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Stable Gold(III) Catalysts by Oxidative Addition of a Carbon-Carbon Bond

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Abstract

Whereas low-valent late transition metal catalysis has become indispensable for chemical synthesis, homogeneous high-valent transition metal catalysis is underdeveloped, mainly due to the reactivity of high-valent transition metal complexes and the challenges associated with synthesizing them. In this manuscript, we report a mild carbon-carbon bond cleavage reaction by a Au(I) complex that generates a stable Au(III) cationic complex. Complementary to the well-established soft and carbophilic Au(I) catalyst, this Au(III) complex exhibits hard, oxophilic Lewis acidity. This is exemplified by 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 in this study provide a strategy for accessing high-valent transition metal catalysis from readily available precursors.

Transition metal catalysis has been developed into an efficient and selective strategy for organic transformations in modern chemistry. Low-valent late transition metal complexes enjoy particularly heavy use due to their stability and usefulness in forming important chemical bonds (C-C, C-O, C-N). However, low oxidation state, late metals struggle with other critical reactions including electrophilic C-H functionalization^{1, 2}. Recent efforts have begun to unlock the potential of high-valent late transition metals, especially Pd(IV), to complement these shortcomings^{3–6}. The major challenges thus far include the typical need for strong oxidants to access the high oxidation state, which limits the functional group tolerance, and the instability of the oxidized metal complexes, which often exist only as

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Author Contributions C.-Y.Wu initiated and developed the organometallic study. C.-Y.Wu and T.H. developed the Lewis acid catalysis. C.-Y.Wu, T.H. and C.B.J. optimized the Lewis acid catalysis study. C.-Y.Wu, T.H. and C.B.J. performed the experiments. C.-Y.Wu, T.H. and C.B.J. and F.D.T wrote the manuscript.

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high-energy intermediates on the catalytic cycle (Fig. 1a). Put broadly, in order to fully explore the undoubtedly rich chemistry of high valent late metals, it will be essential to develop easily prepared, stable, tunable catalysts.

In this regard, we have searched for a route to stable, catalytically active Au(III) complexes with the goal of complementing the ever-increasing library of Au(I)-catalyzed reactions. Whereas homogeneous Au(I) catalysis has seen great progress over the last decade^{7–11}, 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 intrinsic high redox potential, leading to facile reduction of Au(III) complexes to Au(I) or metallic Au(0) species in the presence of electron-rich reagents^{13–18}. In cases where the ligands are capable of stabilizing the highly oxidizing metal, the resulting complex is often rendered catalytically inert. For example, the oxidative addition product, L-AuX₃, formed from L-AuX (X = halogen) is a poor catalyst by itself, and the abstraction of a halide to increase reactivity enables a facile reduction to the lower oxidation states^{15, 16}. Moreover, while complexes of the type Au(III)(C^ΛL)(X)(Y) are available through multi-step synthetic sequences^{19–21}, their instability in the cationic form and the difficulties in readily tuning the coordination environment has severely limited their applications in catalysis.

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.

Based on the reported examples²², we reasoned that the transmetalation of Sn(biphenyl)(^tBu)₂ 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 NHCs (*N*-heterocyclic carbenes) inspired us to examine them as supporting ligands²³. In an effort to access such compounds, attempts to perform the transmetalation of Sn(biphenyl)(^tBu)₂ to IPr-AuCl₃ (**2**) (IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]) gave us no desired product (Fig. 2). Although the replacement of IPrAuCl₃ with (THT)AuCl₃ (THT = tetrahydrothiophene) 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^{24–26} (Fig. 1b). The concept was appealing for its simplicity, 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(II) intermediates^{18, 27–28} or complexes with specially designed ligands^{29–30}. 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 IPrAuCl with AgSbF₆ resulting in the precipitation of AgCl in CD₂Cl₂ at room temperature. Reaction of the resulting electrophilic IPrAu(I)(SbF₆) species with biphenylene resulted in the immediate and quantitative

formation of the coordination complex, (IPrAu-biphenylene)(SbF₆) **4** (Fig. 2), along with a small amount of the Au(III) aqua complex, [IPrAu(III)(biphenyl)(H₂O)]SbF₆ **5**, both of which were observed by ¹H nuclear magnetic resonance (NMR) spectroscopy³¹. Nearly full conversion of the Au(I) cationic species to the desired Au(III) complex **5** was observed after 1.5 hours (see Supplementary Information, Figure S1 and Table S1). In contrast, most reported examples of this type of C-C bond cleavage requires more redox-active metals (e.g. Rh, Ir, Ni, Ru, Fe) and have been carried out under harsh reaction conditions^{24, 25}, suggesting that the sterically unencumbered cationic IPrAu(I) complex might enjoy a comparatively fast rate of coordination and subsequent oxidative addition.

The oxidative addition of IPrAu(I)SbF₆ with the more electron-rich 2,3,6,7-tetramethylbiphenylene (Me₄-biphenylene) was also examined. Full conversion to [IPrAu(III)(Me₄-biphenyl)(H₂O)][SbF₆] **7** was observed in 5 min at room temperature. When replacing AgSbF₆ with AgOTf, the oxidative addition was complete after 6 hours to give [IPrAu(III)(Me₄-biphenyl)OTf] **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(I) complex is the first step in the formation of **5**. The thermodynamic driving force for this reaction comes from the cleavage of the strained biphenylene C-C bond (BDE = 65.4 kcal/mol) via oxidative addition to Au(I) yielding two Au-C(Ar) bonds^{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 ⁿBu₄NCl in dichloromethane resulted in the coordination of chloride and yielded IPrAu(III)(biphenyl)Cl **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_s-symmetric distorted square-planar complex with one IPr carbene ligand, one chloride and two cyclometalation bonds from the biphenyl ligand defining the d⁸ Au(III) geometry shown in Fig. 2. The Au-C bond distances of the gold-biphenyl, Au(1)-C(1) and Au(1)-C(12), are 2.028(12) and 2.046(11) Å, respectively, are shorter than the gold-carbene bond length of 2.117(11) Å (see Supplementary Information). The relatively short bond distances exhibit the strong bonding energy between high oxidation Au(III) and its ligands. Consistent with our hypothesis, introduction of the cyclometallated biaryl ligand and one NHC 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 1 equiv. of AgSbF₆ caused immediate precipitation of AgCl in CD₂Cl₂ and the formation of **5** as observed by ¹H NMR. This feature allows **3** to be used as a stable precatalyst of cationic Au(III).

To gain more insight on the coordination chemistry of cationic Au(III) complex with oxygen-based ligands, treatment of complex **5** with 1.1 equiv. of *N,N*-dimethylformamide (DMF) led to a substantial boost in stability, and allowed the isolation of [IPrAu(III)(biphenyl)(Me₂NC(O)H)][SbF₆] **6** via coordination of a lone pair of electrons on the carbonyl oxygen. As shown by the crystal structure of complex **6** (Fig. 2), the IPr, biphenyl and DMF ligands enforce a distorted square planar geometry around the Au(III) center, with the oxygen coordination from DMF in a distance of 2.140(3) Å. 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 LAu(I) complexes. This was further exemplified by measuring the Lewis acidities of **1** and **3** by the Gutmann-Beckett method (see Supplementary Information, Figure S3). The DMF in **6** is located in the pocket created by the IPr and biphenyl ligands. This environment is substantially more crowded than 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 α,β -unsaturated aldehydes.

Lewis acid-catalyzed 1,4-additions to α,β -unsaturated aldehydes remain challenging as 1,2-additions generally predominate^{32–34}. Yamamoto and colleagues have reported a unique strategy for Lewis acid promoted 1,4-addition to a α,β -unsaturated aldehyde using aluminum reagents with sterically demanding ligands³⁵. 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 **8** under ambient reaction condition. As an initial result, 1,4-adduct was obtained as the major product (1,4-/1,2-adduct = 75/25) in 98% NMR yield when catalyzed by IPrAu(III)(biphenyl)(SbF₆) (see Supplementary Information, Table S2). Replacing AgSbF₆ with AgOTf gave 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 **9** was attempted as nucleophile instead of **8**. The corresponding γ -nitro aldehyde was isolated in 78% yield with excellent selectivity (Fig. 3b). Employing *trans*-2-hexenal **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, Table S2). 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(I)(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(I)Cl, AgOTf, and Me₄-biphenylene (30 mol%) led to the formation of active catalyst IPrAu(III)(Me₄-biphenyl)(OTf) **12** within 1 hour. Subsequent addition of cinnamaldehyde and silyl ketene 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 *in situ* generated catalyst as opposed to 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 silyl ketene acetal and aldehyde functionalities. As an illustration, replacement of biphenylene with Br₂ or PhICl₂ for the oxidation of IPrAu(I)SbF₆ yielded no 1,2-/1,4-adducts in the Mukaiyama–Michael reaction, and only 8% conversion to the 1,2-adduct was obtained with XeF₂ (Fig. 3c).

The ability to generate the Au(III) catalyst *in situ* under mild conditions further suggested to us the alluring possibility of performing successive Au(I)- and Au(III)-catalyzed reactions in a single pot. Thus, we explored a one-pot tandem reaction starting from propargyl alcohol **13** (Fig. 3d). First, the IPrAu(I)(SbF₆) catalyzed Meyer–Schuster rearrangement of propargyl alcohol **13** gave an unsaturated aldehyde. Subsequent oxidative addition of biphenylene afforded the IPrAu(III) cation **5**, which catalyzed the Mukaiyama–Michael addition of silyl ketene 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 different oxidation state catalysts originating from a single precursor is a remarkable feature of the newly developed methods.

Furthermore, a successive Au(III)-catalyzed 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)³⁶. After removal of the excess furan, **5** catalyzed 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 γ,δ -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.^{37, 38}

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 as an oxidant. For the reduction reaction with Hantzsch ester (Fig 4a), catalyst **5** also demonstrated excellent selectivity for the remote reduction of $\alpha,\beta,\gamma,\delta$ -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 bulky Lewis and Brønsted acid catalysts (See Supplementary Information, Table S5 and e.g. ref. 32–34).

Moreover, we also performed the Diels–Alder reaction of 2,4-hexadienal **16** with cyclopentadiene³⁹. Only the γ,δ -functionalized product **19a** was obtained in 85% yield (*endo:exo* = 88:12) employing IPrAu(III)(biphenyl)(NTf₂) as catalyst (Fig. 4b). γ,δ -selective Diels–Alder reactions are unprecedented since α,β -selectivity normally predominates in such Lewis acid catalyzed reactions⁴⁰. Notably, neither IPrAu(I)(NTf₂), Ag(NTf₂) nor organocatalysts provided any product with **16a** and cyclopentadiene (see Supplementary Information, Table S3) further illustrating the novel reactivity of this gold(III)-based catalytic system. Furthermore, *in situ* generation of Au(III) catalyst from Au(I) (Fig 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 γ,δ -adducts with a *endo:exo* of up to 86/14 employing [IPrAu(III)(biphenyl)(H₂O)]SbF₆ generated *in situ* from IPrAu(I)(SbF₆) and biphenylene.

To increase the practicality of the developed procedure we also showed that the amount of biphenylene oxidant can be lowered to 15 mol% (1.5 equivalents as compared to Au(I)). Using these conditions, the *in situ* formed Au(III) catalyst produced product **19b** without significant decline in yield and selectivity.

Whereas [2 + 2] cycloadditions of α,β -unsaturated carbonyl compounds and allenes have been carried out with photochemical conditions⁴¹ there are no examples of Lewis acid catalysis performing such reactions. Therefore, we next attempted to carry out the intramolecular [2 + 2] cycloaddition of *cis*-unsaturated aldehyde-allene **20** (Fig. 5). When **3** with AgSbF₆ was employed, only [2 + 2] cycloadduct was obtained in 70% yield (*cis* : *trans* = 89 : 11). Investigations showed that neither IPrAu(I)(SbF₆), Ag(SbF₆), MeAlCl₂, hv, nor organocatalysts catalyzed the [2 + 2] cycloaddition (see Supplementary Information, Table S4); 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(III)(biphenyl)(η^1 -cinnamaldehyde)] [SbF₆] **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^1 -coordination cinnamaldehyde. The *s-trans*-cinnamaldehyde is buried in the pocket created by the IPr and biphenyl ligands. One of the 2,6-diisopropyl phenyl units is tilted away from the cinnamaldehyde plane due to steric hindrance. As a result, the carbonyl moiety is effectively shielded from nucleophilic attack and by this means, the IPrAu(III)(biphenyl) cation exhibits excellent remote selectivity as a catalyst in additions to unsaturated aldehydes.

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). While oxidative additions with gold(I) have been previously viewed as kinetically challenging,⁴²⁻⁴³ this striking 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 α,β -unsaturated or $\alpha,\beta,\gamma,\delta$ -diunsaturated aldehydes: Mukaiyama–Michael additions, nitronate Michael additions, a thiol addition, Hantzsch ester reductions, Diels-Alder reactions and a [2 + 2] cycloaddition all proceed good yield and excellent selectivity. Whereas commonly employed Au(III) catalysts like AuCl₃ exhibit harsh, nonselective acidity⁴⁴, 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 exquisite 1,4- over 1,2-selectivity in the case of the Michael additions, δ -selectivity in the thiol addition and reduction reactions as well as γ,δ -selectivity in the Diels-Alder reactions of dienals. None of these reactions are feasible with gold(I)-

based catalysts nor traditional bulky Lewis and Brønsted acid catalysts (see Supplementary Information, Table S5 and e.g. ref. 32–34). Furthermore, the catalysts can be generated *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)-catalyzed reactions in a single reaction vessel. In other words, one can take a single precursor and switch between two different reaction manifolds by simple *in situ* catalyst modification. In view of all these features, the methods presented herein should aid in unlocking the potential of high oxidation state gold catalysis.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

Supplementary Material

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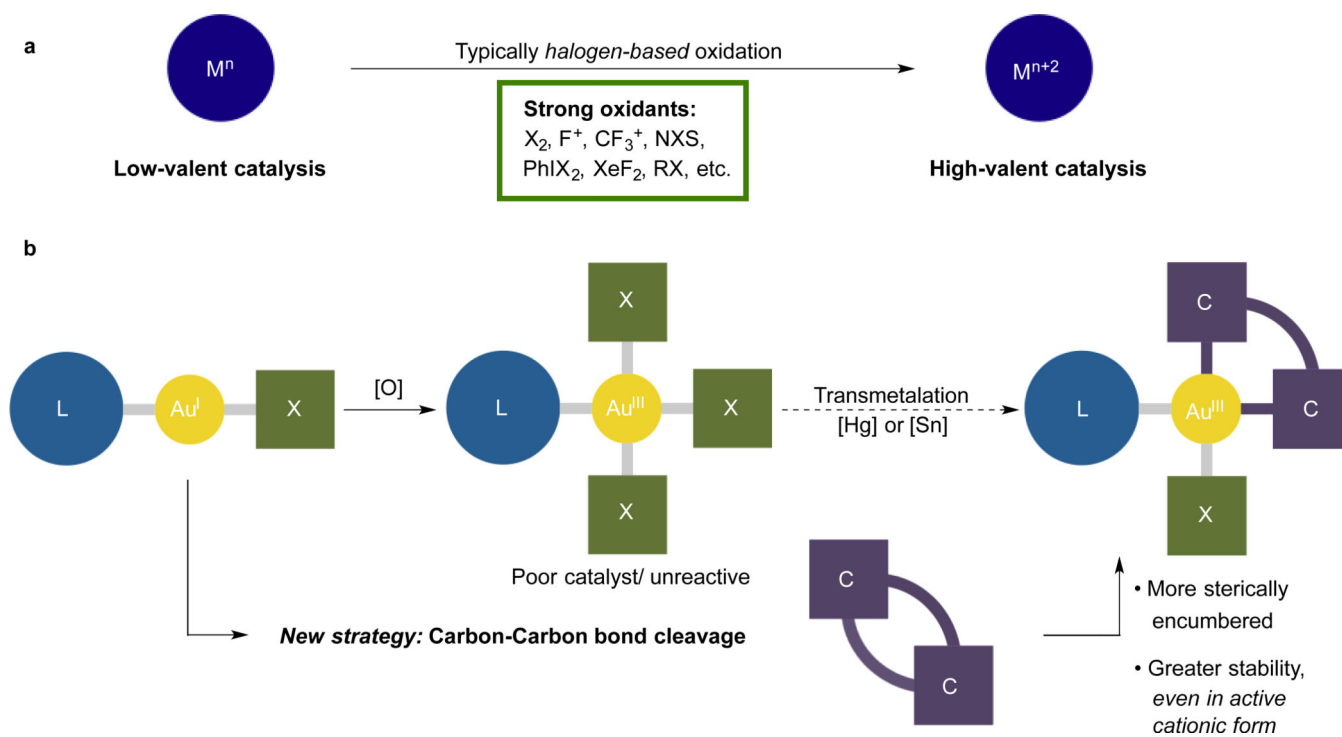


Figure 1. Routes to high-valent metal complexes

a. Standard route to high-valent metal complexes using halogen-based oxidants. **b.** Hypothetically synthetic pathway for accessing Au(III)-C bond-stabilized Au(III) complexes.

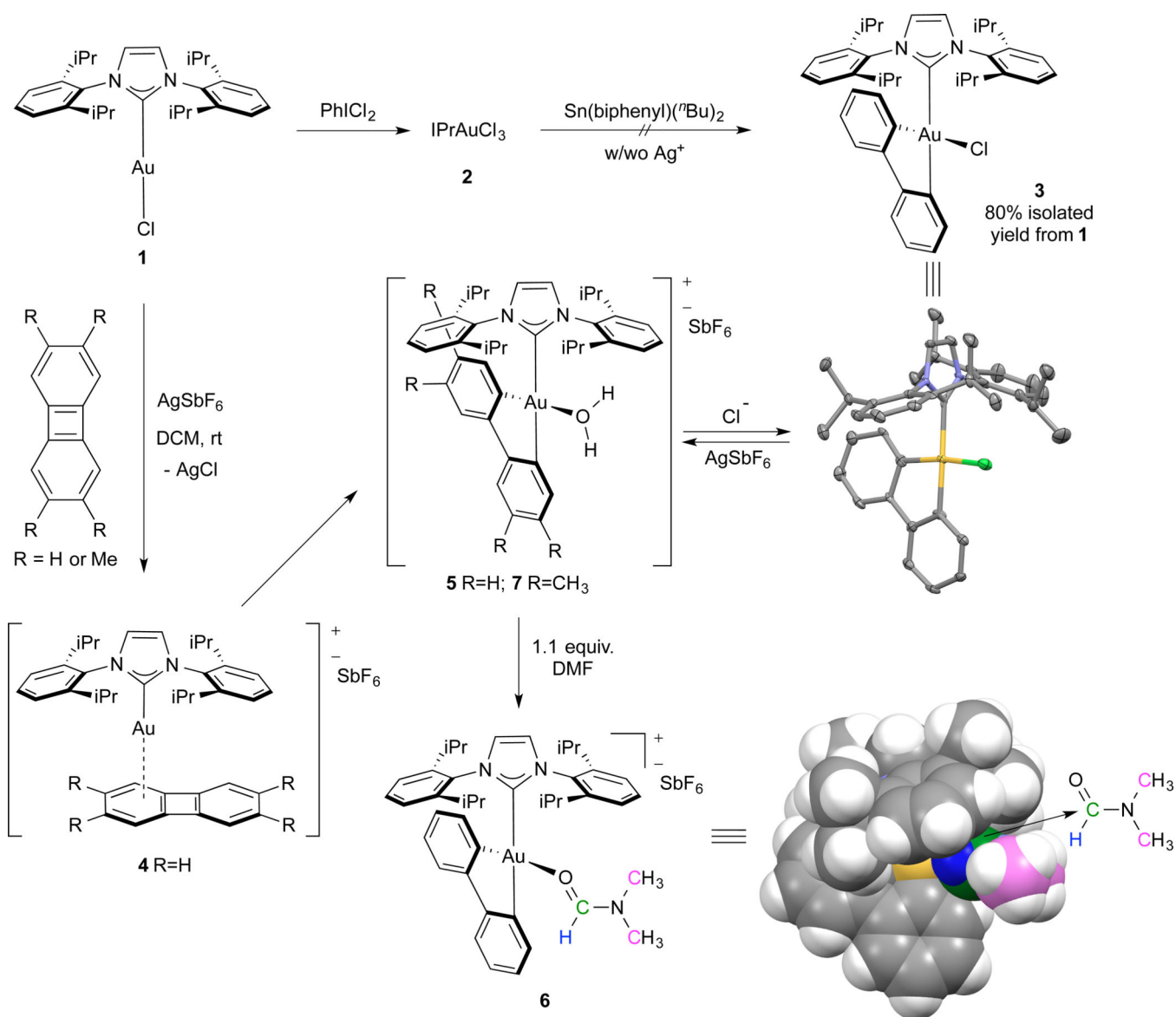


Figure 2. Accessing gold(III) via oxidative addition of a carbon-carbon bond

Attempted access to complex **3** via transmetalation of $\text{Sn(biphenyl)(}^t\text{Bu)}_2$ with IPrAuCl_3 **2**. Proposed pathway for the oxidative addition of IPrAu(I) complex with biphenylene/2,3,6,7-tetramethylbiphenylene. Coordination chemistry of $\text{IPrAu(III)(biphenyl)}$ complex **3** and **6**. X-ray structure of $\text{IPrAu(III)(biphenyl)Cl}$, complex **3** and $[\text{IPrAu(III)(biphenyl)(Me}_2\text{NC(O)H)}][\text{SbF}_6^-]$ complex **6**, SbF_6^- anion is omitted for clarity.

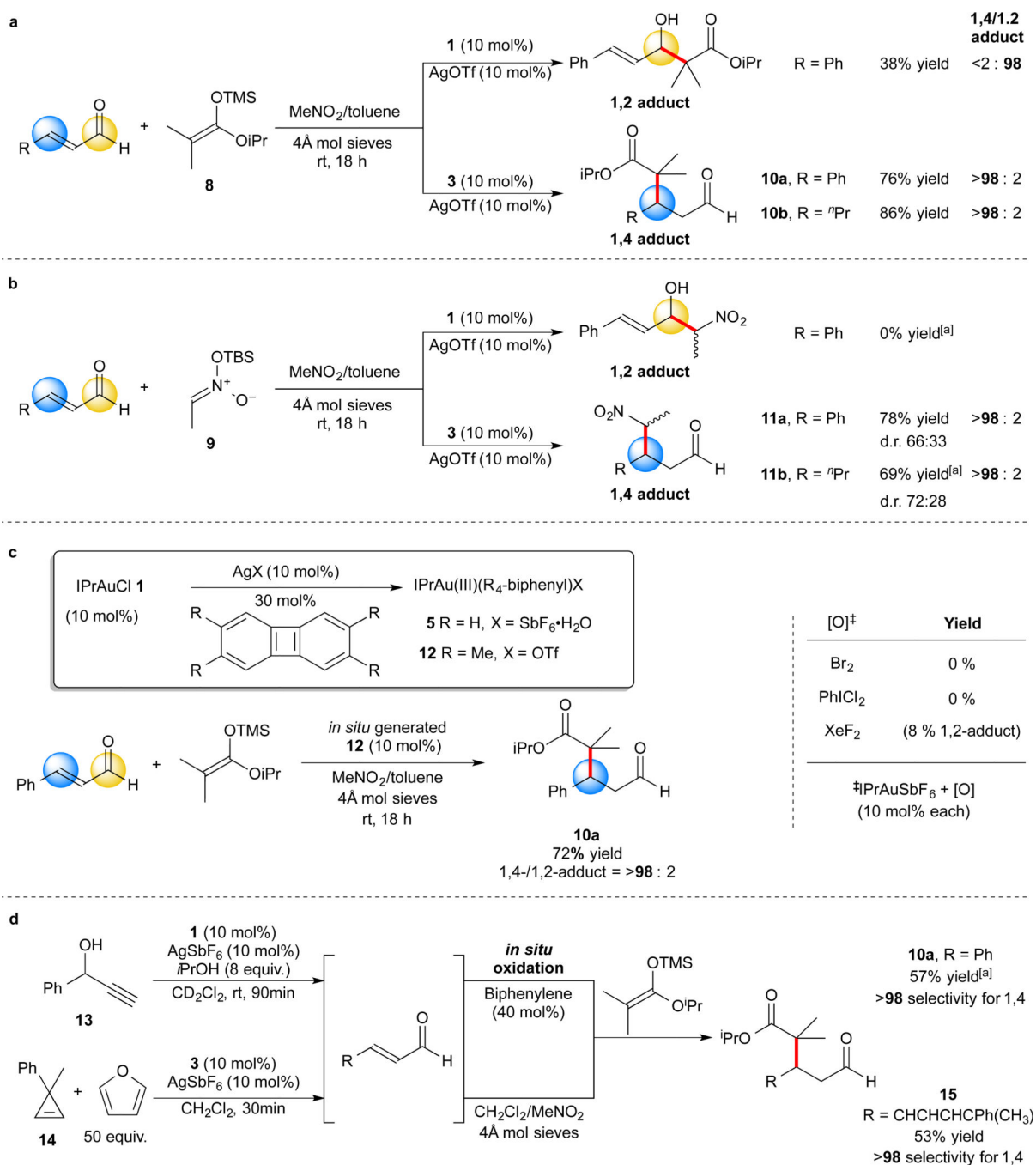


Figure 3. Examples of selective Au(III)-catalyzed 1,4-additions

a, Mukaiyama-Michael addition. **b**, Nitronate Michael-addition. **c**, *In situ* generation of IPrAu(III)(Me₄-biphenyl) catalyst for Mukaiyama-Michael addition. **d**, One-pot tandem Au(I)/Au(III) and Au(III)/Au(III)-catalyzed reactions. [a] NMR yield.

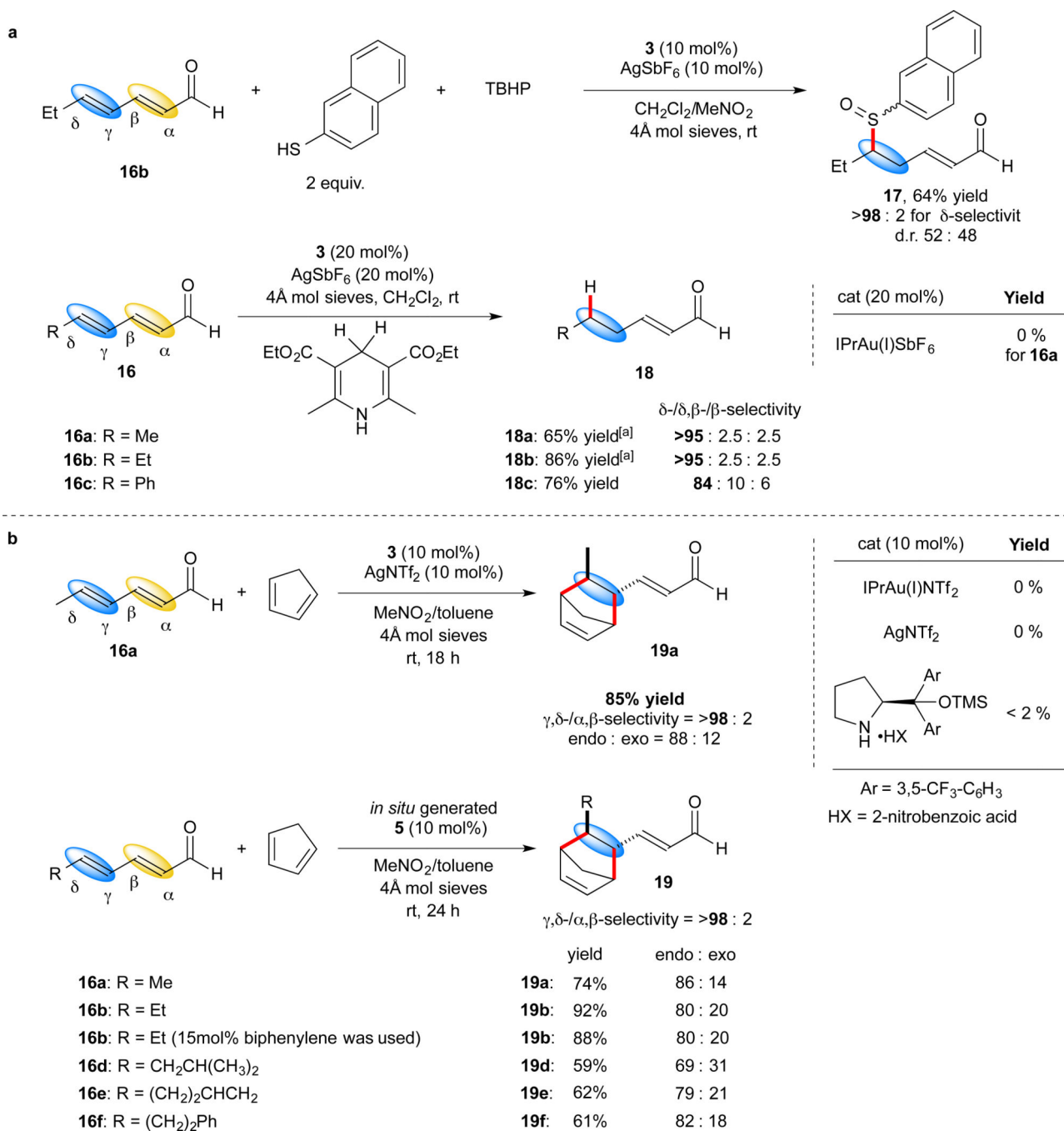


Figure 4. Remote selectivity in gold(III) catalyzed additions to dienals
a, δ-selective thiol addition and reduction reactions. **b**, γ, δ-selective Diels–Alder reaction and *in situ* generation of IPrAu(III)(biphenyl) catalyst for Diels–Alder reactions.

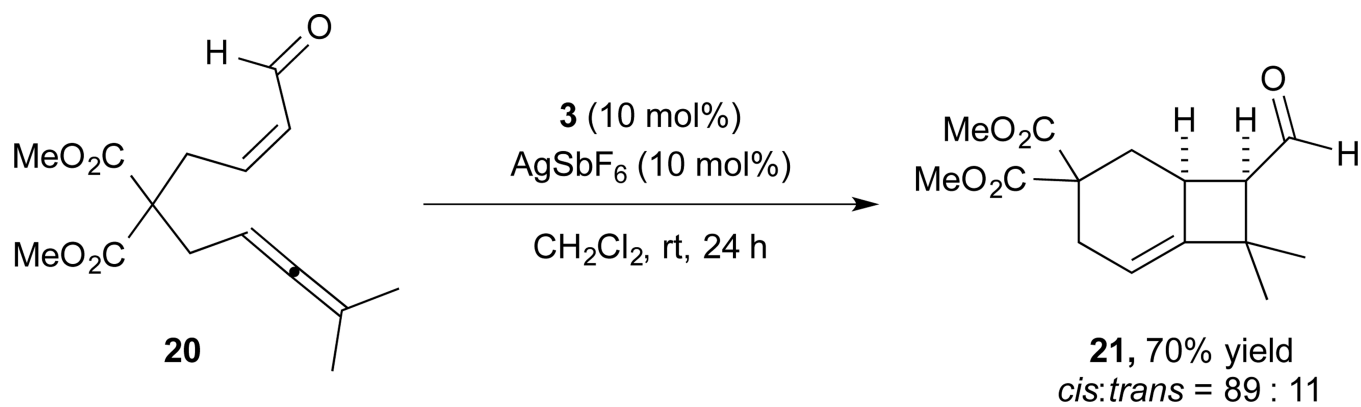


Figure 5. Gold(III) catalyzed [2 + 2] cycloaddition of an allene-aldehyde

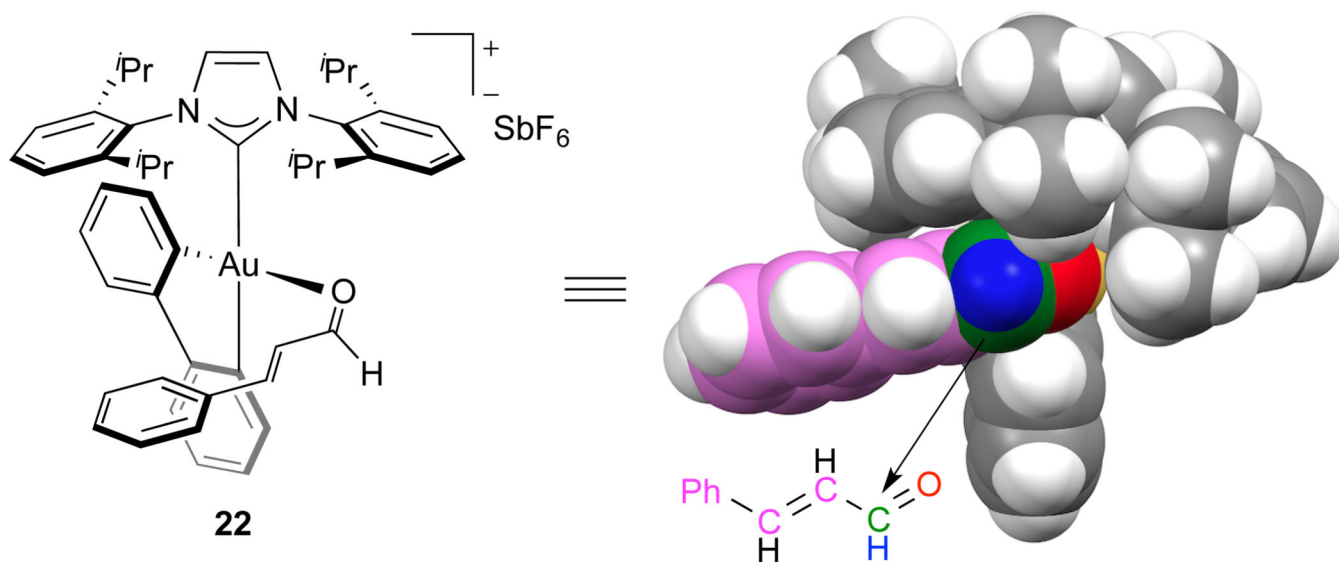


Figure 6. A model for the obtained selectivity

X-ray structure of [IPrAu(III)(biphenyl)(η^1 -cinnamaldehyde)][SbF₆] complex 22. SbF₆⁻ anion is omitted for clarity.