ARTICLE

doi:10.1038/nature14104

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

Chung-Yeh Wu[1]*, Takahiro Horibe[1]*, Christian Borch Jacobsen[1] & F. Dean Toste[1]

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 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 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 decade[7–11], Au(III) catalysis is still mainly limited to the use of inorganic Au(III) salts[12]. 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 reagents[13–18]. In cases where the ligands are capable of stabilizing the highly oxidizing metal, the resulting complex is often rendered

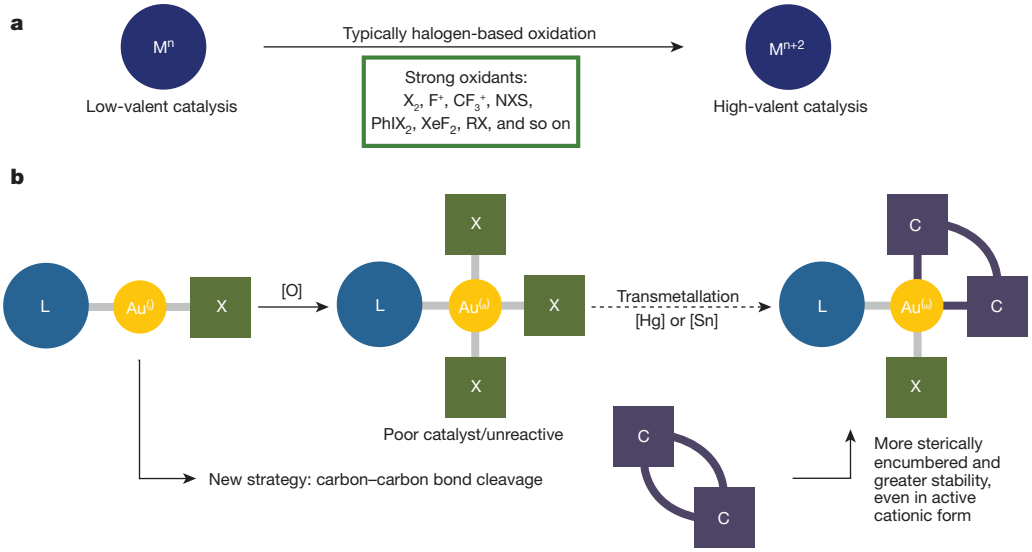

Figure 1 | Routes to high-valent metal complexes. **a**, Standard route to high-valent metal complexes using halogen-based oxidants. n, oxidation state; NXS, N-halosuccinimide; M, metal. **b**, Hypothetically synthetic pathway for accessing Au(III)–C bond-stabilized Au(III) complexes. X, heteroatom;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

[1]Department of Chemistry, University of California, Berkeley, California 94720, USA.
*These authors contributed equally to this work.

catalytically inert. For example, the oxidative addition product, L-AuX_3, 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[15,16]. 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[19–21], their instability in the cationic form and the difficulties in readily tuning the coordination environment has 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[22], we reasoned that the transmetallation of Sn(biphenyl)(^{n}Bu)$_2$ (where Bu is butyl) to L-AuX_3 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[23]. In an effort to access such compounds, attempts to perform the transmetallation of Sn(biphenyl)(^{n}Bu)$_2$ to IPr-$AuCl_3$ (compound **2**) (where IPr is [1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene]) gave no desired product (Fig. 2). Although the replacement of IPrAuCl_3 with (tetrahydrothiophene)AuCl_3 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 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(II) intermediates (for examples see ref. 27 and references therein, and refs 18 and 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)(SbF_6) was generated *in situ* by reacting IPrAuCl with $AgSbF_6$, resulting in the precipitation of AgCl in CD_2Cl_2 at room temperature. Reaction of the resulting electrophilic IPrAu(I)(SbF_6) species with biphenylene resulted in the immediate and quantitative formation of the coordination complex (IPrAu-biphenylene)(SbF_6) (compound **4** in Fig. 2), along with a small amount of the Au(III) aqua complex [IPrAu(III)(biphenyl)(H_2O)]SbF_6 (compound **5**), both of which were observed by ^{1}H nuclear magnetic resonance (NMR) spectroscopy[31]. 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

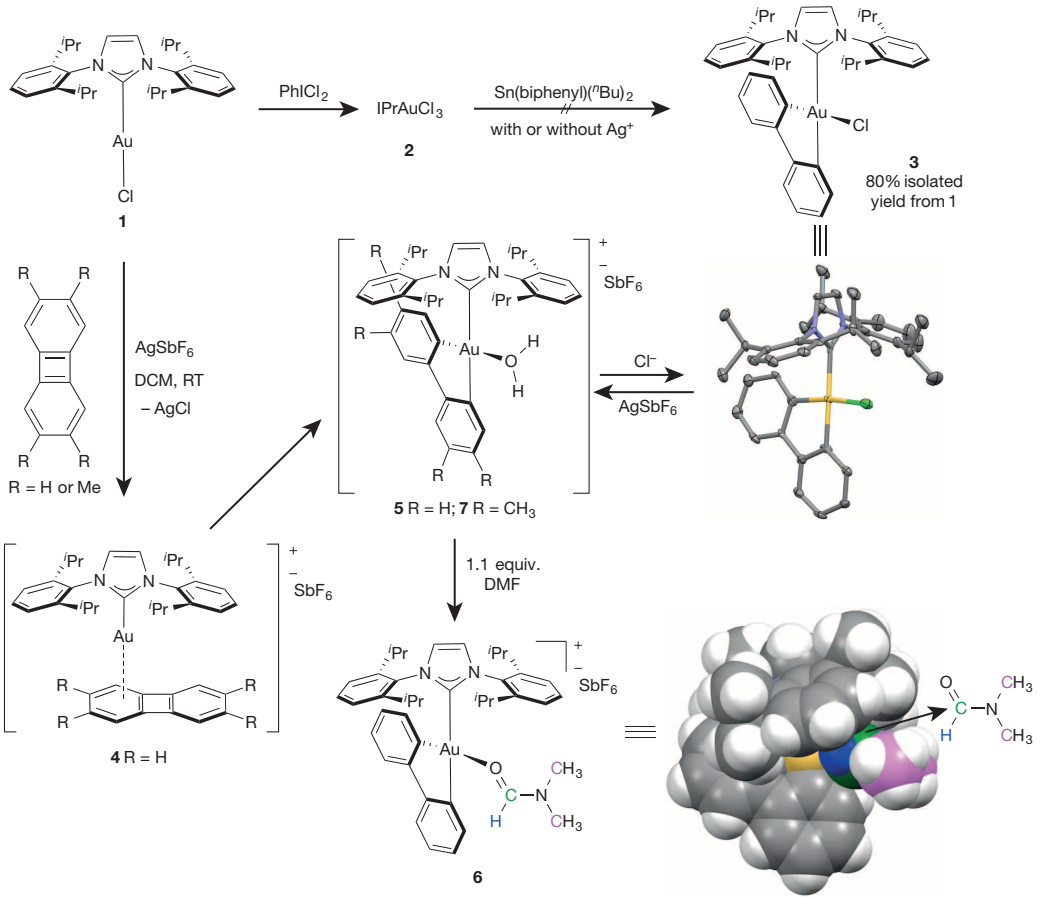

Figure 2 | Accessing Au(III) via oxidative addition of a carbon–carbon bond. Attempted access to complex **3** via transmetallation of Sn(biphenyl)(^{n}Bu)$_2$ with IPrAuCl_3 (compound **2**) is shown. (DCM, dichloromethane; RT, room temperature (approx. 23 °C); –AgCl, removal of AgCl). The proposed pathway for the oxidative addition of IPrAu(I) complex with biphenylene/2,3,6,7-tetramethylbiphenylene is shown. The coordination chemistry of IPrAu(III)(biphenyl) complexes **3** and **6** is shown. The X-ray structures of IPrAu(III)(biphenyl)Cl (complex **3**) and [IPrAu(III)(biphenyl)($Me_2NC(O)H$)][SbF_6] (complex **6**) are shown; the SbF_6^- anion is omitted for clarity. In the crystal structure of **3**: gold, Au; green, Cl; blue, N; grey, C; H is omitted for clarity. In the space-filling model of **6**: gold, Au; green, the specified carbonyl carbon; pink, the specified carbons; blue, the specified hydrogen; grey, all other carbons; white, all other hydrogens. 'equiv.', equivalents. ^{n}Bu, normal butyl; ^{i}Pr, isopropyl.

redox-active metals (such as Rh, Ir, Ni, Ru and Fe) and have been carried out under harsh reaction conditions[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)(H_2O)][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(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 (bond dissociation energy, BDE = 65.4 kcal mol^{-1}) 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 $^nBu_4NCl$ 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_s-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–carbene 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 CD_2Cl_2 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 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)($Me_2NC(O)H$)][SbF_6] (compound **6**) via coordination of a lone pair of electrons on the carbonyl oxygen. As shown by the crystal structure of complex **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 α,β-unsaturated aldehydes.

Gold(III) complexes as selective Lewis-acid catalysts

Lewis-acid-catalysed 1,4-additions to α,β-unsaturated aldehydes remain challenging because 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 aluminium reagents with sterically demanding ligands[35]. 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 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 γ-nitro aldehyde was isolated in 78% yield with excellent selectivity (Fig. 3b). Employing *trans*-2-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(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 Me_4-biphenylene (30 mol%) led to the formation of the active catalyst IPrAu(III)(Me_4-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 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.

Futhermore, 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)[36]. 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 α,β,γ,δ-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 α,β,γ,δ-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].

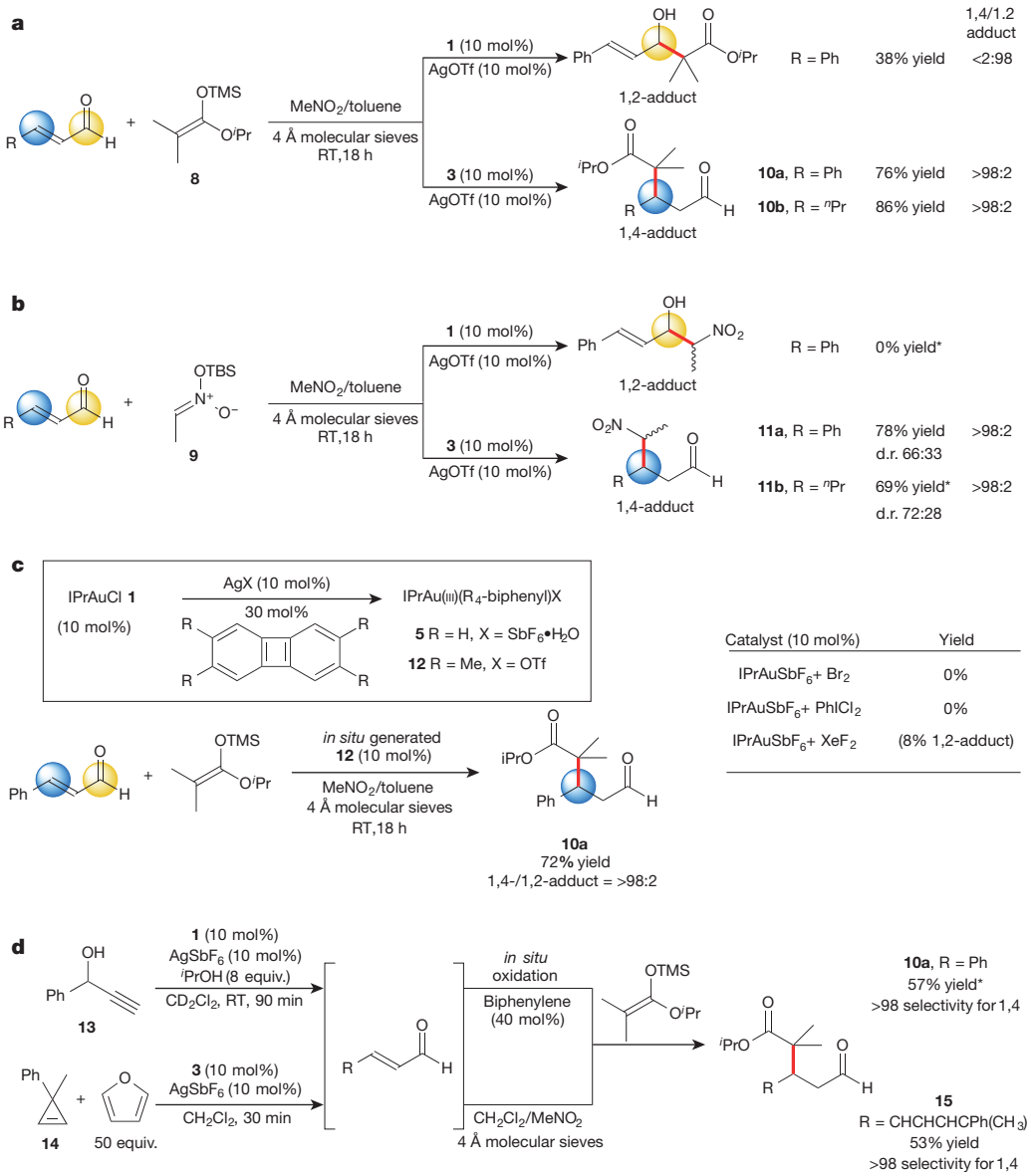

Figure 3 | Examples of selective Au(III)-catalysed 1,4-additions. **a**, Mukaiyama–Michael addition. Tf, trifluoromethanesulfonate. **b**, Nitronate Michael-addition. d.r., diastereomeric ratio; TBS, *tert*-butyl dimethyl silyl. **c**, *In situ* generation of IPrAu(III)(Me_4-biphenyl) catalyst for Mukaiyama−Michael addition. **d**, One-pot tandem Au(I)/Au(III)- and Au(III)/Au(III)-catalysed reactions. *The yield is determined by NMR.

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 $AgSbF_6$, 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 bulky Lewis- and Brønsted-acid catalysts (see Supplementary Information, Supplementary Table 5 and refs 32–34, for example).

Moreover, we also performed the Diels–Alder reaction of 2,4-hexadienal (**16**) with cyclopentadiene[39]. Only the γ,δ-functionalized product **19a** was obtained in 85% yield (diastereomeric ratio *endo*:*exo* = 88:12), employing IPrAu(III)(biphenyl)(NTf_2) as catalyst (Fig. 4b). γ,δ-selective Diels–Alder reactions are unprecedented because α,β-selectivity normally predominates in such Lewis-acid-catalysed reactions[40]. Notably, neither IPrAu(I)(NTf_2), Ag(NTf_2) nor organocatalysts provided any product with **16a** 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 γ,δ-adducts, with an *endo*:*exo* ratio of up to 86:14, employing [IPrAu(III)(biphenyl)(H_2O)]SbF_6 generated *in situ* from IPrAu(I)(SbF_6) 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 Au(III) catalyst formed *in situ* produced product **19b** without a notable decline in yield and selectivity.

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 $AgSbF_6$ was employed, only the [2 + 2] cycloadduct was obtained in 70% yield (*cis*: *trans* = 89: 11). Investigations showed that

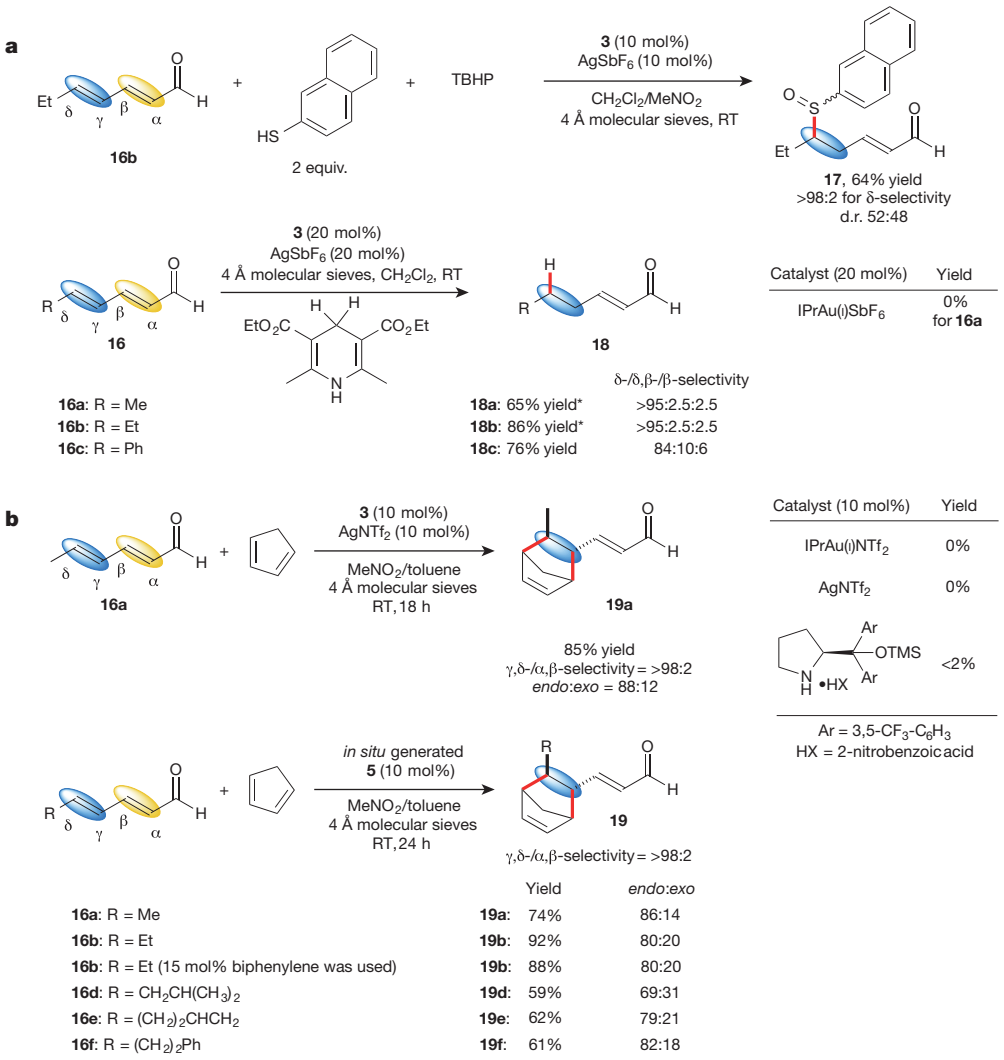

Figure 4 | Remote selectivity in Au(III)-catalysed additions to dienals. **a**, δ-selective thiol addition and reduction reactions. Et, ethyl; cat, catalyst. **b**, γ, δ-selective Diels–Alder reaction and *in situ* generation of the IPrAu(III)(biphenyl) catalyst for Diels–Alder reactions.

neither IPrAu(I)(SbF_6), Ag(SbF_6), $MeAlCl_2$, *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(III)(biphenyl)(η^1-cinnamaldehyde)][SbF_6] (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^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 owing to steric hindrance. As a result, the carbonyl moiety is effectively shielded from nucleophilic attack and thus the IPrAu(III)(biphenyl) cation exhibits

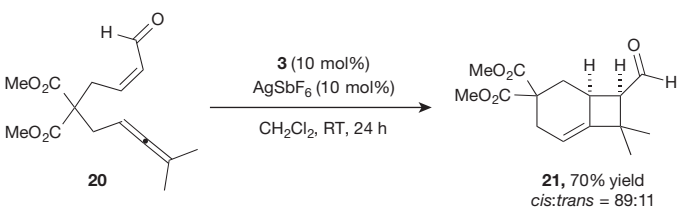

Figure 5 | Au(III)-catalysed [2 + 2] cycloaddition of an allene-aldehyde.

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[42,43], 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 α,β-unsaturated or α,β-γ,δ-diunsaturated aldehydes: Mukaiyama–Michael additions, nitronate Michael additions, a thiol addition, Hantzsch ester reductions, Diels–Alder reactions and a [2 + 2] cycloaddition all have good yield and excellent selectivity. Whereas often-used Au(III) catalysts like $AuCl_3$

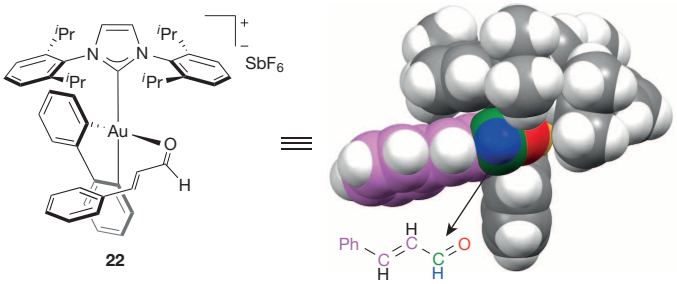

Figure 6 | A model for the obtained selectivity. X-ray structure of the [IPrAu(III)(biphenyl)(η^1-cinnamaldehyde)][SbF_6] complex (**22**). The SbF_6^- anion is omitted for clarity.

exhibit harsh, nonselective acidity[44], 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 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 Au(I)-based catalysts or traditional bulky Lewis- and Brønsted-acid catalysts (see Supplementary Information and Supplementary Table 5 and refs 32–34, for example). 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)-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 *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.

Received 24 June; accepted 19 November 2014.

1. Hickman, A. J. & Sanford, M. S. High-valent organometallic copper and palladium in catalysis. *Nature* **484,** 177–185 (2012).
2. Furuya, T., Kamlet, A. S. & Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **473,** 470–477 (2011).
3. Lee, E. *et al.* A fluoride-derived electrophilic late-stage fluorination reagent for PET imaging. *Science* **334,** 639–642 (2011).
4. Furuya, T. *et al.* Mechanism of C-F reductive elimination from palladium(IV) fluorides. *J. Am. Chem. Soc.* **132,** 3793–3807 (2010).
5. Whitfield, S. R. & Sanford, M. S. Reactivity of Pd(II) complexes with electrophilic chlorinating reagents: Isolation of Pd(IV) products and observation of C−Cl bond-forming reductive elimination. *J. Am. Chem. Soc.* **129,** 15142–15143 (2007).
6. Alsters, P. L. *et al.* Rigid five- and six-membered C,N,N′-bound aryl-, benzyl-, and alkylorganopalladium complexes: sp^2 vs. sp^3 carbon-hydrogen activation during cyclopalladation and palladium(IV) intermediates in oxidative addition reactions with dihalogens and alkyl halides. *Organometallics* **12,** 1831–1844 (1993).
7. Wang, Y.-M., Lackner, A. D. & Toste, F. D. Development of catalysts and ligands for enantioselective gold catalysis. *Acc. Chem. Res.* **47,** 889–901 (2014).
8. Krause, N. & Winter, C. Gold-catalyzed nucleophilic cyclization of functionalized allenes: a powerful access to carbo- and heterocycles. *Chem. Rev.* **111,** 1994–2009 (2011).
9. Corma, A., Leyva-Pérez, A. & Sabater, M. J. Gold-catalyzed carbon-heteroatom bond-forming reactions. *Chem. Rev.* **111,** 1657–1712 (2011).
10. Hamilton, G. L., Kang, E. J., Mba, M. & Toste, F. D. A powerful chiral counterion strategy for asymmetric transition metal catalysis. *Science* **317,** 496–499 (2007).
11. Gorin, D. J. & Toste, F. D. Relativistic effects in homogeneous gold catalysis. *Nature* **446,** 395–403 (2007).
12. Schmidbaur, H. & Schier, A. Gold(III) compounds for homogeneous catalysis: preparation, reaction conditions, and scope of application. *Arabian J. Sci. Eng.* **37,** 1187–1225 (2012).
13. Oliver-Meseguer, J. *et al.* Small gold clusters formed in solution give reaction turnover numbers of 10^7 at room temperature. *Science* **338,** 1452–1455 (2012).
14. Leyva-Pérez, A. & Corma, A. Similarities and differences between the "relativistic" triad gold, platinum, and mercury in catalysis. *Angew. Chem. Int. Ed.* **51,** 614–635 (2012).
15. Gaillard, S. *et al.* Synthetic and structural studies of [$AuCl_3$(NHC)] complexes. *Organometallics* **29,** 394–402 (2010).
16. de Frémont, P., Singh, R., Stevens, E. D., Petersen, J. L. & Nolan, S. P. Synthesis, characterization and reactivity of *N*-heterocyclic carbene gold(III) complexes. *Organometallics* **26,** 1376–1385 (2007).
17. Hashmi, A. S. K., Blanco, M. C., Fischer, D. & Bats, J. W. Gold catalysis: evidence for the *in situ* reduction of gold(III) During the cyclization of allenyl carbinols. *Eur. J. Org. Chem.* 1387–1389 (2006).
18. Wolf, W. J., Winston, M. S. & Toste, F. D. Exceptionally fast carbon–carbon bond reductive elimination from gold(III). *Nature Chem.* **6,** 159–164 (2013).
19. Vicente, J., Bermúdez, M.-D., Carrión, F.-J. & Jones, P. G. Synthesis and reactivity of some nitroaryl complexes of Hg^{II} and Au^{III} — synthesis of a substituted biphenyl by C–C coupling-crystal structure of [$Hg(C_6H_4NO_2$-3,*O*n*Bu*-6)$_2$]. *Chem. Ber.* **129,** 1395–1399 (1996).
20. Roşca, D.-A., Smith, D. A., Hughes, D. L. & Bochmann, M. A thermally stable gold(III) hydride: synthesis, reactivity, and reductive condensation as a route to gold(II) complexes. *Angew. Chem. Int. Ed.* **51,** 10643–10646 (2012).
21. Hashmi, A. S. K. Fire and ice: a gold(III) monohydride. *Angew. Chem. Int. Ed.* **51,** 12935–12936 (2012).
22. Usón, R., Vicente, J., Cirac, J. A. & Chicote, M. T. Synthesis and reactivity of dibenzometallole complexes of gold(III) and platinum(II). *J. Organomet. Chem.* **198,** 105–112 (1980).
23. Pyykkö, P. & Runeberg, N. Comparative theoretical study of N-heterocyclic carbenes and other ligands bound to Au^I. *Chem. Asian J.* **1,** 623–628 (2006).
24. Jones, W. D. Mechanistic studies of transition metal-mediated C–C bond activation. *Top. Curr. Chem.* **346,** 1–31 (2013).
25. Perthuisot, C. *et al.* Cleavage of the carbon–carbon bond in biphenylene using transition metals. *J. Mol. Catal. Chem.* **189,** 157–168 (2002).
26. Darmon, J. M. *et al.* Oxidative addition of carbon–carbon bonds with a redox-active bis(imino)pyridine iron complex. *J. Am. Chem. Soc.* **134,** 17125–17137 (2012).
27. Levin, L. D. & Toste, F. D. Gold-catalyzed allylation of aryl boronic acids: accessing cross-coupling reactivity with gold. *Angew. Chem. Int. Ed.* **53,** 6211–6215 (2014).
28. Fackler, J. P. Jr. Metal-metal bond formation in the oxidative addition to dinuclear gold(I) species. Implications from dinuclear and trinuclear gold chemistry for the oxidative addition process generally. *Polyhedron* **16,** 1–17 (1997).
29. Guenther, J. *et al.* Activation of aryl halides at gold(I): practical synthesis of (P,C) cyclometalated gold(III) complexes. *J. Am. Chem. Soc.* **136,** 1778–1781 (2014).
30. Joost, M. *et al.* Facile oxidative addition of aryl iodides to gold(I) by ligand design: bending turns on reactivity. *J. Am. Chem. Soc.* **136,** 14654–14657 (2014).
31. Weber, S. G., Rominger, F. & Straub, B. F. Isolated silver intermediate of gold precatalyst activation. *Eur. J. Inorg. Chem.* 2863–2867 (2012).
32. North, M., Usanov, D. L. & Young, C. Lewis acid catalyzed asymmetric cyanohydrin synthesis. *Chem. Rev.* **108,** 5146–5226 (2008).
33. Yamamoto, H. (ed.) *Lewis Acids in Organic Synthesis* 1–995 (Wiley, 2000).
34. Mahrwald, R. Diastereoselection in Lewis-acid-mediated aldol reactions. *Chem. Rev.* **99,** 1095–1120 (1999).
35. Maruoka, K., Imoto, H., Saito, S. & Yamamoto, H. Virtually complete blocking of α,β-unsaturated aldehyde carbonyls by complexation with aluminum tris(2,6-diphenylphenoxide). *J. Am. Chem. Soc.* **116,** 4131–4132 (1994).
36. Hadfield, M. S. & Lee, A.-L. Gold(I)-catalyzed synthesis of conjugated trienes. *Chem. Commun.* **47,** 1333–1335 (2011).
37. Akagawa, K., Nishi, N., Sen, J. & Kudo, K. Peptide-catalyzed consecutive 1,6- and 1,4-additions of thiols to α,β,γ,δ-unsaturated aldehydes. *Org. Biomol. Chem.* **12,** 3581–3585 (2014).
38. Akagawa, K., Sen, J. & Kudo, K. Peptide-catalyzed regio- and enantioselective reduction of α,β,γ,δ-diunsaturated aldehydes. *Angew. Chem. Int. Ed.* **52,** 11585–11588 (2013).
39. Ahrendt, K. A., Borths, C. J. & MacMillan, D. W. C. New strategies for organic synthesis: the first highly enantioselective organocatalytic Diels-Alder reaction. *J. Am. Chem. Soc.* **122,** 4243–4244 (2000).
40. Hayashi, Y., Okamura, D., Umemiya, S. & Uchimaru, T. Organocatalytic 1,4-addition reaction of α,β,γ,δ-diunsaturated aldehydes versus 1,6-addition reaction. *ChemCatChem* **4,** 959–962 (2012).
41. Alcaide, B., Almendros, P. & Arancillo, C. Exploiting [2 + 2] cycloaddition chemistry: achievements with allenes. *Chem. Soc. Rev.* **39,** 783–816 (2010).
42. Hashmi, A. S. K. *et al.* On homogeneous gold/palladium catalytic systems. *Adv. Synth. Catal.* **354,** 133–147 (2012).
43. Livendahl, M., Goehry, C., Maseras, F. & Echavarren, A. M. Rationale for the sluggish oxidative addition of aryl halides to Au(I). *Chem. Commun.* **50,** 1533–1536 (2014).
44. Hashmi, A. S. K., Frost, T. M. & Bats, J. W. Highly selective gold-catalyzed arene synthesis. *J. Am. Chem. Soc.* **122,** 11553–11554 (2000).

Supplementary Information is available in the online version of the paper.

Acknowledgements We gratefully acknowledge the NIHGMS (RO1 GM073932) for financial support. C.-Y.W. thanks the Taiwan National Science Council for a postdoctoral fellowship (2011-2012). T.H. thanks the Uehara Memorial Foundation for a postdoctoral fellowship. C.B.J. is grateful to the Lundbeck Foundation for a postdoctoral fellowship. We thank A. DiPasquale (at the College of Chemistry X-ray Crystallography Facility of the University of California, Berkeley) for X-ray crystallographic data collection and we acknowledge support from the NIH Shared Instrumentation Grant S10-RR027172. We thank H.-J. Liu for his generous donation of the biphenylene.

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

Author Information X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under code CCDC 1002525-1002527. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of the paper. Correspondence and requests for materials should be addressed to F.D.T. (fdtoste@berkeley.edu).