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Electrophilic activation of unsaturated systems: Applications to selective organic synthesis*

Samuel Suárez-Pantiga and José M. González‡

Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, 33071 Oviedo, Spain

Abstract: Selected examples from previous work on iodonium-triggered approaches for the functionalization of unsaturated systems, which summarize innovative transformations, are presented. This section is mostly focused on C–C bond-forming processes from alkynes that are directly bonded to relevant heteroatoms, such as iodine, silicon, or sulfur. Besides, recent advances related to iodonium-promoted C–H functionalization reactions are briefly outlined. A second section shows representative examples of our current research activity on electrophilic reactions aimed at the activation of unsaturated systems, which now are built upon the potential offered by the so-called carbophilic catalysis. More specifically, a new catalytic cyclopentannulation sequence from *N*-tosylimines and propargyl tosylates and novel C–H functionalization processes from related tosylates are studied. Likewise, representative examples for the intermolecular Au(I)-catalyzed [2 + 2] cycloaddition reaction of sulfonylallenamides with activated alkenes are given, including the first enantioselective reaction of this type, which is also among the first examples of an intermolecular asymmetric gold-catalyzed reaction. The discussion of the reported iodonium and gold chemistry emphasizes a search for new intermolecular processes, although intramolecular reactions are also pursued and developed.

Keywords: alkynes; allenes; gold; heterocyclic chemistry; iodonium.

INTRODUCTION

Heteroatom-driven reactions are key processes for organic synthesis. Molecules such as enamines, organosulfurs, aziridines, organosilanes, and others have become quite popular in preparative organic chemistry. Besides, the discovery of organic reactions promoted by reactive forms of elements such as iodine or gold falls within the broad borderlines limiting this topic. In fact, electrophiles based on these two elements are among the most popular and widely used nowadays, and a comparison of their potential to initiate electrophilic transformations from different unsaturated systems has recently been traced in the literature [1].

Most of the initial work from our laboratory in this field relates to the development of the synthetic potential of the tetrafluoroborate of bis(pyridine)iodonium(I) (IPy_2BF_4), which is now known and credited as "Barluenga's reagent" [2]. More recently, we became interested in further developing related

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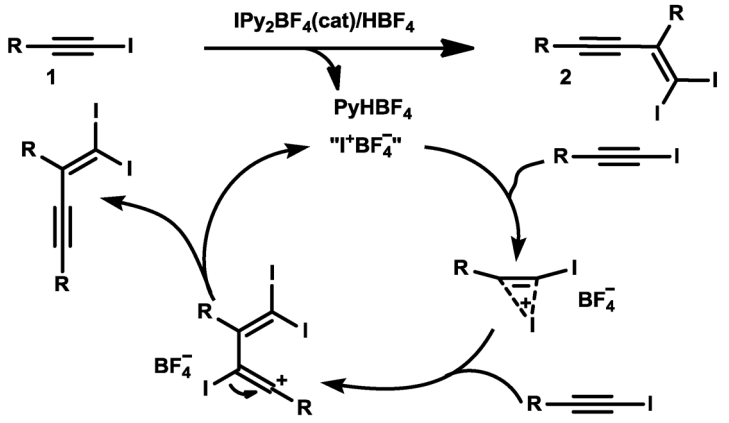
‡Corresponding author: E-mail: jmgd@uniovi.es

chemistry touching on the growing area of Au(I) catalysis, which has demonstrated superb selectivity for the functionalization of carbon-based unsaturated systems, in particular, alkynes and allenes [3].

This account is organized according to the nature of the electrophile used to activate the process and that of the unsaturated hydrocarbon being transformed. First, iodonium-promoted C–C bond-forming reactions from heterosubstituted alkynes are revised. Intramolecular arylation reactions of allenes provide ground for the use of both electrophiles in related transformations. Next, gold-catalyzed domino sequences starting from propargyl tosylates are summarized, and, finally, recent catalytic [2 + 2] cycloaddition reactions of allenyl sulfonamides are covered. The accomplished chemistry with different electrophiles is intended to be analyzed in a complementary rather than competitive manner. Thus, the advantages of each of the processes are proper synthetic tools to access the desired target transformation depending on its ultimate intended application. Altogether, this contribution summarizes work that offers a personal view of a long-lasting journey through this rewarding and broad research topic.

Uncommon coupling reactions of alkynes assisted by classic iodonium chemistry

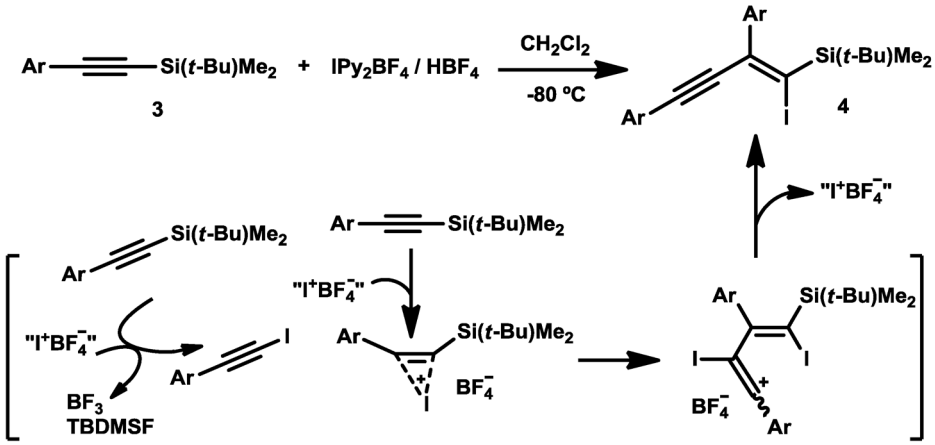
The documented potential for iodination reactions to approach the formation of C–C bonds is mainly confined to intramolecular reactions [4], while their utility to promote related intermolecular processes has been scantily documented. The iodonium-catalyzed dimerization of 1-aryl-2-iodoalkynes **1** represents an early example for the latter type of process [5] (Scheme 1).



Scheme 1 Iodonium-catalyzed head-to-tail dimerization of iodoalkynes.

It was established that addition of 1-aryl-2-iodoalkynes at –80 °C to a solution containing a catalytic amount of IPy_2BF_4 and HBF_4 (1:2 molar ratio, respectively) in dichloromethane furnished selectively, upon stirring and warming the reaction mixture for several additional hours, the dimers **2** arising from a selective head-to-tail coupling mode. The substitution onto the aryl ring proved to be important for the outcome of the process. According to the electrophilic nature of the dimerization, alkynes substituted by more electron-rich arenes undergo the reaction more easily. The reaction of 1-iodo-2-(4-methoxyphenyl)ethyne (50 mmol) with IPy_2BF_4/HBF_4 (1 mmol/2 mmol) in CH_2Cl_2 (100 mL) for 5 h, from –80 to –60 °C, gave the corresponding dimer in 94 % isolated yield. For the intermediate resulting from the coupling step of the two alkynes, a likely interaction between the remote iodine at C-1 and the vinyl cation could play a role in the noticed selectivity, precluding further oligomerization reactions to occur. The reaction failed with iodo derivatives of aliphatic alkynes, but it can be implemented over related iodoenynes.

The reaction of silyl-substituted alkynes **3** towards the Barluenga's reagent was also investigated. It was found that the ancillary ligands attached to silicon play a major role in controlling the selectivity of the process. For instance, from trimethyl(phenylethynyl)silane the sole formation of (iodoethynyl)benzene was noticed, the product arising from an electrophilic ipso-substitution process. However, when the related *tert*-butyldimethyl(phenylethynyl)silane was exposed to equimolecular amounts of the iodinating reagent and tetrafluoroboric acid, a different C–C bond-making process took place efficiently at low temperature (Scheme 2). Functionalized enynes **4** are the result of this stereoselective C–C coupling reaction [6].

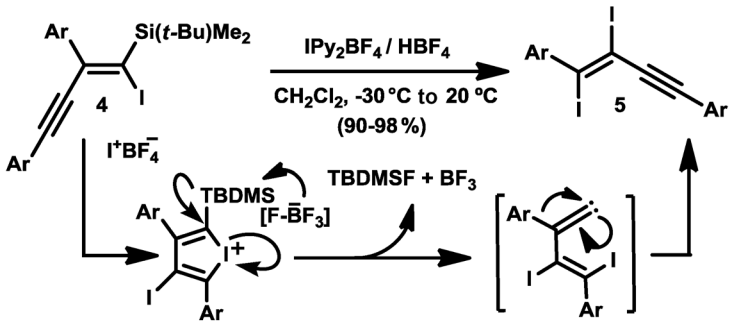


Scheme 2 Intermolecular iodonium-promoted coupling of alkynylsilanes.

A balanced combination of an iododesilylation and a simple iodonium activation of the alkyne was proposed to account for the observed transformation. The iodoalkyne resulting from the former process would be a proper nucleophile to trap the reactive vinylcationic species derived from the electrophilic activation of the silyl-substituted alkyne, which enjoy the stabilization imparted by the iodonium bridge and, additionally, benefit from the preference of silicon to furnish intermediate β-cationic species, matching the observed regioselectivity. The related synthesis of enynes **4** containing two different arenes in a cross-coupling reaction of iodoalkynes with an excess of an alkynylsilane provides further support to this proposal.

The above-depicted coupling reaction runs efficiently using 1:1 molar ratio of the alkynylsilane and the iodinating agent. Nevertheless, at the time of delivering enynes **4**, the overall process releases one equivalent of free iodonium ion into the solution. On this basis, it was proven that the control of the temperature is critical to define the reaction product. So, mixing the reagents at –80 °C and allowing the reaction mixture to rise up to –30, 0 °C for the less electron-rich (arylethynyl) silanes gives the above-reported silicon-containing enynes, in almost quantitative yield. On the other hand, when the reaction mixture is allowed to warm to 20 °C a new and selective transformation occurred. It gives rise to the formation of diiodinated enyne scaffolds **5**. Formally, the structure of these molecules is that one anticipated as the result of a selective "head-to-head" coupling of iodoalkynes. The same result was obtained when pure samples of enynes **4** are allowed to react with the iodonium donor activated by the added acid, from –30 °C to room temperature, see Scheme 3.

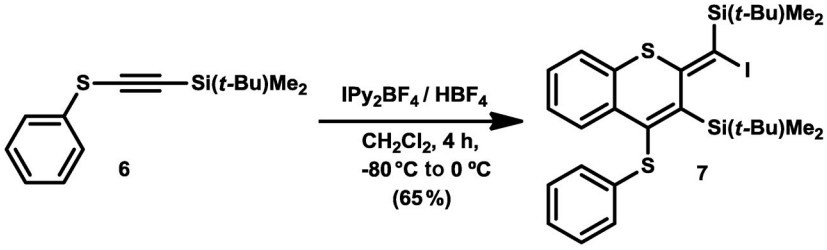
So, in terms of the regioselectivity, for the preparation of diiodinated conjugated enynes using iodonium activation, this overall coupling sequence is complementary to the catalytic dimerization of iodoalkynes (see Schemes 1 and 3).



Scheme 3 Formal access to the head-to-head dimers of iodoalkynes: evidence for the formation of an intermediate iodolium ion in the rearrangement of 1-iodo-1-trialkylsilylenynes.

The mechanism for this reaction was investigated, and an iodolium ion was identified as a key intermediate. It results from the 1,4-neighboring assistance of the remote iodine in the electrophilic activation of the alkyne by the added iodonium ion. This intermediate was characterized by NMR from an experiment using trifluoromethanesulfonate as counter anion. The standard combination of silicon and fluoride (tetrafluoroborate could act as a gentle source of fluoride for this reagent [7]) provides a way to advance this intermediate to the final product through the Fritsch–Buttenberg–Wiechell rearrangement.

The alkyne **6**, featuring sulfur substitution at the terminal position, was also investigated in this context. The high reactivity of this alkyne towards its electrophilic activation associated with the presence of this additional heteroatom determines a new "domino sequence" that comprises two C–C bond-forming steps at the expense of the added electrophile, namely, the alkyne coupling process and a subsequent Friede–Crafts capture of the resulting cationic intermediate (Scheme 4).

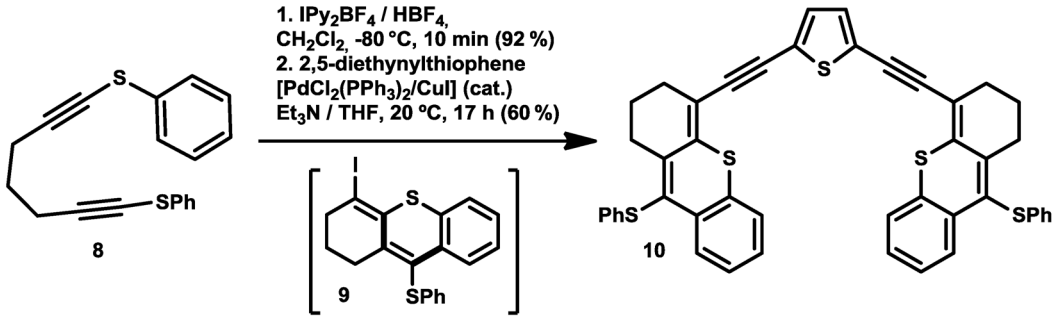


Scheme 4 "Domino" assembly of a 2-methylene-4-(phenylthio)-2*H*-thiochromene scaffold.

The high steric congestion of the selectively assembled 1,4-diene moiety in **7** is reflected in the large value (74.1°) for the torsional angle between the exocyclic double bond and the C–Si bond present in the assembled 2-methylene-4-(phenylthio)-2*H*-thiochromene skeleton [8].

This iododonium-promoted domino sequence was applied to related systems, defining an entirely intramolecular process. For α,ω-diynyl-arylsulfide derivatives, as for instance **8** (Scheme 5), the scarcely observed *exo–endo*-cyclization mode was identified and different polycyclic structures were elaborated in a very fast reaction at low temperature.

The synthetic potential of the formed C–I bond was recognized and used for accessing molecular diversification of the assembled skeleton in **9** using robust contemporary transition-metal-catalyzed transformations, as for the rapid preparation of **10**.



Scheme 5 Molecular diversity: merging iodonium and transition-metal reactions to define selective sequences for C–C bond formation.

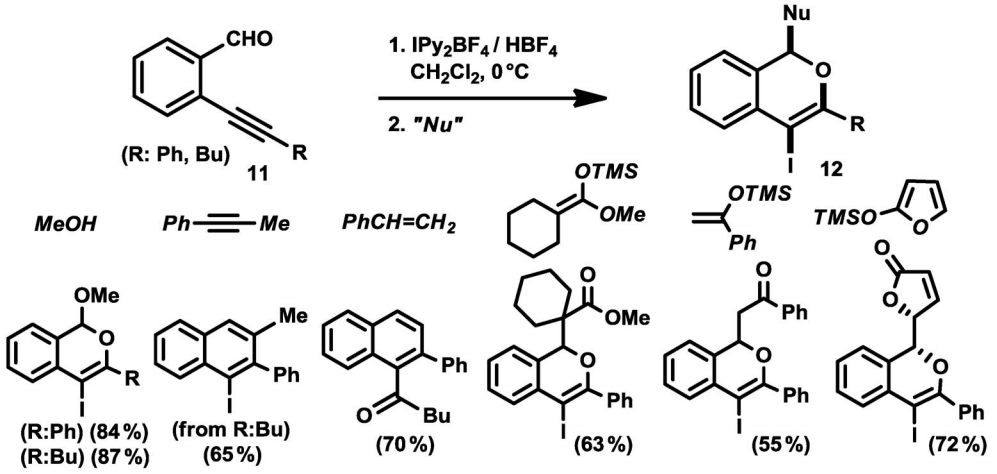
All these facts make the overall sequence amenable for a rapid synthesis of collections of compounds using predictable and modular designing principles, and offering clear potential for targeting interesting applications.

IODONIUM-PROMOTED ACTIVATION OF ALKYNES AS A SYNTHETIC TRIGGERING DEVICE FOR THE ADDITION OF NUCLEOPHILES TO ALDEHYDES: SYNTHETIC APPLICATIONS

During the past decade, our laboratory was interested in establishing processes that upon a selective alkyne activation step promoted by either iodonium ions or carbophilic metal catalysts show useful synthetic complementarity in their results. Some of those transformations were identified and showed the utility of the iodonium-based approach for the application of the resulting building blocks in accessing further molecular diversity [9].

A particularly attractive parallel development was related to the reactivity found associated with the electrophilic functionalization of *o*-alkynyl-benzaldehyde derivatives, a topic in which Yamamoto's group, as well as Larock's laboratory, have been mostly active [10].

The iodonium chemistry allowed functionalization by several external nucleophiles, such as alcohols, alkynes, and alkenes, to take place [11] (Scheme 6).

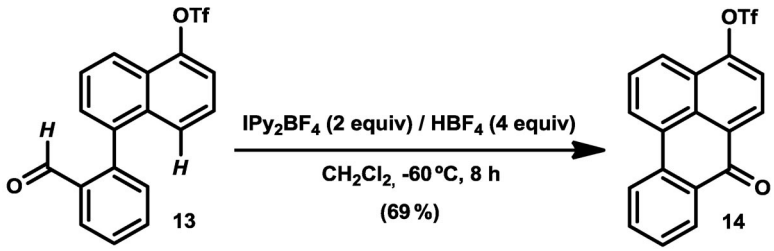


Scheme 6 Flexible iodonium-triggered reaction of *o*-alkynylbenzaldehyde derivatives.

Furthermore, the fluorinating ability of the reaction media was found useful to facilitate additional and distinctive C–C bond-forming reactions using silylated pronucleophiles, as also depicted in Scheme 6. This blend of heteroatoms outlines a set of activating conditions that turns out to be crucial to define a selective combination from these reactive chemical compounds, and that allows defining a collection of unique transformations featuring three different types of bonds being assembled in just a single synthetic operation.

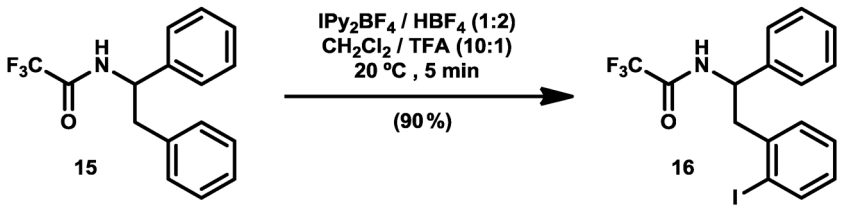
IODONIUM-MEDIATED SELECTIVE C–H FUNCTIONALIZATION REACTIONS OF ARENES

The reactivity of this iodinating agent was exploited to establish different arene C–H functionalization processes, transformations that take place according to a Friedel–Crafts reaction path [12]. In this context, a direct intramolecular arylation of aldehydes leading to benzocyclic ketones has been reported [13], a representative example is given below, see Scheme 7.



Scheme 7 Synthesis of benzocyclic ketones by iodonium-promoted aldehyde arylation reaction.

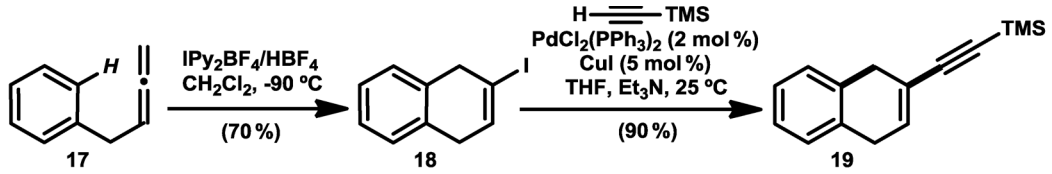
The great capability of the IPy_2BF_4 reagent to perform aromatic iodination reactions was used to furnish a selective postsynthetic modification of small peptides [14]. In this context, the unusual *o*-selectivity found for the iodination of phenylalanine residues in peptides prompted us to search for proper small-molecule fragments that mimic such a directing control over this C–H functionalization reaction. Masking the amino function as the corresponding trifluoroacetamide derivative for phenylalanine and for β- or γ-aryl-alkylamines (see **15**, Scheme 8), was recognized as a convenient option to drive the iodination of these molecules to the desired *ortho*-position [15].



Scheme 8 Trifluoroacetamide as key directing group for a selective *ortho*-iodination.

Synthetic sequences based on this C–H functionalization approach, involving iodination followed by further exploiting the reactivity of the resulting C–I bond, open a powerful route for the selective *ortho*-functionalization of relevant bioactive molecular skeletons [16].

Furthermore, the potential of iodonium-promoted chemistry has been recently exploited to determine advances for the direct C–H functionalization reaction of arenes with allenes [17]. The intermolecular iodoarylation requires electron-rich arenes and ultimately gives substituted 2-iodo-allylated



Scheme 9 Allene iodoarylation reaction: an alternative approach to arene C–H functionalization.

derivatives for the parent arene. The intramolecular process furnishes a powerful entry into the elusive 2-iodo-1,4-dihydronaphthalene scaffold **18**. Partly dehydrogenated aromatic derivatives can be obtained using the rich chemistry of the assembled C(sp^2)-I bond (Scheme 9).

Although formally related with the above-described electrophilic functionalization reaction of unsaturated systems, the discussion on related processes based on gold-catalyzed transformations is deferred to a later section.

So far, different C–C bond-forming reactions summarizing early activity on the iodonium activation of alkynes and allenes have been discussed. The implications of some of these studies for the borderline with the rapidly growing field of metal-mediated C–H bond functionalization have been also analyzed. Besides, this work provides roots to our current research activity aimed to devise new but related electrophilic transformations for alkynes and allenes, this time relying on catalytic processes using different Au(I) complexes to trigger the carbophilic activation of these unsaturated motifs. Again, emphasis is devoted to the search for transformations taking place intermolecularly, although the design and the applications of selected intramolecular processes will also be incorporated to the discussion of this manuscript.

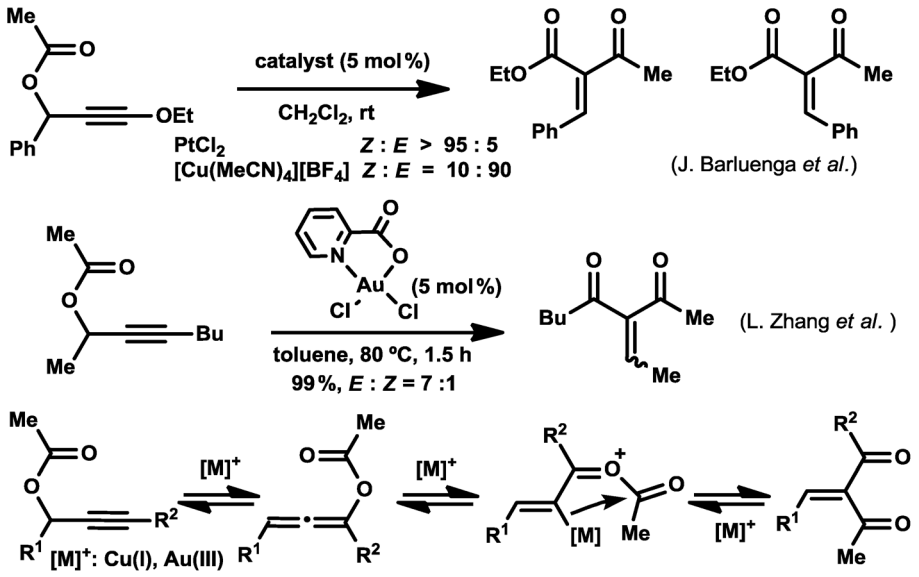
Au(I)-CATALYZED REACTION OF PROPARGYL TOSYLATES WITH IMINES

The idea of electrophilic activation of unsaturated systems comprises a diversity of reactions. Certainly, it represents a powerful and practiced approach to access C–C bond formation through polar reactions. Nowadays, a collection of chemical transformations with potential for selective organic synthesis has been developed on the basis of gold-catalyzed reactions. It is now well established that this research field has rapidly emerged and built upon representative examples of innovative chemical transformations [18].

Recently, it has been shown that esters derived from simple propargylic alcohols are unique substrates to define new chemical transformations through metal catalysis, some of them relating with prior isomerization to functionalized allenes [19]. Furthermore, it has been established that those precursors give Knoevenagel-like adducts upon exposition to Au(III), Cu(I), or Pt(II) catalysts [20] (Scheme 10).

The key intermediate for these transformations is a compound having a σ-metal-C(sp^2) bond. It arises from the rearrangement of the propargylic ester to a propa-1,2-dien-1-yl acetate derivative and its subsequent activation by the electrophilic metal. Upon formation of the π-complex, this system evolves to generate a cationic intermediate that contains the metal attached to the central carbon of the former allene (see Scheme 10). The acetoxy group plays a key role in the reaction by providing stabilization to the generated electronic deficiency at C-1 at the time of prompting the generation of an acylium ion, which eventually will supply the required electrophile that is intramolecularly captured by the organometallic reagent placed at C-2, leading to the formation of the noticed products.

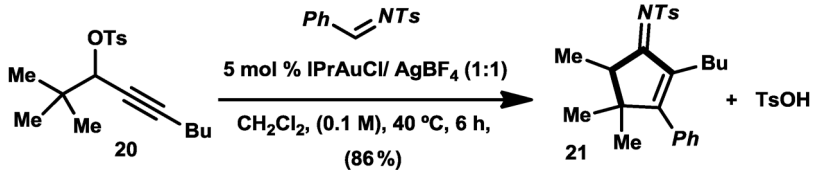
Thus, we reasoned that modifying the nature of the capping acid in the ester functionality might allow for both the discovery of alternative transformations from simple propargylic alcohols and the search for intermolecular reactions based on previously recognized ways of generating organo-gold intermediates.



Scheme 10 Knoevenagel-like adducts from metal-catalyzed rearrangements of propargyl acetates.

Interestingly, a family of propargyl tosylates was found useful to verify this hypothesis. A new cyclization was shown from the Au(I)-catalyzed intermolecular reaction of propargyl tosylates with *N*-tosylaldimines [21].

It gives rise to the formation of cyclopent-2-enimines as the result of a major reorganization of both components and provides formal examples of the rare [4 + 1] cyclization mode. The molecular structure of the assembled adduct was established by X-ray analysis (Scheme 11).

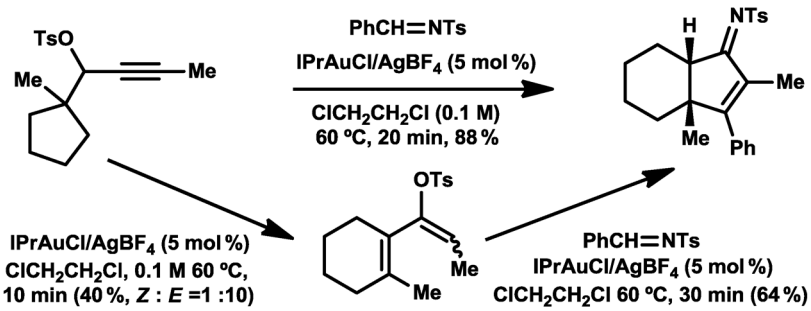


Scheme 11 Au(I)-catalyzed formal [4 + 1] cyclization of propargyl tosylates and aldimines.

A quick optimization of the process revealed that the reaction of Au(I) chloride complex with the *N*-heterocyclic carbene (NHC) ligand IPr [IPr: 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene] supplies an active and convenient catalytic system upon activation by Ag(I) tetrafluoroborate. Alternatively, conducting the reaction in 1,2-dichloroethane, at 60 °C, allows the reaction time to be reduced. Under these conditions, it was shortened to 1 h, furnishing the product **21** in comparable yield.

Moreover, the reaction poses an interesting mechanistic question as both components undergo noticeable changes for the assembling of the reaction product. An exploratory study of the reactivity of the propargylic tosylate under the influence of the gold catalyst, in the absence of the imine, was clarifying. It revealed that the overall process is a Au(I)-catalyzed domino sequence that comprises several precisely concatenated reaction steps.

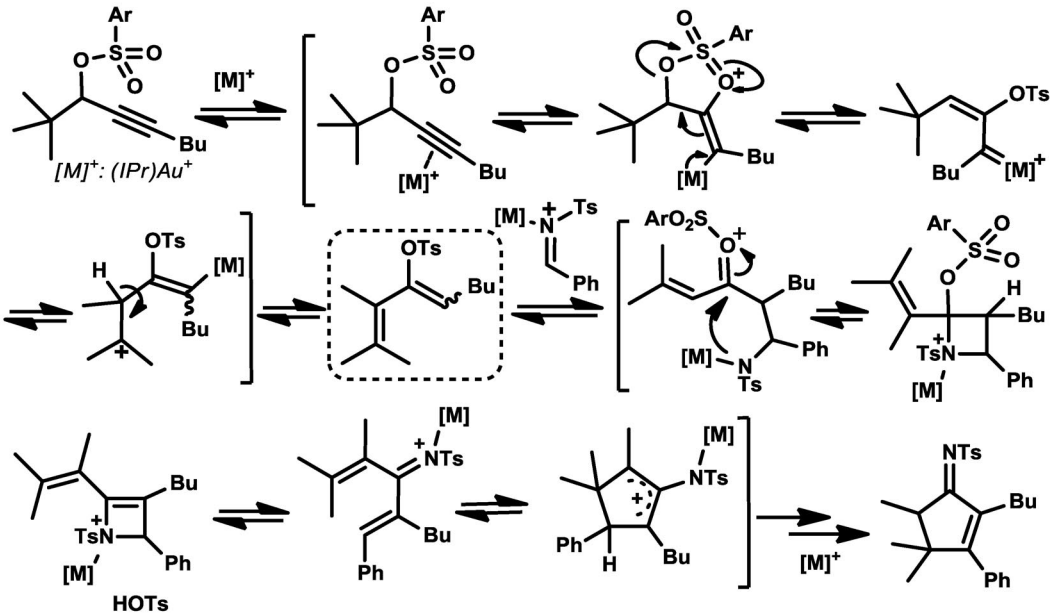
Among them, a catalytic sequence involves an stepwise and clean isomerization of the starting propargyl tosylate into a related 2-tosyloxy-1,3-butadiene derivative. A representative of this class of conjugated dienes has been isolated and characterized from the Au(I)-catalyzed isomerization of a



Scheme 12 Au(I)-catalyzed "domino" reaction: Synthesis of cyclopent-2-enimine derivatives from propargyl tosylates and *N*-tosylimines.

propargyl tosylate (Scheme 12). Subsequent exposure of the isolated 2-tosyloxy-1,3-diene to the imine under the influence of the catalytic system led to a cyclopent-2-enimine derivative having the same structure that was assembled upon reacting the parent propargyl tosylate with the corresponding imine.

The initial isomerization process comprises a Au(I)-promoted 1,2-tosyl rearrangement that induces further 1,2-vicinal migration of hydrogen or alkyl, as a function of the structure of the starting tosylate. Subsequent elimination of a proton and eventual protonation of the C–Au bond renders the tosyloxy diene and closes an initial catalytic cycle. Interestingly, the cyclization of the imine with the generated 2-tosyloxy-1,3-diene entails another catalytic and complex reaction sequence that, among others, includes a formal imine metathesis and one of the early examples of an aza-Nazarov cyclization event (Scheme 13).



Scheme 13 Detailed proposed steps behind the synthesis of cyclopent-2-enimines.

Besides, the reaction has been found compatible with various *N*-tosylaldimines, both derived from aliphatic and aromatic aldehydes. For the acetylenic fragment, it requires a secondary or tertiary

homopropargylic system. Among other products, C-4 spiro-substituted derivatives of the cyclopent-2-enimine core have been prepared. A selective 1,2-hydrogen shift is involved in this transformation. Interestingly, a clean ring expansion from a cylopenta- to a cyclohexane fused frame has been also encompassed within the overall process, furnishing the *N*-tosyl imine derivative of the 3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one scaffold.

HYDROARYLATION OF ARENES WITH ELECTRON-WITHDRAWING SUBSTITUENTS: APPLICATIONS IN HETEROCYCLIC CHEMISTRY

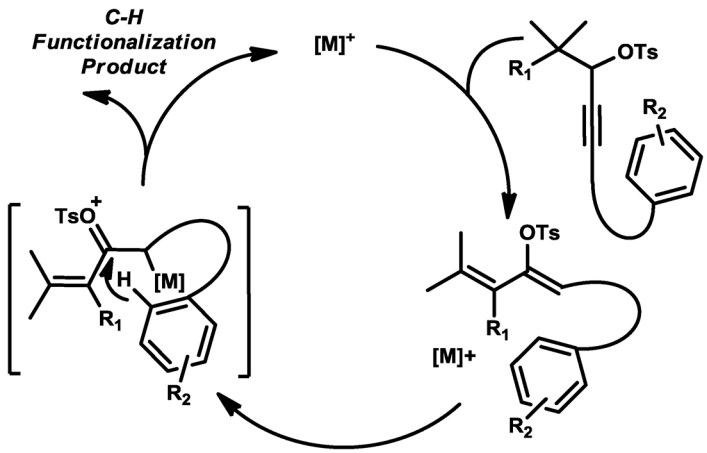
The recognition of the above isomerization, which precedes the ultimate intermolecular cyclization with the *N*-tosylimine, prompted us to further attempt to exploit its potential for a different synthetic purpose.

Metal-catalyzed alkyne hydroarylation processes offer a powerful entry for the synthesis of hetero- and carbocyclic benzofused compounds. In general, this kind of process is restricted to electron-rich arenes.

Mechanistically differentiated alternatives have been devised to override this constraint, and, though yet scant, seminal examples to conduct hydroarylation reactions of alkynes with electron-poor arenes are known [22].

We reasoned that propargyl tosylates can be a proper class of active partners for catalytic intramolecular arylation studies. The initial isomerization step could be followed by a subsequent and selective activation of the tosyloxy-1,3-diene moiety.

All this would result in the generation of cationic species that would be reactive towards properly located arenes to render the desired C–H functionalized product for a variety of arenes (Scheme 14).

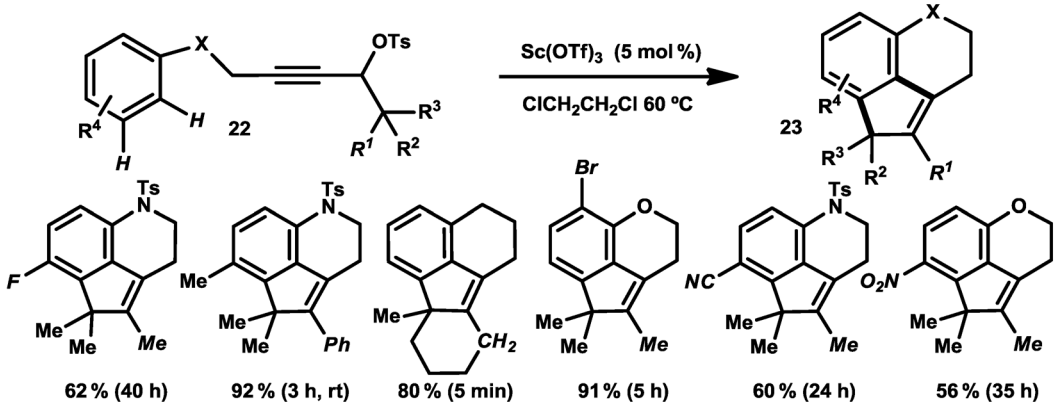


Scheme14 Metal-catalyzed intramolecular C–H functionalization of ω-aryl propargyl tosylates.

To verify this hypothesis, several tosylates containing structural features reminiscent of those early used in the previous [4 + 1] cycloaddition with imines were prepared, and their catalytic transformation were assayed [23].

Different catalysts were tested along the exploratory screening, and the more robust and general results were obtained using $Sc(OTf)_3$ this time.

Au(I) complexes were active and efficient to furnish derivatives from all-carbon as well as *N*-linked precursors, but failed to produce cyclization from the related *O*-linked starting material that, instead, suffers from major propargylic cleavage.



Scheme 15 Catalytic electrophilic C–H bifunctionalization from ω-aryl propargyl tosylates.

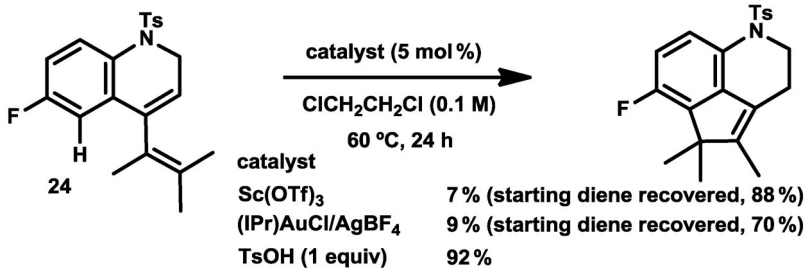
The cyclization products **23** that were accessed have several interesting features (Scheme 15), among them, the structure of the resulting product that is the result of not just one but two consecutive functionalization processes.

Also, the process was found tolerant with the use of aromatic rings that, apart from the tethering element, bear additional electron-withdrawing substituents. Selected examples are given within Scheme 15.

The mechanism of the reaction was studied in detail. Interestingly, from the reaction of a propargylated derivative of *N*-tosyl-4-fluoroaniline, more specifically the 6-[*N*-(4-fluorophenyl)-4-methylphenylsulfonamido]-2,2-dimethylhex-4-yn-3-yl 4-methylbenzenesulfonate, which gives the doubly functionalized derivative as the main reaction product, it was possible to isolate a minor amount of the corresponding mono-functionalized compound **24**.

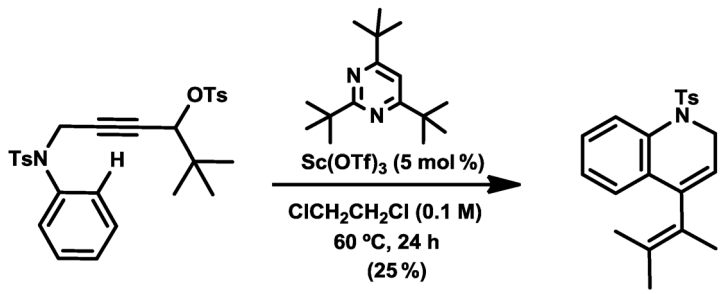
So, this molecule was then used for further investigation of the reaction mechanism. It was found that the initial cyclization step requires the activation provided by the externally added catalyst, either $Sc(OTf)_3$, that showed broader scope, or catalytic systems based on the activation of IPrAuCl by $AgBF_4$. Alternative protic acids were not adequate for this purpose.

For the second cyclization, it was found that sulfonic acid is a competent and highly efficient promoter (Scheme 16). It should be noticed that for the overall process, sulfonic acid is produced in stoichiometric amount as the result of the first catalytic cycle.



Scheme 16 Domino bifunctionalization of ω-aryl propargyl tosylates: the second step.

Thus, the invoked mechanistic proposal comprises an initial catalytic cyclization relying on the activation of the propargylic tosylate by the added metal catalyst followed by a subsequent cyclization promoted by the generated sulfonic acid, which is released as the byproduct of the first cyclization.



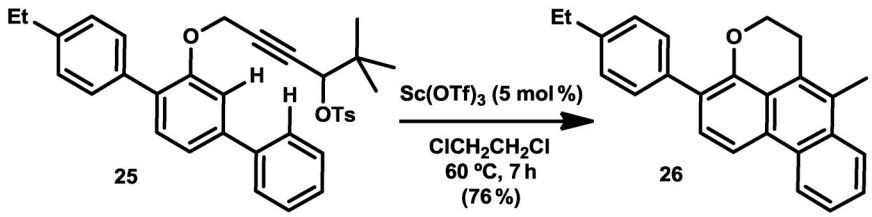
Scheme 17 Suppression of the second catalytic step by addition of a base.

This rationalization was further supported by two types of independent experiments that were explored. In this regard, upon addition of a proper base (2,4,6-tri-*tert*-butylpyrimidine, TTBP) the second cyclization was suppressed (Scheme 17).

Furthermore, the results obtained from the labeling experiments also support the proposed mechanistic rationalization for the noticed overall C–H bifunctionalization process.

The possibility of replacing the late annulation that occurs on the same ring by another potential cyclization event was explored. Thus, the structure of the starting compound was slightly modified to target the synthesis of a different molecular scaffold.

The substrate **25** was delineated and prepared with the aim of activating two different aromatic units, properly located within the same molecule, in one synthetic operation. This possibility was accomplished as shown in Scheme 18.

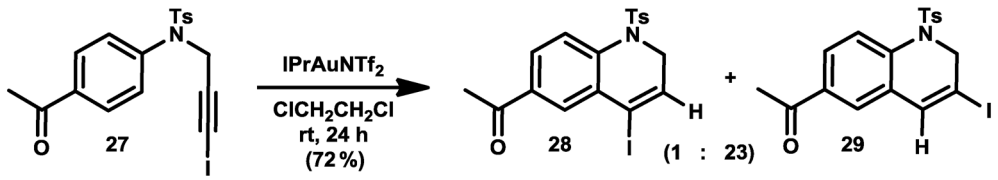


Scheme 18 Domino bifunctionalization of two different aromatic rings in one catalytic process.

The outcome of the reaction was rationalized assuming that the first and the second cyclizations will evolve following the same paths explained above. The difference will relate to the size of the cyclic structure to be formed in second place, which this time is a six-membered ring, as a consequence of the topology of the precursor.

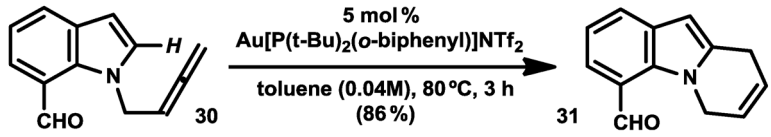
Now, the overall domino sequence comprises an additional step, which is a retro-ene reaction that will smoothly afford to the formation of the noticed polycylic compound **26** at the expense of the release of a molecule of propene.

Our group has a long-standing interest in the elaboration of heterocyclic compounds using the heteroatom as a convenient tethering element and relying on a selective C–C bond-forming operation for the late ring-closing process. On this ground we investigated additional transformations based on Au(I) catalysis. Among them, transformations that exploited the potential offered by plausible Au(I) vinylidene intermediates to generate various *N*-tosyl derivatives of the 3-iodo-1,2-dihydroquinoline core by the catalytic hydroarylation of *N*-(3-iodoprop-2-ynyl)-*N*-tosylanilines **27**, a class of compounds which cannot be accessed by direct iodoarylation of the parent alkyne [24] (Scheme 19).



Scheme 19 Heterocyclic synthesis from catalytic C–C formation through gold vinylidenes.

Also related, the privileged skeleton of indole was selectively modified upon clean and catalytic cycloisomerization of differently substituted 1-(2,3-butadienyl)-1*H*-indoles **30** to produce valuable pyrido[1,2-*a*]-1*H*-indole derivatives **31** (Scheme 20).



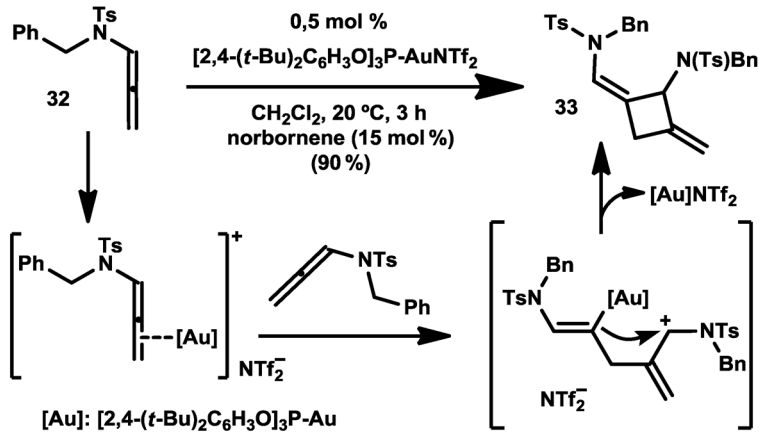
Scheme 20 Heterocyclic modification via 6-*endo* allene hydroarylation.

The mechanism for this reaction was further investigated in detail. The study included kinetic, labeling, and NMR-monitoring experiments, but these results will not be detailed here [25]. Also worth mentioning, an interesting observation was made when the cyclization of related *N*-allenyl-*N*-aryl-sulfonamide derivatives was explored. For the cyclization of these compounds having nitrogen directly attached to the reactive unsaturation, a significant solvent effect was noticed. When rather than using toluene their cyclization was attempted in methylene chloride a clearly differentiated evolution was noticed and functionalized cyclobutane frames were formed [26], as it will be outlined and discussed in the following section.

GOLD-CATALYZED DIMERIZATION OF *N*-ALLENYL SULFONAMIDES AND [2 + 2] CYCLOADDITION REACTIONS WITH ACTIVATED ALKENES

The discovery of selective chemical transformations associated with cyclobutane frames is the subject of current attention, and the synthesis of this structural unit keeps on receiving attention. For this purpose, through cycloaddition reactions with alkenes, allenes are unique substrates [27], but the intermolecular [2 + 2] cycloaddition involving both partners being electron-rich systems is an elusive transformation [28]. As quoted above, while dealing with gold-catalyzed hydroarylation reactions of allenes, it was discovered that different types of *N*-allenyl sulfonamide derivatives **32** can be selectively dimerized [26]. For this purpose, it was found that addition of a co-catalytic amount of norbornene was beneficial to improving the desired process, as it minimizes a fast consumption of the starting allene, likely via its competitive evolution through an extensive oligomerization process. Using this approach, functionalized alkylidenecylobutane derivatives **33** were smoothly obtained from the catalytic homodimerization reaction of *N*-allenyl sulfonamides, a process that occurs in a regio- and stereoselective manner. An example is depicted in Scheme 21.

The formation of the [2 + 2] cycloadduct **33** was rationalized assuming a stepwise reaction in agreement with the precedents for gold-catalyzed addition reactions to allenes [29]. The activation of the allenamide by the Au(I) catalyst determines a certain degree of positive charge at the allene distal carbon atom, which promotes the first C–C bond-forming step by electrophilic attack to the second molecule of an allenamide generating a new cation, and with gold remaining bonded to the central carbon

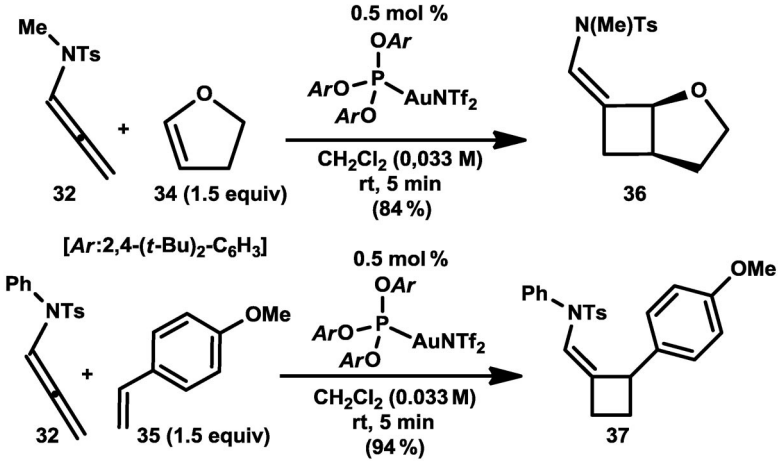


Scheme 21 Au(I)-catalyzed selective homodimerization of *N*-allenyl sulfonamides.

of the initially activated allene. Subsequent ring-closing furnishes the cyclobutane and closes the catalytic cycle by the attack of the C–Au bond to the cationic center developed on the second allene.

On this basis, exploring the possibility of replacing the second allene by another type of nucleophilic partner that could actively take place in the cyclization would be of synthetic relevance.

Our focus was on enol ethers **34** and other activated alkenes **35**, for the reason given above. After some experimental optimization, it was possible to identify suitable conditions to carry out this elusive [2 + 2] cycloaddition reaction under gold catalysis, using a reasonable experimental protocol [26] (Scheme 22).



Scheme 22 Phosphite-Au(I) catalyzed [2 + 2] intermolecular cycloaddition of *N*-allenyl sulfonamides and activated alkenes.

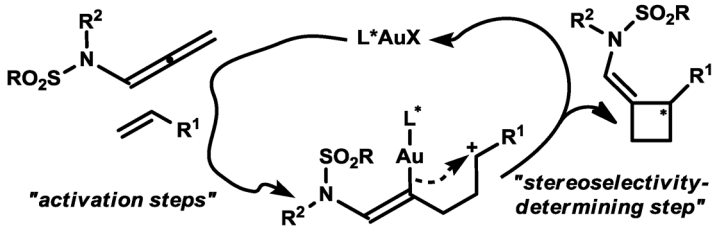
It was found that using the depicted phosphite ligand, better performances were accomplished than using other gold catalysts based on alternative standard ligand, always using the bis[(trifluoromethane)sulfonyl]amide (NTf_2) as counter anion that provides a silver-free active catalytic system, as early documented by Gagosz [30].

This cyclization of allenyl sulfonamides with activated alkenes does not require the presence of any additive or other chemical entities as dehydrating agents.

Both terminal and internal allenyl sulfonamides are reactive, and the remaining substituent on nitrogen could be aliphatic, aromatic, or even benzylic groups.

Also, *tert*-butyl(diphenyl)silyl 1,2-propadienyl ether was successfully assayed and co-cyclized with 2,3-dihydrofuran in 88 % isolated yield. For the alkene, differently substituted enol ethers and vinyl arenes have been identified as useful partners.

Furthermore, another interesting opportunity is associated with the possibility of using Au(I) complexes with enantiopure chiral ligands to attempt a catalytic asymmetric synthesis of related alkylidenecyclobutane derivatives. This hypothesis is graphically outlined in Scheme 23.



Scheme 23 A possible catalytic asymmetric Au-catalyzed [2 + 2] intermolecular cycloaddition.

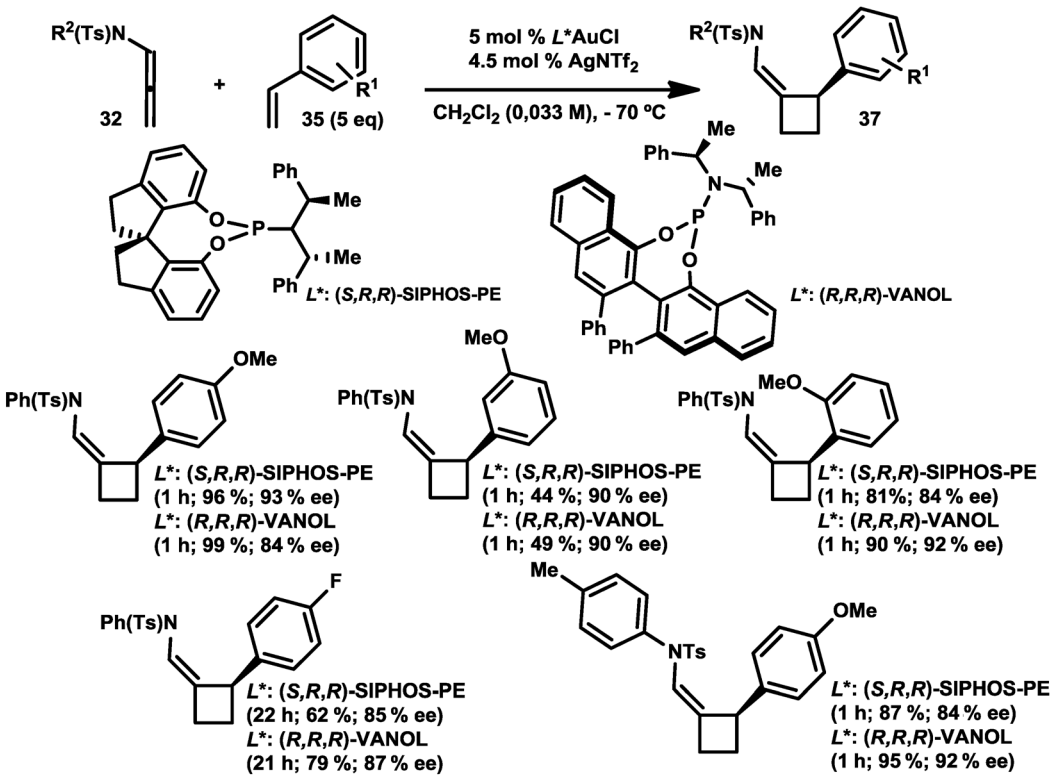
An exploratory study to define proper experimental conditions was conducted using the *N*-allenyl sulfonamide derived from aniline and 4-methoxystyrene. Those substrates were chosen as models on the basis of their superior performance in the previously investigated racemic version, for which these two partners gave the highest turnover number (TON) and turnover frequency (TOF) values (188 and 2256 h^{-1}, respectively). An experimental survey to identify suitable ligands to control the absolute stereochemistry of this stepwise cycloaddition led to good results for two known phosphoramidite ligands [31]. Specifically, those derived from the interaction of (*R*,*R*)-bis(1-phenylethylamine) and either (*R*)-VANOL or (*S*)-1,1'-spirobiindane-7,7'diol that furnish (*S*)-SIPHOS-PE. Their Au(I) complexes were found to produce the same enantiomer for a representative collection of starting *N*-allenyl-*N*-aryl sulfonamides and vinyl arenes, some of them are depicted in Scheme 24 [32].

The influence of the substitution at the sulfonyl group over the enantioselectivity was also investigated. It was found that the use of a tosyl group offers a balanced situation with respect to both the chemical yield and the enantiomeric excess (ee). Also of synthetic interest, the phosphoramidites obtained from the same chiral amine upon reaction with (*S*)-VANOL or simple (*S*)-BINOL allow the complementary preparation of the opposite enantiomer.

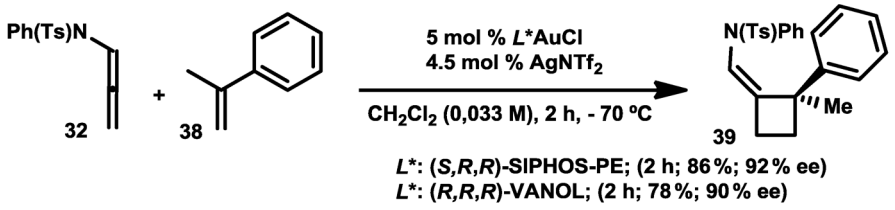
Another synthetic question that was explored was the possibility of accessing chiral quaternary centers with reasonable enantiocontrol using this reaction. Now, 2-phenylpropene **38** was tested as the alkene. This is a challenging situation as for the previous cases the stereoselection derives from discrimination between hydrogen and an aromatic ring, and now hydrogen is replaced by a methyl group. The first successful example is presented in Scheme 25.

This time, the catalyst based on SIPHOS was more active than the one based on VANOL, contrary to most of the situations presented previously in the precedent Scheme 24. This trend was also found for the reaction of the related allenyl sulfonamide derived from benzylamine. In this case, the yields were in the range of the 70s and the ee values in the mid-80s, but again slightly in favor for the same chiral ligand.

Overall, the first examples of an intermolecular Au(I)-catalyzed asymmetric synthesis of cyclobutane derivatives from reaction of allenes and alkenes were obtained.



Scheme 24 Phosphoramidite-Au(I) catalyzed [2 + 2] cycloaddition of allenamides and styrenes.



Scheme 25 Enantioselective access to a quaternary carbon by [2 + 2] cycloaddition.

SUMMARY AND CONCLUSION

Iodine and gold are borderline elements with respect to the aim of ICHAC Conferences, still falling within the limit of the general interest for this event. This article summarizes work done along the years in our laboratory on research aimed at the discovery of synthetically useful transformations, which are triggered by reactive compounds based on those elements. The electrophilic nature of all those processes is a major and distinctive common feature of the included transformations. There are many differences between chemical entities based on those elements, but iodonium ions and Au(I) cationic species share a remarkable capability to selectively activate unsaturations based on carbon. Thus, it is reasonable and desirable to attempt to exploit the potential offered by these reactive species to trigger new processes that start from this kind of unsaturation. Closely associated to each of them is an inherently diverse selectivity for the initial activation and different operation modes for stabilizing the resulting intermediates. All this can be nicely exploited to implement a diversity of transformations. To this

end, rather than contending approaches they might be considered as allied tools in searching for reaction discovery, sometimes giving nice complementarity.

For the case of iodonium-based chemistry, both inter- and intra-molecular reactions leading to C–C bond formation have been discussed, with emphasis on a versatile elaboration of heterocyclic compounds that is planned for rapid diversification by further catalytic modification of the C–I bond. Also for iodine, most of the reactions are stoichiometric, though some catalytic C–C bond formation was also documented, which suggests an attractive but complex scenario for further advancement of the field. Au(I) complexes are known to offer unique opportunities for establishing related catalytic approaches directed towards the assembly of synthetically relevant building blocks from coupling of common precursors. The [4 + 1] intermolecular cyclization of propargyl tosylates with imines is a clear example of this notion. At the same time, different types of Au(I)-catalyzed C–H functionalization and cycloisomerization reactions are presented to provide smooth access to otherwise elusive substitution patterns of common heterocyclic frames. The possibility that the remaining spectator ligand on the Au(I) catalyst offers to transmit key information to control both the activation and the stereo-differentiating steps has been exploited for the construction of chiral cyclobutane frames from the intermolecular [2 + 2] cycloaddition of allenyl sulfonamides with vinylbenzene derivatives.

Altogether, this work is just another example of the power that heteroatom chemistry still holds for reaction discovery in organic synthesis.

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REFERENCES

1. (a) Y. Yamamoto, I. D. Gridnev, N. T. Patil, T. Jin. *Chem. Commun.* 5075 (2009); (b) S. Hummel, S. F. Kirsch. *Beilstein J. Org. Chem.* **7**, 847 (2011).
2. For key references on selected synthetic application of the IPy_2BF_4 reagent not addressed in this article, see: for aromatic iodination: (a) J. Barluenga, J. M. González, M. A. García-Martín, P. J. Campos, G. Asensio. *J. Org. Chem.* **58**, 2058 (1993); for oxidative opening of cycloalkanols: (b) J. Barluenga, F. González-Bobes, S. R. Ananthoju, M. A. García-Martín, J. M. González. *Angew. Chem., Int. Ed.* **40**, 3389 (2001); for oxidation of alcohols to carbonyls: (c) J. Barluenga, F. González-Bobes, M. C. Murguía, S. R. Ananthoju, J. M. González. *Chem.—Eur. J.* **10**, 4206 (2004).
3. For selected recent reviews, see: (a) A. Corma, A. Pérez-Leyva, M. Sabater. *Chem. Rev.* **111**, 1657 (2011); (b) H. Huang, Y. Zhou, H. Liu. *Beilstein J. Org. Chem.* **7**, 897 (2011).
4. For selected examples of intramolecular reactions, see: (a) J. Barluenga, J. M. González, P. J. Campos, G. Asensio. *Angew. Chem., Int. Ed. Engl.* **27**, 1546 (1988); (b) M. B. Goldfinger, T. M. Swager. *J. Am. Chem. Soc.* **116**, 7895 (1994); (c) S. A. Worlikar, T. Kesharwani, T. Yao, R. C. Larock. *J. Org. Chem.* **72**, 1347 (2007); (d) B. Crone, S. F. Kirsch, D. Umland. *Angew. Chem., Int. Ed.* **49**, 4661 (2010).
5. J. Barluenga, J. M. González, I. Llorente, P. J. Campos. *Angew. Chem., Int. Ed. Engl.* **32**, 893 (1993).

6. J. Barluenga, I. Llorente, L. J. Álvarez-García, J. M. González, P. J. Campos, M. R. Díaz, S. García-Granda. *J. Am. Chem. Soc.* **119**, 6933 (1997).
7. J. Barluenga, P. J. Campos, J. M. González, J. L. Suárez, G. Asensio. *J. Org. Chem.* **56**, 2234 (1991).
8. J. Barluenga, G. P. Romanelli, L. J. Álvarez-García, I. Llorente, J. M. González, E. García-Rodríguez, S. García-Granda. *Angew. Chem., Int. Ed. Engl.* **37**, 3136 (1998).
9. For instance, for the intramolecular addition of N–H to alkynes to give indoles (iodination): (a) J. Barluenga, M. Trincado, E. Rubio, J. M. González. *Angew. Chem., Int. Ed.* **42**, 2406 (2003); (gold catalysis): (b) A. Arcadi, G. Bianchi, F. Marinelli. *Synthesis* 610 (2004); 5-*endo-dig* carbocyclization of alkynes with dicarbonyl compounds (gold catalysis): (c) S. T. Staben, J. J. Kennedy-Smith, F. D. Toste. *Angew. Chem., Int. Ed.* **43**, 5350 (2004); (iodination): (d) J. Barluenga, D. Palomas, E. Rubio, J. M. González. *Org. Lett.* **9**, 2823 (2007).
10. For a selection of representative papers in the field, see: (a) N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto *J. Am. Chem. Soc.* **124**, 12650 (2002); (b) K. R. Roesch, R. C. Larock. *J. Org. Chem.* **67**, 86 (2002); (c) N. Asao, T. Nogami, S. Lee, Y. Yamamoto. *J. Am. Chem. Soc.* **125**, 10921 (2003); (d) T. Yao, X. Zhang, R. C. Larock. *J. Am. Chem. Soc.* **126**, 11164 (2004); (e) N. Asao, H. Aikawa. *J. Org. Chem.* **71**, 5249 (2006).
11. (a) J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González. *J. Am. Chem. Soc.* **125**, 9028 (2003); (b) J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González. *Org. Lett.* **5**, 4121 (2003); for applications to the elaboration of indole and mechanistic studies, see: (c) J. Barluenga, H. Vázquez-Villa, A. Ballesteros, J. M. González. *Adv. Synth. Catal.* **347**, 526 (2005); (d) J. Barluenga, H. Vázquez-Villa, I. Merino, A. Ballesteros, J. M. González. *Chem.—Eur. J.* **12**, 5790 (2006).
12. (a) J. Barluenga, M. Trincado, E. Rubio, J. M. González. *J. Am. Chem. Soc.* **126**, 3416 (2004); (b) J. Barluenga, M. Trincado, M. Marco-Arias, E. Rubio, A. Ballesteros, J. M. González. *Chem. Commun.* 2008 (2005).
13. J. Barluenga, M. Trincado, E. Rubio, J. M. González. *Angew. Chem., Int. Ed.* **45**, 3140 (2006).
14. G. Espuña, G. Arsequell, G. Valencia, J. Barluenga, J. Álvarez-Gutiérrez, A. Ballesteros, J. M. González. *Angew. Chem., Int. Ed.* **43**, 325 (2004).
15. J. Barluenga, J. Álvarez-Gutiérrez, A. Ballesteros, J. M. González. *Angew. Chem., Int. Ed.* **46**, 1281 (2007).
16. For closely related studies, see: J.-J. Li, T.-S. Mei, J.-Q. Yu. *Angew. Chem., Int. Ed.* **47**, 6452 (2008).
17. J. Barluenga, E. Campos-Gómez, A. Minatti, D. Rodríguez, J. M. González. *Chem.—Eur. J.* **15**, 8946 (2009).
18. For selected reviews: (a) A. S. K. Hashmi. *Chem. Rev.* **107**, 3180 (2007); (b) A. Fürstner, A. P. Davies. *Angew. Chem., Int. Ed.* **46**, 3410 (2007); (c) Z. Li, C. Brouwer, C. He. *Chem. Rev.* **108**, 3239 (2008); (d) A. Arcadi. *Chem. Rev.* **108**, 3266 (2008); (e) A. Jiménez-Núñez, A. M. Echavarren. *Chem. Rev.* **108**, 3326 (2008); (f) D. J. Gorin, B. D. Sherry, F. D. Toste. *Chem. Rev.* **108**, 3351 (2008); (g) A. Fürstner. *Chem. Soc. Rev.* **38**, 3208 (2009).
19. (a) N. Marion, S. P. Nolan. *Angew. Chem., Int. Ed.* **46**, 2750 (2007); (b) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan. *J. Am. Chem. Soc.* **129**, 9868 (2007); (d) Y. Peng, L. Cui, G. Zhang, L. Zhang. *J. Am. Chem. Soc.* **131**, 5062 (2009); (d) P. Mauleón, J. Krinsky, F. D. Toste. *J. Am. Chem. Soc.* **131**, 4513 (2009).
20. (a) S. Wang, L. Zhang. *J. Am. Chem. Soc.* **128**, 8414 (2006); (b) J. Barluenga, L. Riesgo, R. Vicente, L. A. López, M. Tomás. *J. Am. Chem. Soc.* **129**, 7772 (2007).
21. S. Suárez-Pantiga, E. Rubio, C. Álvarez-Rúa, J. M. González. *Org. Lett.* **11**, 13 (2009).
22. For seminal work, see: (a) N. Chernyak, V. Gevorgyan. *J. Am. Chem. Soc.* **130**, 5636 (2008); (b) N. Marion, S. Díez-González, P. de Frémont, A. R. Noble, S. P. Nolan. *Angew. Chem., Int. Ed.* **45**, 3647 (2006).

23. S. Suárez-Pantiga, D. Palomas, E. Rubio, J. M. González. *Angew. Chem., Int. Ed.* **48**, 7857 (2009).
24. P. Morán-Poladura, S. Suárez-Pantiga, M. Piedrafita, E. Rubio, J. M. González. *J. Organomet. Chem.* **696**, 12 (2011).
25. J. Barluenga, M. Piedrafita, A. Ballesteros, A. L. Suárez-Sobrino, J. M. González. *Chem.—Eur. J.* **16**, 11827 (2010).
26. S. Suárez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio, J. M. González. *Adv. Synth. Catal.* **354**, 1651 (2012).
27. B. Alcaide, P. Almendros, C. Aragoncillo. *Chem. Soc. Rev.* **39**, 783 (2010).
28. For ongoing activity, see: (a) X.-X. Li, L.-L. Zhu, W. Zhou, Z. Chen. *Org. Lett.* **14**, 436 (2012); (b) H. Faustino, P. Bernal, L. Castedo, F. López, J. L. Mascareñas. *Adv. Synth. Catal.* **354**, 1658 (2012); (c) M. Ebisawa, H. Kusama, N. Iwasawa. *Chem. Lett.* **41**, 7868 (2012).
29. For reviews, see, for instance: (a) A. S. K. Hashmi, M. Bührle. *Aldrichim. Acta* **43**, 27 (2010); (b) N. Krause, C. Winter. *Chem. Rev.* **111**, 1994 (2011).
30. N. Mézailles, L. Ricard, F. Gagosz. *Org. Lett.* **7**, 4133 (2005).
31. For reviews on phosphoramidite ligands in asymmetric catalysis, see: (a) J. Teichert, B. L. Feringa. *Angew. Chem., Int. Ed.* **49**, 2486 (2010); for a selected example on the early use of these ligands in gold catalysis, see: (b) I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas. *J. Am. Chem. Soc.* **131**, 13020 (2009); for a recent study, see: (c) H. Teller, M. Corbet, L. Mantilli, G. Gopakumar, R. Goddard, W. Thiel, A. Fürstner. *J. Am. Chem. Soc.* **134**, 15331 (2012).
32. S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio, J. M. González. *Angew. Chem., Int. Ed.* **51**, 11552 (2012).

