



HAL
open science

Au(I)/Au(III) Catalytic Allylation Involving π -Allyl Au(III) Complexes

Jessica Rodriguez, David Vesseur, Alexis Tabey, Sonia Mallet-Ladeira, Karinne Miqueu, Didier Bourissou

► **To cite this version:**

Jessica Rodriguez, David Vesseur, Alexis Tabey, Sonia Mallet-Ladeira, Karinne Miqueu, et al.. Au(I)/Au(III) Catalytic Allylation Involving π -Allyl Au(III) Complexes. ACS Catalysis, 2022, 12 (2), pp.993-1003. 10.1021/acscatal.1c04580 . hal-03543277

HAL Id: hal-03543277

<https://univ-pau.hal.science/hal-03543277v1>

Submitted on 9 Oct 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Au(I)/Au(III) Catalytic Allylation Involving π -Allyl Au(III) Complexes

*Jessica Rodriguez,^{‡[a]} David Vesseur,^{‡[a]} Alexis Tabey,^{‡[a]} Sonia Mallet-Ladeira,^[b] Karinne
Miqueu,^[c] Didier Bourissou^{*[a]}*

[a] Dr. J. Rodriguez, D. Vesseur, Dr. A. Tabey, Dr. D. Bourissou

Laboratoire Hétérochimie Fondamentale et Appliquée (LHFA, UMR 5069) CNRS/Université Paul
Sabatier 118 Route de Narbonne, 31062 Toulouse Cedex 09, France

[b] S. Mallet-Ladeira

Institut de Chimie de Toulouse (FR 2599) 118 Route de Narbonne, 31062 Toulouse Cedex 09 France

[c] Dr. K. Miqueu

CNRS/Université de Pau et des Pays de l'Adour, E2S-UPPA Institut des Sciences Analytiques et
Physico-Chimie pour l'Environnement et les Matériaux (IPREM, UMR 5254) Hélioparc, 2 Avenue du
Président Angot, 64053 Pau Cedex 09, France

‡ These authors contributed equally to this work.

Dedicated to Christian Bruneau for his outstanding contribution to catalysis.

KEYWORDS:

π -allyl, gold, homogeneous catalysis, indoles, (P,N) ligands

ABSTRACT:

The (MeDalphos)AuCl complex was found to efficiently catalyze the cross-coupling of indoles and allyl acetates/alcohols. The reaction tolerates many functional groups and selectively affords the branched C3-allylated products from both α - and γ -substituted allyl substrates. It takes advantage of the hemilabile character of the P[^]N ligand. The C(sp²)-C(sp³) coupling operates via a Au(I)/Au(III) redox cycle and involves a dicationic π -allyl Au(III) complex as key intermediate. In this case, the allyl moiety adopts an asymmetric σ + π -coordination mode, as substantiated by NMR spectroscopy and DFT calculations.

Introduction

Transition metal-catalyzed allylation reactions are extremely powerful and versatile transformations widely used in synthesis.^[1] Here, palladium, ruthenium and iridium are the key players, but the unique carbophilic properties and functional group tolerance of gold makes it a valuable candidate, and Au-catalyzed allylation reactions have started to emerge over the past 15 years. The field has been recently reviewed comprehensively by Bandini *et al.*^[2] Figure 1 shows selected examples representative of the different reactivities of the allyl moiety (nucleophilic, electrophilic) as well as the different gold species involved, *ie* Au(I) complexes, Au(III) complexes, Au nanoparticles. Campagne *et al.* reported in 2005 the nucleophilic substitution of propargyl alcohols with allyltrimethylsilane catalyzed by gold(III) salts such as NaAuCl₄.^[3] Patil *et al.* later developed a dual photoredox gold catalyzed allylation reaction. The combination of (Ph₃P)AuCl and Ru(bipy)₃(PF₆)₂ under irradiation efficiently promotes the coupling of aryl diazonium salts and allyltrimethylsilane.^[4] Allylstannanes are also suitable substrates for gold-

catalyzed allylation, as recently substantiated by Peters *et al.* upon C(sp³)–C(sp³) Stille coupling with gold nanoparticles supported on active carbon.^[5] Allylation reactions involving electrophilic substrates (typically referred as nucleophilic allylic substitutions) are both more challenging and more interesting synthetically. Here, the first hint dates back to 2009 when Bandini *et al.* achieved the enantioselective intramolecular allylation of indoles with dinuclear Au(I) complexes deriving from chiral diphosphines.^[6] According to experimental and computational studies, the reaction operates as a Friedel-Crafts alkylation *via* a stepwise S_N2'-type mechanism in which the gold(I) complex activates the C=C double bond.^[7] In 2014, Toste *et al.* reported the allylation of aryl boronic acids with allyl bromides catalyzed by a dinuclear Au(I) complex bridged by a bis(phosphino)amine ligand.^[8,9] This is the first time cross-coupling was catalyzed by gold complexes without using a strong oxidant or light assistance. Here, the two metal centers act in concert and Au(II)–Au(II) complexes were proposed as key intermediates. In 2021, Xie *et al.* extended the use of binuclear gold complexes to the allylation of cyclopropenes with allyl bromides.^[9] Another elegant oxidant-free approach has been recently developed by Shi *et al.* to carry out the thioallylation of alkynes.^[10] Nucleophilic addition of allyl thioethers to the π -activated alkyne first forms vinyl Au(I) species. The allyl group is then transferred from sulfur to gold with Au(I) to Au(III) oxidation.

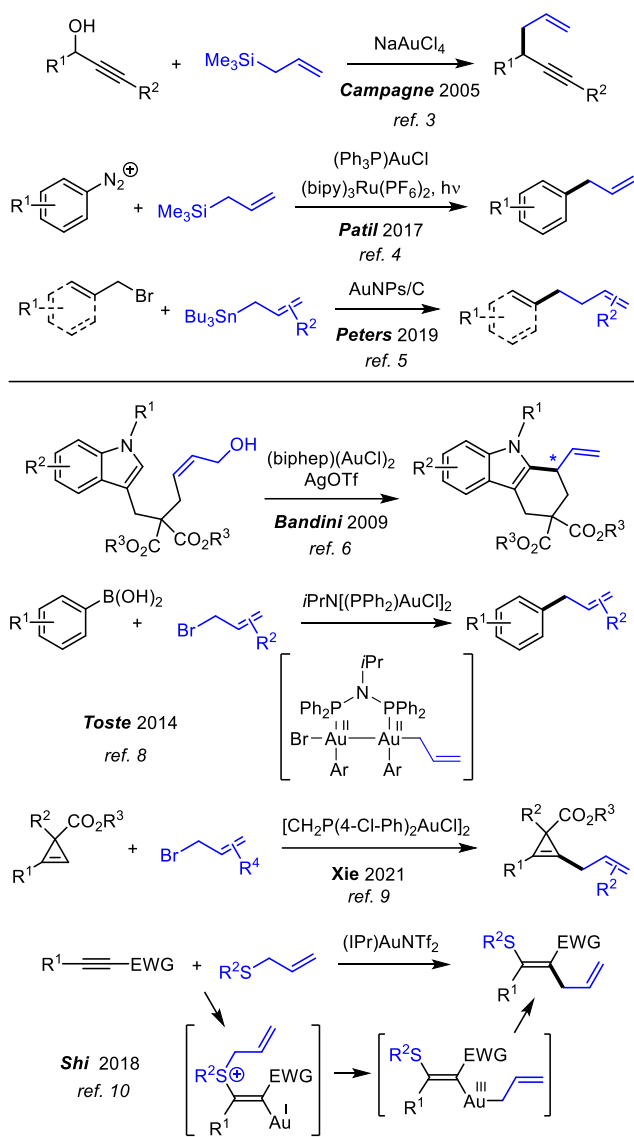
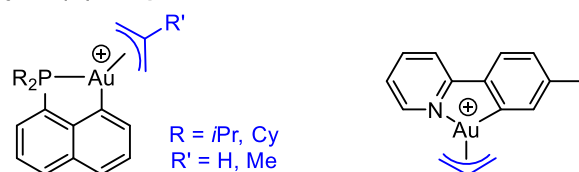


Figure 1. Representative examples of gold-catalyzed allylation reactions.

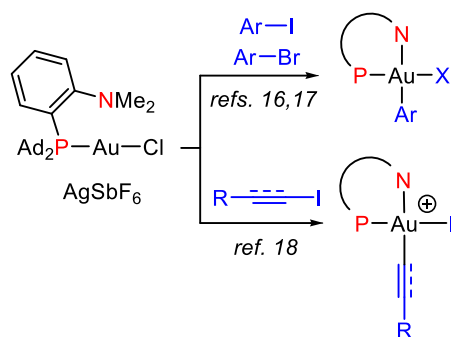
It is striking to note that none of these gold-catalyzed allylation reactions operate *via* π -allyl complexes, as is classically the case with Pd, Ru and Ir catalysts. In fact, it was not until last year that the first gold π -allyl complexes were prepared and unambiguously authenticated in two parallel studies by Tilset and our group (Figure 2).^[11-14] In addition, we have shown the P,C-cyclometalated Au(III) π -allyl complexes to display rich reactivity towards β -keto enolates. Nucleophilic attack can occur at the terminal and central positions of the allyl as well as gold itself

to give ultimately the C–C coupling product.^[15] These achievements suggest it may be possible to develop a catalytic transformation involving π -allyl Au(III) complexes. This was the aim of this work. We have recently demonstrated that P[^]N hemilabile ligands such as MeDalphos triggers the oxidative addition of C(sp²) and C(sp)[–]X bonds (X = I; Br) to gold under mild conditions.^[16-18] This reactivity is amenable to catalysis and several Au(I)/Au(III)-catalyzed arylation/vinylation cross-couplings were developed.^[16-26] The P[^]N ligands also support the π -coordination and activation of alkenes (and alkynes) at Au(I), as substantiated by the isolation of a variety of π -complexes and their application to the C3-alkylation of indoles.^[28] Here, we sought to extend the ligand-enabled approach to C(sp³)–X bond activation and Au(I)/Au(III)-catalyzed allylation. As reported thereafter, the allylation of indoles^[29] can indeed be achieved efficiently using (MeDalphos)AuCl as catalyst. The reaction selectively affords the branched C3-allylated products and tolerates many functional groups. It involves dicationic Au(III) π -allyl complexes as key intermediates, which have been spectroscopically authenticated. Their structure has been computationally analyzed and compared to those of the previously reported N,C/P,C-cyclometalated species.

Known π -allyl Au(III) complexes refs. 11,12



Ligand-enabled oxidative additions to gold & Au(I)/Au(III) transformations



Au(I)/Au(III) catalytic allylation via Au(III) π -allyl complexes (this work)

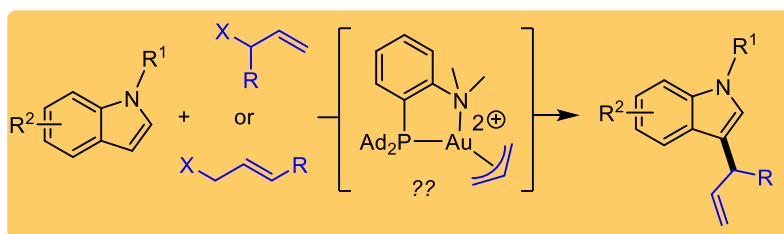


Figure 2. Known π -allyl Au(III) complexes, Au(I)/Au(III) transformations triggered by the P^N ligand and targeted Au(I)/Au(III)-catalyzed allylation.

Results and Discussion

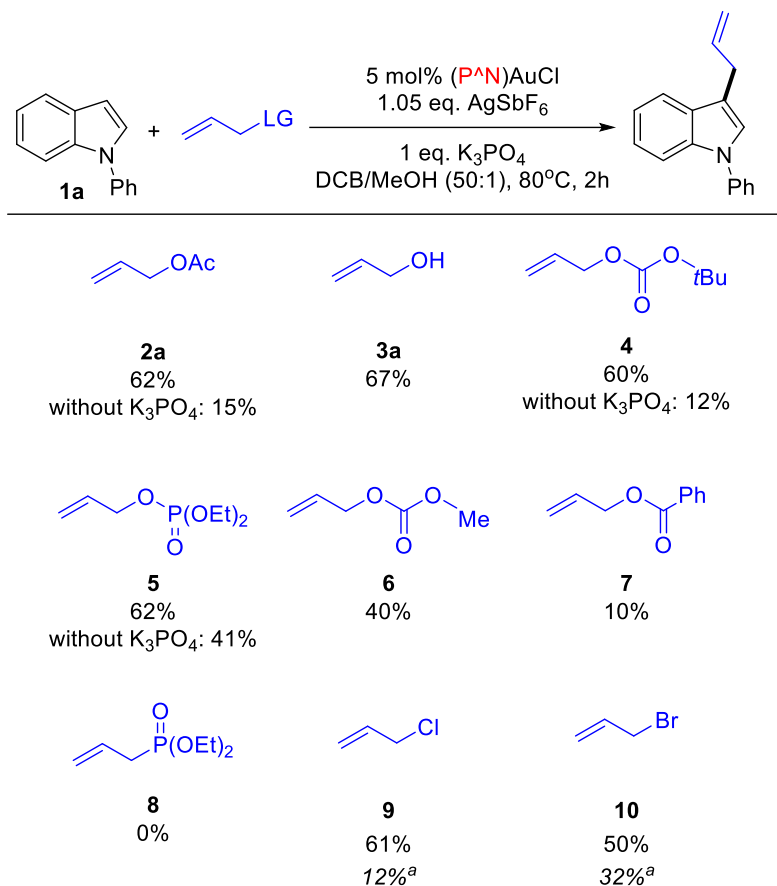
Initial results and optimization

To start with, the allylation of *N*-phenyl indole **1a** with allyl acetate **2a** was tried under the same conditions we used for the Au(I)/Au(III)-catalyzed arylation of indoles with aryl iodides^[17]: 5 mol% (MeDalphos)AuCl, 1.05 eq. AgSbF₆, 1 eq. K₃PO₄ in *o*-DCB/MeOH (50:1), 80°C, 2 h. This reaction resulted in complete conversion of *N*-phenyl indole **1a** but partial consumption of allyl acetate **2a**, and afforded a single allylation product in 37% yield. Mass spectrometry analysis

and ^1H NMR spectroscopy confirmed cross-coupling of the substrates. Further analysis of the NMR data enabled to unambiguously authenticate the product as the C3-allylated *N*-phenyl indole. Most diagnostic is the disappearance of the ^1H NMR for the proton in C3 position of the indole. Selective C3-allylation of indoles is a common feature of all transition metals. It results from the higher nucleophilicity of this position of indoles with respect to C2.^[29a,30] Using 2 equivalents of *N*-phenyl indole **1a** resulted in full conversion of the allyl acetate **2a** and improved the yield to 62% while maintaining complete C3 selectivity. No improvement could be achieved using different halide scavengers, bases, solvents and temperatures (see Table S1).^[31] No cross-coupling product was detected using the (P[^]N)AuCl catalyst alone, showing that a silver salt is required. AgSbF₆ is presumed to activate the gold complex and to assist the activation of the allyl substrate (see the stoichiometric studies below). When using only 0.5 equivalent, the C3 allylated indole was obtained in a lower yield of 40%. Conversely, the silver salt alone does not promote the indole allylation either.^[32] When doubling the catalyst loading from 5 to 10 mol%, only a small increase to 68% yield was observed while lowering the loading to 2.5 mol% gave a significantly decreased yield of 33%.

Allyl substrates with different leaving groups were then tested and compared (Scheme 1). Allyl alcohol **3a**, the corresponding *tert*-butyl carbonate **4** and diethyl phosphate **5** all performed well with yields of 60 to 67%, similar to that observed with allyl acetate **2a**. Lower yields were obtained with allyl methyl carbonate **6** and allyl benzoate **7**, 40 and 10%, respectively. No coupling product was observed with the allyl diethyl phosphonate **8**. The leaving group of the allyl substrate can potentially act as an internal base. The reactions were thus also performed without K₃PO₄, but significantly lower yields were obtained: 15% with the acetate **1a**, 12% with the *tert*-butyl carbonate **4** and 41% with the diethyl phosphate **5**. Lastly, allyl chloride **9** and allyl bromide **10**

were tested. Both works (61 and 50% yields, respectively). An unidentified allylation side product was observed in the case of allyl bromide **10**, which explains the lower yield compared to the allyl chloride **9**. Control experiments showed that the reaction with the allyl halides also proceeds to some extent in the absence of (P[^]N)AuCl, with allyl bromide **10** giving a 32% yield.

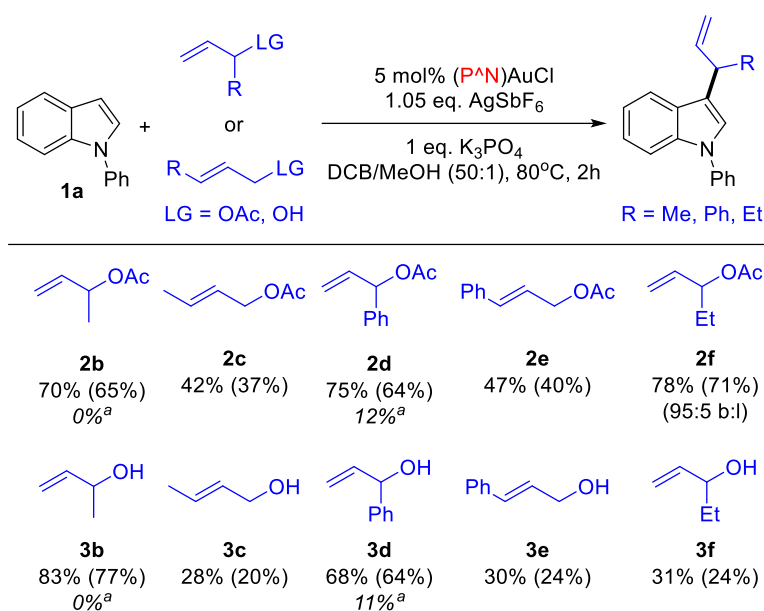


Scheme 1. Gold-catalyzed allylation of *N*-phenyl indole: scope of leaving groups at the allyl substrate. Yields determined by ¹H NMR spectroscopy with diethyl terephthalate as internal standard. ^aIn the absence of (P[^]N)AuCl.

The scope of the reaction was then investigated, focusing on allyl alcohols and acetates, which are the more attractive substrates in terms of availability, structural modularity and atom economy.^[33]

Scope and limitations

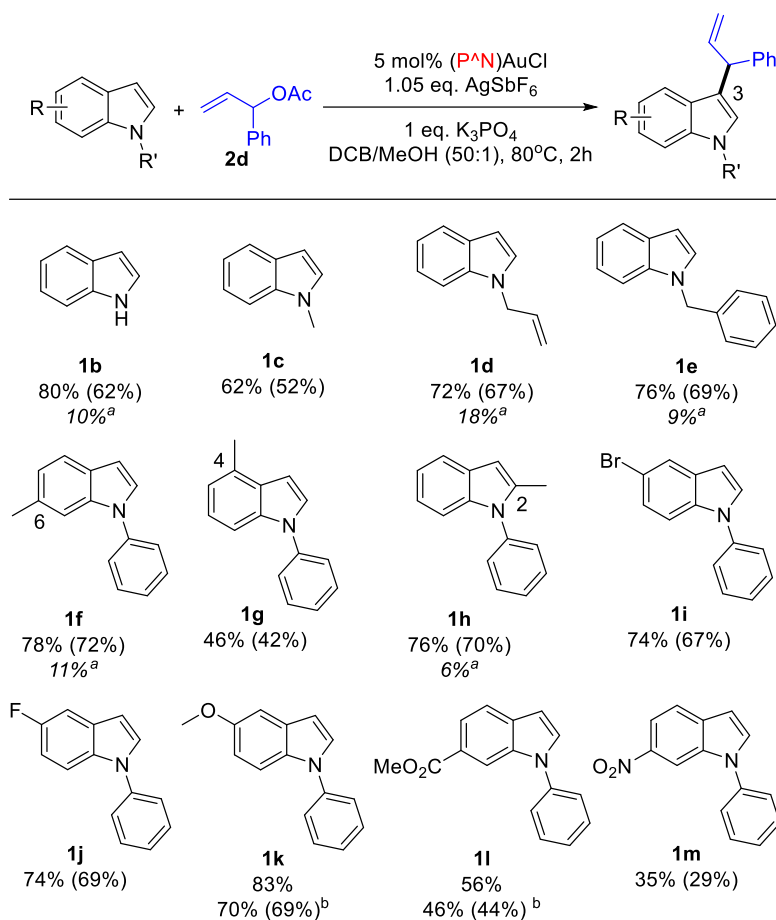
The reaction of *N*-phenyl indole with α - and γ -substituted allyl substrates was then investigated to probe the involvement of π -allyl Au(III) complexes as intermediates. In such a case, similar outcomes are indeed expected from branched and linear substrates, as typically observed with Pd, Ru and Ir-based catalysts.^[34] α -Methyl allyl acetate **2b** was tried first. ¹H NMR spectroscopy showed the formation of a unique coupling product (70% yield) featuring a terminal CH=CH₂ moiety. The C–C coupling is selective for C3 branched allylation of the indole. Using the γ -methyl allyl acetate **2c** also resulted in a single allylation product, the same branched product, *albeit* obtained in lower yield (42%). The difference in reactivity between branched and linear allyl substrates may result from less favoured coordination of the alkene to the (P[^]N)Au⁺ fragment when internal *vs* terminal.^[35] The formation of the same coupling product from **2b** and **2c** is likely to result from a common Au(III) π -allyl intermediate. To confirm this hypothesis, the α - and γ -phenyl allyl acetates **2d** and **2e** were then tested. In both cases, the reaction gave selectively the corresponding branched allylated indole, in 75 and 47% yield, respectively. Selective formation of the branched allylation product is thus observed with both alkyl and aryl substituents. Good results were also obtained with the α -ethyl allyl acetate **2f**: 78% yield with high branched/linear selectivity (95/5). Switching to allyl alcohols (methyl and phenyl-substituted substrates **3b-3e**) gave very comparable results. The C3-branched allylation product was obtained selectively, from both the branched and linear substrate. The α -ethyl allyl alcohol **3f** led to a lower yield than the corresponding acetate **2f**, but with again very high selectivity for the branched allyl indole (the linear product was not detected in this case). To confirm the crucial role of the gold catalyst, controlled reactions were carried out with silver only for **2b**, **2d**, **3b** and **3d**, which gave either no or a very low yield of allylation product.



Scheme 2. Gold-catalyzed allylation of *N*-phenyl indole: scope of α - and γ -substituted allyl acetates/alcohols. Yields determined by 1H NMR spectroscopy with diethyl terephthalate as internal standard. Isolated yields in parentheses. ^aIn the absence of $(P^N)AuCl$ catalyst.

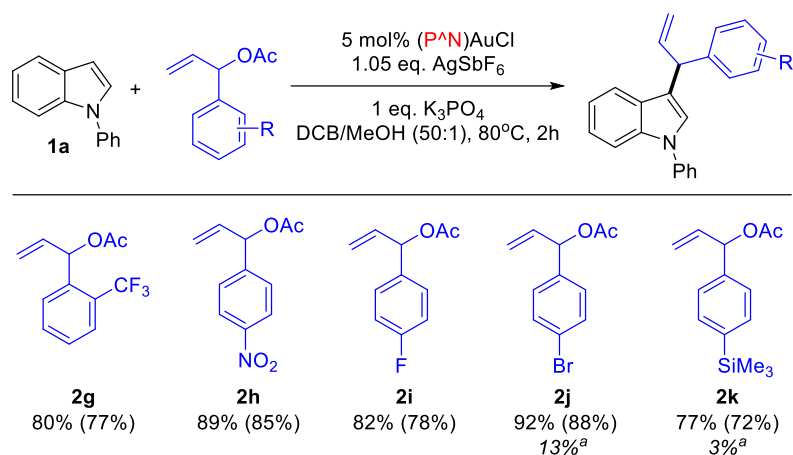
It is worth comparing the branched selectivity observed in the allylation of indole catalyzed by the $(P^N)AuCl$ complex with the behavior of common Pd, Ru and Ir-based catalysts. In contrast with the C3 site-selectivity which is dictated by the innate properties of indoles, the linear/branched selectivity of the introduced allyl moiety varies markedly with the catalyst. The general trend^[34e] is that Pd complexes favor the formation of linear products, especially with aryl substituents (mixtures of branched and linear products are generally obtained with alkyl substituents),^[34a-c] while Ir-based catalysts usually drive the reaction to the branched products.^[30b,34e,36,37] The behavior of Ru-based catalysts is somewhere in between and depends strongly on the ligand and substrate. Formation of mixtures as well as high selectivities in favor of either the branched or the linear isomers have been reported.^[30a,34d,38]

We then investigated the scope of indoles (Scheme 3). The α -phenyl allyl acetate **2d** was chosen as reaction partner so as to assess simultaneously the generality of the branched selectivity as observed with *N*-phenyl indole. The NH-indole **1b** gave the C3-allylated product in good yield (80%) with no competitive *N*-allylation. The reaction also works well with indoles **1c-1e** featuring methyl, allyl and benzyl instead of phenyl substituent at nitrogen. Substitution of the backbone of *N*-phenyl indole was then studied. Methylation of the C6 position (indole **1f**) has no effect (78% yield), while a decrease in yield was observed with the C4-methylated indole **1g**, likely due to steric shielding of the C3 position. Pleasingly, the reaction works well with the C2-methylated indole **1h** (76% yield). This is in stark contrast with the absence of arylation we observed previously when trying to couple indoles and iodobenzene under similar conditions.^[17] Five functionalized indoles **1i-1m** were then tested, illustrating the good functional group compatibility of the transformation. The reaction tolerates C–F and C–Br bonds (74% yields from indoles **1i,j**). It is most efficient with electron-enriched substrates (83% yield from indole **1k**). It works also with electron-deprived indoles *albeit* giving lower yields (56% from the carbomethoxy derivative **1l**, 35% from the nitro compound **2m**). In all cases, the indoles are allylated with complete C3 and branched selectivity. In addition, control experiments with **1b**, **1d**, **1e**, **1f** and **1h** showed that the presence of the gold catalyst is crucial (with much lower yields obtained using the silver salt alone).



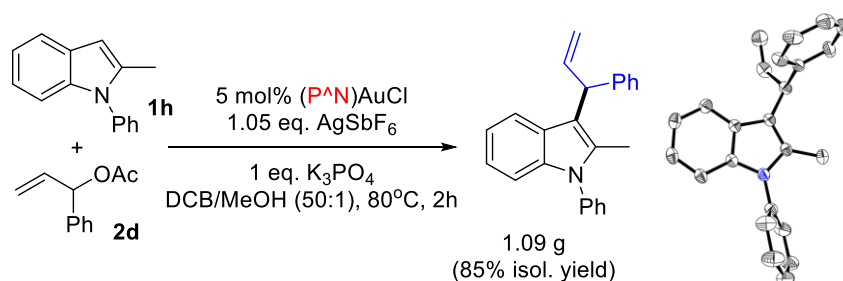
Scheme 3. Gold-catalyzed allylation: scope of indoles. Yields determined by ¹H NMR spectroscopy with diethyl terephthalate as internal standard. Isolated yields in parentheses. ^aIn the absence of (P^N)AuCl catalyst. ^bWith 1 equivalent of indole

Next, substitution of the aromatic group of α -phenyl allyl acetate was investigated, using *N*-phenyl indole as coupling partner (Scheme 4). Varying the steric and electronic profile (CF₃, NO₂ and F-substituted substrates **2g**, **2h** and **2i**) did not affect the reaction and resulted in good to excellent yields (80-89%). The tolerance to functional group was then probed. Bromide and trimethylsilyl substitutions can lead to undesirable side reactions in palladium-catalyzed cross-coupling reactions. Gold usually shows higher compatibility, as substantiated here by the allylation of *N*-phenyl indole with **2j** and **2k** (92 and 77% yield, respectively).



Scheme 4. Gold-catalyzed allylation of *N*-phenyl indole: scope of α -phenyl allyl acetates. Yields determined by 1H NMR spectroscopy with diethyl terephthalate as internal standard. Isolated yields in parentheses. ^aIn the absence of $(P^N)AuCl$ catalyst.

Finally, to demonstrate the practical interest of the transformation, the coupling of **1h** and **2d** was scaled up to 4 mmol (Scheme 5). The increased scale of the reaction did not reduce the yield. The product was isolated in 85% yield (1.09 g), while maintaining complete branched and C3 selectivity. Crystals were then grown and characterized by X-ray diffraction which unambiguously confirmed the connectivity of the coupling product.^[31]



Scheme 5. Gold-catalyzed allylation of the *N*-phenyl 2-methyl indole **1h** on 4 mmol scale. Molecular structure of the C3-branched allylated indole shown on the right (thermal ellipsoids at 50% probability; hydrogen atoms omitted for clarity).

Once established the scope of the gold-catalyzed allylation of indoles, we were keen to gain some mechanistic insight. On the basis of previous reports on arylation/vinylation reactions catalyzed by the (P[^]N)AuCl complex^[16-26] as well as recent studies on Au(III) π -allyl complexes,^[11,12,15] we envisioned the Au(I)/Au(III) cycle depicted in Figure 3, with the π -allyl (P[^]N)Au(III) complex **II** as key intermediate. Accordingly, the reaction would start by coordination of the allyl substrate to give a π -alkene Au(I) complex **I**.^[28] Then, cleavage of the C–O bond with gold oxidation would generate the π -allyl Au(III) complex **II**. Finally, C–C coupling would result from nucleophilic attack of the indole to the π -allyl moiety. Of note, detailed mechanistic investigations of the addition of β -diketo enolates to π -allyl (P,C)Au(III) complexes have shown the feasibility of nucleophilic attack at the terminal and central positions of the π -allyl as well as gold, but the last two paths proved reversible.^[15]

To support the existence and catalytic relevance of the key π -allyl Au(III) complexes **II**, stoichiometric reactions were performed (Scheme 6). First, the π -alkene Au(I) complex **A**^[28,39] was synthesized, isolated and fully characterized (NMR, EA).^[31] Its structure was analyzed computationally, showing in-plane coordination of the C=C double bond to gold.^[31] The cleavage of the allyl–OAc bond (formal oxidative addition)^[40] is not spontaneous, as it is usually with L₂Pd(0) complexes.

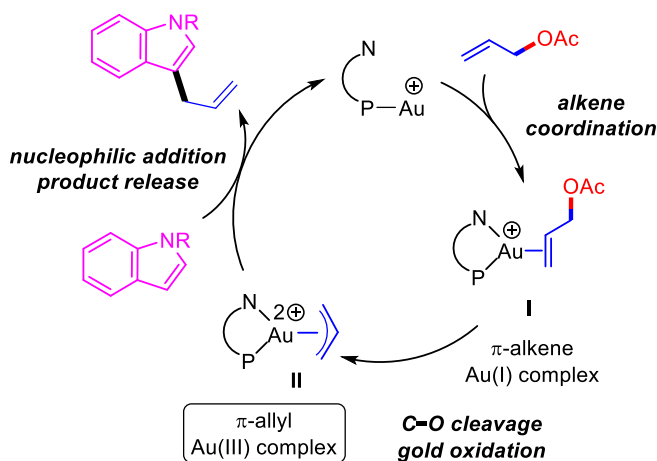
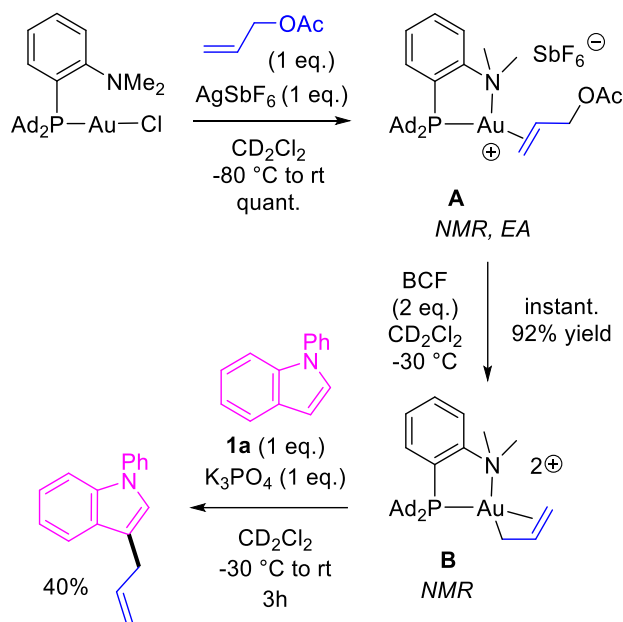


Figure 3. Au(I)/Au(III) cycle proposed to account for the gold-catalyzed allylation of indoles.

This is because the $(P^N)Au^+$ fragment is less prone to be oxidized and to form the π -allyl Au(III) complex, despite the enhanced π -backdonating ability of gold induced by bending.^[41,42] To assist the activation of the allyl substrate,^[43] complex **A** was reacted with tris(pentafluorophenyl)borane (BCF), a strong Lewis acid. BCF was chosen as a soluble surrogate for the silver salt used in the catalytic transformations. *In situ* monitoring by ^{31}P and 1H NMR spectroscopy revealed instantaneous abstraction of the acetate at -30 °C to give a major product (92% yield). The ensuing complex proved too unstable to be isolated (it decomposed above -30 °C), but it could be unequivocally authenticated as the dicationic π -allyl Au(III) complex **B** thanks to multi-nuclear NMR analyses. The ^{31}P NMR signal appears at $\delta 92.3$ ppm, deshielded by 33 ppm with respect to complex **A**. Oxidation of gold and coordination of the NMe_2 group are clearly apparent from the associated 1H and ^{15}N NMR signals. For **B**, they appear at $\delta 3.7$ and 66.2 ppm, respectively, in the same typical ranges as those of $(P^N)Au(III)$ aryl complexes.^[16,19] Most diagnostic of the change in the coordination of the allyl moiety from **A** to **B** are the large downfield shifts of the signals for the central CH group. The 1H NMR signal shifts from 5.05 to 6.98 ppm, while the ^{13}C NMR shifts from 92.0 to 136.9 ppm. Of note, the two terminal CH_2 groups resonate

at very different fields in ^{13}C NMR (δ 66.9/114.5 ppm), suggesting a highly asymmetric η^3 -allyl coordination (see below).



Scheme 6. Formation, NMR characterization and reaction of the Au(III) π -allyl complex **B**. Yields determined by ^1H NMR with *n*-dodecane as internal standard.

The structure of the π -allyl Au(III) complex **B** was further assessed computationally (Figure 4a). DFT calculations were performed on the real complex (with the exact MeDalphos ligand) at the SMD(CH_2Cl_2)-B3PW91/SDD+f(Au),6-31G**(other atoms) level of theory, taking into account dichloromethane solvation.^[31] The ground-state structure of **B** is an η^3 structure (the corresponding η^1 form is much less stable, by >35 kcal/mol). It shows inequivalent C–C bond distances in the π -allyl ligand (1.437 vs 1.385 Å), and inequivalent Au–CH₂ distances (2.134 Å *trans* to N vs 2.405 Å *trans* to P). This is indicative of a highly asymmetric π -allyl complex. It is best represented by the Lewis structure shown in Scheme 6, with a Au–CH₂ σ -bond *trans* to N and a CH=CH₂ moiety π -coordinated to Au *trans* to P. This view was further supported by Atoms-In-Molecules (AIM) calculations (Figure 4b). Only one bond critical point (BCP) was found between

Au and the allyl ligand, with the CH₂ moiety *trans* to N. Consistently, a CHCH₂ bond of the allyl, the one *trans* to P, displays more double bond character, as apparent from the Bader's delocalization indices (1.415 vs 1.173).

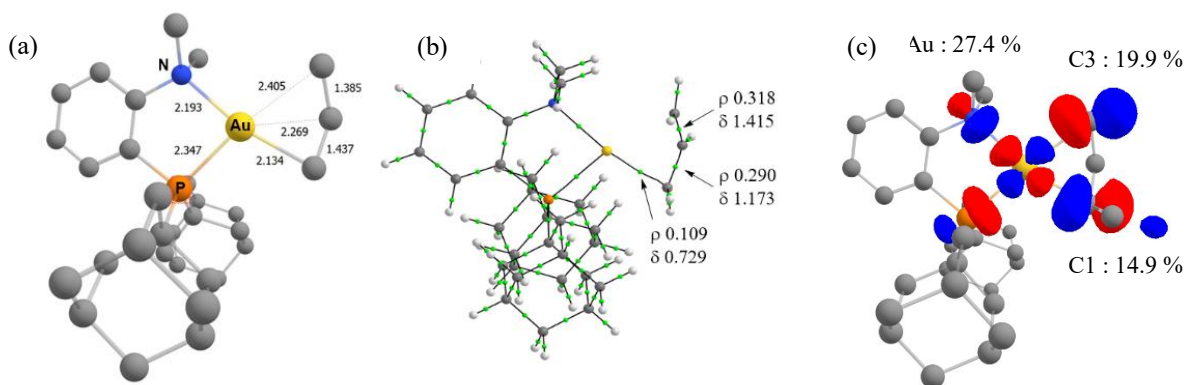


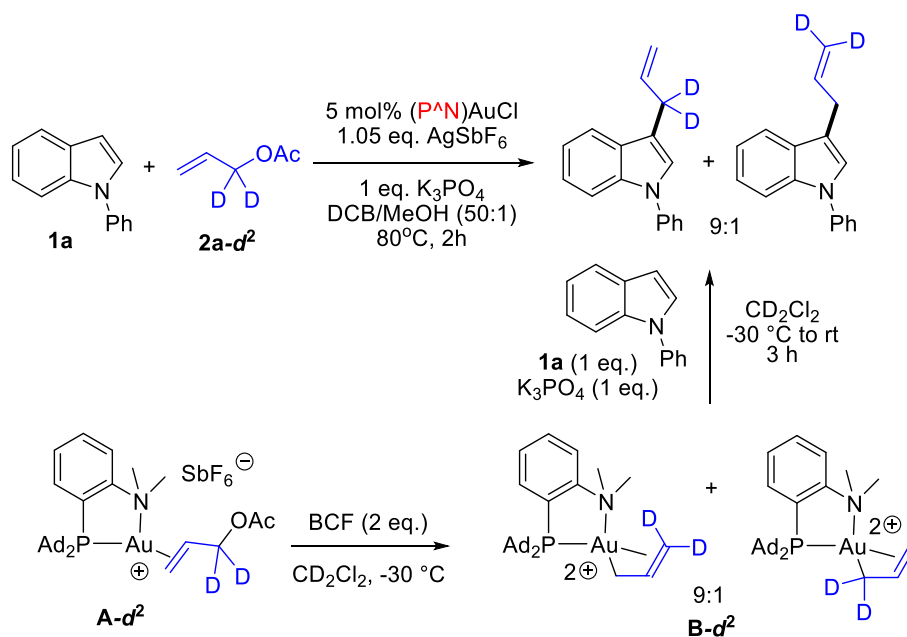
Figure 4. (a) Optimized geometry of the π -allyl Au(III) complex **B** at the SDM(CH₂Cl₂)-B3PW91/SDD+f(Au),6-31G**(other atoms) level of theory (distances in Å). (b) Associated AIM molecular graph with relevant bond paths, bond critical points (BCP, green circles), electron densities (ρ in e/bohr³) and Bader's delocalization indices (δ). (c) Plot of the LUMO (cutoff : 0.05) with key atomic contributions in %.

The asymmetric $\sigma+\pi$ -coordination encountered in complex **B** contrasts with the symmetric η^3 -coordination we found in P,C-cyclometalated Au(III) π -allyl complexes,^[12,15] but it is reminiscent of that observed by Tilset *et al.* in related N,C-cyclometalated complexes.^[11] Thus the bonding mode of the π -allyl moiety strongly depends on the ancillary ligand and it actually conveys its electronic features. While the (P,C) ligand is about symmetric electronically, the (P[^]N) and (N,C) ligands are highly asymmetric, P and C being significantly more donating than N. Inspection of the vacant molecular orbitals of complex **B** provides useful insights. The LUMO is centered on gold and on the terminal carbon atoms, with a larger contribution from the position *cis*

to N (19.9 vs 14.9%) (Figure 4c). The LUMO+1 and LUMO+2 show larger contributions from the central carbon atom (12.6 and 16.5%, respectively) than from the terminal ones (< 6%), but they are significantly higher in energy ($\geq 1.3\text{eV}$),^[31] in contrast to the (P,C)Au(π -allyl)⁺ complex.^[15] Having established the existence of (P[^]N)(π -allyl) Au(III) complexes, we sought to demonstrate their ability to react with indoles to give the corresponding C3-allylation products. To this end, an *in situ* and freshly generated sample of the π -allyl Au(III) complex **B** was treated with *N*-phenyl indole **1a** and K₃PO₄ (1 eq. each) at -30 °C. ³¹P and ¹H NMR monitoring revealed immediate and complete consumption of the π -allyl complex **B** with formation of the C3-allylated indole (40% yield). Taken together, these experiments support the proposed 2-electron redox catalytic cycle and the involvement of the π -allyl Au(III) complexes **II** (resulting from coordination and activation of allyl acetates at gold) as key intermediates.

Some D-labeling experiments were also carried out with the allyl acetate **2a-d²** and allyl alcohol **3a-d²** (Scheme 7). In both cases, the catalytic allylation of indole **1a** led to the a 90:10 mixture of the corresponding product, the one with the CD₂ group directly bonded to indole being predominant. The fate of the D-labeling was also probed under stoichiometric conditions. The π -alkene Au(I) complex **A-d²** was reacted with B(C₆F₅)₃ at low temperature to give a 90:10 mixture of the π -allyl Au(III) complex **B-d²** with the CD₂ group predominantly in the position *trans* to P. Upon addition of **1a** and K₃PO₄, a 85:15 mixture of the C3-allylated indoles was obtained. Thus, partial D-scrambling is consistently observed under catalytic and stoichiometry conditions, supporting further the involvement of the π -allyl Au(III) complex as key intermediate in the catalytic transformation. The D-labeling experiments indicate that there is some “memory” effect with allyl acetate **2a**. The π -allyl complex and C3-allylated indole keeps trace of the position of the D-labeling in the allyl substrate. This may be due to competition between SN₂ and SN₂'

pathways in the transformation of the π -alkene Au(I) complex into the π -allyl Au(III) complex. However, the complete regioselectivity in favor of the branched product observed with 1- and 3-substituted allyl acetates/alcohols suggests that this picture cannot be generalized to other substrates.



Scheme 7. Deuterium labeling experiments under catalytic and stoichiometric conditions.

To assess the influence of the allyl substitution on the coordination and reactivity of the allyl group, calculations have been performed on the (P^N)Au[H₂CC(H)CH(CH₃)]²⁺ complex (Figure 5). Accordingly, the most stable form was found to be the one with the Me group sitting in pseudo-equatorial position, *cis* to the NMe₂ group. The coordination of the π -allyl is highly dissymmetric, even more than in complex **B**. The LUMO is also centered on the Au, C1 and C3 atoms, with an even larger contribution from the C atom *cis* to N (the one bearing the Me substituent), 20.7 %. This picture is consistent with a nucleophilic attack of indoles at the substituted carbon atom of the allyl, in line with the branched regioselectivity observed experimentally.

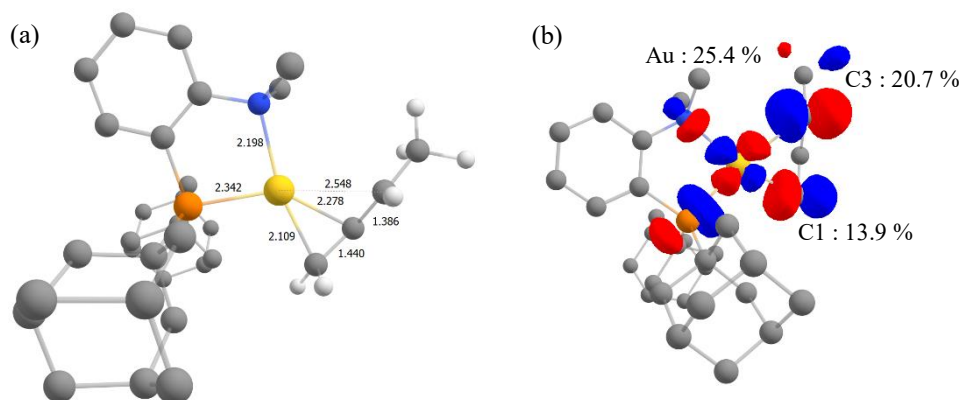


Figure 5. (a) Optimized geometry of the π -allyl Au(III) complex $(P^N)Au[H_2CC(H)CH(CH_3)]^{2+}$ at the SDM(CH₂Cl₂)-B3PW91/SDD+f(Au),6-31G**(other atoms) level of theory (distances in Å). (b) Plot of the LUMO (cutoff : 0.05) with key atomic contributions in %.

Conclusion

The use of strong oxidants or photoredox conditions was long considered mandatory to achieve catalytic cross-coupling with gold complexes. The use of bidentate ligands able to stabilize both Au(I) and Au(III) complexes has recently opened a new path in Au(I)/Au(III) catalysis. We previously showed that P^N hemilabile ligands such as MeDalphos trigger oxidative addition of $C(sp^2)$ and $C(sp)-X$ bonds ($X = I; Br$) to gold under mild conditions, and we applied them in several Au(I)/Au(III)-catalyzed arylation/vinylation cross-couplings. In this work, we have extended this ligand-enabled approach to $C(sp^3)-X$ bond activation and Au(I)/Au(III)-catalyzed allylation. The (MeDalphos)AuCl was found to efficiently catalyze the allylation of indoles. The reaction works with allyl acetates as well as alcohols. It selectively affords the branched C3-allylated products and tolerates many functional groups. The key intermediates are dicationic Au(III) π -allyl complexes, which have been spectroscopically authenticated. Because of the

electronic dissymmetry of the P^N ligand, the allyl moiety adopts an asymmetric $\sigma+\pi$ -coordination mode.

This transformation represents the first example of a gold-catalyzed allylation reaction operating *via* a Au(I)/Au(III) cycle and involving π -allyl complexes. As such, this work bridges the gap between gold and the transition metals prevailing in catalytic allylation, namely palladium, ruthenium and iridium which all operate classically *via* π -allyl complexes.^[44] Future work will aim to develop further the ligand-enabled approach in Au(I)/Au(III) catalysis, so as to expand the arsenal of C–C/C–X bond cross-coupling reactions.

ASSOCIATED CONTENT

Details for the synthesis and characterization of all the new compounds, the X-ray structure for *N*-phenyl-2-methyl-3-(1-phenyl-2-propen-1-yl)-1*H*-indole, and the DFT calculations details are available free of charge via the Internet at <http://pubs.acs.org> (PDF, CIF).

AUTHOR INFORMATION

Corresponding Author

Didier Bourissou – Email: dbouriss@chimie.ups-tlse.fr ORCID: 0000-0002-0249-1769

ORCID

Jessica Rodriguez – ORCID: 0000-0002-3814-6588

David Vesseur – ORCID: 0000-0002-9594-6741

Alexis Tabey – ORCID: 0000-0002-6960-3542

Miqueu Karinne – ORCID: 0000-0002-5960-1877

Author Contributions

J.R.[‡], D.V.[‡] and A.T.[‡] performed all the experimental work and spectroscopic analyses. S.M.-L. carried out the X-ray diffraction analyses. K.M. performed the DFT calculations. All authors analyzed the data and contributed to manuscript preparation. D.B. conceived and supervised the project. ‡These authors contributed equally.

ACKNOWLEDGMENT

Financial support from the Centre National de la Recherche Scientifique, the Université de Toulouse and the Agence Nationale de la Recherche Scientifique (Gold-III, ANR-19-CE07-0037) is gratefully acknowledged. J.R. thanks the European Commission for a MCIF (Gold3Cat-799606). The “Direction du Numérique” of the Université de Pau et des Pays de l’Adour, MCIA (Mésocentre de Calcul Intensif Aquitain) and CINES under allocation A009080045 made by Grand Equipement National de Calcul Intensif (GENCI) are acknowledged for computational facilities. E. D. Sosa Carrizo is thanked for preliminary calculations. The NMR service of ICT (P. Lavedan, M. Vedrenne) is acknowledged for assistance with the low-temperature NMR experiments.

REFERENCES

- [1] For selected reviews, see: a) B. M. Trost, M. L. Crawley, Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis. *Chem. Rev.* **2003**, *103*, 2921–2944; b) B. F. Straub in *Organotransition Metal Chemistry: From Bonding to Catalysis*, 1st ed. (Eds: John F. Hartwig), University Science Books, Sausalito, **2010**, pp. 7622–7622; c) J. F. Hartwig, M. J. Pouy, Iridium-Catalyzed Allylic Substitution. *Top. Organomet. Chem.* **2011**, *38*, 169–208; d) O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, J. Bäckvall, A. Pfaltz, M. A. Pericàs, M. Diéguez, Recent Advances in Enantioselective Pd-Catalyzed Allylic Substitution: From Design to Applications. *Chem. Rev.* **2021**, *121*, 4373–4505.
- [2] A. Quintavalla, M. Bandini, Gold-Catalyzed Allylation Reactions. *ChemCatChem* **2016**, *8*, 1437–1453.
- [3] M. Georgy, V. Boucard, J.-M. Campagne, Gold (III)-catalyzed nucleophilic substitution of propargylic alcohols. *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181.
- [4] M. O. Akram, P. S. Mali, N. T. Patil, Cross-coupling reactions of aryldiazonium salts with allylsilanes under merged gold/visible-light photoredox catalysis. *Org. Lett.* **2017**, *19*, 3075–3078.
- [5] J. Holz, C. Pfeffer, H. Zuo, D. Beierlein, G. Richter, E. Klemm, R. Peters, In situ generated gold nanoparticles on active carbon as reusable highly efficient catalysts for a C–C stille coupling. *Angew. Chem. Int. Ed.* **2019**, *58*, 10330–10334.
- [6] M. Bandini, A. Eichholzer, Catalytic functionalization of indoles in a new dimension. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644.

- [7] M. Bandini, A. Bottoni, M. Chiarucci, G. Cera, G. P. Miscione, Mechanistic insights into enantioselective gold-catalyzed allylation of indoles with alcohols: the counterion effect. *J. Am. Chem. Soc.* **2012**, *134*, 20690–20700.
- [8] M. D. Levin, F. D. Toste, Gold-Catalyzed Allylation of Aryl Boronic Acids: Accessing Cross-Coupling Reactivity with Gold. *Angew. Chem. Int. Ed.* **2014**, *53*, 6211–6215.
- [9] K. Liu, T. Li, D.Y. Liu, W. Li, J. Han, C. Zhu, J. Xie, Dinuclear gold-catalyzed CH bond functionalization of cyclopropenes. *Sci. China Chem.* **2021**, *64*, 1958–1963.
- [10] J. Wang, S. Zhang, C. Xu, L. Wojtas, N. G. Akhmedov, H. Chen, X. Shi, Highly Efficient and Stereoselective Thioallylation of Alkynes: Possible Gold Redox Catalysis with No Need for a Strong Oxidant. *Angew. Chem. Int. Ed.* **2018**, *57*, 6915–6920.
- [11] M. S. M. Holmsen, A. Nova, S. Øien-Ødegaard, R. H. Heyn, M. Tilset, A Highly Asymmetric Gold(III) η^3 -Allyl Complex. *Angew. Chem. Int. Ed.* **2020**, *59*, 1516–1520.
- [12] J. Rodriguez, G. Szalóki, E. D. Sosa Carrizo, N. Saffon-Merceron, K. Miqueu, D. Bourissou, Gold (III) π -Allyl Complexes. *Angew. Chem. Int. Ed.* **2020**, *59*, 1511–1515.
- [13] For π -allyl Au(III) complexes detected in the gas phase by mass spectrometry, see: a) W. Nakanishi, M. Yamanaka, E. Nakamura, Reactivity and stability of organocopper (I), silver (I), and gold (I) ate compounds and their trivalent derivatives. *J. Am. Chem. Soc.* **2005**, *127*, 1446–1453; b) N. J. Rijs, N. Yoshikai, E. Nakamura, R. A. J. O’Hair, Gas-phase reactivity of group 11 dimethylmetallates with allyl iodide. *J. Am. Chem. Soc.* **2012**, *134*, 2569–2580.
- [14] For σ -allyl Au(III) complexes, see: a) S. Komiya, S. Ozaki, Isolation of the first allylic gold (III) complex having a triphenylphosphine ligand. *Chem. Lett.* **1988**, *17*, 1431–1432; b) M.

D. Levin, T. Q. Chen, M. E. Neubig, C. M. Hong, C. A. Theulier, I. J. Kobylanskii, M. Janabi, J. P. O'Neil, F. D. Toste, A catalytic fluoride-rebound mechanism for C (sp³)-CF₃ bond formation. *Science* **2017**, *356*, 1272–1276; c) M. D. Levin, F. D. Toste, Gold-Catalyzed Allylation of Aryl Boronic Acids: Accessing Cross-Coupling Reactivity with Gold. *Angew. Chem. Int. Ed.* **2014**, *53*, 6211–6215.

[15] J. Rodriguez, M. S. M. Holmsen, Y. García-Rodeja, E. D. Sosa Carrizo, P. Lavedan, S. Mallet-Ladeira, K. Miqueu, D. Bourissou, Nucleophilic Addition to π -Allyl Gold (III) Complexes: Evidence for Direct and Undirect Paths. *J. Am. Chem. Soc.* **2021**, *143*, 11568–11581.

[16] A. Zeineddine, L. Estévez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, Rational development of catalytic Au (I)/Au (III) arylation involving mild oxidative addition of aryl halides. *Nat. Commun.* **2017**, *8*, 1–8.

[17] J. Rodriguez, A. Zeineddine, E. D. Sosa Carrizo, K. Miqueu, N. Saffon-Merceron, A. Amgoune, D. Bourissou, Catalytic Au(I)/Au(III) arylation with the hemilabile MeDalpos ligand: unusual selectivity for electron-rich iodoarenes and efficient application to indoles. *Chem. Sci.* **2019**, *10*, 7183–7192.

[18] J. Rodriguez, A. Tabey, S. Mallet-Ladeira, D. Bourissou, Oxidative additions of alkynyl/vinyl iodides to gold and gold-catalyzed vinylation reactions triggered by the MeDalpos ligand. *Chem. Sci.* **2021**, *12*, 7706–7712.

[19] J. Rodriguez, N. Adet, N. Saffon-Merceron, D. Bourissou, Au (I)/Au (III)-Catalyzed C–N coupling. *Chem. Commun.* **2020**, *56*, 94–97.

[20] M. Rigoulet, O. Thillaye du Boullay, A. Amgoune, D. Bourissou, Gold (I)/Gold (III) Catalysis that Merges Oxidative Addition and π -Alkene Activation. *Angew. Chem. Int. Ed.* **2020**, *59*, 16625–16630.

[21] M. O. Akram, A. Das, I. Chakrabarty, N. T. Patil, Ligand-Enabled Gold-Catalyzed C(sp²)-N Cross-Coupling Reactions of Aryl Iodides with Amines. *Org. Lett.* **2019**, *21*, 8101–8105.

[22] A. G. Tathe, C. C. Chintawar, V. W. Bhoyare, N. T. Patil, Ligand-enabled gold-catalyzed 1, 2-heteroarylation of alkenes. *Chem. Commun.* **2020**, *56*, 9304–9307.

[23] C. C. Chintawar, A. K. Yadav, N. T. Patil, Gold-Catalyzed 1,2-Diarylation of Alkenes. *Angew. Chem. Int. Ed.* **2020**, *59*, 11808–11813.

[24] A. G. Tathe, Urvashi, A. K. Yadav, C. C. Chintawar, N. T. Patil, Gold-Catalyzed 1,2-Aminoarylation of Alkenes with External Amines. *ACS Catal.* **2021**, *11*, 4576–4582.

[25] S. Zhang, C. Wang, X. Ye, X. Shi, Intermolecular Alkene Difunctionalization via Gold-Catalyzed Oxyarylation. *Angew. Chem. Int. Ed.* **2020**, *59*, 20470–20474.

[26] For recent reviews dealing with oxidant-free Au(I)/Au(III) catalysis, see: a) M. O. Akram, S. Banerjee, S. S. Saswade, V. Bedi, N. T. Patil, Oxidant-free oxidative gold catalysis: the new paradigm in cross-coupling reactions. *Chem. Commun.* **2018**, *54*, 11069–11083; b) B. Huang, M. Hu, F. D. Toste, Homogeneous Gold Redox Chemistry: Organometallics, Catalysis, and Beyond. *Trends Chem.* **2020**, *2*, 707–720; c) V. W. Bhoyare, A. G. Tathe, A. Das, C. C. Chintawar, N. T. Patil, The interplay of carbophilic activation and Au(I)/Au(III) catalysis: an emerging technique for 1,2-difunctionalization of C–C multiple bonds. *Chem. Soc. Rev.* **2021**, *50*, 10422–10450; d) P.

R. Font, S. X. Ribas, Fundamental Basis for Implementing Oxidant-Free Au(I)/Au(III) Catalysis. *Eur. J. Inorg. Chem.* **2021**, *26*, 2556–2569.

[27] For reviews dealing with oxidative Au(I)/Au(III) catalysis, see: a) J. Miró, C. del Pozo, Fluorine and Gold: A Fruitful Partnership. *Chem. Rev.* **2016**, *116*, 11924–11966; b) S. Banerjee, V. W. Bhojare, N. T. Patil, Gold and hypervalent iodine(III): liaisons over a decade for electrophilic functional group transfer reactions. *Chem. Commun.* **2020**, *56*, 2677–2690; c) A. Nijamudheen, A. Datta, Gold-Catalyzed Cross-Coupling Reactions: An Overview of Design Strategies, Mechanistic Studies, and Applications. *Chem. Eur. J.* **2020**, *26*, 1442–1487. For a recent review dealing with gold photocatalysis, see: d) S. Witzel, A. S. K. Hashmi, J. Xie, Light in Gold Catalysis. *Chem. Rev.* **2021**, *121*, 8868–8925.

[28] a) M. Navarro, A. Toledo, M. Joost, A. Amgoune, S. Mallet-Ladeira, D. Bourissou, π Complexes of P[^] P and P[^] N chelated gold (I). *Chem. Commun.* **2019**, *55*, 7974–7977; b) M. Navarro, A. Toledo, S. Mallet-Ladeira, E. D. Sosa Carrizo, K. Miqueu, D. Bourissou, Versatility and adaptative behaviour of the P[^] N chelating ligand MeDalphos within gold (I) π complexes. *Chem. Sci.* **2020**, *11*, 2750–2758.

[29] For reviews on transition metal-catalyzed C–H allylation reactions, see: a) N. K. Mishra, S. Sharma, J. Park, S. Han, I. S. Kim, Recent Advances in Catalytic C(sp²)–H Allylation Reactions. *ACS Catal.* **2017**, *7*, 2821–2847; b) S. Dutta, T. Bhattacharya, D. B. Werz, Transition-Metal-Catalyzed C–H Allylation Reactions. *Chem.* **2021**, *7*, 555–605.

[30] Catalytic C2-allylation of indoles was achieved using directing groups or blocking the C3 position: a) X. Wu, H. Ji, Ruthenium (II)-Catalyzed Regio- and Stereoselective C–H Allylation of Indoles with Allyl Alcohols. *Org. Lett.* **2018**, *20*, 2224–2227; b) J. A. Rossi-Ashton, A. K. Clarke,

J. R. Donald, C. Zheng, R. J. K. Taylor, W. P. Unsworth, S.-L. You, Iridium-Catalyzed Enantioselective Intermolecular Indole C2-Allylation. *Angew. Chem. Int. Ed.* **2020**, *59*, 7598–7604.

[31] See Supplementary information for details.

[32] For stoichiometric allylation reactions promoted by silver salts, see: X. Xiong, J. Wong, Y.-Y. Yeung, Silver Salt-Mediated Allylation Reactions Using Allyl Bromides. *J. Org. Chem.* **2021**, *86*, 6974–6982.

[33] For reviews on transition metal-catalyzed nucleophilic allylic substitution with allyl alcohols, see: a) B. Sundararaju, M. Achard, C. Bruneau, Transition metal catalyzed nucleophilic allylic substitution: activation of allylic alcohols via π -allylic species. *Chem. Soc. Rev.* **2012**, *41*, 4467–4483; b) N. A. Butt, W. Zhang, Transition metal-catalyzed allylic substitution reactions with unactivated allylic substrates. *Chem. Soc. Rev.* **2015**, *44*, 7929–7967.

[34] For examples in Pd and Ru-catalyzed allylation of indoles, see: a) M. Kimura, M. Futamata, R. Mukai, Y. Tamaru, Pd-catalyzed C3-selective allylation of indoles with allyl alcohols promoted by triethylborane. *J. Am. Chem. Soc.* **2005**, *127*, 4592–4593; b) I. Usui, S. Schmidt, M. Keller, B. Breit, Allylation of N-Heterocycles with Allylic Alcohols Employing Self-Assembling Palladium Phosphane Catalysts. *Org. Lett.* **2008**, *10*, 1207–1210; c) Y. Gumrukcu, B. de Bruin, J. N. H. Reek, Hydrogen-Bond-Assisted Activation of Allylic Alcohols for Palladium-Catalyzed Coupling Reactions. *ChemSusChem* **2014**, *7*, 890–896; d) B. Sundararaju, M. Achard, B. Demerseman, L. Toupet, G. Sharma, C. Bruneau, Ruthenium (iv) complexes featuring p, o-chelating ligands: Regioselective substitution directly from allylic alcohols. *Angew. Chem. Int. Ed.* **2010**, *49*, 2782–2785; For Ir-catalyzed allylation, see: e) J. F. Hartwig, L. M. Stanley, Mechanistically driven

development of iridium catalysts for asymmetric allylic substitution. *Acc. Chem. Res.* **2010**, *43*, 1461–1475.

[35] The binding energy of the γ -methyl allyl acetate **2b** to the (P[^]N)Au⁺ fragment was predicted to be >2 kcal/mol larger than those of the α -methyl allyl acetates *E* and *Z-2c*.^[31]

[36] W.-B. Liu, H. He, L.-X. Dai, S.-L. You, Ir-catalyzed regio- and enantioselective Friedel–Crafts-type allylic alkylation of indoles. *Org. Lett.* **2008**, *10*, 1815–1818.

[37] W.-B. Liu, H. He, L.-X. Dai, S.-L. You. Synthesis of 2-Methylindoline- and 2-Methyl-1,2,3,4-tetrahydroquinoline-Derived Phosphoramidites and Their Applications in Iridium-Catalyzed Allylic Alkylation of Indoles. *Synthesis* **2009**, 2076–2082.

[38] S. Gruber, A. B. Zaitsev, M. Wörle, P. S. Pregosin, L. F. Veiros, Facile ruthenium (IV)-catalyzed single and double allylation of indole compounds using alcohols as substrates: Aspects of ruthenium (IV) allyl chemistry. *Organometallics* **2008**, *27*, 3796–3805.

[39] For a review dealing with 3-coordinate π -alkene Au(I) complexes, see: M. Navarro, D. Bourissou, π -Alkene/alkyne and carbene complexes of gold (I) stabilized by chelating ligands. *Adv. Organomet. Chem.* **2021**, *76*, 101–144.

[40] Rigorously, the oxidative addition terminology should be restricted to elementary transformations in which a X–Y bond adds to a metal center to give a M(X)(Y) complex. This is not the case in the transformation **A**→**B**, the OAc group does not bind to gold. A similar situation is typically met upon reaction of complexes with aryl diazonium salts: a M–aryl bond is formed, the metal is oxidized and N₂ is released.

[41] M. Joost, L. Estévez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, Enhanced π -Backdonation from Gold (I): Isolation of Original Carbonyl and Carbene Complexes. *Angew. Chem. Int. Ed.* **2014**, *53*, 14512–14516.

[42] A. Zeineddine, F. Rekhroukh, E. D. Sosa Carrizo, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, Isolation of a Reactive Tricoordinate α -Oxo Gold Carbene Complex. *Angew. Chem. Int. Ed.* **2018**, *57*, 1306–1310.

[43] For recent examples of σ -bond activations at transition metals assisted by external Lewis acids, see: a) D. You, H. Yang, S. Sen, F. P. Gabbaï, Modulating the σ -accepting properties of an antimony z-type ligand via anion abstraction: remote-controlled reactivity of the coordinated platinum atom. *J. Am. Chem. Soc.* **2018**, *140*, 9644–9651; b) H. Kameo, H. Yamamoto, K. Ikeda, T. Isasa, D. Bourissou, Fluorosilane Activation by Pd/Ni \rightarrow Si–F \rightarrow Lewis Acid Interaction: An Entry to Catalytic Sila-Negishi Coupling. *J. Am. Chem. Soc.* **2020**, *142*, 14039–14044; c) H. Kameo, A. Mushiake, T. Isasa, H. Matsuzaka, D. Bourissou, Pd/Ni-Catalyzed Germa-Suzuki coupling via dual Ge–F bond activation. *Chem. Commun.* **2021**, *57*, 5004–5007.

[44] For a recent review dealing with metal-dependent selectivity (Au vs other metals) in catalysis, see: C. C. Chintawar, A. K. Yadav, A. Kumar, S. P. Sancheti, N. T. Patil, Divergent Gold Catalysis: Unlocking Molecular Diversity through Catalyst Control. *Chem. Rev.* **2021**, *121*, 8478–8558.