Gold-Catalyzed C(sp^2)—H Bond Functionalization

Xun-Shen Liu and Lu Liu

School of Chemistry and Molecular Engineering, East China Normal University, Shanghai, PR China

1 Introduction

Carbon–hydrogen bond is one of the most fundamental chemical bonds in organic molecules. The direct conversion of C—H bond into C—X (X = C, N, O, S, etc.) bond, termed C—H bond functionalization, which is regarded as the "Holy Grail" in chemistry, has been emergent as an efficient approach for the construction of complex molecules because of the atom and step economy [1–10]. Both aromatic compounds and olefins, such as phenol, toluene, and ethylene, which represent the most abundant chemical feedstocks, contain a mass of the C(sp^2)—H bond. Furthermore, the carbon–carbon double bond, which possesses the sp^2 carbon, is the most important scaffold in organic synthesis and is prevalent in bioactive compounds, drugs, dyes, functional materials, and fine chemicals. Thus, the development of new reaction methodologies of C(sp^2)—H bond functionalization is highly desirable in which it is a vital issue to control the functionalization of specific one among many C—H bonds.

For a long time in history, gold is regarded as a symbol of wealth because gold is very stable and cannot be used in chemical reactions. However, during the past two decades, gold catalysis has attracted much attention for the discovery of novel organic transformations by the π-activation of unsaturated carbon–carbon bonds due to the excellent carbophilic π-acidic and catalytic activities of both gold(I) or gold(III) complexes [11–18]. Gold complexes can also catalyze the C—H bond functionalization. In 2000, Hashmi and coworkers developed the intermolecular C(sp^2)—H bond functionalization of arenes with olefins [19]. In 2004, He and coworkers developed the gold(III)-catalyzed C(sp^2)—H bond functionalization of arenes with primary alcohol sulfonate esters in which they present the pathway of the formation of phenylgold(III) species via C—H bond activation [20]. Compared to the other commonly used transition metals, e.g. palladium, rhodium, and ruthenium, in C—H bond functionalization reaction, which generally need the extra installation of directing groups to achieve the site-selectivity via coordination with the metal catalysts, gold catalysts are used in an "undirected" approach. Recently, gold catalysts exhibit more and more specific reactivity in C(sp^2)—H bond

Handbook of CH-Functionalization, First Edition. Edited by Debabrata Maiti.

DOI: 10.1002/9783527834242.chf0097

functionalization, because many parameters, such as ligands, counter anions, and additives, can be tuned to control the chemo- and site-selectivities in gold catalysis. In this article, we focus on C(sp^2)—H bond functionalization via gold catalysis. We cover the milestones and the recent advance in this research field and show the different chemo- and site-selectivities under various reaction conditions.

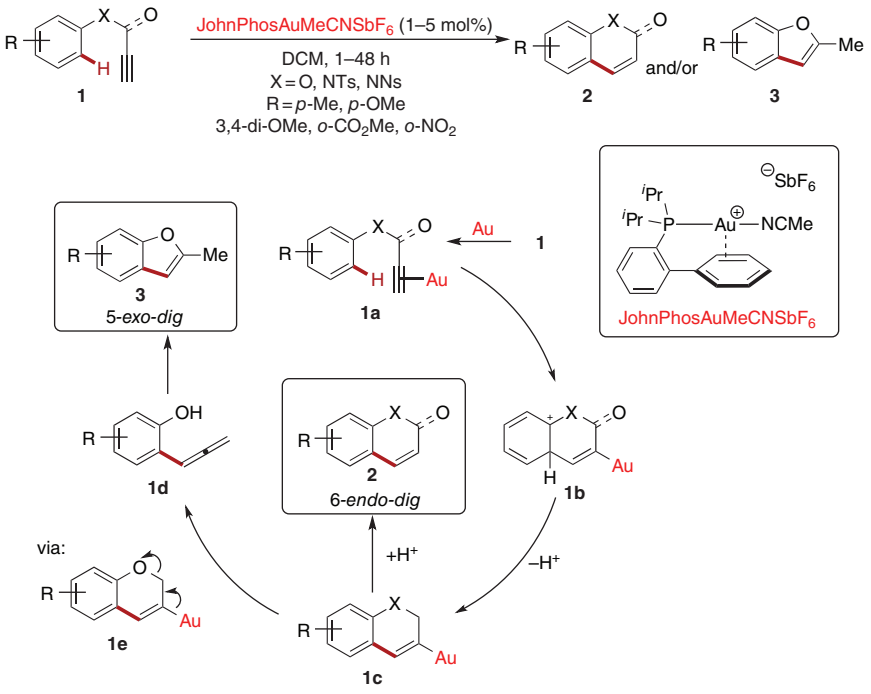
2 Gold-Catalyzed Intramolecular C(sp^2)—H Functionalization

Fused hetero- and carbocycles are important motifs found in numerous natural products, bioactive molecules, functional materials, and so on. Thus, the potential usage of these structures has greatly motivated scientists to aim at the development of novel, efficient, economical, and selective synthetic approaches for the construction of these compounds. In this regard, gold-catalyzed intramolecular C(sp^2)—H functionalization reaction between aromatic rings and electrophiles is one of the most straightforward strategies to access these scaffolds. Over the past two decades, spectacular achievements have been reached in this field of Au-catalyzed C—H bond functionalization process.

Gold complexes, which normally played the role as π Lewis acid, have excellent and specific abilities to activate the unsaturated carbon–carbon bonds. Then, the activated unsaturated C—C bonds, especially the alkynyl and allenyl, can undergo the addition of aromatic rings, which might include rearrangement reactions. In 2009, Banwell et al. reported the gold-catalyzed aromatic C(sp^2)—H bond of phenyl rings with intramolecular terminal alkynyl groups, delivering various important fused heterocyclic motifs. As shown in Scheme 1, in most cases, the six-membered-ring products **2** were the major products via the *6-endo-dig* cyclization catalyzed by JohnPhosAu(CH_3CN)SbF_6. In some cases, the benzofurans **3** were obtained via the tandem [3,3]-Claisen rearrangement/*5-exo-dig* cyclization reactions of aryl propargyl ethers. In the formation of benzofurans **3**, *ortho*-allenyl phenols **1d** or the corresponding phenolic anions were the important intermediates, which could be stabilized by the electron-withdrawing substituents on the phenyl ring through resonance. Thus, benzofurans **3** were obtained as the major products using aryl propargyl ethers with the strong electron-withdrawing groups, such as CO_2Me and NO_2, at the ortho-position of the oxygen atom as the substrates [21]. In 2011, Stratakis and coworkers disclosed that the [3,3]-Claisen rearrangement could be hindered by switching the JohnPhos gold complex to $Ph_3PAuNTf_2$, yielding exclusively 2*H*-chromenes **2** [22].

Thus, this gold-catalyzed highly regioselective cyclization of phenyl rings had become an efficient strategy to construct various benzoheterocyclic compounds, such as coumarin and quinine, by tuning the gold catalysts and the alkynyl-containing benzene substrates, which had been reported by Arcadi, Banwell, Goggiamani, and other researchers (Scheme 2) [23–34]. Besides the commonly used homogeneous gold complexes, heterogeneous gold catalysts were also used in this transformation. In 2013, Litinas group disclosed that the gold nanoparticles,

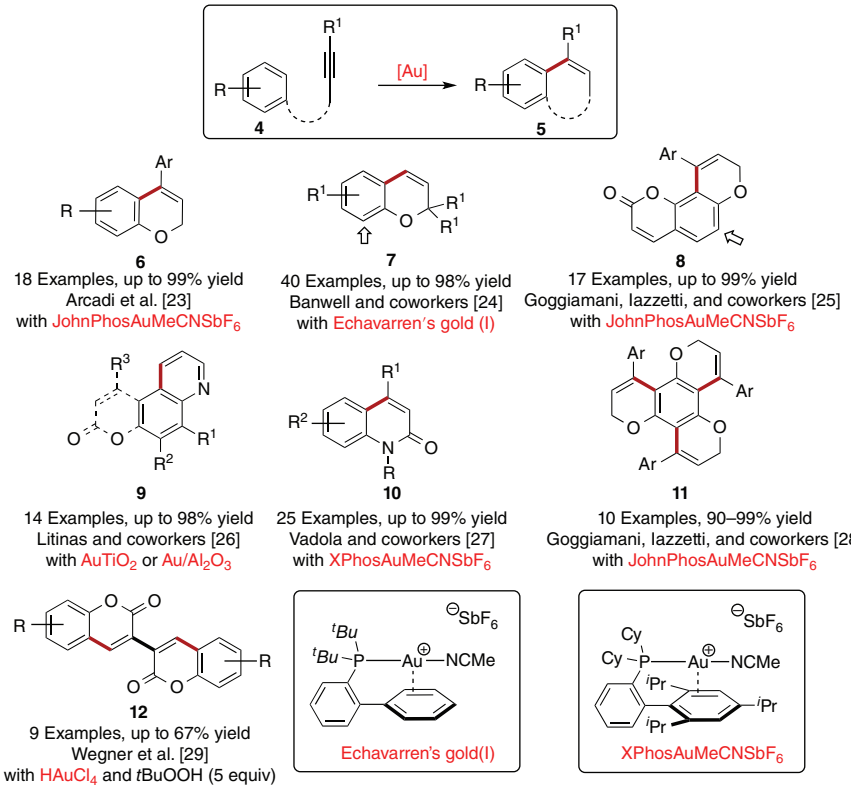
Banwell and coworkers [21]



Scheme 1 Gold-catalyzed cyclization reaction via C(sp²)—H functionalization.

which were supported on TiO_2 and Al_2O_3, were efficient catalysts to convert *N*-propargyl anilines and coumarins into the corresponding quinolines and fused pyridocoumarins **9** under mild conditions [26]. Wegner et al. developed an Au-catalyzed domino cyclization/oxidative coupling reaction by combining $HAuCl_4$ and *tert*-butyl hydroperoxide (TBHP) as the catalysts. In this reaction, the gold catalyst performed two different functions via the catalytic cycle between Au(I) and Au(III), affording a series of dicoumarins **12** [29]. In addition, gold-catalyzed intramolecular hydrogen arylation also exhibits huge potential in natural product synthesis [33, 35–37].

Besides the O- and N-containing heterocycles, P-containing heterocycles could also be reached by this method [38–40]. In 2021, the synthesis of phosphorus atom containing benzo six-membered heterocycles **14** was reported by Pirat, Virieux, and coworkers (Scheme 3a) [38]. In this reaction, the regioselective *6-endo-dig* cyclization of P-containing phenyl alkynes **13** was promoted by PPh_3AuCl and triflate acid under the activation of microwave. Meanwhile, Kamikawa group reported the synthesis of P-containing seven-membered rings **16** from 2-ethynyl triaryl quaternary phosphonium salts **15** under the catalysis of IPrAuCl/AgOTf with triflate acid as the promoter (Scheme 3b). The *6-exo-dig* product **17** was preferred using terminal alkynes [39].

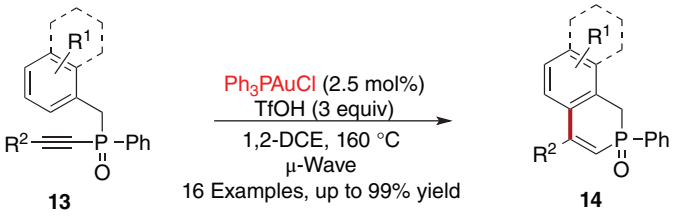


Scheme 2 Gold-catalyzed *6-endo-dig* cyclization. Source: Adapted from Arcadi et al. [23], Cervi et al. [24], Arcadi et al. [25], Symeonidis et al. [26], Vacala et al. [27], Arcadi et al. [28], Wegner et al. [29], Nevado and Echavarren [30], Xiao et al. [31], Morán-Poladura et al. [32], Jiang et al. [33], Yin et al. [34].

Allene is another functional group, which can be activated by gold catalysts similar to alkyne. When alkynyl was replaced with allenyl in the substrates containing phenyl rings, hydroarylation could also take place with the catalysis of gold to construct benzocyclic motifs (Scheme 4) [41–44]. In 2007, Fujii, Ohno, and coworkers developed a gold-catalyzed hydroarylation reaction of allenic phenol and aniline derivatives catalyzed by gold, producing various chromene and dihydroquinoline scaffolds **20** and **21** under mild conditions [41]. In 2013, Alcaide and Almendros disclosed a gold-catalyzed chemo- and regioselective *9-endo* carbocyclization to construct fused tricyclic β-lactams **22** through introducing a long linker between the phenyl and the allenyl groups [43].

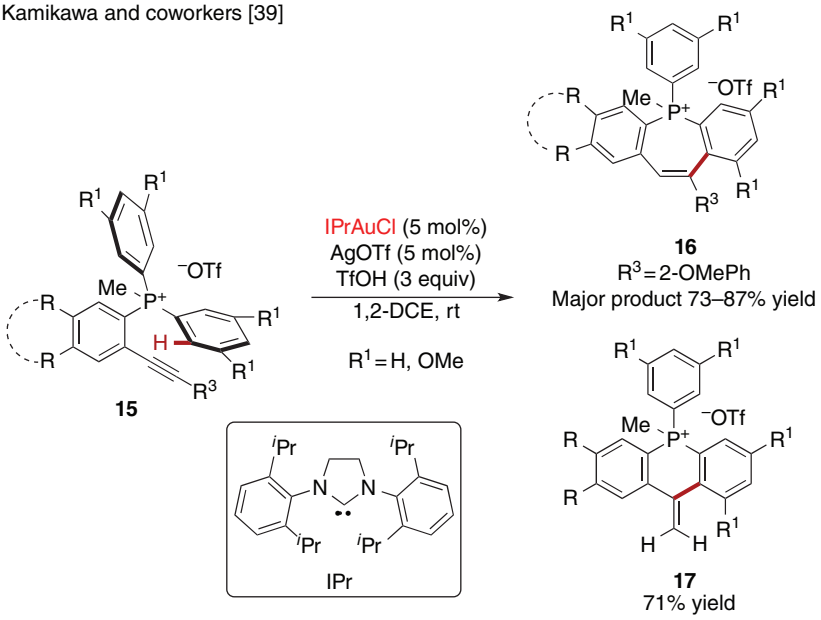
The gold-catalyzed C—H bond arylation is an efficient method to obtain benzocyclic compounds. In 2016, Lloyd-Jones and coworkers reported gold-catalyzed intramolecular C(sp^2)—H bond arylation of arenes with arylsilanes, generating annelated biaryls **24** with five- to nine-membered rings under mild conditions (Scheme 5) [45].

(a) Pirat and coworkers [38]:



13 14

(b) Kamikawa and coworkers [39]

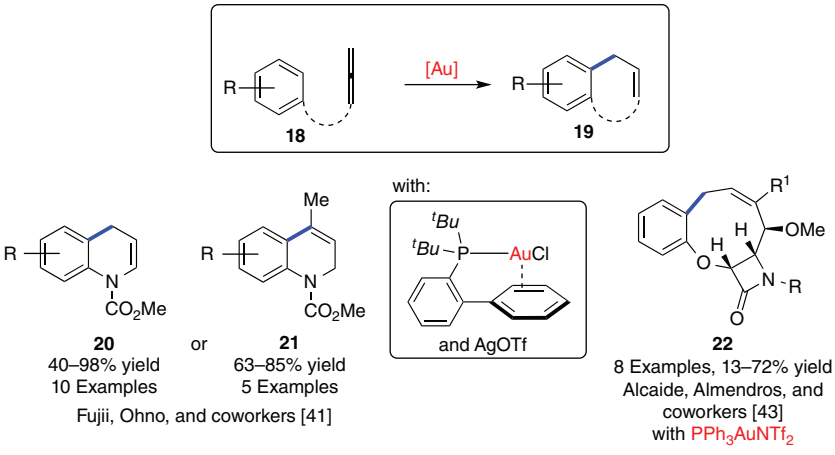


15

16
R3 = 2-OMePh
Major product 73–87% yield

17
71% yield

Scheme 3 Synthesis of P-containing heterocycles via Gold-catalyzed cyclization. Source: Hariri et al. [38], Tsurusaki et al. [39].



18 19

20
40–98% yield
10 Examples

or

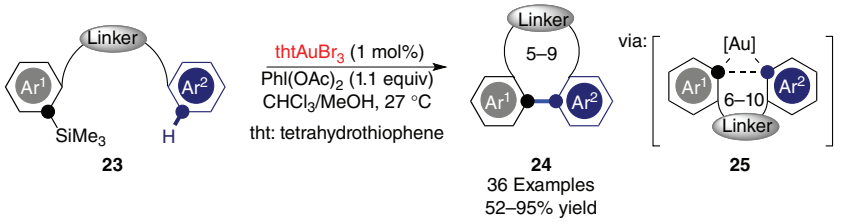
21
63–85% yield
5 Examples

Fujii, Ohno, and coworkers [41]

22
8 Examples, 13–72% yield
Alcaide, Almendros, and coworkers [43]
with PPh_3AuNTf_2

Scheme 4 Gold-catalyzed hydroarylation reaction of allenes. Source: Adapted from Watanabe et al. [41], Alcaide et al. [43].

Lloyd-Jones and coworkers [45]

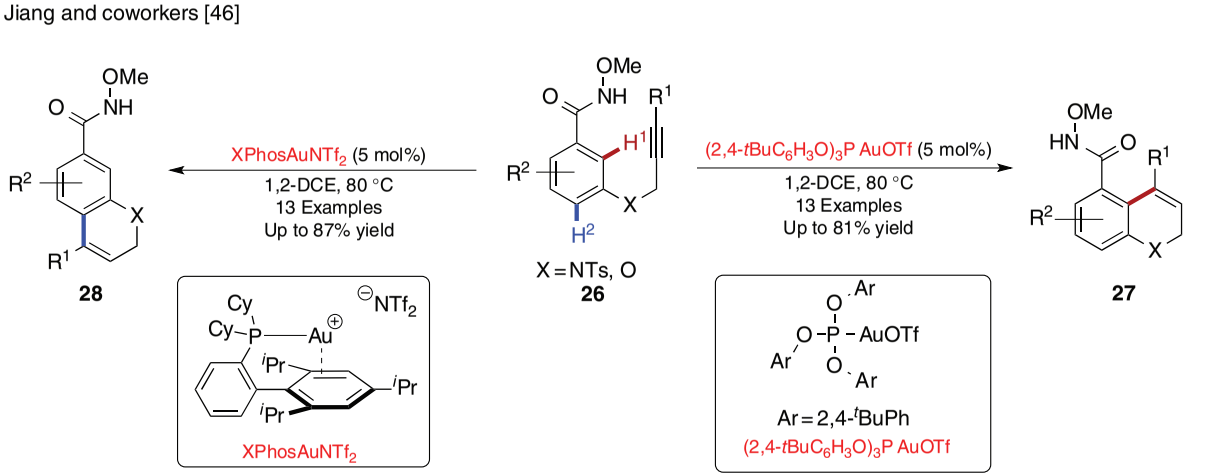


Scheme 5 Gold-catalyzed intramolecular C(sp²)—H bond arylation. Source: Corrie et al. [45]/American Chemical Society.

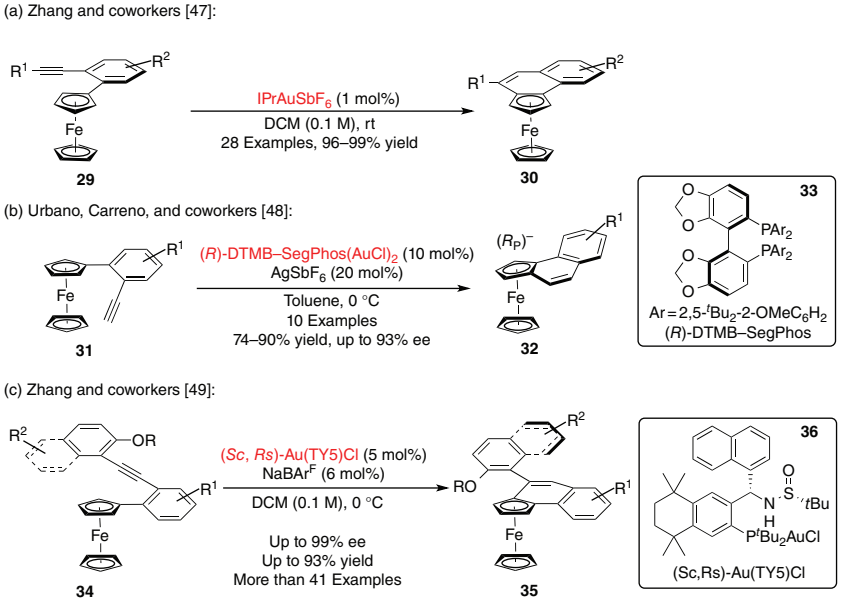
The site-selectivity of the aromatic C(sp²)—H bond could be controlled by the reaction conditions, when the gold-catalyzed intramolecular hydroarylation could result in two C(sp²)—H bond functionalization products for the unsymmetric phenyl ring. In 2016, a regiodivergent cyclization reaction was reported by Jiang et al. by tuning the gold catalysts (Scheme 6). In this reaction, the authors proposed that the electronic property and steric hindrance of the gold catalyst were vital for the site-selectivity. When the electron-deficient phosphite ligand $(2,4\text{-}^{t}BuC_6H_3O)_3P$ was used, the electrophilicity of the gold center was increased, which could be easily trapped by the lone-pair electrons of substituted amino group, resulting in the ortho-selective C(sp²)—H[1] bond functionalization product **27**. Moreover, when the bulky and electron-abundant phosphine ligand XPhos was used, the electrophilicity of the gold center was lowered, delivering the para-selective C(sp²)—H[2] bond functionalization product **28** [46].

This approach is also suitable for C(sp²)—H bonds of other aromatic rings. In 2016, Li, Zhang, and coworkers reported a gold-catalyzed hydroarylation reaction using *ortho*-alkynylferrocene derivatives **29** to synthesis a novel series of naphthoferrocene derivatives **30** (Scheme 7a) [47]. Urbano and Carreno achieved the asymmetric version using the substrates with terminal alkynyl **31** in the presence of the chiral phosphine ligand (R)-DTBM-Segphos **33** (Scheme 7b) [48]. In 2021, Zhang's group reported an asymmetric hydroarylation reaction of *ortho*-alkynylferrocene derivatives **34** to build axial and planar chiralities together. Under the catalysis of a novel TY-Phos-derived gold complex **36**, the product **35** was obtained with high yield and high diastereo- and enantioselectivity (Scheme 7c) [49].

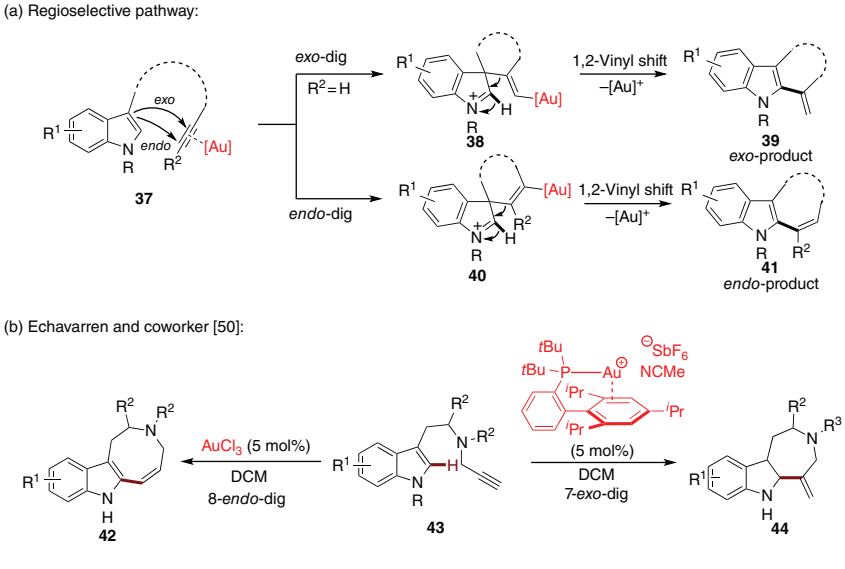
Similarly, heterocyclic aromatic compounds, such as indole and furan, are also suitable for gold-activated hydroarylation due to their nucleophilicity. The normal reaction pathways are shown in Scheme 8a. However, how to control the regioselectivity was vital in organic synthesis. In 2005, Echavarren group reported the first regiodivergent cyclization of indole-based alkyne **43** by tuning the gold catalysts. The *8-endo* product **42** could be obtained in the presence of $AuCl_3$, while the high-hindrance Au(I) complex resulted in the *7-exo* product **44** (Scheme 8b) [50]. Later, the same group also reported the gold-catalyzed intramolecular reaction of indoles with alkynes, giving the indole-fused annulated compounds that ranged from six- to eight-membered rings [51, 52].



Scheme 6 Gold-catalyzed region-divergent intramolecular 6-endo-dig cyclization. Source: Ding et al. [46]/American Chemical Society.



Scheme 7 Gold-catalyzed intramolecular *6-endo-dig* cyclization of ferrocene. Source: (a) Zhang et al. [47]/John Wiley & Sons, (b) Urbano et al. [48], (c) Zhang et al. [49].



Scheme 8 Gold-catalyzed aromatic C—H functionalization of heterocycles with alkynes. Source: (b) Echavarren et al. [50].

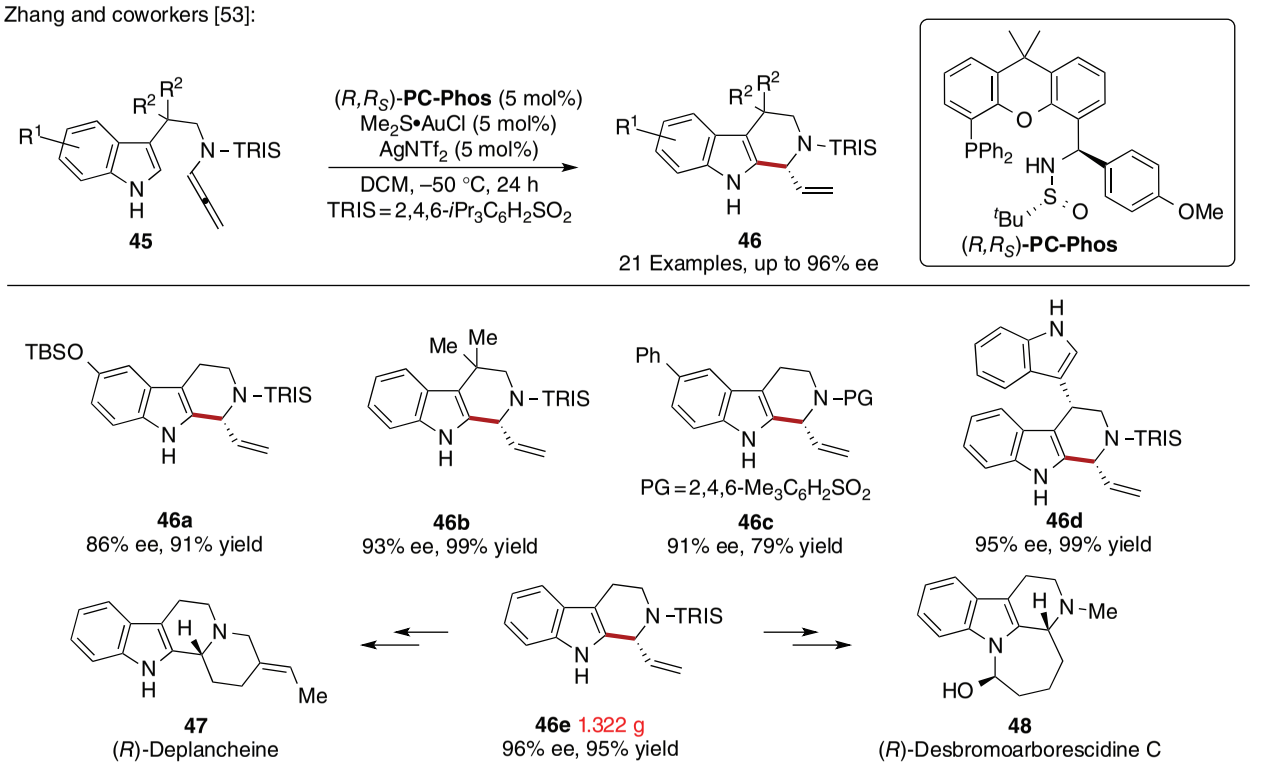
The similar cyclization was observed by replacing the alkynyl group with allenic group. Moreover, this reaction could construct a new chiral center. In 2017, Zhang's group reported an efficient approach to synthesize chiral tetrahydrocarboline **46** via indole-based *N*-allenamides **45** (Scheme 9). This method was achieved using the gold catalyst and a type of novel designed phosphine ligand PC-Phos. The protecting group on *N*-allenamides was crucial to the control of chirality due to steric hindrance. Excellent stereoselectivity was reached when the easily removable protecting group, such as 2,4,6-iPr$_3$C$_6$H$_2$SO$_2$ and 2,4,6-Me$_3$C$_6$H$_2$SO$_2$, was used. The enantioselective desymmetrization of *N*-allenamides also worked, which gave the tetrahydrocarboline **46d** containing two chiral centers. Gram-scale synthesis was also carried out smoothly. Furthermore, the products could be easily turned into the key intermediates of several natural products, which exhibited the application potential of this transformation [53].

In 2012, Hashmi group presented a 1,2-acyl amino-transfer mode in this indole-alkyne cyclization. As shown in Scheme 10, when the spiro intermediate **52** was generated via *6-endo-dig* cyclization of indolyl alkyne **49**, the resonance species **53** (**53′**) was formed via aromatization of the indole ring. Then, the Friedel–Crafts reaction occurred at the 2-position of indole, giving the final product **50** [54].

The linker could also be installed on the 1-position of indole, which could afford the corresponding 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indole core (Scheme 11) [54, 55]. In 2010, Barluenga et al. reported gold-catalyzed cycloisomerization of 1-(2,3-butadienyl)-1*H*-indole derivatives **55** via *6-endo* allene hydroarylation, giving various isolable pyrido [1,2-*a*]-1*H*-indole derivatives **56** (Scheme 11a) [55]. In 2021, Ma and coworkers developed a gold-catalyzed intramolecular cycloisomerization of *N*-1,3-disubstituted allenyl indoles, delivering a series of functionalized 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indoles directly. In this reaction, the chiral 6,9-dihydro-pyrido[1,2-*a*]-1*H*-indoles could be obtained with high yields and ee values via the transfer of the axial chirality to the central chirality (Scheme 11b) [56].

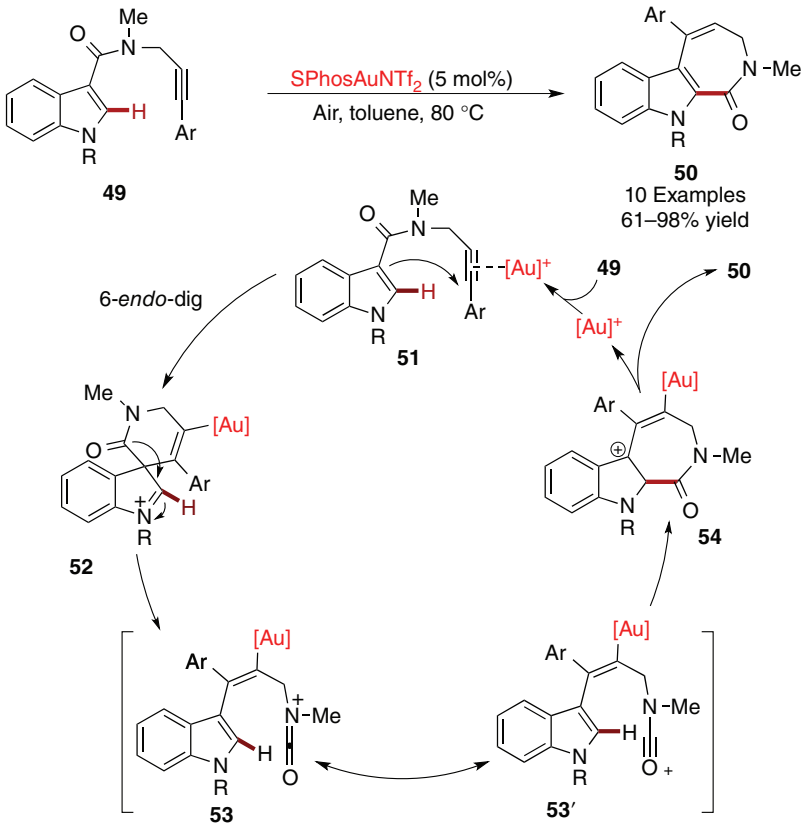
Furthermore, the C4 position-occupied indole could also undergo the similar cycloisomerization reaction. In 2013, Van der Eycken's group disclosed that the indoles-installed alkynyl amide on the C4 position **63** could undergo the C3-selective C(sp^2)—H functionalization via *8-endo-dig* cyclization in the presence of IPrAuCl/AgNTf$_2$, affording the corresponding tricyclic azocino-[*c*,*d*]indolone core **64**. However, in the presence of In(OTf)$_3$, another regioselective tricyclic azepino-[*c*,*d*]indolone product **65** was obtained via *7-exo-dig* cyclization (Scheme 12) [57]. In addition, this type of reaction can also be extended to other heterocyclic compounds including pyrrole and furan, providing a new strategy for the construction of heterocyclic bioactive molecules [58–62].

The aromatic C(sp^2)—H functionalization was also achieved by the active intermediate from the alkynyl group. In 2009, Liu and Zhang reported a gold-catalyzed cycloisomerization of *ortho*-alkynyl phenyl enones **66** to produce the benzo[α]-fluorenol **67** in good efficiency. In the proposed mechanism, the second cyclization of phenyl ring was due to the formation of alkenyl



Scheme 9 Gold-catalyzed asymmetric C—H functionalization of indoles with allenes. Source: Wang et al. [53]/John Wiley & Sons.

Hashmi et al. [54]:

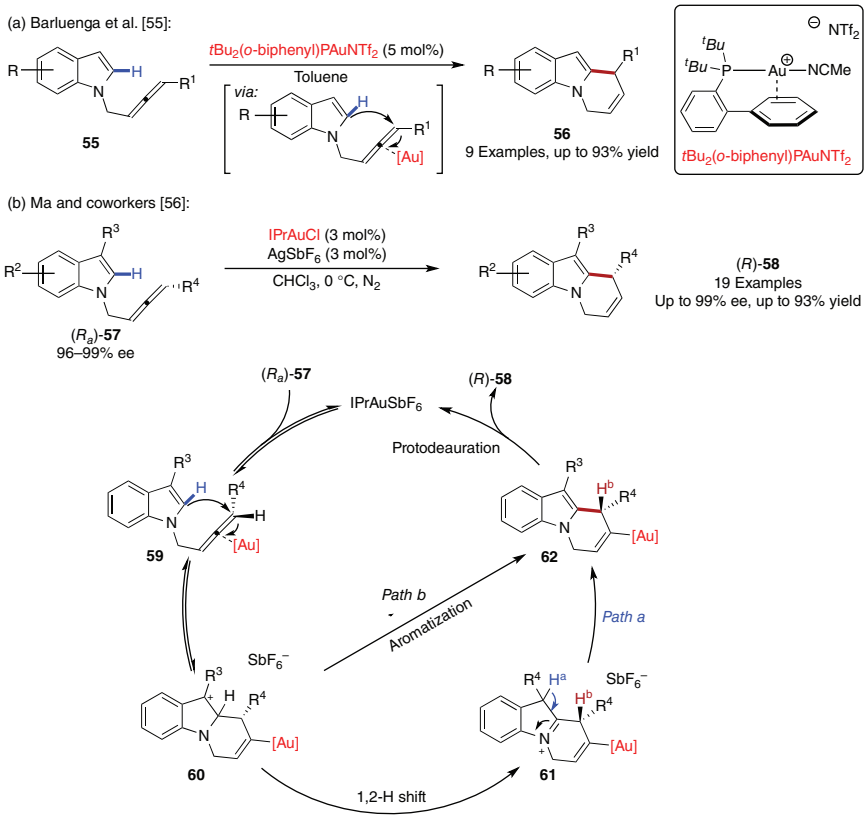


Scheme 10 Gold-catalyzed C—H functionalization of indoles via 1,2-acyl amino transfer. Source: Hashmi et al. [54]/John Wiley & Sons.

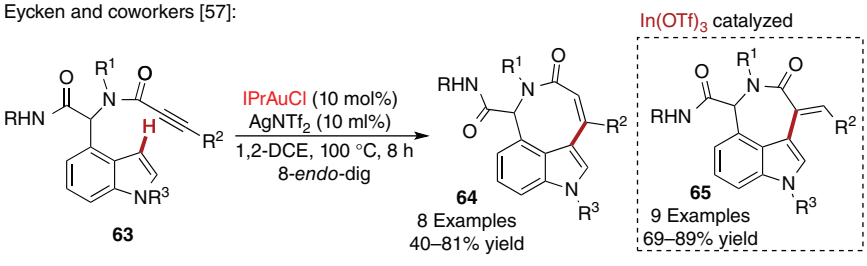
cation **69** which was generated via the gold-catalyzed alkyne–carbonyl coupling (Scheme 13) [63].

Besides the aromatic rings, the C(sp²)—H bond functionalization of alkenes was also realized by gold catalysis. In 2012, Zhang disclosed a gold-catalyzed intramolecular C(sp²)—H functionalization of enynyl azide **71**. The key intermediate was the α-imino gold carbene **78**, which was generated via the cyclization of azide in the presence of gold catalyst. The intermediate **78** could be easily converted to get 2,3-dihydro-1*H*-pyrrolizines **72** through the apparent electrocyclic ring closure (Scheme 14) [64].

The formation of this gold carbene intermediate containing diene-type motifs was also through the intermolecular reaction of alkynes with oxidants. In 2012, Liu's group reported a method to build furan derivatives **83** via the 3-en-1-ynamides **80** and 8-methylquinoline oxide **81** catalyzed by gold (Scheme 15a) [65]. In this reaction, gold-stabilized allylic cation intermediate **82** was important, which underwent



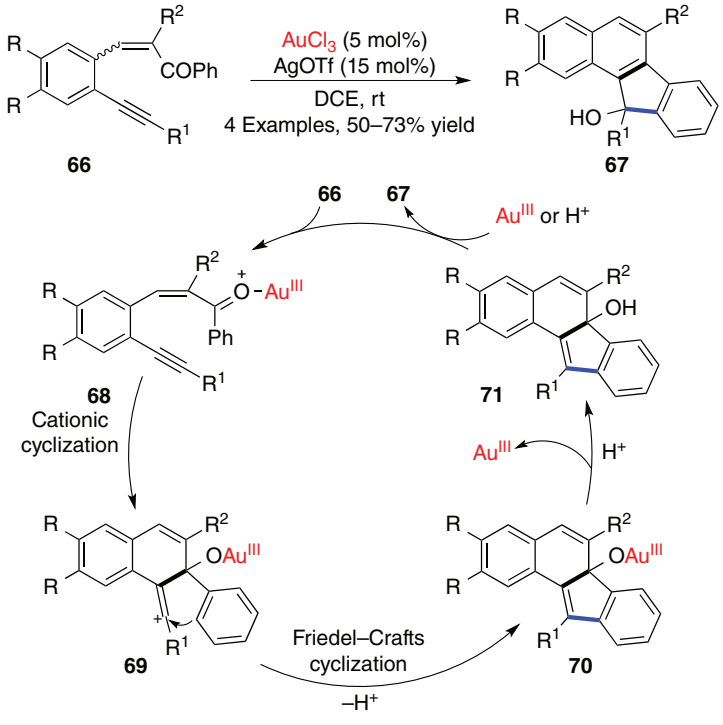
Scheme 11 C2-selective C—H functionalization of indoles with allenes. Source: (a) Barluenga et al. [55]/John Wiley & Sons, (b) Jiang et al. [56]/Royal Society of Chemistry.



Scheme 12 C3-selective C(sp^2)—H functionalization via *8-endo-dig* cyclization. Source: Kumar et al. [57]/Royal Society of Chemistry.

the oxa-Nazarov cyclization to construct the furan products **83**. In 2016, Ye and coworkers replaced 8-methylquinoline oxide **81** with azides **85** subject to the similar substrates **84**. 2-Aminopyrrole derivative **87** was obtained from the α-imino gold carbene intermediate **86** via the similar gold–carbene formation/Nazarov-type cyclization (Scheme 15b) [66].

Liu and Zhang [63]:



Scheme 13 Gold-catalyzed cycloisomerization of (*o*-alkynyl)phenyl enones. Source: Liu and Zhang [63]/John Wiley & Sons.

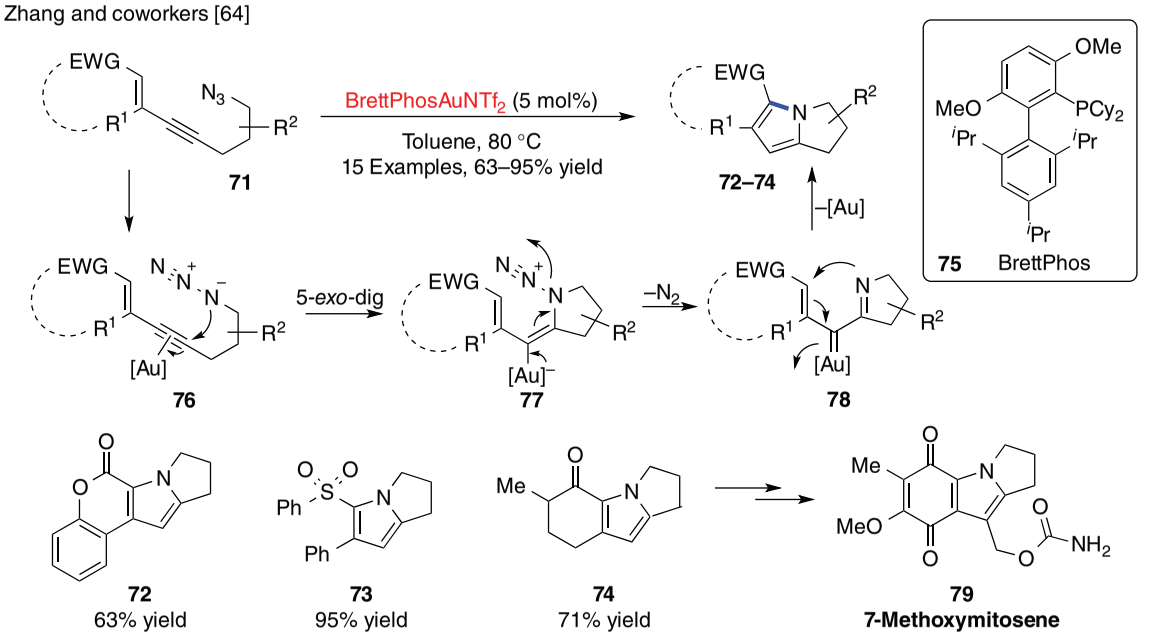
3 Gold-Catalyzed Intermolecular C(sp²)—H Functionalization

Compared to the intramolecular reaction, the intermolecular version is more difficult. In general, the intermolecular reaction needs the substrates to have more reactivity. Furthermore, the site-selectivity of C(sp²)—H bond is more challenging.

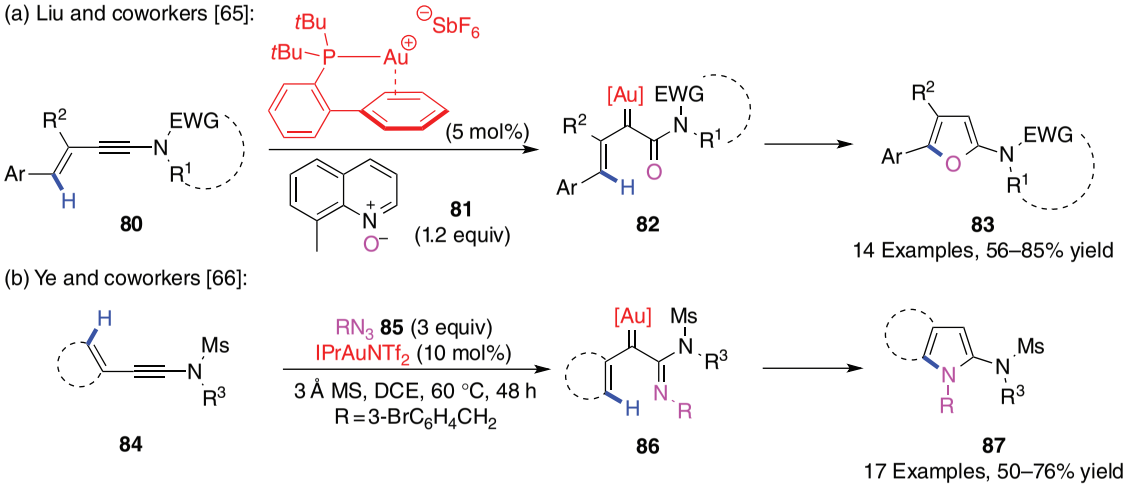
3.1 Carbon–Heteroatom Bond Formation

In 2009, Wang's group reported a bromination reaction of aromatic C(sp²)—H bond of phenyl rings with *N*-bromosuccinimide (NBS) under the catalysis of $HAuCl_4$. This reaction could take place under mild condition in high efficiency with good para-selectivity, producing a series of bromobenzene derivatives. Although good yield was observed for the reaction of toluene, the regioselectivities of the ortho- and para-position were not good (Scheme 16) [67].

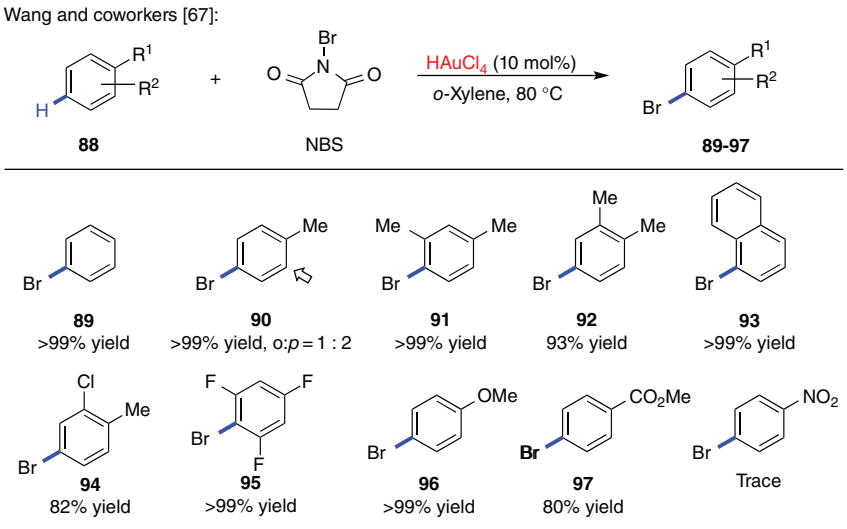
In 2014, DeBoef's group reported an efficient method to synthesize aniline derivatives via site-selective C—H bond amination. The combination of Cy_3PAuCl and the



Scheme 14 Gold-catalyzed C(sp^2)—H bond functionalization of alkenes via α-imino gold-carbene. Source: Yan et al. [64]/John Wiley & Sons.

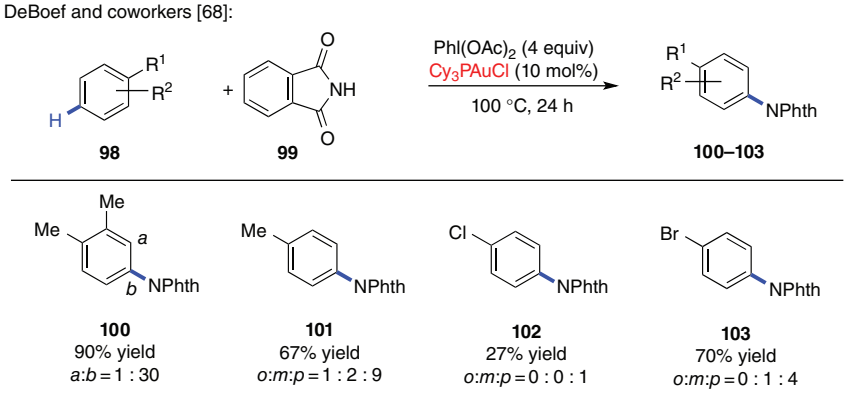


Scheme 15 C(sp^2)—H bond functionalization of alkenes to build heterocyclic compounds. Source: (a) Dateer et al. [65]/Royal Society of Chemistry, (b) Shu et al. [66]/American Chemical Society.



Scheme 16 Gold-catalyzed aromatic C(sp^2)—H bromination. Source: Mo et al. [67].

oxidant $PhI(OAc)_2$ could promote the C—H bond functionalization of arenes with phthalimide to access a variety of substituted anilines in good yields. The proposed mechanism suggests that the position of electrophilic aromatic metalation will determine the regioselectivity of the amination (Scheme 17) [68].

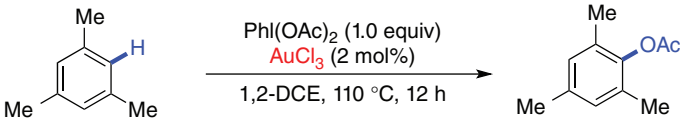


Scheme 17 Gold-catalyzed aromatic C(sp^2)—H amination. Source: Marchetti et al. [68]/American Chemical Society.

In 2011, Wang's group reported the acetoxylation of electron-rich arenes under the catalysis of $AuCl_3$ using iodobenzene diacetate as the acetoxylation reagent, delivering the corresponding products **105** in good yield (Scheme 18a) [69]. Later, Toullec and Michelet disclosed the Ph_3PAuCl-catalyzed acyloxylation of nonactivated hindered aromatic rings with di(acetoxy)iodobenzene as the oxidant (Scheme 18b) [70]. In this reaction, the acyloxyl groups were from the corresponding carboxyl acid as

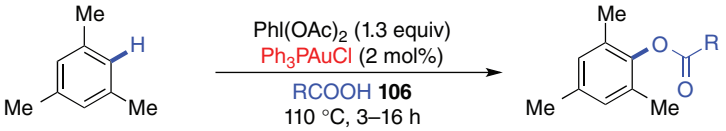
the solvent. The catalytic cycle between Au(I) and Au(III) was the key issue for the success of these two reactions.

(a) Wang and coworkers [69]:



104 **105**
75% yield

(b) Toullec, Michelet, and coworker [70]:



104 **107**
32–80% yield

Scheme 18 Gold-catalyzed C(sp²)—H acetoxylation reaction. Source: (a) Qiu et al. [69]/American Chemical Society. (b) Pradal et al. [70]/American Chemical Society.

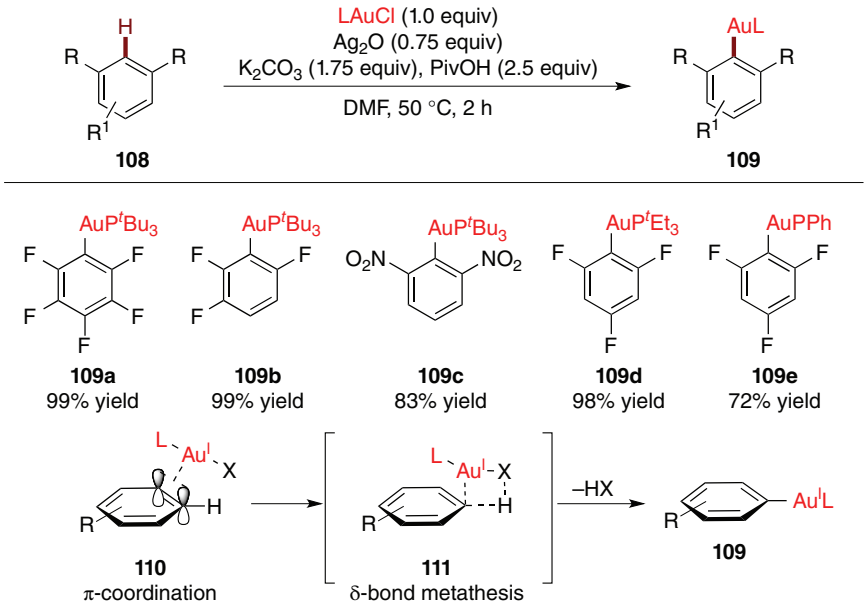
In 2010, Larrosa's group achieved C(sp²)—H functionalization of electron-deficient arenes **108** using stoichiometric gold complexes to construct the C—Au bond. The Au(I) complexes strongly coordinate to the π bond of arenes, followed by the σ-bond metathesis (SBM) to form the final Au-containing arenes **109**. The large primary kinetic isotope experiment (KIE) of 5 indicates that the C—H bond activation step in the reaction occurs during the rate-determining step (Scheme 19) [71].

3.2 Carbon–Carbon Bond Formation

3.2.1 C(sp²)—C(sp) Bond Formation

Alkynes are well known as versatile building blocks and important functional groups for the molecules of value in biochemistry and material science. The alkynylation reactions of C(sp²)—H bond enable the construction of alkynyl-containing conjugated systems, such as enynes and aromatic alkynes, which attract wide interest of chemists. A neutral benziodoxolone-derived alkynylation reagent containing hypervalent iodine (1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one, TIPS-EBX) was developed by Waser's group in 2009. Under the catalysis of AuCl, TIPS-EBX became an ideal alkynylation reagent for electron-rich and heterocyclic aromatics. In 2009, Waser reported the C(sp²)—H bond alkynylation of indoles and pyrroles **112** with TIPS-EBX in the presence of AuCl, affording the corresponding products **113** in good to excellent yields with excellent regioselectivity (Scheme 20a) [72]. Later, the same group developed the direct alkynylation of thiophene derivatives catalyzed by gold with the trifluoroacetic acid (TFA) as an additive at room temperature (Scheme 20b) [73]. All the regioselectivities were high, which occurred at the most electron-rich position. Then, they also developed a highly para-selective

Larrosa and coworkers [71]:



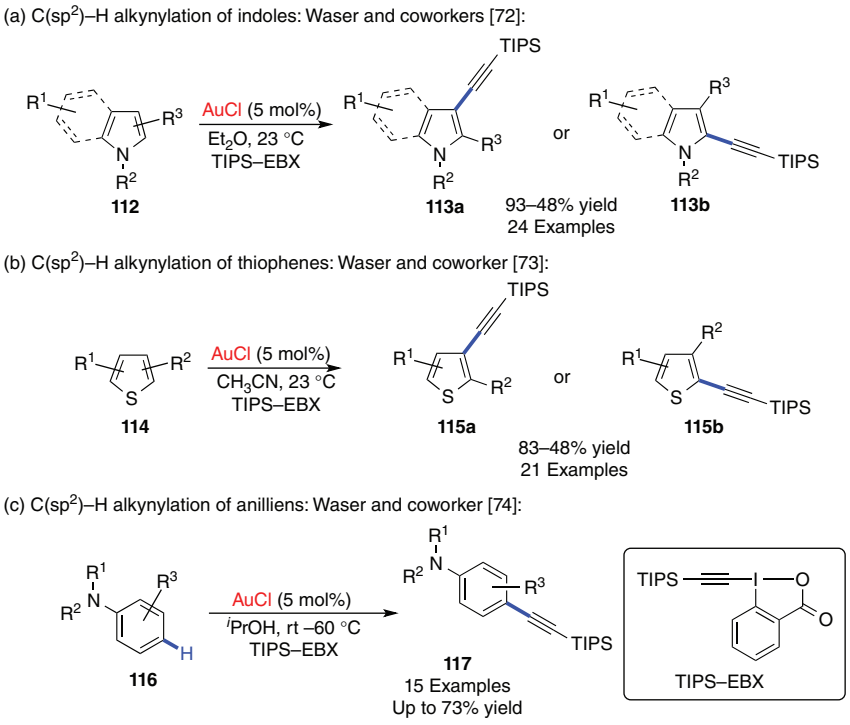
Scheme 19 The formation of C—Au bond via C(sp²)—H functionalization. Source: Lu et al. [71]/American Chemical Society.

C(sp²)—H bond alkynylation of aniline derivatives (Scheme 20c) [74]. Besides these heteroatom-containing aromatics, Tolnai, Novák, and coworkers reported a similar C(sp²)—H bond alkynylation of azulenes with TIPS-EBX with good regioselectivity in 2017, which was an alternative for the traditional cross-coupling reaction [75].

Furthermore, many research works showed that the regioselectivities of C(sp²)—H bond alkynylation under gold catalysts were different with the same reaction under other noble metal catalysts. Bolm discovered that the site-selective alkynylation of indole at the C3 position occurred in the presence of AuCl in mixer mills, while the C2-selective product **119b** was obtained catalyzed by Rh complex (Scheme 21a) [76]. Li realized a regiodivergent (C5 or C6) C(sp²)—H bond alkynylation of 2-pyridones under Au(I) and Rh(III) catalysis (Scheme 21b) [77]. Patil reported a site-divergent C(sp²)—H bond alkynylation of isoquinolones under the catalysis of gold and rhodium complexes, providing a facile access to either C-4- or C-8-alkynylated isoquinolones (Scheme 21c) [78].

The terminal alkynes could also be used as the alkynylation reagent. In 2010, Nevado and coworker realized the first C(sp²)—H bond alkynylation of electron-rich arenes **125** with terminal alkynes **126** in the presence of gold catalyst with $PhI(OAc)_2$ as the oxidant. In this reaction, both C(sp²)—H and C(sp)—H bonds were activated together. This transformation provides an efficient protocol for the synthesis of aromatic propiolates difficult to prepare by other methods (Scheme 22) [79].

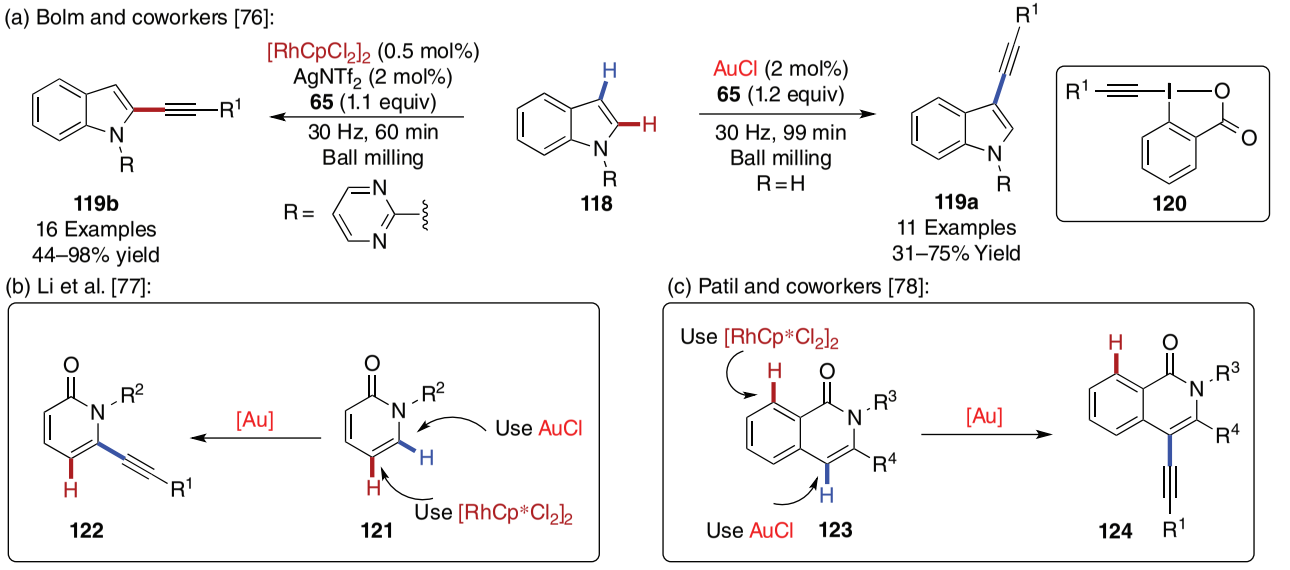
The C(sp²)—H bond alkynylation also occurs at the alkenyl group under gold catalysis. In 2018, Hashmi's group achieved the C(sp²)—H alkynylation



Scheme 20 Gold-catalyzed C(sp²)—H alkynylation with TIPS–EBX. Source: (a) Brand et al. [72]/John Wiley & Sons, (b) Brand and Waser [73]/John Wiley & Sons, (c) Brand and Waser [74]/American Chemical Society.

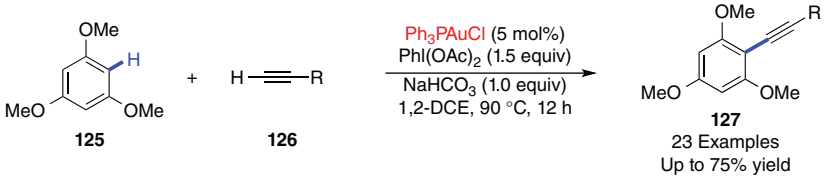
of cyclopropene **127** via dual gold/silver catalysis. Furthermore, the mechanistic investigation suggested that this reaction pathway was different from the previous C(sp²)—H alkynylation via gold only. As shown in Scheme 23, this reaction included two catalytic cycles. At the beginning, the active gold species **130** is generated by ligand exchange, followed by oxidative addition to give alkynylgold(III) complex **132**. Then, the alkoxyl is transferred from Au to Ag to form silver complex **137**, which undergoes C—H activation to generate the cyclopropenyl silver species **135**. The cyclopropenyl gold **134** is formed via the transmetalation group, which forms the alkynylated cyclopropane product **129** and regenerates the active (Phen)AuL **130** by reductive elimination (Scheme 23) [80].

Later, Hashmi and coworkers developed gold-catalyzed C(sp²)—H bond alkynylation reaction to synthesize tetra-substituted 1,3-enyne **139** from noncyclic olefins **138** with the same hypervalent iodine reagent **128**. The similar Au(I)/Au(III) catalytic cycle was involved in this transformation. This reaction expanded the gold-catalyzed C(sp²)—H bond alkynylation to synthesize multisubstituted olefins due to the mild conditions and good functional group compatibility (Scheme 24) [81].



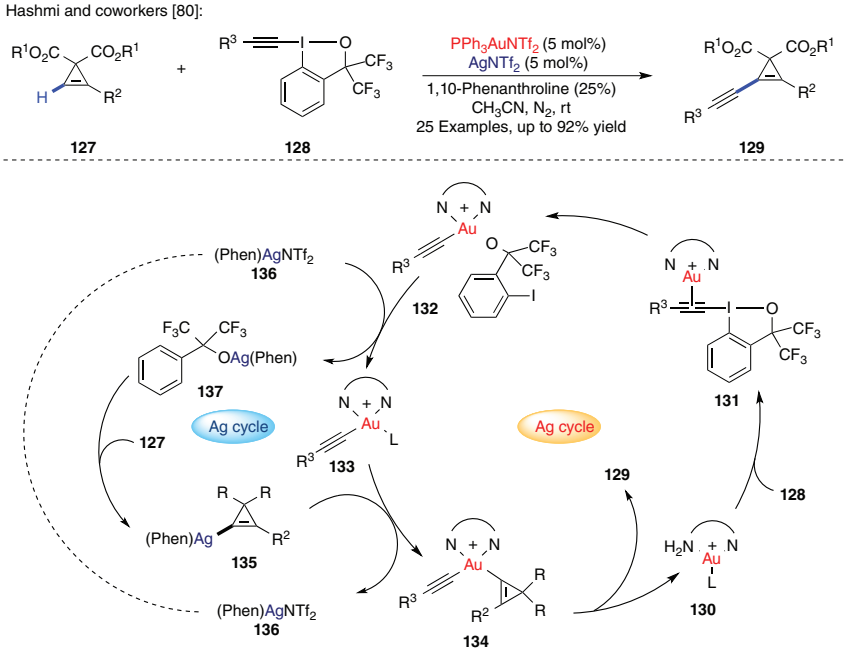
Scheme 21 Regio-divergent C—H bond alkynylation of heterocycles. Source: (a) Hermann et al. [76]/John Wiley & Sons, (b) Li et al. [77], (c) Shaikh et al. [78].

Nevado and coworker [79]:



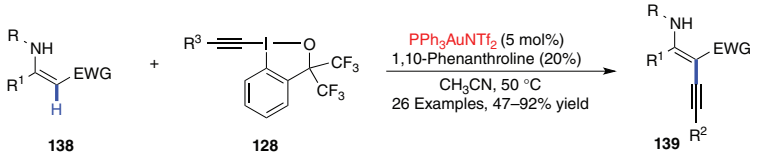
Scheme 22 Gold-catalyzed C(sp²)—H alkynylation of electron-rich arenes with terminal alkynes. Source: Haro et al. [79]/American Chemical Society.

Hashmi and coworkers [80]:



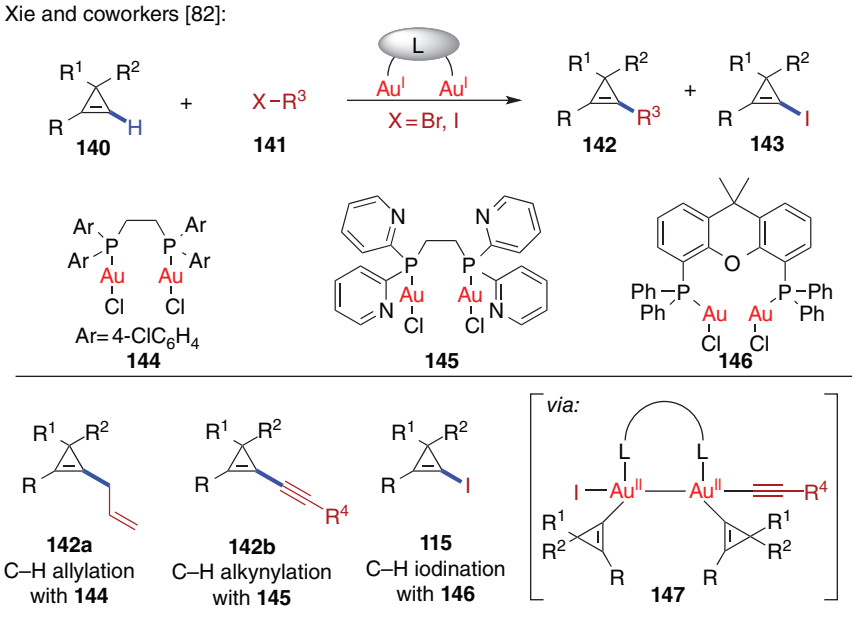
Scheme 23 C(sp²)—H alkynylation of cyclopropenes via the cooperative gold/silver catalysis. Source: Yang et al. [80]/John Wiley & Sons.

Hashmi and coworkers [81]:



Scheme 24 Gold-catalyzed C(sp²)—H alkynylation of enamines. Source: Han et al. [81]/American Chemical Society.

In 2021, Xie reported C(sp²)—H bond functionalization of cyclopropene via binuclear gold complexes, including C—H alkylation, halogenation, and allylation products. In this work, the ligands were important for the formation of different reductive elimination products (Scheme 25) [82].

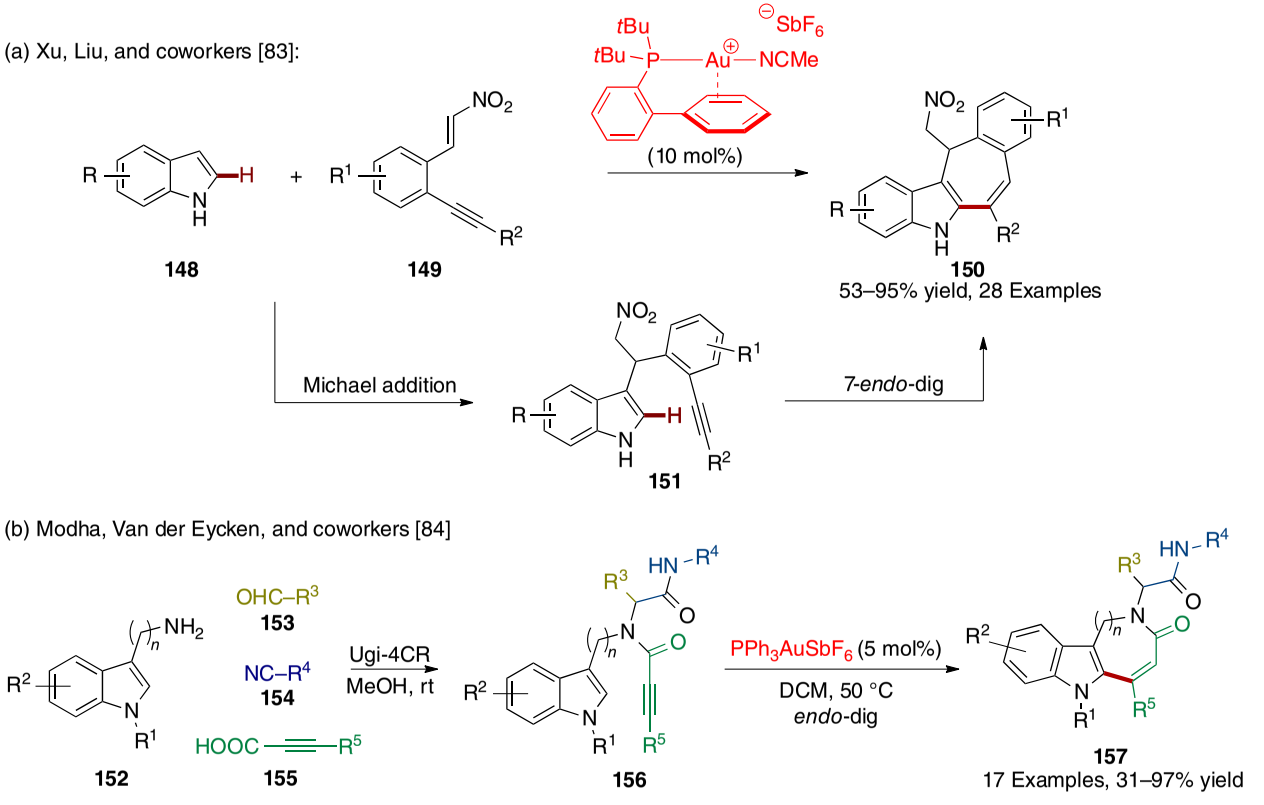


Scheme 25 C(sp²)—H bond functionalization of cyclopropene via binuclear gold complexes. Source: Liu et al. [82]/Springer Nature.

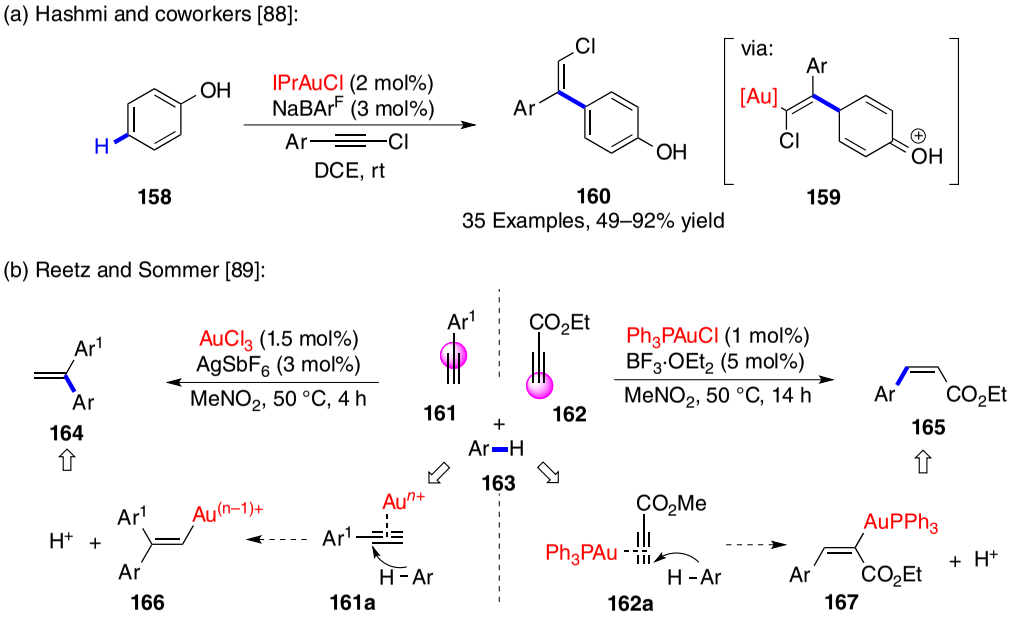
3.2.2 C(sp²)—C(sp²) Bond Formation

An indirect strategy to realize the intermolecular C(sp²)—H bond alkenylation is via a sequential reaction, which includes the coupling reaction of aromatic rings and alkynes as well as the intramolecular hydroarylation [73–86]. In 2013, Liu, Xu, and coworkers reported a gold-catalyzed C(sp²)—H bond alkenylation of indole **148** and enyne **149** via tandem intermolecular Michael addition and intramolecular hydroarylation reaction (Scheme 26a) [83]. Van der Eycken and coworkers constructed the similar indole-fused rings via the tandem Ugi four-component reaction/cyclization (Scheme 26b) [84].

The direct intermolecular hydroarylation reactions of aromatic compounds and alkynes are more efficient than the indirect version [85–93]. In 2019, Hashmi and coworkers used IPrAuCl–NaBAr^F as a catalyst to achieve a highly chemo- and site-selective C(sp²)—H bond alkenylation of phenol **158** to obtain various derivatives of *Z*-chlorovinyl phenol **160** (Scheme 27a) [88]. Reetz's group reported a regiodivergent C(sp²)—H hydroarylation between electron-rich aromatics and electron-rich alkyne **161** and electron-poor alkyne **162** (Scheme 27b) [89]. He and



Scheme 26 Gold-catalyzed intermolecular C(sp^2)—H alkenylation of indoles. Source: (a) Xu et al. [83] (b) Vachhani et al. [84].



Scheme 27 Gold-catalyzed intermolecular C(sp^2)—H alkenylation of arenes with alkynes. Source: (a) Adak et al. [88] (b) Reetz et al. [89].

coworkers also developed an efficient $AuCl_3$/3AgOTf-catalyzed hydroarylation reaction of arenes with electron-deficient alkynes [90].

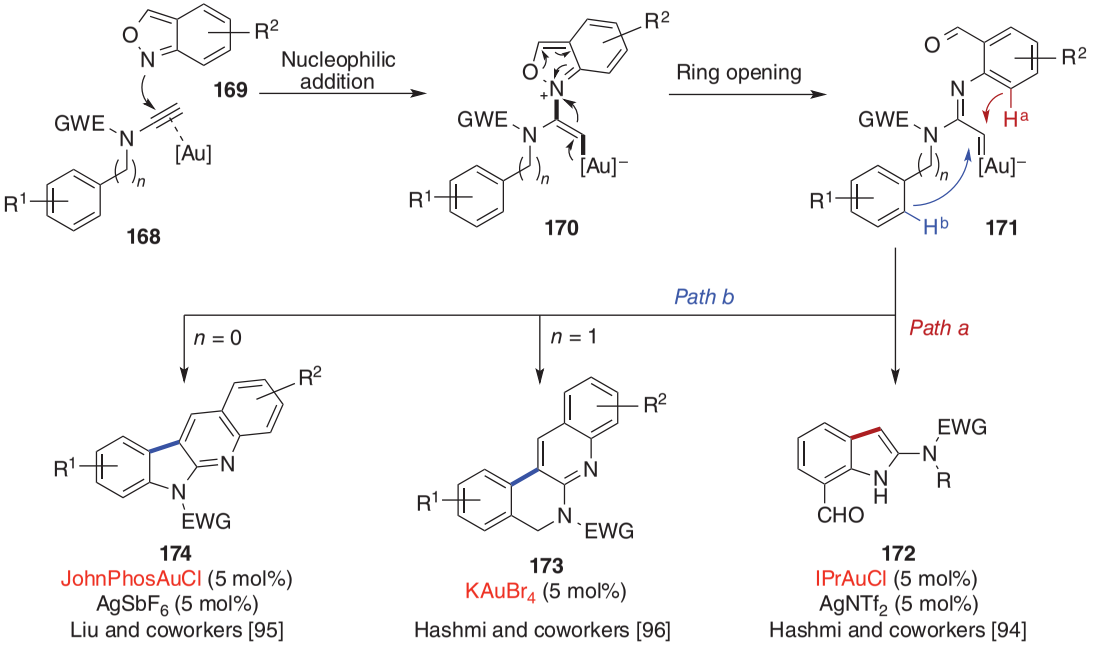
Another strategy to achieve the C(sp^2)—H bond functionalization is the formation of gold–carbene intermediate. Several regioselective C(sp^2)—H bond alkenylations, whose products could be controlled by substrates, had been achieved successively via gold–carbene intermediates from alkynes with anthranils **169** (Scheme 28) [94–97]. In these reactions, the α-imino gold–carbenes **171** were produced via the nucleophilic attacking of anthranil **169** to gold-activated alkynyl group and the rearrangement shown in Scheme 28. If the *ortho*-aryl C—H bond insertion occurred, various 7-formyl indoles **172** could be afforded via path a [94]. If the phenyl groups on ynamides were electron-rich phenyl rings, the domino C—H bond insertion/aldol reaction occurred, affording the fused 6*H*-indolo[2,3-*b*]quinoline frameworks **174** [95]. Hashmi reported the similar tandem cyclization using the *N*-benzyl ynamides, affording a series of quinoline-fused polyazaheterocycles **173** [96].

In 2015, Ye disclosed that the gold-catalyzed reaction of ynamides **175** and azides **176/178** was an efficient strategy for the formation of α-imino gold–carbene. Based on this gold-carbene intermediates, versatile 2-aminoindoles **179** and 3-amino-β-carbolines **177** were synthesized in good to excellent yields with excellent site-selectivity. In addition, the authors proposed the mechanistic rationale for the regioselectivity, which was also strongly supported by density functional theory (DFT) computations (Scheme 29) [98].

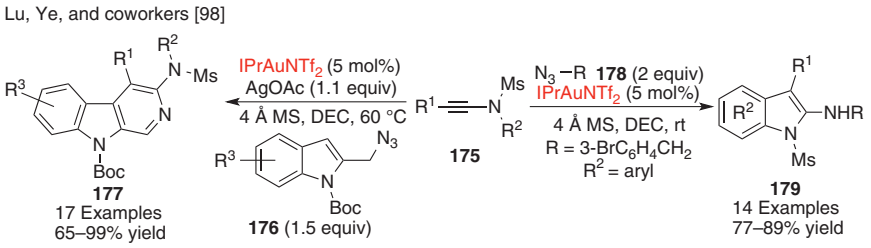
Biaryl, which is another important motif in pharmaceuticals, agrochemicals, and organic materials, could be obtained by the gold-catalyzed intermolecular C(sp^2)—H bond arylation of aromatic compounds (Scheme 30) [98–102]. In 2012, Lloyd-Jones, Russell, and coworker developed the gold-catalyzed C—H bond arylation of arenes with arylsilanes [99]. In 2017, Nevado and coworkers disclosed a gold-catalyzed oxidative cross-coupling of arenes with aryl boronates [102]. In general, the catalytic cycle can be initiated by the transmetalation of [Au] to form an arylgold(I) complex **183**. Then, this intermediate **183** can be oxidized by the oxidant $ArI(OAc)_2$ to afford the bis(acetate)arylgold(III) complex **184**. The C—H bond activation of the arene **181** occurs by an S_EAr process to generate a bis(aryl)gold-(III) species **185**, which undergoes the subsequent reductive elimination to produce the final heterocoupling product **182** and regenerates the gold(I) catalyst. Alternatively, the oxidation of gold(I) to gold(III) might occur before transmetalation in some cases [100].

Compared to the coupling reaction using aryl metal reagent **180**, the double C—H bond activation is more atom economical in organic synthesis. In 2008, Tse and coworkers reported a gold-catalyzed oxidative coupling of arenes using $PhI(OAc)_2$ as the oxidant [103, 104].

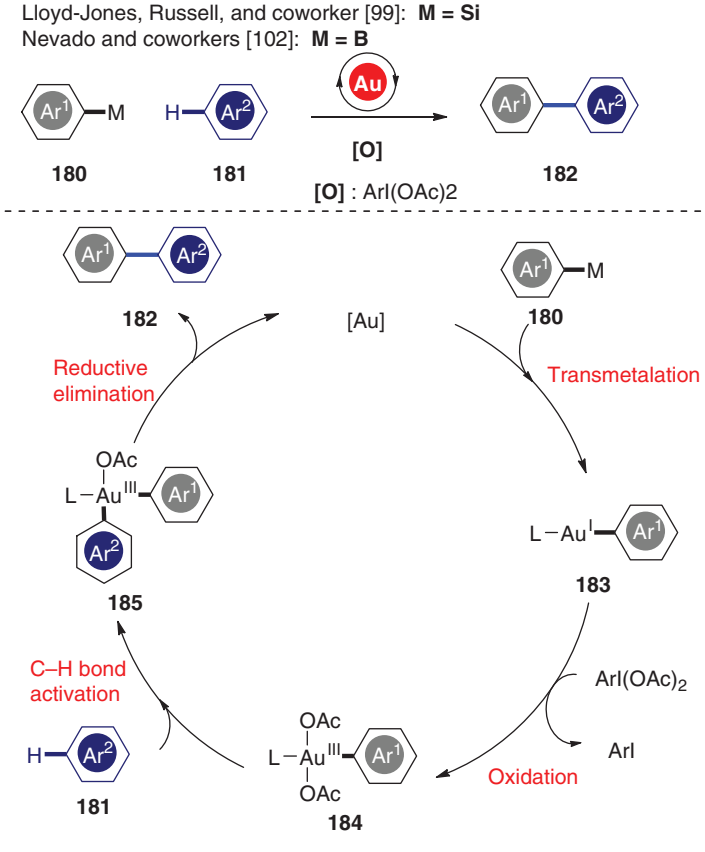
However, only homocoupling products were obtained in this reaction, which limited the utilization of this strategy. In 2015, Larrosa and coworkers developed an efficient gold-catalyzed oxidative cross-coupling of arenes via double C—H activation, which simplified the preparation of biaryls because this protocol did not need directing groups or a large excess of one of arenes (Scheme 31a) [105]. The



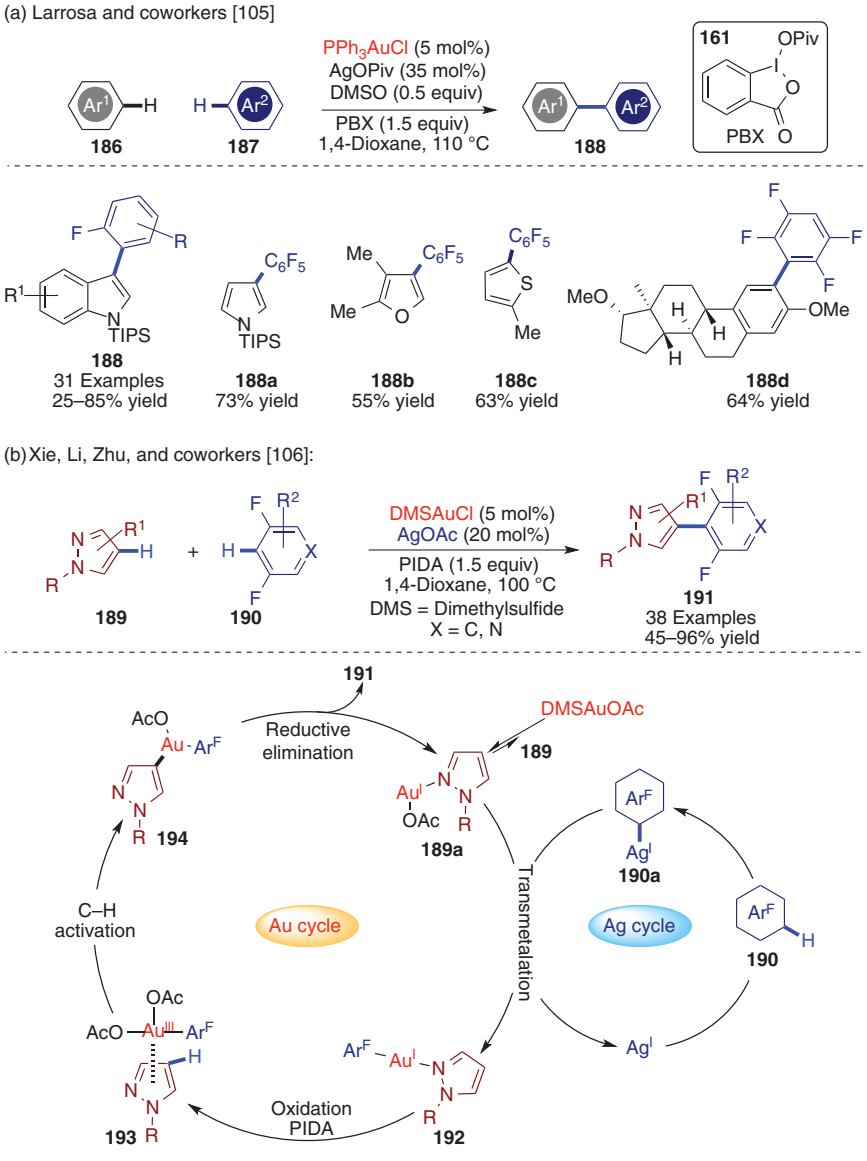
Scheme 28 Regioselective C(sp^2)—H alkenylations via gold-carbene intermediate. Source: Jin et al. [94], Tsai et al. [95], and Zeng et al. [96].



Scheme 29 Gold-catalyzed C(sp²)—H alkenylations of ynamides and azides.
Source: Shu et al. [98].



Scheme 30 Gold-catalyzed intermolecular C(sp²)—H arylation via cross-coupling reaction.
Source: Ball et al. [99], and Hofer et al. [102].



Scheme 31 Gold-catalyzed oxidative cross-coupling of arenes. Source: (a) Cambeiro et al. [105]. (b) Li et al. [106].

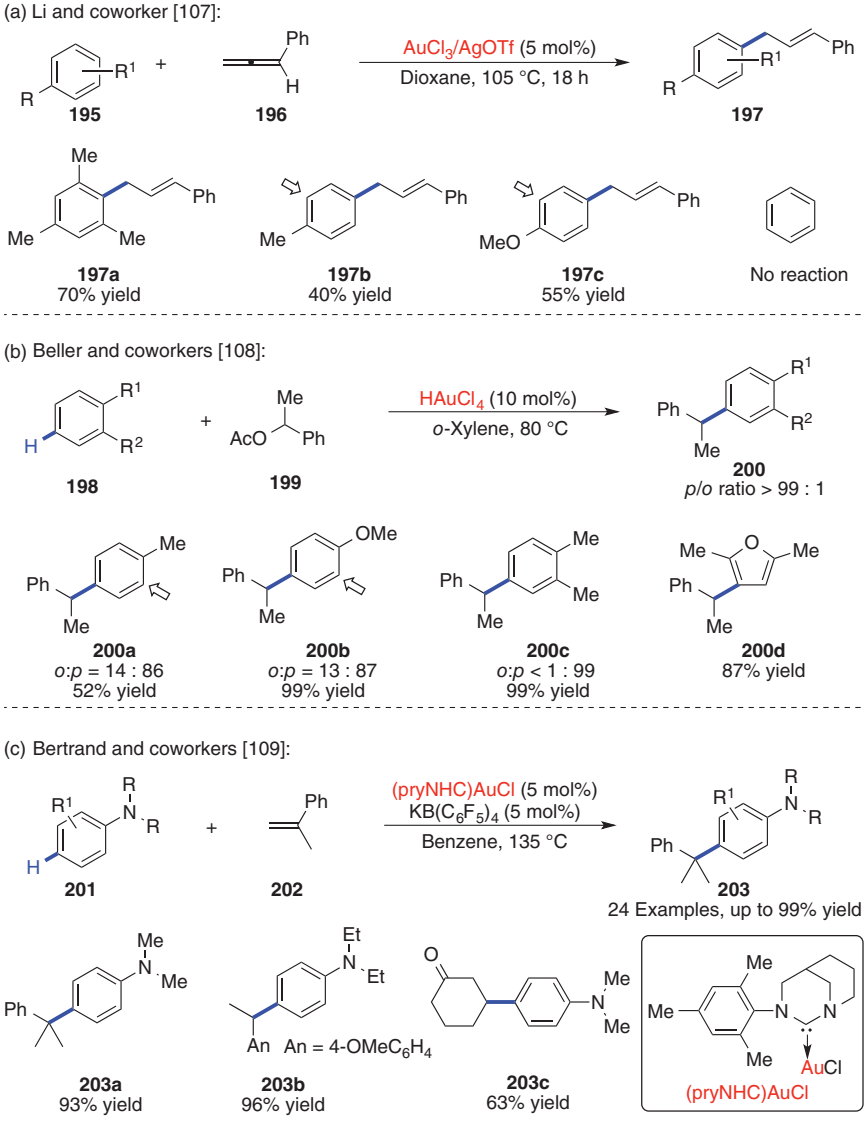
excellent selectivity is because this cross-coupling needs one electron-rich arene and one electron-poor arene containing a relatively acidic C—H bond. In 2018, Xie and coworkers developed a highly selective double C—H bond functionalization between pyrazoles **189** and fluoroarenes **190** under the cooperative catalysis of Au/Ag bimetals. The mechanistic insight proved that silver salts were not only the halogen scavenger for gold complex but also an important catalytic species in reaction pathway, which is different from the previously reported Au(I)/Au(III)

catalytic mode. The authors proposed that Ag(I) was the actual catalytic species for the C—H bond activation of electron-poor arene **190** to generate arylsilver intermediate **190a** via a concerted metalation–deprotonation (CMD) process. The AcOAu–pyrazole complex **189a** was formed via ligand exchange, which would go through transmetalation to form two aryl gold species **192**. Then, the oxidation of Au(I) species **192** by PIDA afforded the formation of an Au(III) intermediate **193**, followed by the C—H activation of *N*-phenylpyrazole via electrophilic aromatic substitution (S_EAr) mechanism. Finally, the reductive elimination from the tricoordinate Au(III) intermediate **194** gave the biaryl products **191** and regenerated the gold catalyst. The proposed reaction pathway was proved by experimental and DFT theoretical studies (Scheme 31b) [106].

3.2.3 C(sp^2)—C(sp^3) Bond Formation

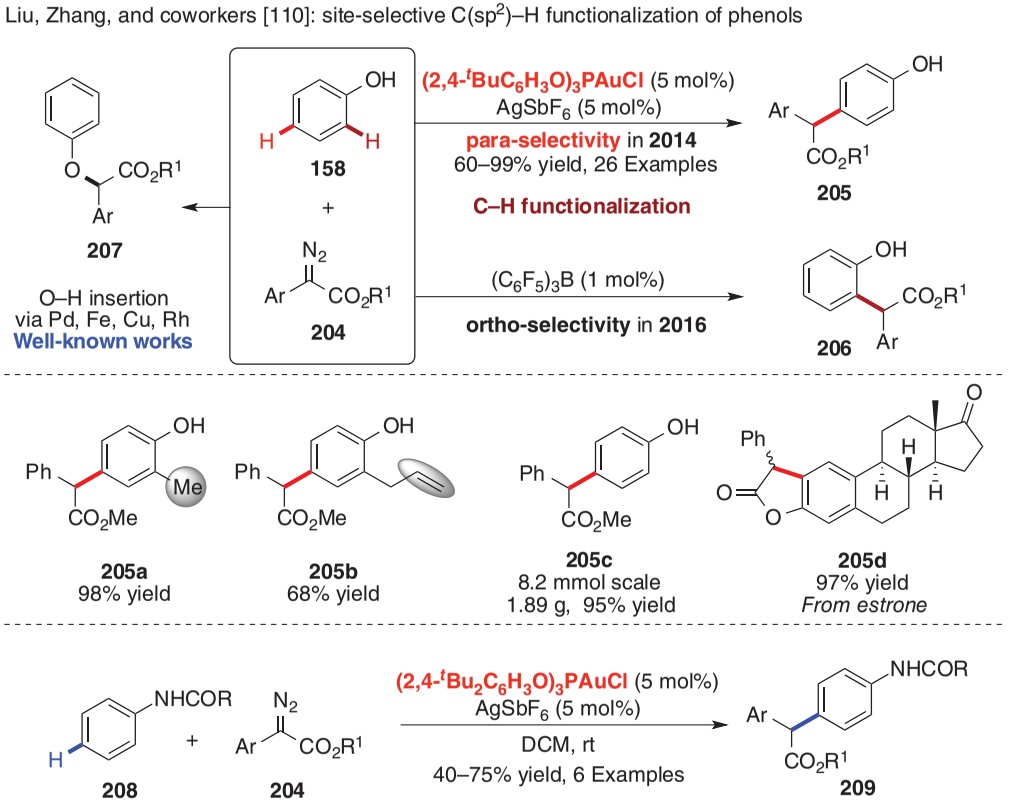
The classical Friedel–Crafts alkylation of aromatic compounds is the most important reaction to construct C(sp^2)—C(sp^3) bond via intermolecular C(sp^2)—H functionalization. However, the substrate scope is limited, and the site-selectivity is not good for this classical approach. Thus, the development of novel methodology, such as gold-catalyzed reaction, is highly desirable. In 2007, Li developed an intermolecular C(sp^2)—H functionalization of mesitylene or 1,3,5-trimethoxybenzene **195** using allene **196** as an electrophile via gold catalyst to afford allyl benzene derivatives (Scheme 32a) [107]. The regioselectivity of allene is at the γ-position, while the site-selectivities of the mono-substituted aromatics were not good. Moreover, the yields decreased drastically to even no reaction for unactivated arenes. Beller's group achieved an $HAuCl_4$-catalyzed site-selective *para*-C(sp^2)—H benzylation of arenes **198** with benzyl acetate **199**. This reaction performed outstanding regioselectivity in most substrates. However, for some challenging substrates, such as toluene and anisole, there still were about 13% ortho-benzylation products (Scheme 32b) [108]. In 2014, Bertrand developed a novel hemilabile cyclic (alkyl)(amino)carbene (CAAC), which was an efficient ligand for gold complex. The (CAAC)AuCl/$KB(C_6F_5)_4$ showed high catalytic activity for the hydroarylation of *N*,*N*-dimethylaniline **201** with alkene **202** with high selectivity (Scheme 32c) [109].

Although many kinds of electrophiles have been utilized in the C(sp^2)—H functionalization of arenes, the site-selectivity remains a challenging issue. The highly selective *para*-C(sp^2)—H functionalization of arenes is still rare, despite that the directing-group-assisted strategy is already successful for ortho- and meta-selective C(sp^2)—H bond functionalization. In 2014, Liu, Zhang, and coworkers developed an elegant gold-catalyzed *para*-C(sp^2)—H functionalization of phenols **158** and anilines **208** with diazo compounds **204** (Scheme 33) [110]. The reaction featured fast reaction rate, high chemo- and site-selectivity, excellent yield, and mild condition. The phosphine ligand $(2,4\text{-}^tBu_2C_6H_3O)_3P$ is crucial in this reaction. When other phosphine ligands were used for gold complex, the O—H insertion product **207** was observed, which is the well-known product for previously reported works using other commonly used metal catalysts. Besides, no *ortho*-C(sp^2)—H functionalization was observed in this reaction. Gram-scale reaction could be easily carried out when the loading of gold catalyst was decreased to 0.5 mol%,



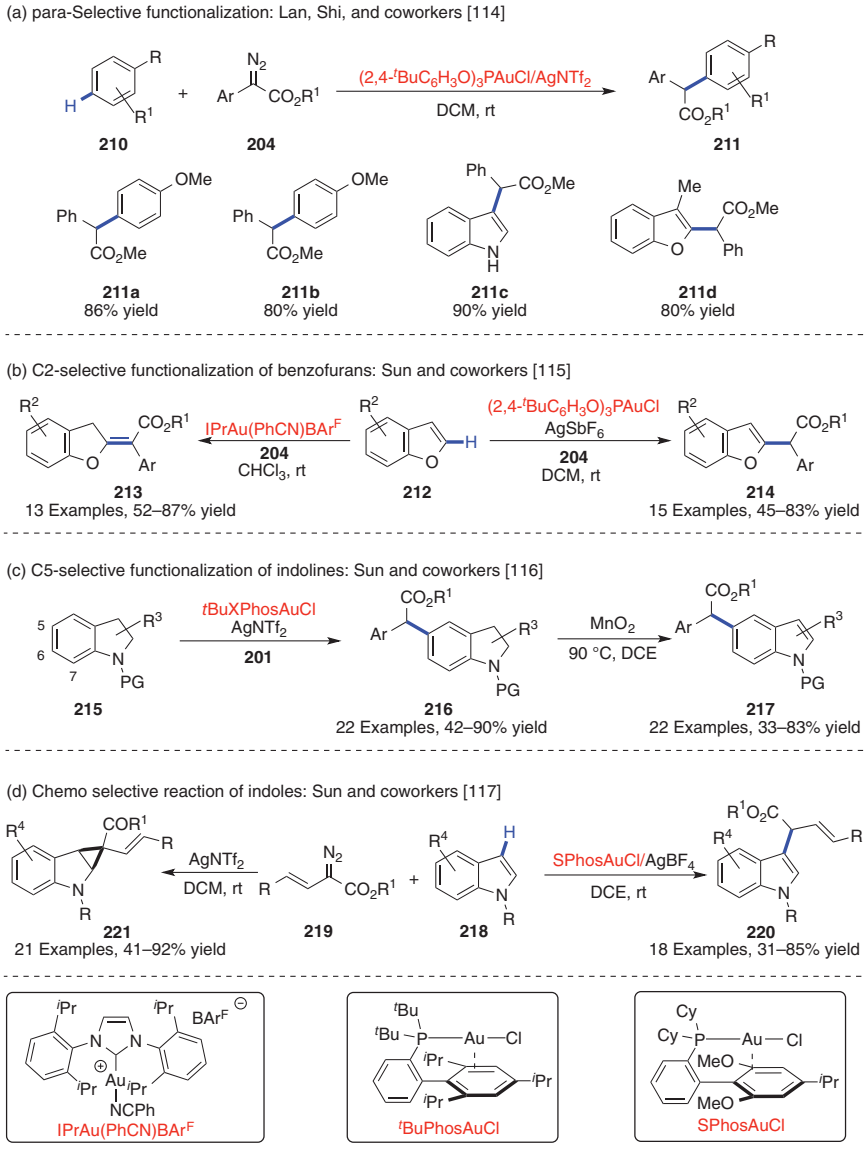
Scheme 32 Gold-catalyzed intermolecular aromatic C—H bond alkylation of arenes. Source: (a) Skouta et al. [107]. (b) Mertins et al. [108]. (c) Hu et al. [109].

and this protocol was also successfully applied to the late-stage modifications of natural products and pharmaceutical molecules because of the mild condition and high functional group compatibility. The reaction mechanism was also studied by experiments and DFT calculation [111]. Later, the supramolecularly regulated gold(I) catalysts were prepared and worked for this reaction [112]. Furthermore, the ortho-selective C(sp²)—H functionalization of phenols with diazo compounds was also achieved by Liu, Zhang, and coworkers in 2016 [113].



Scheme 33 Gold-catalyzed *para*-C(sp^2)—H functionalization of phenols and anilines with diazo compounds. Source: Yu and Ma et al. [110].

Shi and coworkers reported a similar gold-catalyzed C(sp²)—H functionalization of electron-rich arenes (Scheme 34a) [114]. In 2018, Sun disclosed a gold-catalyzed C—H bond functionalization of benzofurans **212** in which the ligands were crucial for chemoselectivity (Scheme 34b) [115]. Later, Sun reported a novel sequential C5-selective C(sp²)—H functionalization/oxidative aromatization for the synthesis of C5-alkylated indole derivatives **217** via gold catalyst (Scheme 34c) [116].



Scheme 34 Gold-catalyzed site-selective C(sp²)—H functionalization with diazo compounds. Source: (a) Lan, Shi, and coworkers [114], (b) Sun and coworkers [115], (c) Sun and coworkers [116], (d) Sun and coworkers [117].

In 2019, the same group developed a catalyst-controlled chemodivergent C(sp^2)—H bond alkylation or cyclopropanation of indoles with vinyl diazo compounds via gold or silver catalysts (Scheme 34d) [117].

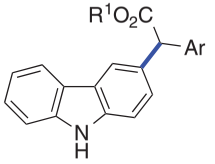
Koenigs and coworkers reported a series of gold-catalyzed C(sp^2)—H functionalizations of nitrogen-containing aromatic rings in high site-selectivity (Scheme 35) [118–122].

In 2019, Liu, Zhang, and coworkers developed a gold-catalyzed site-divergent C(sp^2)—H functionalization of naphthols **228** controlled by ligands and anions. The site-selectivity could be tuned by the coordinating states between the gold complexes and the hydroxyl group. For 2-naphthol, the C1-selective C(sp^2)—H bond alkylation product **232** was obtained under the catalysis of JohnPhosAuCl/AgOTf (Scheme 36) [123]. Interesting, Nemoto disclosed the tandem C—H functionalization/lactonization of 2-naphthols via $Ph_3PAuCl/AgSbF_6$ [124].

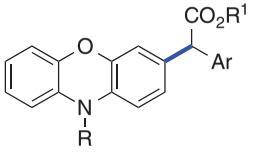
Compared to the electron-rich aromatic compounds, the neutral arenes, such as benzene and toluene, are the challenging substrates for the site-selective C(sp^2)—H bond functionalization, because they lack nucleophilicity, and substituted alkyls on phenyl rings normally do not have the interaction with catalysts. The reactions of toluene derivatives with diazo compounds catalyzed by transition metals, e.g. rhodium, copper, and iron, were well known, leading the Buchner reaction, benzylic C(sp^3)—H bond insertion, and nonselective C(sp^2)—H functionalization (Scheme 37a). In 2011, Díaz-Requejo, Pérez, and coworkers reported $IPrAuBr_3$-catalyzed chemoselective aromatic C—H bond alkylation of alkyl-substituted benzenes using the methodology of carbene transfer. However, the regioselectivity was not good [125]. In 2017, Liu and Zhang achieved the highly chemo- and regioselective *para*-C—H functionalization of benzene derivatives with diazo compounds catalyzed by $(2,4\text{-}^tBu_2C_6H_3O)_3$ $PAuPhCNSbF_6'$. The introduction of trifluoroethyl group to diazo ester could enhance the electrophilicity of the gold–carbene intermediate. This reaction featured broad substrate scope, which included monoalkyl benzenes, benzene, and monohalogen benzene (Scheme 37b) [126]. Furthermore, it also worked to switch the electron-withdrawing group from ester to phenyl ring catalyzed by gold, which was efficient to synthesis the product installed with complex alcohols, such as sugar and menthol (Scheme 37c) [127].

These C—H bond functionalizations are useful to construct the complex cyclic molecules via tandem reaction. In 2015, Liu, Zhang, and coworkers developed a gold-catalyzed tandem C—H bond functionalization/aldol reaction to construct indanol and tetrahydronaphthalenol derivatives **241**. If the chiral phosphine ligand was used, the asymmetric catalysis worked, giving the chiral products in moderate enantioselectivity (Scheme 38a) [128]. Later, due to the specific catalytic activities to alkynes of gold catalysts, Liu, Zhang, and coworkers disclosed an efficient domino C—H functionalization/*5-endo-dig* cyclization of alkynyl diazoesters **242** with various arenes, delivering a series of indene derivatives **243** in highly chemo- and site-selective manner (Scheme 38b) [129]. In 2020, the same authors developed an intermolecular [4 + 1] spiroannulation reaction via chemo- and site-selective C(sp^2)—H functionalization/dearomatization of phenol derivatives with *ortho*-alkynylaryl-α-diazoesters **244** under gold(I) catalysts (Scheme 38c) [130].

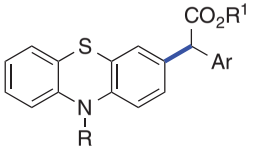
Koenigs and coworkers [118–122]:



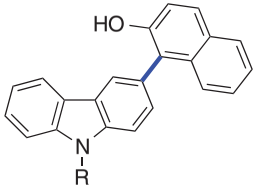
222
>60 Examples, up to 98% yield
with tBu$_3$PAuCl / AgSbF$_6$
in **2020**



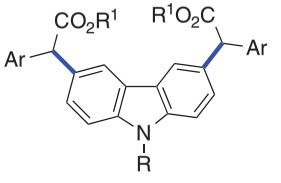
223
4 Examples, up to 74% yield
with (2,4-^{t}Bu$_2$C$_6$H$_3$O)PAuCl / AgSbF$_6$
in **2020**



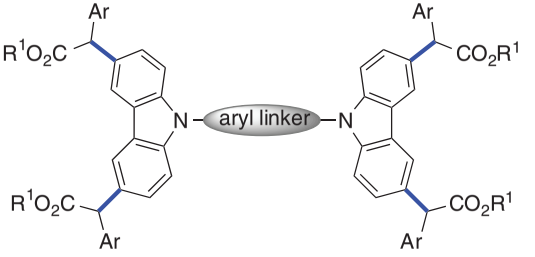
224
>30 Examples, up to 83% yield
with (2,4-^{t}Bu$_2$C$_6$H$_3$O)PAuCl / AgSbF$_6$
in **2020**



225
17 Examples, up to 80% yield
with IPrAuCl / AgSbF$_6$
in **2021**



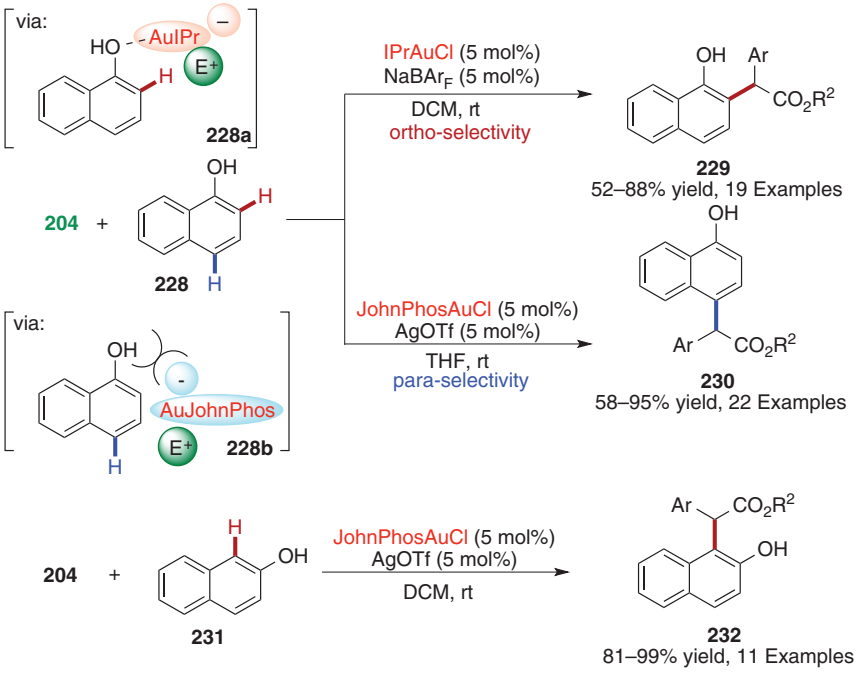
226
13 Examples, up to 85% yield
with (2,4-^{t}Bu$_2$C$_6$H$_3$O)PAuCl / AgSbF$_6$
in **2021**



227
5 Examples, up to 78% yield
with (2,4-^{t}Bu$_2$C$_6$H$_3$O)PAuCl / AgSbF$_6$
in **2021**

Scheme 35 Gold-catalyzed site-selective C(sp^2)—H functionalization of nitrogen-containing heterocycles. Source: Jana et al. [118–120], Bera et al. [121], He et al. [122].

Liu, Zhang, and coworkers [123]:



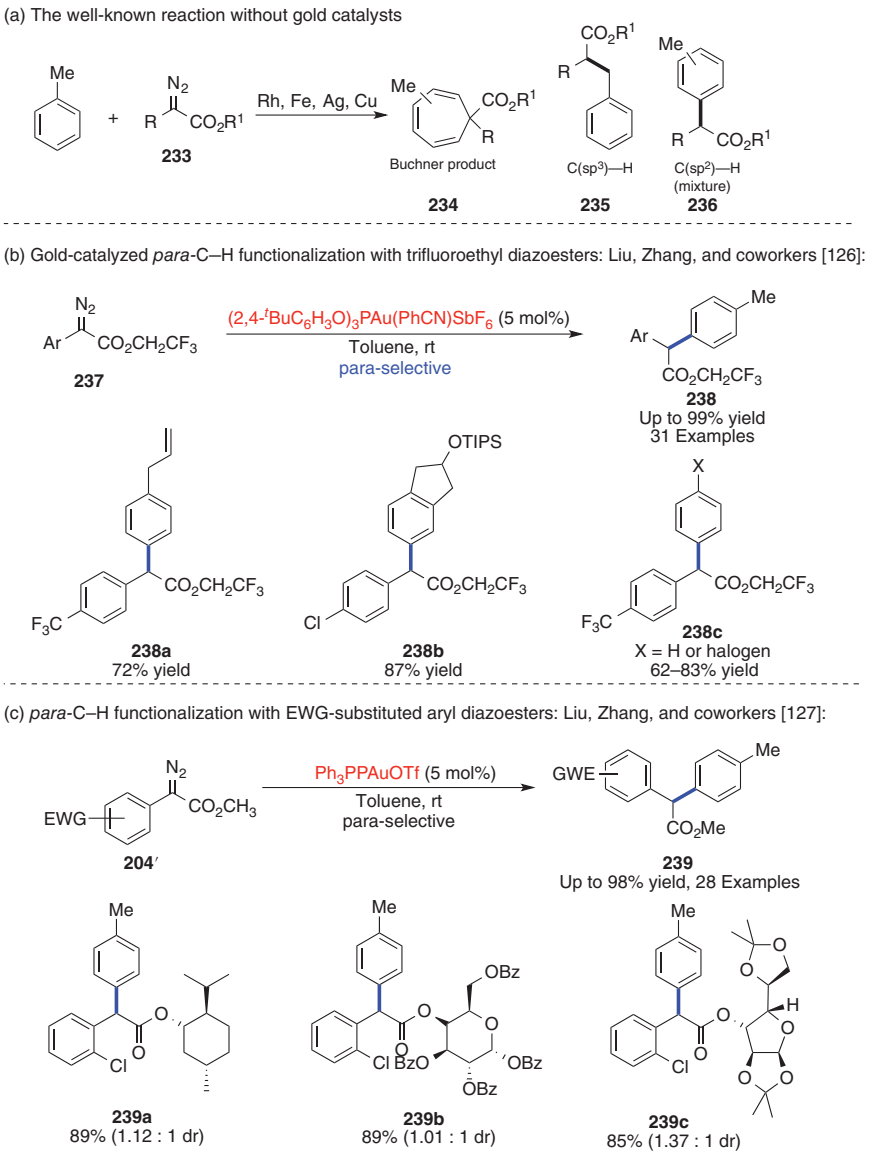
Scheme 36 Gold-catalyzed regio-divergent C(sp^2)—H functionalization of naphthols. Source: Yu et al. [123].

As shown in Scheme 38d, the intermediate **246** was formed via the C—H bond functionalization. If R^1 is not H, the alkynyl could be used with gold strongly, and the *5-endo-dig* carbocyclization occurred very fast, furnishing the indane product **243**. If R^1 is H, the enol group of **246** was easily converted to the ester group, which favored the dearomatization cyclization to afford the spiro product **245**.

In 2019, Patil, Baik, and coworkers reported a novel strategy to synthesize 3-substituted chromone derivatives **251** via gold-catalyzed C(sp^2)—H bond alkylation of enaminones with diazo compounds. The combined experimental and computational mechanistic investigations showed that the *ortho*-hydroxyl group served as a directing group to assist the C(sp^2)—H bond alkylation (Scheme 39) [131].

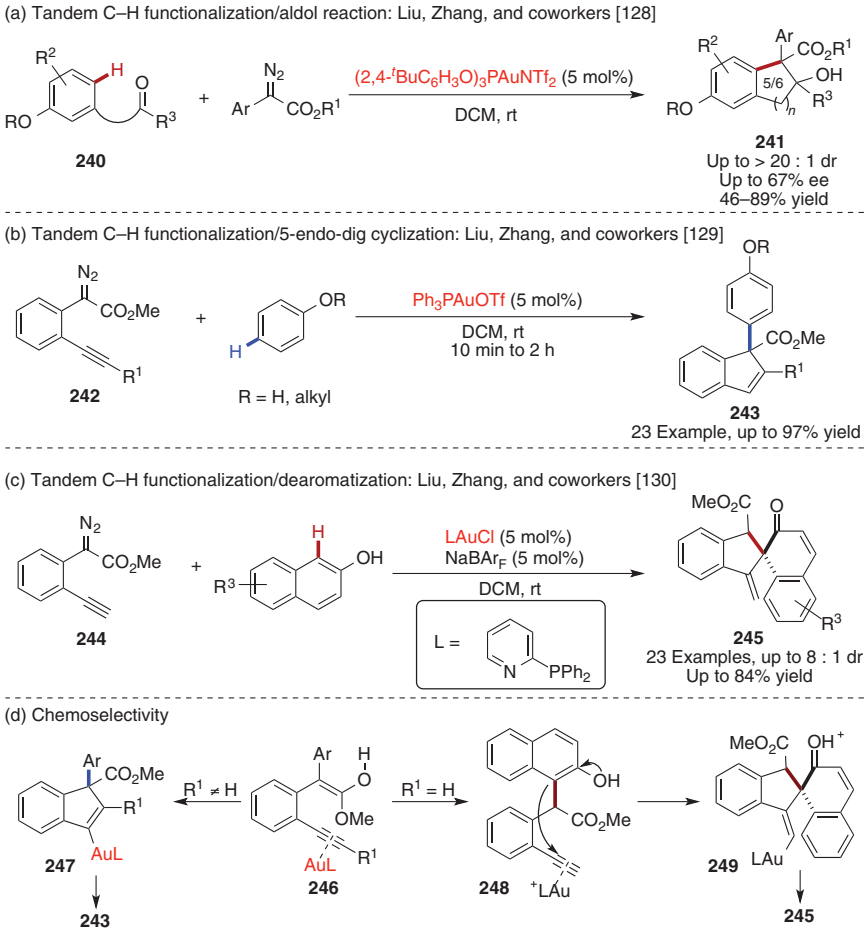
4 Summary and Perspective

In this article, we have described the gold-catalyzed C(sp^2)—H bond functionalization of aromatic compounds and olefins from historical landmarks to recent advances. Over the past two decades, much progress has been made to directly convert the C—H bond to C—X bonds, including carbon–carbon, carbon–halogen, and carbon–oxygen bonds, under the catalysis of gold. Moreover, it is not required

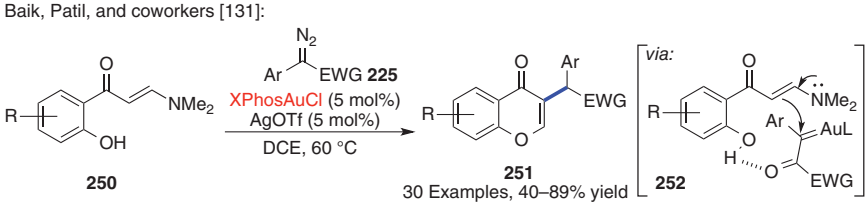


Scheme 37 Gold-catalyzed *para*-C(sp²)—H of non-active arenes. Source: (b) Ma et al. [126]. (c) Ma et al. [127].

to install the extra directing group on the substrates for achieving the high selectivity. The strategy features good functional group tolerance, high reaction efficiency, and excellent chemo-, regio-, and stereoselectivity, which has already become a useful synthetic tool for the construction of a broad variety of complex molecules and late-stage functionalization of bioactive compounds and drugs.



Scheme 38 Gold-catalyzed tandem reactions involving C(sp^2)—H functionalization. Source: (a) Liu, Zhang, and coworkers [128], (b) Liu, Zhang, and coworkers [129], (c) Liu, Zhang, and coworkers [130].



Scheme 39 Gold-catalyzed C(sp^2)—H alkylation of enamines. Source: Bagle et al. [131].

However, the utilization of gold catalysis for C(sp^2)—H bond functionalization is still at its infancy, and several breakthrough fronts should gain momentum in the future: (i) Enantioselectivity. Only a few gold-catalyzed enantioselective C(sp^2)—H bond functionalizations were reported. The development of more chiral ligands and the cooperative catalysis of gold and other chiral catalysts might address this issue. (ii) Substrate scope. For the intermolecular C(sp^2)—H bond functionalization, the site-selectivity of arenes is normally according to the electronic effects of the substituted groups on phenyl rings. It is important and useful to achieve more regiodivergent reaction by tuning the gold catalysts. Overall, we believe that the unique catalytic activity of gold complexes should offer new opportunities for the development of new organic transformations based on C(sp^2)—H bond functionalization.

Related Articles

Palladium/Norbornene Cooperative Catalytic C—H Functionalization
Iron-Catalyzed Nitrene Insertion of C—H Bonds
Rh-Catalyzed Arene Distal *meta*- and *para*-C—H Functionalization
Rhodium(II)-Carboxylate-Catalyzed Carbene Transfer Reactions: Toward C—H Functionalizations
Ruthenium-Catalyzed C–Heteroatom Bond Formation Through C(sp^2)—H Functionalization
Gold-Catalyzed C—C Bond Formation Through C—H Functionalization
Mechanistic Understandings of Gold-Catalyzed C—H Functionalization
Gold-Catalyzed C(sp^2)—H Functionalization under Au(I)/Au(III) Catalysis
Gold-Catalyzed C—H Activation/Functionalization Reactions
Intra- and Inter-Molecular Carbene and Nitrene Insertion by Metalloenzymes into C—H Bond
Ag-, Au-, and Pt-Catalyzed C—H Functionalization
Catalytic Aromatic C—H Functionalization Involving Metal Carbene
Diazo Compounds as Cross-Coupling Partners in C(sp^2)—H Bond Functionalization
Steric Effects in *ortho* C—H Activation of Aromatic Systems
Aromatic C—H Bond Functionalization with Carbene Precursors

References

1 Sinha, S.K., Guin, S., Maiti, S. et al. (2022). *Chem. Rev.* 166 (6): 5682–5841. doi: 10.1021/acs.chemrev.1c00220.
2 Dong, Z., Ren, Z., Thompson, S.J. et al. (2017). *Chem. Rev.* 117: 9333–9403.
3 Gensch, T., Hopkinson, M.N., Glorius, F., and Wencel-Delord, J. (2016). *Chem. Soc. Rev.* 45: 2900–2936.
4 Sambiagio, C., Schönbauer, D., Blieck, R. et al. (2018). *Chem. Soc. Rev.* 47: 6603–6743.
5 Rej, S., Das, A., and Chatani, N. (2020). *Coord. Chem. Rev.* 431: 213683.

6 Dutta, U., Maiti, S., Bhattacharya, T., and Maiti, D. (2021). *Science* 372: eabd5992.
7 Rogge, T., Kaplaneris, N., Chatani, N. et al. (2021). *Nat. Rev. Dis. Primers* 1: 43.
8 Saint-Denis, T.G., Zhu, R.-Y., Chen, G. et al. (2018). *Science* 359: eaao4798.
9 Goswami, N., Bhattacharya, T., and Maiti, D. (2021). *Nat. Rev. Chem.* 5: 646–659.
10 Lu, L. and Junliang, Z. (2017). *Chin. J. Org. Chem.* 37: 1117–1126.
11 Campeau, D., Rayo, D.F.L., Mansour, A. et al. (2021). *Chem. Rev.* 121: 8756–8867.
12 Chintawar, C.C., Yadav, A.K., Kumar, A. et al. (2021). *Chem. Rev.* 121: 8478–8558.
13 Fürstner, A. (2018). *Angew. Chem. Int. Ed.* 57: 4215–4233.
14 Rudolph, M. and Hashmi, A.S.K. (2012). *Chem. Soc. Rev.* 41: 2448–2462.
15 Zi, W. and Toste, F.D. (2016). *Chem. Soc. Rev.* 45: 4567–4589.
16 Hashmi, A.S.K. and Toste, F.D. (2012). *Modern Gold Catalyzed Synthesis*. Weinheim: Wiley-VCH.
17 Lu, L. and Junliang, Z. (2016). *Chem. Soc. Rev.* 45: 506–516.
18 Ma, B., Liu, L., and Zhang, J. (2018). *Asian J. Org. Chem.* 7: 2015–2025.
19 Hashmi, A.S.K., Schwarz, L., Choi, J.-H., and Frost, T.M. (2000). *Angew. Chem. Int. Ed.* 39: 2285–2288.
20 Shi, Z. and He, C. (2004). *J. Am. Chem. Soc.* 126: 13596–13597.
21 Menon, R.S., Findlay, A.D., Bissember, A.C., and Banwell, M.G. (2009). *J. Org. Chem.* 74: 8901–8903.
22 Lykakis, I.N., Efe, C., Gryparis, C., and Stratakis, M. (2011). *Eur. J. Org. Chem.* 2011: 2334–2338.
23 Arcadi, A., Blesi, F., Cacchi, S. et al. (2012). *Org. Biomol. Chem.* 10: 9700–9708.
24 Cervi, A., Vo, Y., Chai, C.L.L. et al. (2021). *J. Org. Chem.* 86: 178–198.
25 Arcadi, A., Ciogli, A., Fabrizi, G. et al. (2019). *Org. Biomol. Chem.* 17: 10065–10072.
26 Symeonidis, T.S., Lykakis, I.N., and Litinas, K.E. (2013). *Tetrahedron* 69: 4612–4616.
27 Vacala, T., Bejcek, L.P., Williams, C.G. et al. (2017). *J. Org. Chem.* 82: 2558–2569.
28 Arcadi, A., Fabrizi, G., Fochetti, A. et al. (2021). *Eur. J. Org. Chem.* 2021: 1676–1687.
29 Wegner, H.A., Ahles, S., and Neuburger, M. (2008). *Chem. Eur. J.* 14: 11310–11313.
30 Nevado, C. and Echavarren, A.M. (2005). *Chem. Eur. J.* 11: 3155–3164.
31 Xiao, F., Chen, Y., Liu, Y., and Wang, J. (2008). *Tetrahedron* 64: 2755–2761.
32 Morán-Poladura, P., Suárez-Pantiga, S., Piedrafita, M. et al. (2011). *J. Organomet. Chem.* 696: 12–15.
33 Jiang, C., Xu, M., Wang, S. et al. (2010). *J. Org. Chem.* 75: 4323–4325.
34 Yin, H., Kong, F., Wang, S., and Yao, Z.-J. (2012). *Tetrahedron Lett.* 53: 7078–7082.
35 Wright, N.E. and Snyder, S.A. (2014). *Angew. Chem. Int. Ed.* 53: 3409–3413.

36 Carreras, J., Gopakumar, G., Gu, L. et al. (2013). *J. Am. Chem. Soc.* 135: 18815–11882.

37 Kirillova, M.S., Muratore, M.E., Dorel, R., and Echavarren, A.M. (2016). *J. Am. Chem. Soc.* 138: 3671–3674.

38 Hariri, M., Darvish, F., Ndong, K.P.M.M. et al. (2021). *J. Org. Chem.* 86: 7813–7824.

39 Tsurusaki, A., Shimatani, H., and Kamikawa, K. (2021). *Asian J. Org. Chem.* 10: 154–159.

40 Kim, C.-E., Ryu, T., Kim, S. et al. (2013). *Adv. Synth. Catal.* 355: 2873–2883.

41 Watanabe, T., Oishi, S., Fujii, N., and Ohno, H. (2007). *Org. Lett.* 9: 4821–4824.

42 Park, C. and Lee, P.H. (2008). *Org. Lett.* 10: 3359–3362.

43 Alcaide, B., Almendros, P., Cembellín, S. et al. (2013). *Chem. Commun.* 49: 1282–1284.

44 Liu, Y., Zhu, J., Qian, J., and Xu, Z. (2012). *J. Org. Chem.* 77: 5411–5417.

45 Corrie, T.J.A., Ball, L.T., Russell, C.A., and Lloyd-Jones, G.C. (2017). *J. Am. Chem. Soc.* 139: 245–254.

46 Ding, D., Mou, T., Feng, M., and Jiang, X. (2016). *J. Am. Chem. Soc.* 138: 5218–5221.

47 Zhang, P.-C., Wang, Y., Qian, D. et al. (2017). *Chin. J. Chem.* 35: 849–852.

48 Urbano, A., Hernández-Torres, G., Hoyo, A.M. et al. (2016). *Chem. Commun.* 52: 6419–6422.

49 Zhang, P.-C., Li, Y.-L., He, J. et al. (2021). *Nat. Commun.* 12: 4609.

50 Ferrer, C. and Echavarren, A.M. (2006). *Angew. Chem. Int. Ed.* 45: 1105–1109.

51 Ferrer, C., Escribano-Cuesta, A., and Echavarren, A.M. (2009). *Tetrahedron* 65: 9015–9020.

52 Ferrer, C., Amijs, C.H.M., and Echavarren, A.M. (2007). *Chem. Eur. J.* 13: 1358–1373.

53 Wang, Y., Zhang, P., Di, X. et al. (2017). *Angew. Chem. Int. Ed.* 56: 15905–15909.

54 Hashmi, A.S.K., Yang, W., and Rominger, F. (2012). *Adv. Synth. Catal.* 354: 1273–1279.

55 Barluenga, J., Piedrata, M., Ballesteros, A. et al. (2010). *Chem. Eur. J.* 16: 11827.

56 Jiang, F., Fu, C., and Ma, S. (2021). *Chem. Sci.* 12: 696–701.

57 Kumar, A., Li, Z., Sharma, S.K. et al. (2013). *Chem. Commun.* 49: 6803–6805.

58 Dong, Z., Liu, C.-H., Wang, Y. et al. (2013). *Angew. Chem. Int. Ed.* 52: 14157–14161.

59 Pan, B., Lu, X., Wang, C. et al. (2014). *Org. Lett.* 16: 2244–2247.

60 Li, X., Xie, X., and Liu, Y. (2016). *J. Org. Chem.* 81: 3688–3699.

61 Hashmi, A.S.K., Yang, W., and Rominger, F. (2011). *Angew. Chem. Int. Ed.* 50: 5762–5765.

62 Menon, R.S. and Banwell, M.G. (2010). *Org. Biomol. Chem.* 8: 5483–5485.

63 Liu, L. and Zhang, J. (2009). *Angew. Chem. Int. Ed.* 48: 6093–6096.

64 Yan, Z.-Y., Xiao, Y., and Zhang, L. (2012). *Angew. Chem. Int. Ed.* 51: 8624–8627.

65 Dateer, R.B., Pati, K., and Liu, R.-S. (2012). *Chem. Commun.* 48: 7200–7202.

66 Shu, C., Wang, Y.-H., Shen, C.-H. et al. (2016). *Org. Lett.* 18: 3254–3257.

67 Mo, F., Yan, J.M., Qiu, D. et al. (2010). *Angew. Chem. Int. Ed.* 49: 2028–2032.

68 Marchetti, L., Kantak, A., Davis, R., and DeBoef, B. (2015). *Org. Lett.* 17: 358–361.

69 Qiu, D., Zheng, Z., Mo, F. et al. (2011). *Org. Lett.* 13: 4988–4991.

70 Pradal, A., Toullec, P.Y., and Michelet, V. (2011). *Org. Lett.* 13: 6086–6089.

71 Lu, P., Boorman, T.C., Slawin, A.M.Z., and Larrosa, I. (2010). *J. Am. Chem. Soc.* 132: 5580–5581.

72 Brand, J.P., Charpentier, J., and Waser, J. (2009). *Angew. Chem. Int. Ed.* 48: 9346–9349.

73 Brand, J.P. and Waser, J. (2010). *Angew. Chem. Int. Ed.* 49: 7304–7307.

74 Brand, J.P. and Waser, J. (2012). *Org. Lett.* 14: 744–747.

75 Székely, A., Péter, Á., Aradi, K. et al. (2017). *Org. Lett.* 19: 954–957.

76 Hermann, G.N., Unruh, M.T., Jung, S.-H. et al. (2018). *Angew. Chem. Int. Ed.* 57: 10723–10727.

77 Li, Y., Xie, F., and Li, X. (2016). *J. Org. Chem.* 81: 715–722.

78 Shaikh, A.C., Shinde, D.R., and Patil, N.T. (2016). *Org. Lett.* 18: 1056–1059.

79 Haro, T. and Nevado, C. (2010). *J. Am. Chem. Soc.* 132: 1512–1513.

80 Yang, Y., Antoni, P., Zimmer, M. et al. (2019). *Angew. Chem. Int. Ed.* 58: 5129–5133.

81 Han, C., Tian, X., Zhang, H. et al. (2021). *Org. Lett.* 23: 4764–4768.

82 Liu, K., Li, T., Liu, D.-Y. et al. (2021). *Sci. China Chem.* 64: 1958–1963.

83 Xu, S., Zhou, Y., Xu, J. et al. (2013). *Green Chem.* 15: 718–726.

84 Vachhani, D.D., Kumar, A., Modha, S.G. et al. (2015). *Synthesis* 47: 1337–1347.

85 Jiang, K.-M., Kang, J.-A., Jin, Y., and Lin, J. (2018). *Org. Chem. Front.* 5: 434–441.

86 Alfonsi, M., Arcadi, A., Chiarini, M., and Marinelli, F. (2011). *Tetrahedron Lett.* 52: 5145–5148.

87 Heffernan, S.J., Tellam, J.P., Queru, M.E. et al. (2013). *Adv. Synth. Catal.* 355: 1149–1159.

88 Adak, T., Schulmeister, J., Dietl, M.C. et al. (2019). *Eur. J. Org. Chem.* 2019: 3867–3876.

89 Reetz, M.T. and Sommer, K. (2003). *Eur. J. Org. Chem.* 2003: 3485–3496.

90 Shi, Z. and He, C. (2004). *J. Org. Chem.* 69: 3669–3671.

91 Baron, M. and Biffis, A. (2019). *Eur. J. Org. Chem.* 2019: 3687–3693.

92 Pirovano, V., Negrato, M., Abbiati, G. et al. (2016). *Org. Lett.* 18: 4798–4801.

93 Timmerman, J.C., Schmitt, W.W., and Widenhoefer, R.A. (2016). *Org. Lett.* 18: 4966–4969.

94 Jin, H., Huang, L., Xie, J. et al. (2016). *Angew. Chem. Int. Ed.* 55: 794–797.

95 Tsai, M.-H., Wang, C.-Y., Raj, A.S.K., and Liu, R.-S. (2018). *Chem. Commun.* 54: 10866–10869.

96 Zeng, Z., Jin, H., Rudolph, M. et al. (2018). *Angew. Chem. Int. Ed.* 57: 16549–16553.

97 Zeng, Z., Jin, H., Sekine, K. et al. (2018). *Angew. Chem. Int. Ed.* 57: 6935–6939.

98 Shu, C., Wang, Y.H., Zhou, B. et al. (2015). *J. Am. Chem. Soc.* 137: 9567–9570.

99 Ball, L.T., Lloyd-Jones, G.C., and Russell, C.A. (2012). *Science* 337: 1644–1648.

100 Ball, L.T., Lloyd-Jones, G.C., and Russell, C.A. (2014). *J. Am. Chem. Soc.* 136: 254–264.

101 Cresswell, A.J. and Lloyd-Jones, G.C. (2016). *Chem. Eur. J.* 22: 12641–12645.

102 Hofer, M., Genoux, A., Kumar, R., and Nevado, C. (2017). *Angew. Chem. Int. Ed.* 56: 1021–1025.

103 Kar, A., Mangu, N., Kaiser, H.M. et al. (2008). *Chem. Commun.* 386–388.

104 Kar, A., Mangu, N., Kaiser, H.M., and Tse, M.K. (2009). *J. Organomet. Chem.* 694: 524–537.

105 Cambeiro, X.C., Ahlsten, N., and Larrosa, I. (2015). *J. Am. Chem. Soc.* 137: 15636–15639.

106 Li, W., Yuan, D., Wang, G. et al. (2019). *J. Am. Chem. Soc.* 141: 3187–3197.

107 Skouta, R. and Li, C.-J. (2008). *Can. J. Chem.* 86: 616–620.

108 Mertins, K., Iovel, I., Kischel, J. et al. (2006). *Adv. Synth. Catal.* 348: 691–695.

109 Hu, X., Martin, D., Melaimi, M., and Bertrand, G. (2014). *J. Am. Chem. Soc.* 136: 13594–13597.

110 Yu, Z., Ma, B., Chen, M. et al. (2014). *J. Am. Chem. Soc.* 136: 6904–6907.

111 Liu, Y., Yu, Z., Zhang, J.Z. et al. (2016). *Chem. Sci.* 7: 1988–1995.

112 Carreras, L., Franconetti, A., Grabulosa, A. et al. (2020). *Org. Chem. Front.* 7: 1626–1634.

113 Yu, Z., Li, Y., Shi, J. et al. (2016). *Angew. Chem. Int. Ed.* 55: 14807–14811.

114 Xi, Y., Su, Y., Yu, Z. et al. (2014). *Angew. Chem. Int. Ed.* 53: 9817–9821.

115 Xu, G., Liu, K., and Sun, J. (2018). *Org. Lett.* 20: 72–75.

116 Zhang, W., Xu, G., Qiua, L., and Sun, J. (2018). *Org. Biomol. Chem.* 16: 3889–3892.

117 Wang, Z., Xu, G., Tang, S. et al. (2019). *Org. Lett.* 21: 8488–8491.

118 Jana, S., Empel, C., Pei, C. et al. (2020). *ACS Catal.* 10: 9925–9931.

119 Jana, S., Empel, C., Pei, C. et al. (2020). *Adv. Synth. Catal.* 362: 5721–5727.

120 Jana, S., Empel, C., Nguyen, T.V., and Koenigs, R.M. (2021). *Chem. Eur. J.* 27: 2628–2632.

121 Bera, S.S., Bahukhandi, S.B., Empel, C., and Koenigs, R.M. (2021). *Chem. Commun.* 57: 6193–6196.

122 He, F., Jana, S., and Koenigs, R.M. (2020). *J. Org. Chem.* 85: 11882–11891.

123 Yu, Z., Li, Y., Zhang, P. et al. (2019). *Chem. Sci.* 10: 6553–6559.

124 Harada, S., Sakai, C., Tanikawa, K., and Nemoto, T. (2019). *Tetrahedron* 75: 3650–3656.

125 Rivilla, I., Gómez-Emeterio, B.P., Fructos, M.R. et al. (2011). *Organometallics* 30: 2855–2860.

126 Ma, B., Chu, Z., Huang, B. et al. (2017). *Angew. Chem. Int. Ed.* 56: 2749–2753.

127 Ma, B., Wu, J., Liu, L., and Zhang, J. (2017). *Chem. Commun.* 53: 10164–10167.

128 Yu, Z., Qiu, H., Liu, L., and Zhang, J. (2016). *Chem. Commun.* 52: 2257–2260.

129 Ma, B., Wu, Z., Huang, B. et al. (2016). *Chem. Commun.* 52: 9351–9354.

130 Li, Y., Tang, Z., Zhang, J., and Liu, L. (2020). *Chem. Commun.* 56: 8202–8205.

131 Bagle, P.N., Mane, M.V., Sancheti, S.P. et al. (2019). *Org. Lett.* 21: 335–339.