Gold-catalyzed decorations of arenes and heteroarenes with C–C multiple bonds

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Synthetic organic chemistry has been markedly affected by the booming of gold catalysis over the past decade. The renaissance of this coinage metal allowed unprecedented transformations to be realized in a highly selective manner and rendered "old chemistry" more accessible from a practical point of view. Particularly, organic compounds containing C–C multiple bonds benefited from the high carbophilicity of gold species, that opened access to a great chemical diversity through direct and selective π-electrophilic activations. Nowadays, the complexity of naturally occurring compounds based on functionalized aromatic frameworks continues to inspire and influence developments in synthetic chemistry. Furthermore, the ubiquitous presence of arene-based systems in pharmaceuticals, agrochemicals, and functional organic materials warrants the growing demand for mild, selective and sustainable synthetic routes to their preparation. In this context, although the peculiar aptitude of gold salts/complexes for interaction with aromatic compounds (*auration process*) has long been known, the direct *catalytic gold decoration of arenes*, has risen to prominence only recently. Here, the extensive use of electrophilic activation of C–C multiple bonds by gold species deserves a prominent mention, and the great strides made in the field over the last few years are described in this *tutorial review*.

1. Introduction

The use of gold(I)/(III) species in catalytic organic transformations has unquestionably entered its *golden age*. Nowadays, in homogeneous as well as heterogeneous processes, enabling techniques in combination with gold catalysts, computational investigations and stereoselective gold-assisted methodologies have become efficient and consolidated tools to develop innovative transformations or to perform *old* reactions in a more sustainable way. Several comprehensive and more

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Marco Bandini received his PhD in chemistry in 2000 from the University of Bologna with Prof. Achille Umani-Ronchi. After several periods of research at the University of North Carolina at Chapel Hill (M. R. Gagné) and University of York (D. Macquarie, Marco Polo Fellowship), he was appointed assistant Professor at the University of Bologna. His research interests include the design and development of new catalytic stereoselective methodologies for the synthesis of heterocyclic compounds.

Marco Bandini

specific treatises have been reported documenting the flourishing role of Au catalysis in modern organic chemistry.[1] However, the still growing impact of gold catalysis in the realization of structural diversity/complexity from simple precursors[2] requires continuous literature updates.

This widespread interest in gold catalysis is primarily ascribable to a number of unique properties of Au(I) and Au(III) species such as: functional group tolerance, mildness of the operating conditions, stability towards oxido-reductive processes (isohypsic nature)† and simultaneous bi-functional acidity (σ and π). Last but not least, the growing availability of chiral organic ligands helps to define gold catalysis as one of more dynamic hot spots in asymmetric synthesis.[3] In particular, the well-recognized aptitude of gold species toward electrophilic activation of π-electron-containing compounds (*e.g.* alkenes, alkynes, allenes)[4] has rapidly revolutionized and expanded the synthetic portfolio for the decoration of aromatic compounds, by reinforcing critical issues such as: mildness, generality, functional compatibility and atom economy.

In the intrinsic diversity of gold-aromatic interactions, two coordination modes, namely η¹ and η², deserve a special mention. The tendency of AuCl₃ to η¹-coordinate aromatic frameworks (usually referred as *auration* reaction of arenes) has long been known.[5] Contrarily, the direct gold(I)-mediated aromatic C–H activation was documented only recently and this is apparently in contrast with the great stability of gold(I) η¹-aryl connections.[6] In the realm of the gold η²-coordination to unsaturated hydrocarbons, gold–arene interactions are weaker than those of Au–[alkene/alkyne/allene]. However,

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† Isohypsic synthetic steps generally refer to chemical processes that avoid redox events.
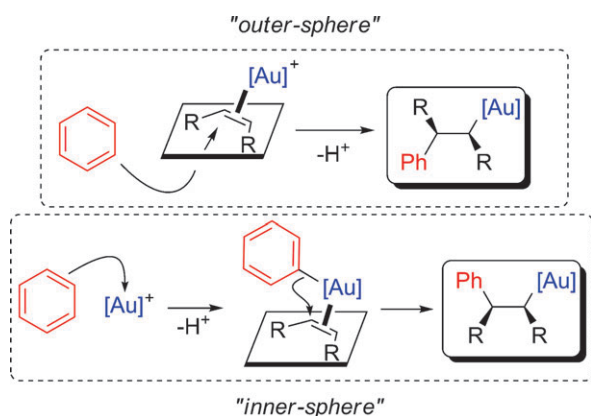
Fig. 1 Inner- (*syn*) and outer-sphere (*anti*) mechanism in gold-catalyzed arene functionalization.

their role has been recognized to be crucial due to their interplay in determining final chemical outcomes and in the fine-tuning of gold-catalysts.[7] Based on such a background, it is not surprising to note the current impact of gold in arene chemistry that allows complex polyfunctionalized molecular scaffolds to be prepared in a straightforward manner.[8]

Mechanistically, gold catalysis is generally expressed through the activation of the electrophilic partner with a consequent *anti* attack of the aromatic compounds (*outer-sphere-type pathway*). However, the possibility of forming discrete aryl gold intermediates makes the *syn* addition process (*inner-sphere-type pathway*) a feasible alternative (Fig. 1).

Basically, AuCl and AuCl$_3$ would show sufficient π-acidity to adequately activate carbon–carbon multiple bonds for the functionalization of aromatic compounds (mainly electron-neutral and electron-"generous" ones). However, a proper fine-tuning of the catalytic properties can be operated by complexing the gold metal center with phosphine, phosphite or *N*-heterocyclic carbene (NHC) ligands and/or *via* cationization of the resulting complexes by means of halogen metathesis with silver salts.

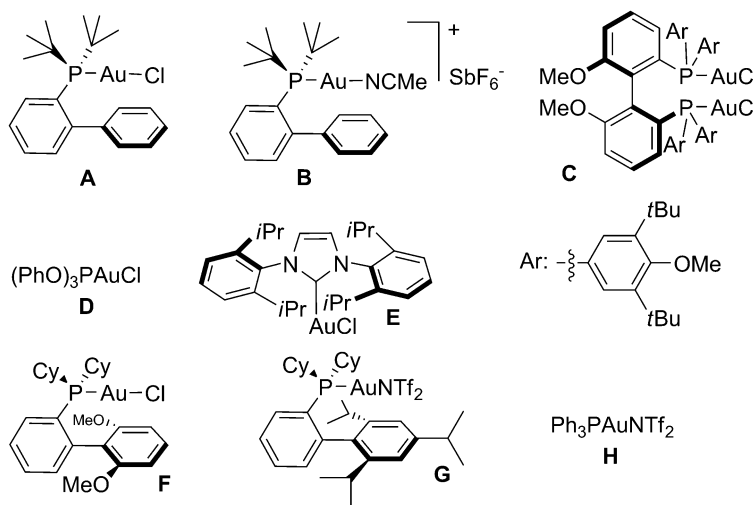In Chart 1, some of the gold catalysts (**A–H**) cited in this tutorial review are collected.

Finally, it should be underlined that, although the massive number of reports nowadays available on gold catalysis constitutes a valuable guideline for entering practitioners, extensive surveys of experimental conditions are still generally required in order to find out best reaction parameters. This aspect is mainly ascribable to the numerous components assembling the pre-catalytic species (*e.g.* ligand, metal source, additives/activators) and to the not fully elucidated operating mechanism of these chemo-, regio- and at times stereoselective transformations.[9]

The present tutorial review deals with some of the more recent reports on the decoration of aromatic compounds *via* electrophilic gold activation of C–C multiple bonds. It is organized according to the families of chemical partners coupled with unfunctionalized arenes under homogeneous conditions. It is not intended to provide a comprehensive treatise of the current topics and only a selection of representative applications will be reported in each section. Particular emphasis will be devoted to the more recent developments, and readers will be redirected to more comprehensive reviews that cover the basics and seminal findings when available. Finally, recent achievements concerning the synthesis of aromatic rings *via* gold-catalyzed cyclization reactions will be not discussed here.

2. Alkynes

2.1 Hydroarylation of alkynes

The addition of electron-neutral and electron-rich arenes to alkynes (*hydroarylation of alkynes*) is a well-established process promoted by late transition metal catalysts, and gold brought new perspective in the field.[10]

Seminal papers accounting for the gold-assisted intra- as well as intermolecular addition of arenes to alkynes appeared in the early 2000s.[11] Here, contrasting mechanistic pathways were somehow proposed, dealing with gold π-activation of the alkyne *via* η^2-coordination or direct *auration* of the arene. Subsequently, gold-catalyzed hydroarylation of alkynes has risen to prominence as one of the most straightforward
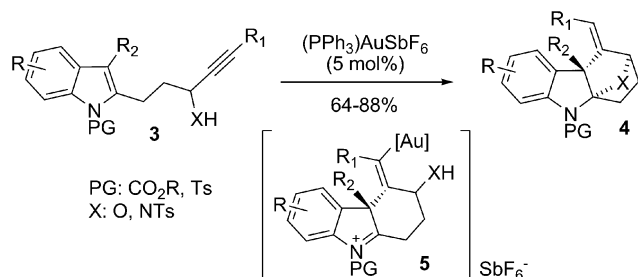

Chart 1
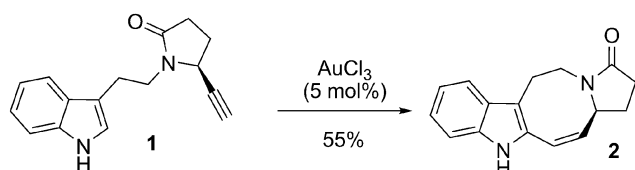
Scheme 1 Regioselective synthesis of azacino[5,4-b]indole derivative **2** *via* AuCl$_3$ catalyzed cyclization of **1**.
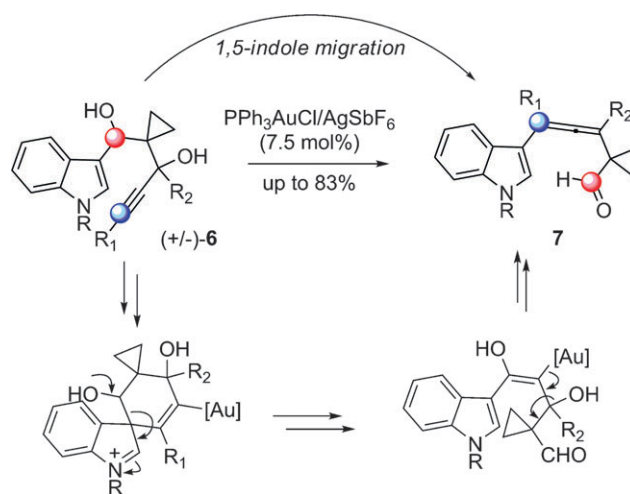
methodologies for the construction of complex aromatic polycyclic architectures. In particular, five-, six-, seven- and even eight-membered rings can be readily accessible in a highly regiochemical fashion. Recently, Echavarren and co-workers extended the scope of pioneering investigations,[12] realizing the synthesis of the molecular skeleton of lunderines *via* regio-selective 8-*endo-dig* AuCl$_3$-catalyzed cyclization of indolyl-alkynes (Scheme 1).[13] Mechanistically, experimental evidence called for the π-activation of the C–C triple bond by the metal center followed by a Friedel–Crafts-type (FC) electro-philic substitution. However, the formation of polycyclic fused cyclopropyl Au-carbene intermediates cannot be ruled out.

The accomplishment of chemical diversity by means of gold-catalyzed hydroarylation of alkynes was elegantly documented by Wang and coworkers, who described a tandem cyclization reaction involving indolyl-propargylic alcohols/amines **3** under mild conditions.[14] A range of diastereomerically pure tetracyclic indolines **4** was obtained by concerting the initial regioselective site-selective indole attack (C3 position) to the C–C triple bond, with the trapping of the iminium ion **5** by *O*- or *N*-based nucleophiles (Scheme 2).

Cascade synthetic sequences are a powerful tool to build up complex architectural motifs, through the formation of multiple strategic interatomic connections in a single synthetic event. Liu *et al.* have successfully applied such a concept to the synthesis of dihydrocyclohepta[b]indoles.[15] Here, a Friedel–Crafts/hydroarylation sequence was performed in the presence of cationic Au(I) species and (*Z*)-2-en-4-yn-1-ols as annulating agents (**34**, see Scheme 10). Shortly after, the same team elegantly documented on the use of indolyl scaffolds as template units to assist gold-catalyzed cascade multiple-bond forming/cleavage processes.[16] Here, properly designed 3-alkynyl-indolyl diols **6** were subjected to consecutive cyclization/fragmentation/elimination processes triggered by PPh$_3$AuCl/AgSbF$_6$ (7.5 mol%). Synthetically versatile C3 allenylated indoles **7** were isolated in good yields and the

proposed intermediates for the 1,5-indole migration reaction are depicted in Scheme 3.

Not only intramolecular but also intermolecular gold-catalyzed addition of indoles to alkynes has been utilized to form bis(aryl)alkanes in a straightforward manner.[12,17,18] Interestingly, the opposite regiochemistry in the nucleophilic attack (terminal *vs.* internal position of the C–C triple bond) could be realized by a proper combination of both gold complex and alkyne structure.

2.2 Rearrangement of propargylic derivatives

Propargylic carboxylates **8** have been object of intensive investigation as valuable synthetic precursors for a rich array of reactivities under gold catalysis.[19] The activation of the C–C triple bond by the gold species generally triggers a migration of the carboxylic group *via* a [3,3]-sigmatropic rearrangement generating a synthetically powerful carboxyallene **9**. Alternatively, 1,2-acyl migration could occur resulting in the α,β-unsaturated gold–carbene **10**. Here, the hypothetical concomitance of multiple mechanistic pathways opens access to a plethora of chemical outputs in the presence of internal or external nucleophiles (Fig. 2).

The mild reaction conditions and the wide functional group tolerance featured by such processes prompted researchers to consider the gold-catalyzed rearrangement of propargylic derivatives as a reliable synthetic route to natural products. In particular, after the illuminating papers by Nolan *et al.* and
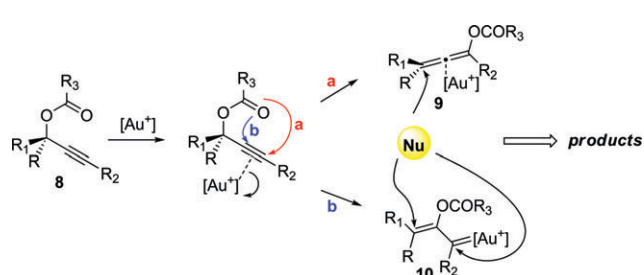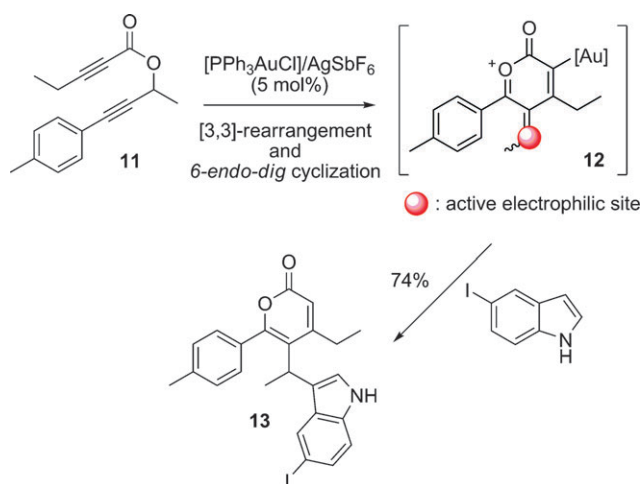

Scheme 3 Au(I)-catalyzed cascade cyclization/fragmentation/elimination reaction for the synthesis of C3-allenylation of indole rings.

Scheme 2 Synthesis of polycyclic indolenines **4** *via* Au(I)-catalyzed cascade cyclization.

Fig. 2 Exploiting the gold-catalyzed 1,3- and 1,2-acyl migration of propargylic carboxylates for generating molecular diversity.
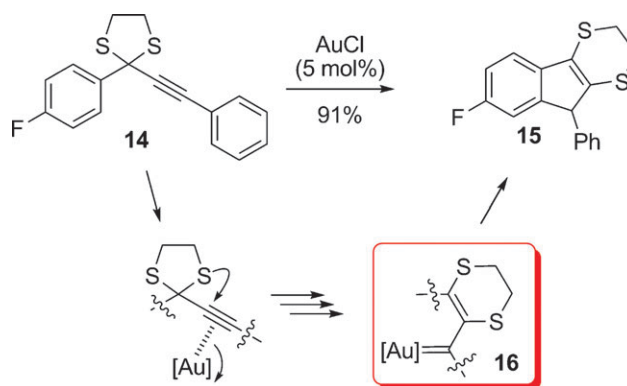
Scheme 4 Synthesis of trisubstituted pyrone **13** initiated by gold(I)-catalyzed rearrangement of the propargyl propiolate **11**.

Zhang on the synthesis of polyfunctionalized indolines and indenes,[20] many studies have been reported exploiting such a strategy for the functionalization of arenes. Among them, the intermolecular condensation of propargyl carboxylates with electron-rich aromatic compounds (*e.g.* indole, 1,3,5-trimethoxybenzene) has been discussed by Echavarren and colleagues.[21] Here, regioselectivity (*i.e.* 1,3-rearrangement *vs.* 1,2-acyl migration) resulted to be substantially affected by both structure of the catalyst and type of propargyl carboxylates.

Other excellent examples of aromatic decoration exploiting gold induced [3,3]-sigmatropic rearrangements of propargylic derivatives, were reported by the groups of Toste and Schreiber, providing a wide chemical diversity/complexity with inter- as well as intramolecular Friedel–Crafts-type processes.[22] For instance, a library of functionalized α-pyrones (**13**) was realized by Schreiber using a gold(I)-catalyzed coupling reaction. Here, the propargylic propiolate **11** underwent a sequential [3,3]-sigmatropic rearrangement and 6-*endo-dig* cyclization, with the final trapping of the resulting oxocarbenium species **12** by electron-rich benzenes or hetero-aromatics (Scheme 4).

Notably, also propargylic sulfides and dithioacetals proved to be competent precursors for Au-catalyzed arene manipulations. In particular, Wang *et al.* reported on the synthesis of sulfur-containing indenes (**15**) under silver-free conditions. Mechanistically, the ring expansion of the starting propargyl dithioacetal **14** was explained by considering the vinylcarbenoid **16** as a plausible reaction intermediate (Scheme 5).[23] It is worth mentioning that these findings elegantly highlighted the competence of sulfur-based compounds in gold-catalyzed transformations despite the well known poisoning effect toward "soft" late transition metal species.

Finally, the gold-promoted rearrangement of propargylic derivatives was utilized by Sanz *et al.* to accomplish an unprecedented 1,2-migration of indoles.[24] The reaction profile involved the consecutive rupture/formation of new C–C bonds and it was dictated by the intrinsic nucleophilicity of the indolyl nucleus. In particular, when 3-propargylic indoles **17** were exposed to catalyst **H** (PPh$_3$AuNTf$_2$, 5 mol%), a

substantial formation of 2-indenyl indoles **20a** and **20b** was recorded *via* tandem 1,2-migration/C–H insertion (**20a**) or 1,2-migration/Nazarov cyclization (**20b**), respectively (Scheme 6). Interestingly, the final outputs resulted from the simultaneous re-functionalization of two aromatic units present in the starting materials **17** (*i.e.* indole and phenyl substituent at the propargylic position). The synthetic potential of the

Scheme 5 Synthesis of sulfur-containing indenes from propargyl dithioacetals.
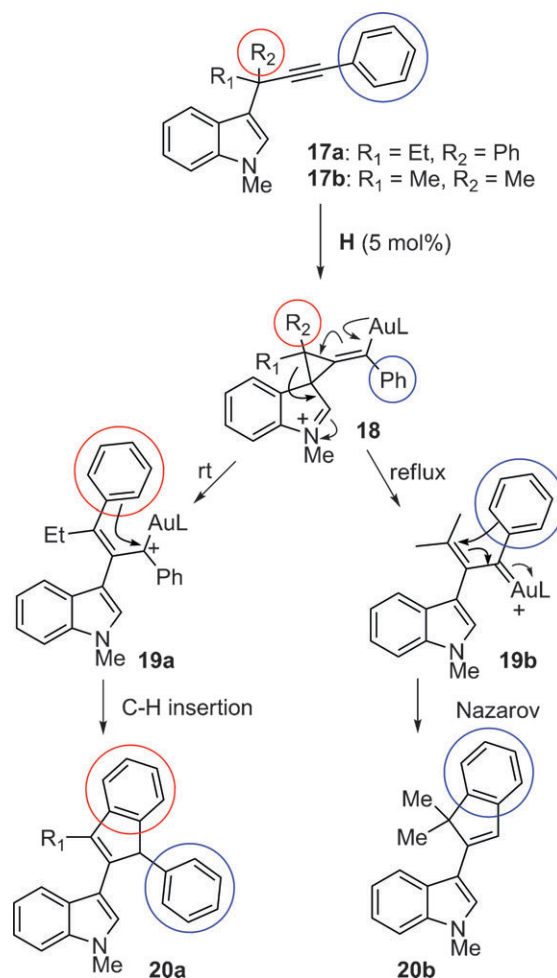
Scheme 6 Synthesis of indenyl-indoles **20a,b** *via* gold(I)-promoted 1,2-migration of indoles.

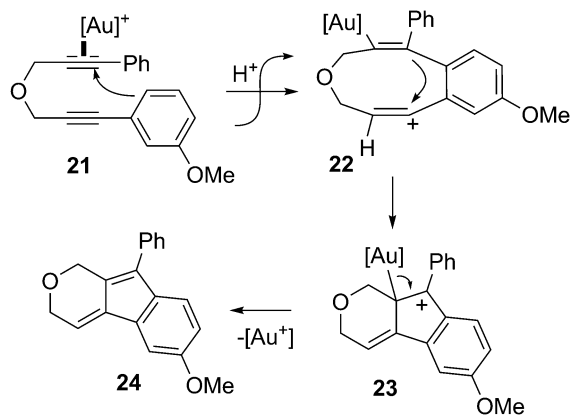present methodology was emphasized further by the broad substrate-scope and excellent chemoselectivity.

2.3 Cycloadditions of areyne-yne

Thermally induced cycloadditions of areynes with unactivated alkynes commonly required harsh reaction conditions ($T > 250\ °C$). The use of late-transition metal catalysis generally allows milder parameters to be operationally accessible, enlarging the synthetic applicability of the method to the preparation of fused polycyclic compounds. In this framework, PPh₃AuSbF₆ (2 mol%) was reported assisting the intramolecular [3 + 2]-cycloaddition of the arenyne-yne 21 at room temperature to give the functionalized indene 24 in good yield.[25] Deuterated labelling experiments provided mechanistic insights and supported the initial nucleophilic attack of the electron-rich arene on the Au(I)-activated alkyne. The deriving vinyl gold(I)-intermediate 22 could undergo a Nazarov-type cyclization followed by deauration reaction (Scheme 7).
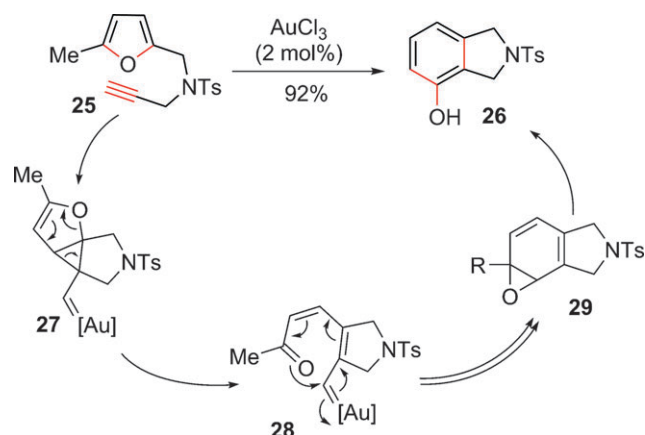
2.4 Alkyne-induced structural reorganizations of aromatic compounds

Hashmi and co-workers first recognized the gold-catalyzed structural reorganizations of functionalized π-compounds, a straightforward synthetic protocol to bicyclic-fused arenes.[26] In particular, the intramolecular cyclization of furyl-alkynes 25 to phenol 26 was efficiently promoted by AuCl₃ (2 mol%), that emerged as the more active species within a range of d⁸ metals. Interestingly, the overall transformation involves the simultaneous breaking of four bonds and the formation of new four interatomic connections with a net intramolecular migration of the furan oxygen atom (Scheme 8).

Subsequently, the scope of the pioneering investigations was substantially expanded through intermolecular variants,[27] detailed mechanistic insights[28] and application to the synthesis of natural compounds such as Junginol and epi-Junginol.[29] More recently, the same team further increased the challenge of the process by introducing stereochemical elements, and both diastereoselective as well as enantioselective variants were reported.[30] In the former case, chiral/racemic tertiary dipropargylic alcohol 30 (model substrate) was subjected to AuCl₃ catalyzed cycloisomerization, and the desired bicyclic phenol 31 was isolated in good yield (92%) as a single


Scheme 8 Phenols from furans *via* gold catalysis.

diastereoisomer (dr = 99:1). In the latter procedure, achiral tertiary alcohol 32 was reacted in the presence of chiral dinuclear gold(I)-complexes, with the final aim to exert an enantiotopic selection between the alkynyl groups. Under best conditions (*i.e.* (R)-C(AuBF₄)₂) phenol 33 was isolated in excellent yield (99%) and moderate enantioselectivity (55%, Scheme 9).

Substituted enones and enals have also been synthesized through similar gold-catalyzed FC-cycloisomerization cascade processes. In particular, by treating α- or β-substituted furans with enynols 34 in the presence of AuCl₃ (5 mol%), the acyclic FC-adduct 36 was isolated predominantly.[31] On the contrary, commercially available silver-free catalyst H (5 mol%) smoothly promoted the tandem synthetic sequence, giving rise to the configurationally pure α,β-unsaturated ketones 35. The overall cycloisomerization pathway led to a final outcome in which the tetrasubstituted aromatic ring incorporated five carbon atoms of the enynol skeleton and the C5 carbon atom of the furan (Scheme 10). The dichotomy on the chemical output, with respect to the previously described phenol synthesis, is rationalized in terms of the alternative formation of 1,3-linked carbenoid species 37b or of 1,2 analogues 37a.

3. Allenes

Metal-catalyzed hydroarylation of allenes has received considerable attention as a highly atom economical synthetic

Scheme 7 Gold-catalyzed [3 + 2]-cycloaddition of arenyne-ynes.
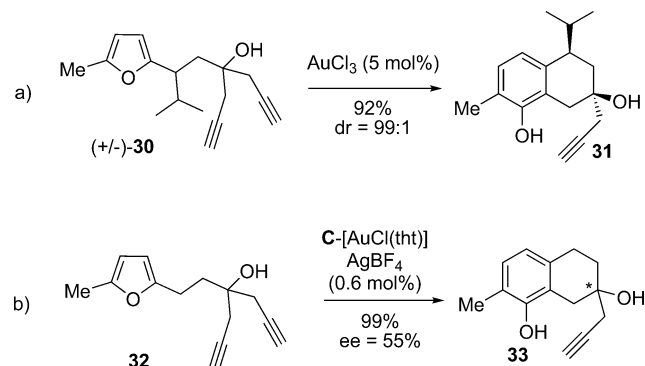
Scheme 9 Stereoselective synthesis of phenols 31 and 33 *via* cycloisomerization of furyl-alkynes 30 and 32 (tht = tetrahydrothiophene).
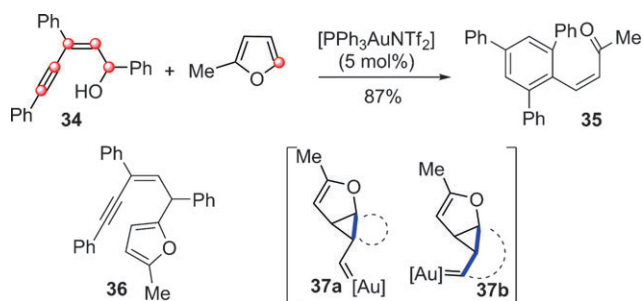
Scheme 10 Stereoselective synthesis of α,β-unsaturated carbonyls *via* gold-catalyzed cascade reactions. The carbon atoms in the reagents that will assemble the tetrasubstituted aromatic ring in **35** have been highlighted. In square brackets 1,2- and 1,3-linked cyclopropyl gold-carbenoids invoked by Hashmi *et al.* and Liu *et al.*, respectively.

procedure to build up chemical diversity in the realm of functionalized aromatic compounds. The higher reactivity of C=C bonds of allenic compounds, with respect to alkenyl analogous, allowed mild reaction conditions and high selectivity to be operationally feasible.[32] Target-oriented synthesis greatly profited by this aspect, and the synthesis of (−)-rhazinilam, *via* stereoselective gold(I)-catalyzed intramolecular addition of pyrrole to enantiomerically pure allenes, still represents one of the leading examples.[33]

Intramolecular gold(I)-catalyzed hydroindolination of allenes was introduced by Widenhoefer and co-workers as a valuable synthetic shortcut to 4-vinyl-tetrahydrocarbazoles **39** (THCs) and analogous.[34] *exo*-Allylic alkylation of indoles was performed *via* regioselective ring-closing reactions of 2-allenyl indoles **38** and perfect axial chirality transfer from **38a** to **39a** was recorded by using catalyst **A**. Analogously, chiral gold(I) complex **C**, containing MeOBIPHEP ligand, provided the THC **39b** in excellent enantiomeric excess (92%, Scheme 11).

Shortly after, Gagné and coworkers elegantly reported on the efficiency of the triphenylphosphite-based catalyst **D** (3 mol%) and AgSbF₆ in promoting the cycloarylation of electron-neutral as well as electron-rich benzenes **40** *via* *exo*-attack of the π-nucleophile on allenylic units. Subsequently, a deep insight into the mechanistic profile was gained by unambiguously determining the resting state of the catalyst. The formation of a diaurated structure **41**, based on a three-center two-electron vinyl architecture, was proved (Scheme 12).[35]

a)

b)
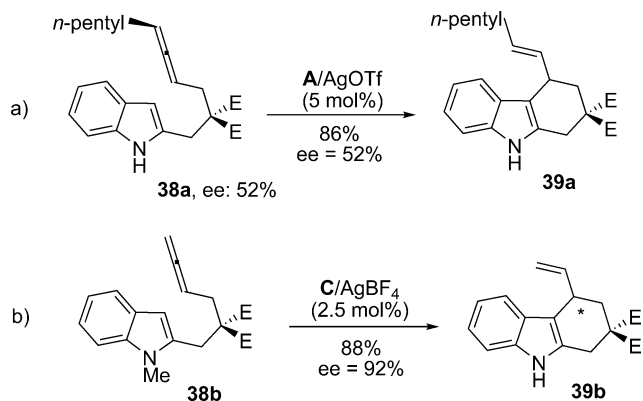
Scheme 11 Transfer of chirality in the hydroindolination of allenes (E = CO₂Me).
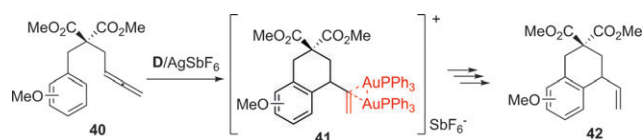
Scheme 12 Three-center diaurated resting state (**41**) in the gold-catalyzed hydroarylation of allenes with electron-rich benzenes.

In addition to the previous 6-*exo* cyclization, an example of intramolecular 6-*endo* hydroarylation of allenes with anilines and phenols was documented by Ohno *et al.*, in the presence of **A**/AgOTf (1–2 mol%) as the catalytic system.[36] Polysubstituted aniline cores underwent the ring-closing process under mild conditions (rt) and short reaction times (minutes). On the contrary, hydroarylation involving less activated arenes required the use of AcOH as the reaction media, in order to achieve synthetically useful reaction conditions. Deuterium experiments allowed light to be shed on the intrinsic role of the protic co-solvent, that turned out to be directly involved in speeding up the final step of proto-deauration (Scheme 13).

Subsequently, the challenging task of intermolecular addition of arenes and indoles to allenes was efficiently addressed by using (4-ClPhO)₃PAuCl/AgBF₄ (5 mol%) and **E**/AgOTf (5–10 mol%) as the pre-catalytic species.[37] Although good chemical as well as optical yields were normally recorded, substrate scope still represents an important issues to be fully solved.

4. Alkenes

4.1 Electron deficient alkenes: Michael-type addition

The catalytic functionalization of aromatic C–H bonds *via* Michael-type additions has recently attracted extensive research efforts.[38] Focusing on gold chemistry, gold(III) chloride proved to be a competent promoting agent for the 1,4-addition of electron-rich arenes (*i.e.* 2-methylfuran, methoxyarenes) to methylvinylketone (MVK) and, although a conclusive mechanistic rational was not provided, experimental controls evidenced that an electrophilic direct C–H activation could be operating in the Friedel–Crafts-type alkylation.[39] As a consequence, more electrophilic Au(III) species were preferred with respect to Au(I)-based systems. In this segment, related studies were also reported by Arcadi *et al.* and He *et al.* independently, that investigated the regioselective Au(III)-catalyzed
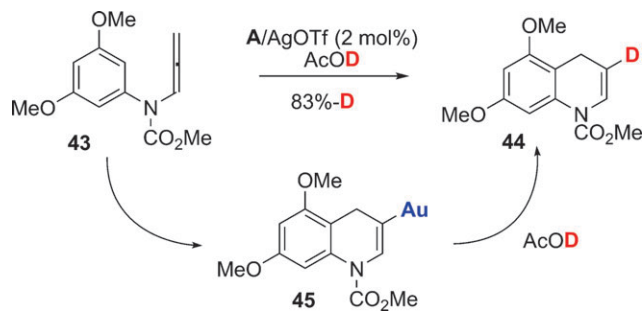

Scheme 13 Synthesis of dihydroquinolines *via* regioselective 6-*endo* hydroarylation of allenes.
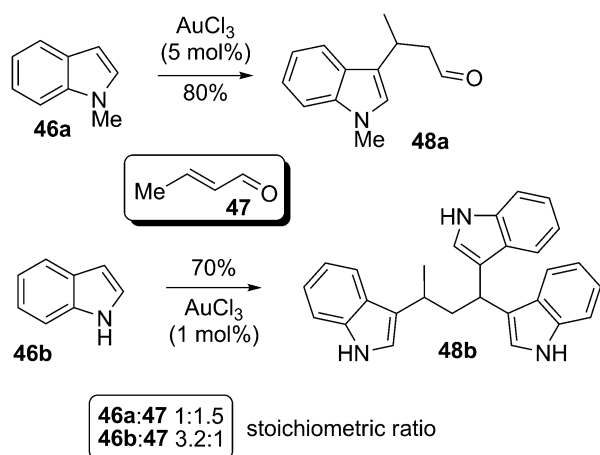
Scheme 14 Stoichiometry makes the difference in the Au(III)-catalyzed alkylation of indoles with croton aldehyde **47**.

(*i.e.* NaAuCl$_4$, AuCl$_3$) 1,4-conjugate addition of indoles to a range of Michael acceptors.[11,40] Here, while an excess of the olefinic counterpart propelled the exclusive formation of the 1,4-adduct **48a**, the use of larger quantities of heteroaromatic compounds (*i.e.* indole, 2-methylfuran) led to the tris-addition product **48b**, predominantly (Scheme 14).

More recently, Urriolabeitia *et al.* provided entry for moisture tolerant alternatives to conventional gold(I) halides. The authors exploited the capability of *C,N*-ligands to stabilize gold species in high oxidation states and readily isolable organogold(III) iminophosphoranes **49** proved efficient in promoting the conjugate addition of several electron-rich arenes to MVK.[41]

49a,b: R = H, Me, X = CH
49c,d: R = Ph, COPh, X = N
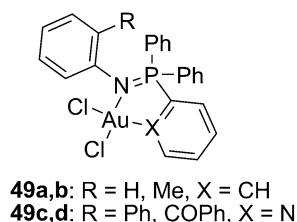
4.2 Dienes

The synthetic versatility of cyclic dienes has also been exploited in gold-catalyzed alkylation of electron-rich arenes. In particular, the catalytic system AuCl$_3$/AgOTf (5/15 mol%) successfully promoted the completely atom-economical annulation reaction between phenols **50** and cyclic dienes to produce the dihydrobenzofurans **51** in high yields. The results are consistent with a mechanism proceeding by the initial gold activation of the C–C double bond followed by the aromatic C–H addition (Scheme 15).[42]
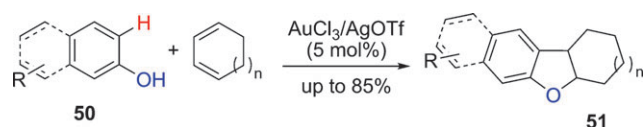
Scheme 15 Atom economical synthesis of dihydrobenzofurans *via* gold-catalyzed activation of dienes.

4.3 Unactivated alkenes

Unactivated carbon–carbon double bonds are commonly reluctant in taking part to hydroarylation reactions involving direct aromatic C–H functionalization.[43] As a matter of fact, high temperatures, prolonged reaction times and relatively high loading of catalyst are routinely required. This stringent aspect is amplified if a comparison with analogous hydro-arylation of allenes is considered. However, very recently remarkable progresses toward substrate scope and mildness of operating conditions have been realized.[44]

On the contrary, the relative inertness of C–C double bonds, combined with the limited examples of enantioselective Au(III)-catalyzed transformations account for the largely unexplored gold-catalyzed enantioselective functionalization of unactivated olefins.[3] Bandini and co-workers have recently documented that allylic alcohols can be efficiently employed as synthetic equivalents of unactivated olefins in the enantioselective FC-type allylic alkylation of indoles. The optimized intramolecular procedure employs the dinuclear complex [MeOBIPHEPAu$_2$OTf$_2$] and both 1-vinyl and 4-vinyl-THCs (**53a,b**) were isolated in highly stereodefined manner (Scheme 16a).[45]

Diastereomerically pure tetrahydro-β-carbolines (THBCs) were also accessible through this methodology starting from enantiomerically pure indolyl-alcohols **54**.[46] Moreover, by merging gold(I) catalysis and ruthenium mediated ring-closing processes, the 9-aza-[3.2.2]nona-2,6-diene bicyclic framework **57** was isolated in 47% yield (Scheme 16b).

### 4.4 Cycloadditions and related transformations with unactivated alkenes

The well known ability of gold(I) species to catalyze 5-*exo-dig* carbocyclizations of 1,6-enynes inspired chemists to exploits such an efficient cycloisomerisation/addition process for the construction of complex molecular skeleton with the concomitant functionalization of electron-rich aromatics.

Echavarren and coworkers[47] and subsequently Michelet and coworkers[48] have pioneered the field by describing the possibility of trapping gold cyclopropyl carbene intermediates **59** *via* intra- as well as intermolecular C–H functionalization of arenes. In particular, the Spanish team emphasized the role of catalyst **F**, combined with AgSbF$_6$ (2 mol%), in promoting a formal [4 + 2] cycloaddition of arylalkyne **58a**. With this approach a range of functionalized polycyclic fused hydro-naphthalenes (**60**) was readily synthesized in highly diastereo-selective fashion (Scheme 17, path a). On the other hand, also 1,6-enynes, comprising terminal alkynes (*i.e.* **58b**), proved to be ideal precursors for a tandem atom economical Friedel–Crafts/carbocyclization reaction in the presence of polymethoxybenzenes as well as heteroarenes. Furthermore, the authors developed an enantioselective variant of this process by employing chiral cationic dinuclear complex **C** as the pre-catalytic species (Scheme 17, path b).

Finally, a very nice illustration of Friedel–Crafts-type trapping of charged intermediates was documented by Odabachiana and Gagosz. Here, a synthetic sequence involving a formal [2 + 2] cycloaddition of poly-yno/enes, FC-alkylation, diene isomerization and Wagner–Meerwein rearrangement was efficiently amalgamated by the silver free catalyst **G**.[49]
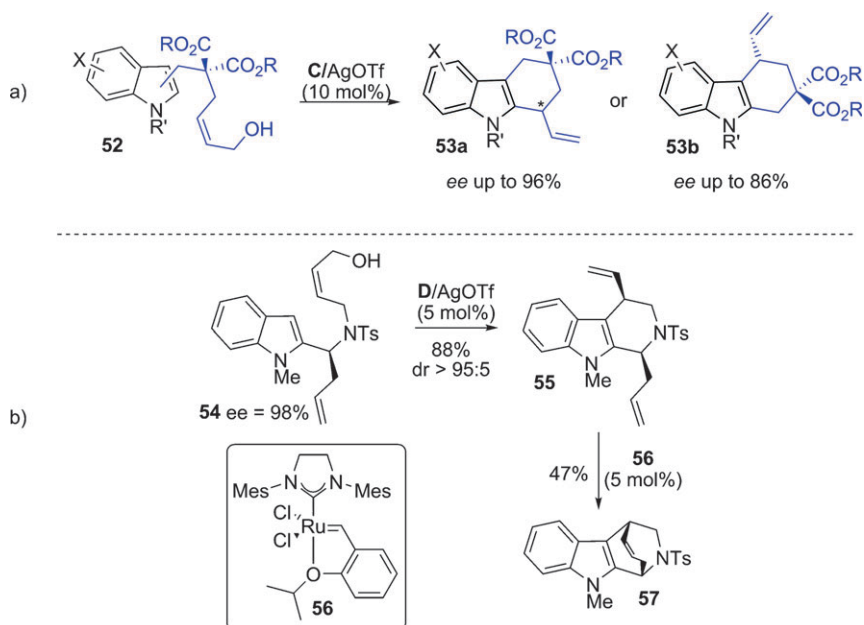
Scheme 16 (a) Catalytic enantioselective FC-type alkylation of indoles with direct activation of allylic alcohols; (b) sequential dual-metal catalyzed (Au, Ru) synthesis of polycyclic alkaloid **57**.
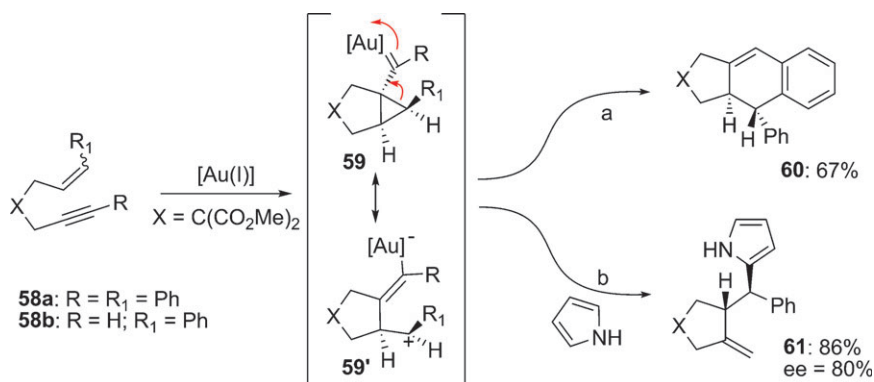
Scheme 17 *Reagents and conditions.* (a) **F**/AgSbF$_6$ (2 mol%); (b) (*R*)-**C**/AgOTf (3 mol%).

4.5 Masked electron-rich olefins

Electron-rich carbon–carbon double bonds, such as enols, have been demonstrated to be optimal reaction intermediates in the gold-catalyzed diastereoselective synthesis of benzo-fused polyclic ethers **63**.[50] The proposed protocol involved a tandem hydroalkoxylation/FC-alkylation sequence starting from benzyl-substituted alkynols **62**. The gold catalyst was proposed to exert a dual function: firstly triggering the forma-tion of enols **64** through coordination to the C–C triple bond, and subsequently promoting the formation of the oxonium intermediate **65**. Finally, the latter positively charged species was trapped *via* intramolecular hydroarylation reaction (Scheme 18). The isolation of the enol ether **64a** supported the previously described tentative mechanism.

5. Catalysis by Au(I)/(III) redox couple

As mentioned in the introduction, the isohypsic nature of gold species is largely considered a peculiarity of this noble

metal. However, some interesting exceptions have been documented in the literature with particular regard to cross-coupling reactions.[51]

A representative example was reported by Wegner and co-workers that exploited the redox couple Au(I)/(III) to synthesize dicoumarin frameworks in moderate to good yields (Scheme 19).[52] The evidence that electron-rich arenes actively took part in the process supported the initial FC-type step triggered by the HAuCl$_4$ activation of propiolate triple bond. Then, the organogold(III) intermediate **68** promoted a second hydroarylation reaction with the formation of labile divinyl-Au(III) species **69**. Thus, final reductive elimination would furnish the desired dimeric product **67** with concomi-tant release of Au(I)-species that can be re-oxidized by *t*-BuOOH.

The same catalytic species was also employed in the oxida-tive coupling of non-activated aromatic rings (homo-coupling process) in the presence of PhI(OAc)$_2$ as the stoichiometric oxidant. Based on experimental controls a direct aromatic C–H activation is assumed to be operating. In the presence of
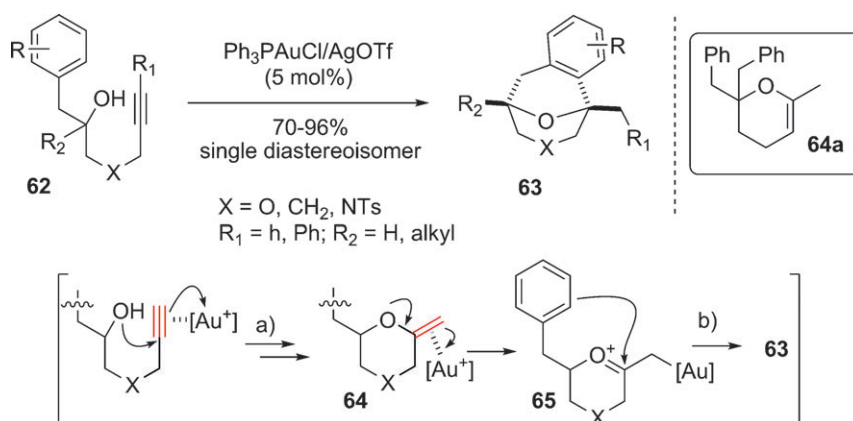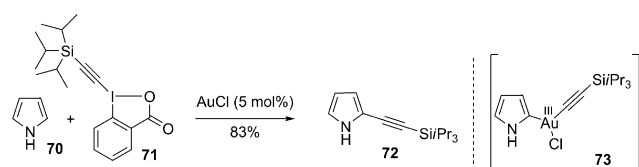
Scheme 18 Diastereoselective synthesis of eight-membered carbocycles *via* tandem gold(I)-catalyzed reaction. (a) Hydroalkoxylation/protodeauration, (b) hydroarylation.
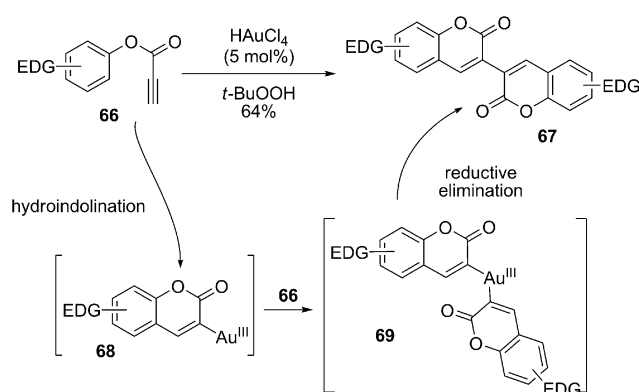
Scheme 19 Gold-catalyzed synthesis of dicoumarins **67** *via* domino hydroarylation of alkynes/oxidative coupling (EDG: electrondonating group).

Au(III) catalysts, several functional groups (*i.e.* halides, alkoxy, esters) were tolerated and preserved during the diaryl formation.[53]

Recently, a study by Waser and co-workers on the alkynylation of indoles and pyrroles has aroused particular interest. Here, ligand and silver-free AuCl catalyst promoted the direct alkynylation of indoles and pyrroles with a range of electrophilic/oxidative alkynyliodonium salts (Scheme 20).[54] Mild reaction conditions, functional group tolerance (*i.e.* OH, CO$_2$H, CN, NO$_2$) and possibility to install free acetylene units represent the main goals of the methodology. Last but not least, although a conclusive picture regarding the operating mechanism was not declared, and a classic gold-promoted π-activation of the triple bond cannot be excluded, the efficiency of oxidative benziodoxolone hypervalent iodine

reagent **71** prompted the authors to hypothesize a pathway involving the redox couple Au(I)/(III).

Conclusions

The latest developments in the use of "fancy" catalysts (*i.e.* carbophilic late-transition metal species) for Friedel–Crafts-type alkylations/alkenylations contributed substantially in pushing "old chemistries" of aromatic compounds into a "new" dimension. In this framework, gold catalysis has emerged recently as a viable response to the ongoing demand for sustainable synthetic methodologies in the manipulation of aromatics *via* C–H activation processes.

However, the presence of still quite unexplored segments, such as Au(III)-asymmetric catalysis, use of unactivated C=C bonds, use of electron-deficient arenes and not fully elucidated mechanistic aspects, suggest that important developments still have to come in this fascinating area, that appears limited only by the scientific creativity.

Acknowledgements

Scheme 20 Direct gold-catalyzed alkynylation of indoles and pyrroles (**73**: hypothetical diorganogold(III) intermediate).

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