Stable gold(III) catalysts by oxidative addition of a carbon–carbon bond

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Low-valent late transition-metal catalysis has become indispensable to chemical synthesis, but homogeneous high-valent transition-metal catalysis is underdeveloped, mainly owing to the reactivity of high-valent transition-metal complexes and the challenges associated with synthesizing them. Here we report a carbon–carbon bond cleavage at ambient conditions by a Au(i) complex that generates a stable Au(III) cationic complex. In contrast to the well-established soft and carbophilic Au(I) catalyst, this Au(III) complex exhibits hard, oxophilic Lewis acidity. For example, we observed catalytic activation of α,β-unsaturated aldehydes towards selective conjugate additions as well as activation of an unsaturated aldehyde–allene for a [2 + 2] cycloaddition reaction. The origin of the regioselectivity and catalytic activity was elucidated by X-ray crystallographic analysis of an isolated Au(III)–activated cinnamaldehyde intermediate. The concepts revealed suggest a strategy for accessing high-valent transition-metal catalysis from readily available precursors.

Transition-metal catalysis has developed into an efficient and selective strategy for organic transformations in modern chemistry. Low-valent late (that is, their periodic table group is more to the right) transition-metal complexes are particularly heavily used owing to their stability and usefulness in forming important chemical bonds (C–C, C–O, C–N). However, low-oxidation-state, late transition metals are less suitable for other critical reactions, including electrophilic C–H functionalization1,2. Recent efforts have begun to unlock the potential of high-valent late transition metals, especially Pd(IV), to complement these shortcomings3–6. The major challenges thus far include the typical need for strong oxidants to access the higher oxidation state, which limits the functional group tolerance, and the instability of the oxidized metal complexes, which often exist only as high-energy intermediates on the catalytic cycle (Fig. 1a). Put broadly, to fully explore the undoubtedly rich chemistry of high-valent late transition metals, there is a need to develop easily prepared, stable, tunable catalysts.

In this regard we searched for a route to stable, catalytically active Au(III) complexes with the goal of complementing the ever-increasing library of Au(i)-catalysed reactions. Whereas homogeneous Au(i) catalysis has seen great progress over the last decade7–11, Au(III) catalysis is still mainly limited to the use of inorganic Au(III) salts12. The synthetic challenge in forming stable, yet catalytically active, organometallic Au(III) complexes derives from the intrinsically high redox potential, leading to the facile reduction of Au(III) complexes to Au(i) or metallic Au(0) species in the presence of electron-rich reagents13–18. In cases where the ligands are capable of stabilizing the highly oxidizing metal, the resulting complex is often rendered

Figure 1 | Routes to high-valent metal complexes. a, Standard route to high-valent metal complexes using halogen-based oxidants. n, oxidation state; NXS, N-halosuccinimide; M, metal. b, Hypothetically synthetic pathway for accessing Au(III)–C bond-stabilized Au(III) complexes. X, heteroatom; L, ligand.

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catalytically inert. For example, the oxidative addition product, L-AuX₃, formed from L-AuX (where X is a halogen and L is ligand) is a poor catalyst by itself, and the abstraction of a halide to increase reactivity enables a facile reduction to the lower oxidation states. Moreover, although complexes of the type Au(III)(C^L)(X)(Y) (C^L is a bidentate ligand coordinating one carbon and one two-electron charge-neutral ligand; X, halogen; Y, X or L) are available through multi-step synthetic sequences, their instability in the cationic form and the difficulties in readily tuning facile reduction to the lower oxidation states, have severely limited their applications in catalysis.

**Formation of stable gold(III) complexes**

To address this challenge, we hypothesized that a multidentate ligand scaffold with strong Au–C bonding energy might be able to stabilize cationic Au(III) organometallic complexes while maintaining catalytic activity. In designing the desired complex, we also hoped to avoid using strong oxidants to maximize the functional group compatibility of the protocol.

From reported examples, we reasoned that the transmetallation of Sn(biphenyl)("Bu)₂ (where Bu is butyl) to L-AuX₃ might afford a stable Au(III) complex with a bidentate ligand containing two strong Au–C bonds (Fig. 1b). The known stabilization of both neutral and cationic Au(I) complexes by N-heterocyclic carbenes inspired us to examine them as supporting ligands. In an effort to access such compounds, attempts to perform the transmetallation of Sn(biphényl)("Bu)₂ to IPr-AuCl₃ (compound 2) (where IPr is [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]) gave no desired product (Fig. 2). Although the replacement of IPr-AuCl₃ with (tetrahydrothiophene)AuCl₃ enabled access to complex 3 in good yield, the two-step procedure was cumbersome, and did not meet the goals of being mild and straightforward.

As an alternative, we imagined that insertion of an Au(I) complex into the strained C–C bond of biphenylene could achieve the desired oxidation and introduction of a stabilizing biphenyl ligand in a single step (Fig. 1b). The concept was appealingly simple, even though oxidative addition to Au(I) complexes with mild oxidants is exceedingly rare, and in general requires either bimetallic complexes generating Au(II)–Au(III) intermediates (for examples see ref. 27 and references therein, and refs 18 and 28) or complexes with specially designed ligands. Moreover, no well defined carbon–carbon bond cleavage reactions with Au(I) complexes have been reported. To investigate the feasibility of this strategy, the coordinatively unsaturated IPrAu(I)(SbF₆) was generated in situ by reacting IPrAuCl₃ with AgSbF₆, resulting in the precipitation of AgCl in CD₂Cl₂ at room temperature. Reaction of the resulting electrophilic IPrAu(I)(SbF₆) with biphenylene resulted in the immediate and quantitative formation of the coordination complex (IPrAu-biphenylene)(SbF₆)(compound 5), both of which were observed by ¹H nuclear magnetic resonance (NMR) spectroscopy. Nearly full conversion of the Au(I) cationic species to the desired Au(III) complex 5 was observed after 1.5 h (see Supplementary Information, Supplementary Fig. 1 and Supplementary Table 1). In contrast, most reported examples of this type of C–C bond cleavage requires more

![Figure 2](image-url)
redox-active metals (such as Rh, Ir, Ni, Ru and Fe) and have been worked out under harsh reaction conditions\cite{24,25}, suggesting that the sterically unencumbered cationic IPrAu(I) complex might display a comparatively fast rate of coordination and subsequent oxidative addition.

We also examined the oxidative addition of IPrAu(I)SbF$_6$ with the more electron-rich 2,3,6,7-tetramethylbiphenylene (Me$_4$-biphenylene). Full conversion to [IPrAu(III)(Me$_4$-biphenyl)](HOTf)SbF$_6$ (compound 7) was observed in 5 min at room temperature. When replacing AgSbF$_6$ with AgOTf, the oxidative addition was complete after 6 h, giving [IPrAu(III)(Me$_4$-biphenyl)]OTf (compound 12). The longer reaction time required in the presence of the more coordinating anion is consistent with the hypothesis that coordination of biphenylene to a cationic coordinatively unsaturated Au(III) complex is the first step in the formation of the complex.

The thermodynamic driving force for this reaction comes from the cleavage of the strained biphenylene C–C bond (bond dissociation energy, BDE = 65.4 kcal mol$^{-1}$) via oxidative addition to Au(I), yielding two Au–C(Ar) bonds\cite{24,25}. This unprecedented C–C bond cleavage by the linear IPrAu(I) cationic complex represents a facile approach for generating strong Au–C(Ar) bonds en route to stable Au(III) complexes. Treatment of 5 with $^7$Bu$_4$NCl in dichloromethane resulted in the coordination of chloride and yielded IPrAu(III)(biphenyl)Cl (compound 3) as a pale yellow powder in 80% isolated yield after column chromatography (Fig. 2).

An X-ray crystal structure of 3 reveals a C$_2$-symmetric distorted square-planar complex with one IPr carbene ligand, one chloride and two cyclometallation bonds from the biphenyl ligand defining the $d^8$ Au(III) geometry shown in Fig. 2. The Au–C bond distances in the gold-biphenyl of 2.028(12) Å and 2.046(11) Å, respectively, are shorter than the gold–carbon bond length of 2.117(11) Å (see Supplementary Information). These relatively short bond distances exhibit the strong bonding energy between high-oxidation-state Au(III) and its ligands. Consistent with our hypothesis, introduction of the cyclometallated biaryl ligand and one N-heterocyclic carbene ligand stabilized this high-oxidation-state Au(III) complex. The air- and moisture-stable complex 3 could be isolated and stored on the benchtop without any decomposition. Reaction of 3 with one equivalent of AgSbF$_6$ caused immediate precipitation of AgCl in CH$_2$Cl$_2$ and the formation of 5 as observed by $^1$H NMR. This feature allows 3 to be used as a stable precatalyst of cationic Au(III).

To gain more insight into the coordination chemistry of the cationic Au(III) complex with oxygen-based ligands, treatment of complex 5 with 1.1 equivalents of N,N-dimethylformamide (DMF) led to a substantial boost in stability, and allowed the isolation of [IPrAu(III)(biphenyl)(Me$_2$N[C(O)H])][SbF$_6$] (compound 6) via coordination of a lone pair of electrons on the carbonyl oxygen. As shown by the crystal structure of compound 6 (Fig. 2), the IPr, biphenyl and DMF ligands enforce a distorted square-planar geometry around the Au(III) centre, with the oxygen atom of DMF at a distance of 2.140(3) Å from the centre. This finding suggests that the IPrAu(III)(biphenyl) cation exhibits a relatively hard, oxophilic Lewis-acidity, which is complementary to the soft Lewis acidity of cationic L-Au(I) complexes. This was further exemplified by measuring the Lewis acidities of 1 and 3 using the Gutmann–Beckett method (see Supplementary Information and Supplementary Fig. 3). The DMF in 6 is located in the pocket created by the IPr and biphenyl ligands. This environment is substantially more crowded than that observed in the linear IPrAuCl complex and effectively shields the DMF carbonyl group. The structural and electronic observations gained from this structure suggested a possible catalytic application of the IPrAu(III)(biphenyl) cation in selective 1,4-additions to $\alpha$-$\beta$-unsaturated aldehydes.

**Gold(III) complexes as selective Lewis-acid catalysts**

Lewis-acid-catalysed 1,4-additions to $\alpha$-$\beta$-unsaturated aldehydes remain challenging because 1,2-additions generally predominate\cite{26,27,28}. Yamamoto and colleagues have reported a unique strategy for Lewis-acid-promoted 1,4-addition to a $\alpha$-$\beta$-unsaturated aldehyde using aluminum reagents with sterically demanding ligands\cite{29}. Although excellent 1,4-selectivity is obtained, stoichiometric amounts of Lewis acid appear to be necessary.

To obtain preliminary information regarding the reactivity of complex 5 prepared from 3 in Lewis-acid catalysis, we initiated our experimental efforts by studying the Mukaiyama–Michael reaction with cinnamaldehyde and ketene silyl acetal (compound 8) under ambient reaction conditions. As an initial result, the 1,4-adduct was obtained as the major product (1,4-/1,2-adduct = 75/25) in 98% NMR yield when catalysed by IPrAu(III)(biphenyl)(SbF$_6$) (see Supplementary Information and Supplementary Table 2). Replacing AgSbF$_6$ with AgOTf gave a 1,4-selectivity exclusively and the product was isolated in 76% yield (1,4-/1,2-adduct = 98/2; Fig. 3a). With the optimized conditions in hand, silyl nitronate (compound 9) was examined as nucleophile instead of 8. The corresponding $\gamma$-nitro aldehyde was isolated in 78% yield with excellent selectivity (Fig. 3b).

Employing trans-$\alpha$-hexenal (compound 18a) as an aliphatic substrate also yielded the corresponding 1,4-adducts with good yield and excellent regioselectivity (Fig. 3a,b). Additionally, the catalyst loading could be decreased to 5 mol% without any loss of yield or selectivity. 10a was isolated in 77% yield with 1,4-/1,2-adduct > 98/2 (see Supplementary Information, Supplementary Table 2). The cationic IPrAu(III)(biphenyl) complex was essential for 1,4-selectivity in these reactions; in control experiments, the corresponding 1,2-adduct was mainly obtained using IPrAu(OTf) and no product was obtained with Ag(OTf) alone. To maximize the convenience and accessibility of our new catalyst, we examined the possibility of *in situ* generation of the IPrAu(III) cation via oxidative addition with biphenylene, followed by its utilization as a catalyst in one-pot reactions (Fig. 3c). Indeed, combining IPrAu(III)Cl, AgOTf, and Me$_2$-biphenylene (30 mol%) led to the formation of the active catalyst IPrAu(III)(Me$_2$-biphenyl)OTf (compound 12) within 1 h. Subsequent addition of cinnamaldehyde and ketene silyl acetal (8) led to the desired Mukaiyama–Michael adduct in 72% yield (1,4-/1,2-adduct = 98/2). Notably, the reactions do not suffer from using an *in situ* generated catalyst as opposed to a preformed Au(III) complex. This flexibility illustrates the power of using biphenylene to generate the Au(III) catalyst: other oxidizing agents are completely incompatible with the sensitive ketene silyl acetal and aldehyde functionalities. As an illustration, replacement of biphenylene with Br$_2$ or PhICl$_2$ for the oxidation of IPrAu(I)SbF$_6$ yielded no 1,2-/1,4-adducts in the Mukaiyama–Michael reaction, and only 8% conversion to the 1,2-adduct was obtained with XeF$_2$ (Fig. 3c).

The ability to generate the Au(III) catalyst in *in situ* under mild conditions suggested the possibility of performing successive Au(I)- and Au(III)-catalysed reactions in a single pot. Thus, we explored a one-pot tandem reaction starting from propargyl alcohol (compound 13 in Fig. 3d). First, the IPrAu(I)SbF$_6$ catalysed Meyer–Schuster rearrangement of propargyl alcohol (13) gave an unsaturated aldehyde. Subsequent oxidative addition of biphenylene afforded the IPrAu(III) cation 5, which catalysed the Mukaiyama–Michael addition of ketene silyl acetal (8) to provide the final product in 57% overall yield (1,4-/1,2-adduct = 98/2). The ability to carry out two distinct reactions with catalysts of different oxidation state originating from a single precursor is a remarkable feature of the newly developed methods.

Furthermore, a successive Au(III)-catalysed ring-opening and Mukaiyama–Michael reaction was conducted. In the first step, 5 activated the ring-opening of the cyclopropene 14, which reacted with furan, to form a functionalized conjugated trienal (Fig. 3d). After removal of the excess furan, 5 catalysed the Mukaiyama–Michael addition of 8 to obtain the final product in 53% isolated yield (>98% 1,4-selectivity).

To demonstrate the generality of this Au(III) catalyst for obtaining remote selectivity, we next performed 1,6-selective thiol addition and reduction reactions of $\alpha$-$\beta$-$\gamma$-$\delta$-diunsaturated aldehydes. We hypothesized that the bulky catalyst ‘aldehyde pocket’ should partially shield the proximal double bond, thus promoting nucleophilic addition at the $\gamma$-$\delta$-double bond. 1,6-additions to $\alpha$-$\beta$-$\gamma$-$\delta$-diunsaturated aldehydes are challenging and especially thiol additions and Hantzsch-ester-mediated reductions are known to proceed with low selectivity to provide a mixture of products\cite{30,31}. ©2015 Macmillan Publishers Limited. All rights reserved
For the thiol addition (Fig. 4a), 1,6-addition of naphthalene thiol to 16b and subsequent oxidation was carried out. With the use of 10 mol% 3 and AgSbF₆, the oxidized 1,6-addition product 17 was obtained with 64% yield and exclusive 1,6-selectivity in the presence of TBHP (tert-butyl hydroperoxide) as an oxidant. For the reduction reaction with Hantzsch ester (Fig. 4a), catalyst 5 also demonstrated excellent selectivity for the remote reduction of α,β,γ,δ-diunsaturated aldehydes 16 to give the α,β-unsaturated aldehydes 18, further showcasing the unique regioselectivity obtained with the Au(III) catalyst compared to traditional Lewis- and Brønsted-acid catalysts (see Supplementary Information and Supplementary Table 5 and refs 32–34, for example).

Moreover, we also performed the Diels–Alder reaction of 2,4-hexadienal and cyclopentadiene (see Supplementary Information and Supplementary Table 3), further illustrating the novel reactivity of this Au(III)-based catalytic system. Furthermore, in situ generation of Au(III) catalyst from Au(I) (Figs 3c and 4b) was also used for the Diels–Alder reaction. Several substrates were shown to provide products in good yield and excellent regioselectivity. The products was isolated in up to 92% yield exclusively as the 1,4-adduct (Fig. 5).

Whereas [2 + 2] cycloadditions of α,β-unsaturated carbonyl compounds and allenes have been carried out with photochemical conditions ⁴¹, there are no examples of Lewis-acid catalysis performing such reactions. Therefore, we next attempted to carry out the intramolecular [2 + 2] cycloaddition of the cis-unsaturated aldehyde-allene 20 (Fig. 5). When 3 with AgSbF₆ was employed, only the [2 + 2] cycloadduct was obtained in 70% yield (cis: trans = 89:11). Investigations showed that...
neither IPrAu(i)(SbF$_6$)$_2$, Ag(SbF$_6$)$_2$, MeAlCl$_2$, hv (irradiation by Hg vapour lamp) nor organocatalysts catalysed the [2 + 2] cycloaddition (see Supplementary Information and Supplementary Table 4); as such, this [2 + 2] cycloaddition is an unprecedented reaction unique to the developed Au(III) catalytic system.

The solid-state structure of the key intermediate [IPrAu(i)(biphenyl) (η$_3$-cinnamaldehyde)][SbF$_6$]$_2$ (compound 22) was determined by X-ray crystallography, as illustrated in Fig. 6. This Au(III)–cinnamaldehyde complex displays a distorted square-planar geometry with a η$_3$-coordination cinnamaldehyde. The s-trans-cinnamaldehyde is buried in the pocket created by the IPr and biphenyl ligands. One of the 2,6-disopropyl phenyl units is tilted away from the cinnamaldehyde plane owing to steric hindrance. As a result, the carbonyl moiety is effectively shielded from nucleophilic attack and thus the IPrAu(i)(biphenyl) cation exhibits excellent remote selectivity as a catalyst for conjugate addition reactions of unsaturated aldehydes.

**Conclusion**

Exploration of the unique catalytic abilities of high-valent late transition metals has been hampered by difficulties in accessing stable complexes with well controlled reactivity. Nowhere is this more evident than in the case of Au(iii), which lags in its infancy compared to the ever-expanding field of Au(i) catalysis. In sharp contrast to previous methods for accessing Au(iii), which rely on strong halogen-based oxidants, we have discovered that stable and catalytically active Au(III) complexes can be obtained by the mild oxidative addition of biphenylene to cationic IPrAu(i). Although oxidative additions with Au(i) have been previously viewed as kinetically challenging, this carbon–carbon bond cleavage proceeds under surprisingly mild reaction conditions, even when compared to previously reported oxidative additions of biphenylene. The resulting IPrAu(iii)(biphenyl) catalyst shows good reactivity as a hard Lewis–acid catalyst, which is complementary to the soft Lewis acidity exhibited by Au(i)-catalysts.

The catalytic reactivity is exemplified by six reactions of unsaturated aldehydes.

**Figure 4** | Remote selectivity in Au(I)-catalysed additions to dienals. a, δ-selective thiol addition and reduction reactions. Et, ethyl; cat, catalyst. b, γ, δ-selective Diels–Alder reaction and in situ generation of the IPrAu(iii)(biphenyl) catalyst for Diels–Alder reactions.

**Figure 5** | Au(III)-catalysed [2 + 2] cycloaddition of an allene-aldehyde.
exhibit harsh, nonselective acidity\(^\text{16}\), these new catalysts possess intermediate reactivity and a sterically defined binding pocket. The ligand environment of the new catalysts, characterized by X-ray crystallography, imparts precise 1,4- over 1,2-selectivity in the case of the Michael addition, \(\delta\)-selectivity in the thiol addition and reaction reactions as well as \(\gamma,\delta\)-selectivity in the Diels–Alder reactions of dienes.

None of these reactions are feasible with Au(I)-based catalysts or traditional bulky Lewis- and Bronsted-acid catalysts (see Supplementary Information and Supplementary Table 5 and refs 32–34, for example). Furthermore, the catalysts can be generated \textit{in situ} from commercially available reagents, thereby eliminating the need for specialized organometallic techniques. The mild nature of the oxidation from Au(I) to Au(III) even permits successive Au(I)- and Au(III)-catalysed reactions in a single reaction vessel. In other words, one can take a single precursor and switch between two different reaction manifolds by simple \textit{in situ} catalyst modification. In view of all these features, the methods presented here should aid in unlocking the potential of high-oxidation-state gold catalysis.

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