Full Paper
doi.org/10.1002/chem.202101751
Chemistry Europe
European Chemical Societies Publishing

Silver-Free Au(I) Catalysis Enabled by Bifunctional Urea- and Squaramide-Phosphine Ligands via H-Bonding

Allegra Franchino,*[a, b] Àlex Martí,[a, b] Stefano Nejrotti,[a, b] and Antonio M. Echavarren*[a, b]

Abstract: A library of gold(I) chloride complexes with phosphine ligands incorporating pendant (thio)urea and squaramide H-bond donors was prepared with the aim of promoting chloride abstraction from Au(I) via H-bonding. In the absence of silver additives, complexes bearing squaramides and trifluoromethylated aromatic ureas displayed good catalytic activity in the cyclization of *N*-propargyl benzamides, as well as in a 1,6-enyne cycloisomerization, a tandem cyclization-indole addition reaction and the hydrohydrazination of phenylacetylene. Kinetic studies and DFT calculations indicate that the energetic span of the reaction is accounted by both the chloride abstraction step, facilitated by the bidentate H-bond donor via an associative mechanism, and the subsequent cyclization step.

Introduction

Activation of gold(I) chloride complexes [LAuCl], required to bring the catalytic activity of Au(I) precatalysts to meaningful levels, is generally performed by chloride abstraction using Ag(I) additives, either in situ or as a separate prior step.[1] While typically very effective, this procedure has the drawback of requiring silver as an additional metal, whose salts are often hygroscopic and light-sensitive. Moreover, if chloride scavenging is done in situ, silver can interfere with the catalysis operated by gold, often with detrimental effects ("silver effect"),[2] although some examples of beneficial Au–Ag cooperative systems have recently been reported.[3] To obviate the practical issues associated with the use of silver salts, the development of silver-free methods for the activation of Au(I) chloride precatalysts has lately become the focus of intense research efforts.[4] Thus, several groups have reported the use of other external activators (e.g. $NaBAr^F_4$, salts of other metals[5] and halogen-bond donors[6]) and self-activating [LAuCl] complexes possessing tailored ligands, such as phosphaalkenes,[7] phosphinines,[8] carbenes or phosphines with redox-switchable metallocenyl groups,[9] pendant Z-type ligands[10] and tethered monodentate H-bond donor (HBD) groups (Figure 1, top).[11,12,13] In this context, the group of Gabbaï disclosed that Au(I) chloride complex **A** bearing a trifluoroacetamide group on a modified PPh_3 scaffold could catalyze the silver-free cyclization of *N*-propargyl benzamide.[11] The activity of **A** was attributed to the ability of the trifluoroacetamide to establish a hydrogen-bond with the chloride ligand, which would facilitate its abstraction from Au(I), thus rendering the metal center catalytically active. Although providing an excellent proof of concept, the study included only a single complex (**A**), whose activity was modest and limited to the cyclization of *N*-propargyl benzamide. Marinetti, Guinchard and coworkers described another isolated example of a phosphine Au(I) chloride complex with a pendant phosphoric acid moiety (**B**), capable of catalyzing the silver-free tandem cycloisomerization-indole addition reaction of 2-alkynyl enones.[12] Regarding NHC-based Au(I) complexes, the group of Helaja very recently presented complexes **C** equipped with an

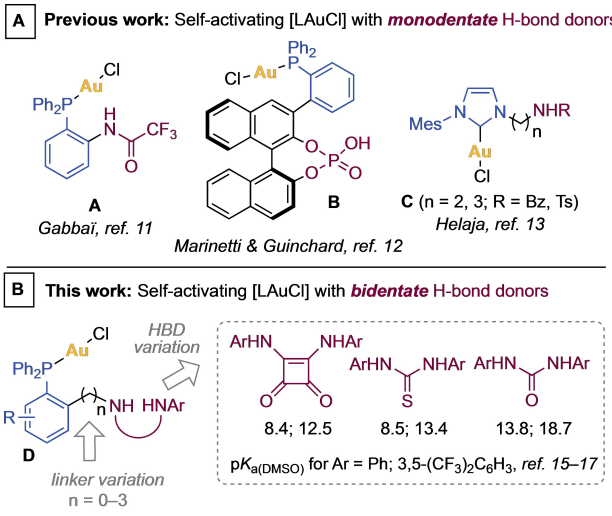


Figure 1. Design of catalytically active Au(I) chloride complexes with tethered H-bond donor (HBD) groups.

[a] Dr. A. Franchino, À. Martí, Dr. S. Nejrotti, Prof. A. M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ)
Barcelona Institute of Science and Technology
Av. Països Catalans 16, 43007 Tarragona (Spain)
E-mail: afranchino@iciq.es
aechavarren@iciq.es

[b] Dr. A. Franchino, À. Martí, Dr. S. Nejrotti, Prof. A. M. Echavarren
Departament de Química Analítica i Química Orgànica
Universitat Rovira i Virgili
C/ Marcel·lí Domingo s/n, 43007 Tarragona (Spain)

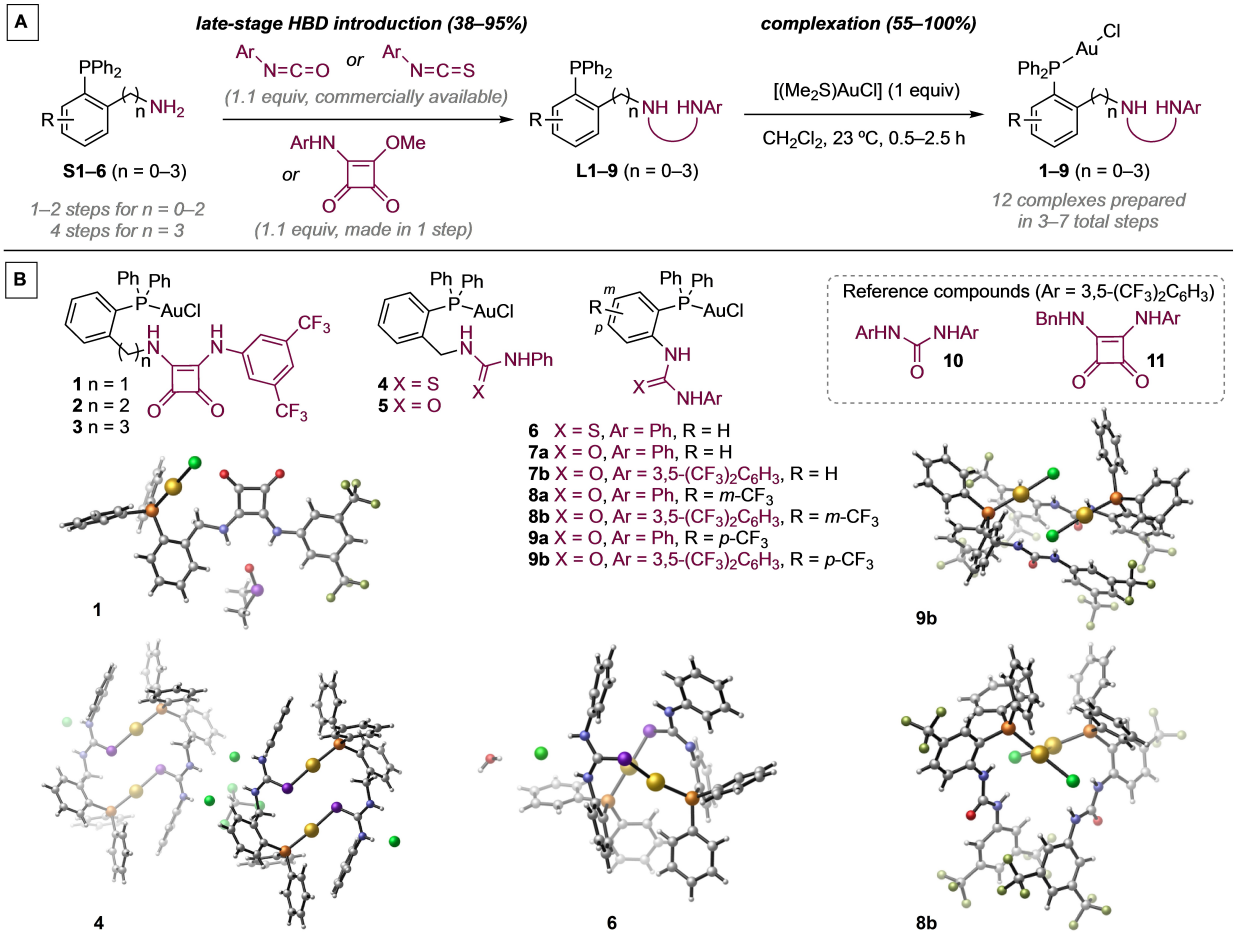
Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202101751

amide side arm, which displayed excellent performances in the absence of additives, but once again only in the cyclization of terminal *N*-propargyl benzamides.[13] Based on calculations, the authors proposed that the NH groups of both the benzamide substrate and the ligand concurred to stabilize the displaced chloride ion.

Complementing these previous reports, we decided to investigate systematically a library of PPh_3-based complexes **D** endowed with classical bidentate H-bond donors (Figure 1, bottom).[14] In order to explore structure-activity relationships, the linker length and the nature of the HBD (squaramides, thioureas and ureas) were varied, covering various geometries and H-bonding abilities (pK_a values[15,16] are shown as an approximate proxy for H-bonding ability[17]). These H-bond donor groups were chosen for their well-known ability to aid chloride abstraction from organic molecules.[18] Herein, we envisaged abstracting the chloride from an electrophilic metal center, with the intention of translating this common "anion-binding" organocatalytic activation strategy to the realm of metal catalysis.[19] This concept sets the present work apart from the very few previous reports on Au(I)[20,21] or Pt(II)[22] complexes with tethered ureas or squaramides, where the pendant HBD groups fulfil the more conventional role of activating organic substrates via H-bonding.[23]

Results and Discussion

Twelve phosphine Au(I) chloride complexes with tethered squaramides (**1**–**3**), thioureas (**4** and **6**) and ureas (**5**, **7**–**9**) were readily prepared in 3–7 steps (Scheme 1A, for details see Supporting Information, Section 2). Late-stage introduction of the HBD groups on the ligands, achieved by reaction of the desired aminophosphines **S1**–**6** with the mixed squarate or iso(thio)cyanate of choice, allowed easy diversification of the key HBD moiety. Ligand exchange with (dimethylsulfide)gold(I) chloride then afforded complexes **1**–**9** as bench-stable solids. All complexes were characterized also by single-crystal X-ray diffraction, which provided valuable information on their connectivity and H-bonding ability in the solid state (Scheme 1B, for details and ORTEP plots see Supporting Information, Section 9).[24] Phosphinosquaramide complexes **1**–**3** display Au–Cl distances of 2.282(1)–2.287(1) Å and a 2-point H-bond between the squaramide and a molecule of DMSO, the

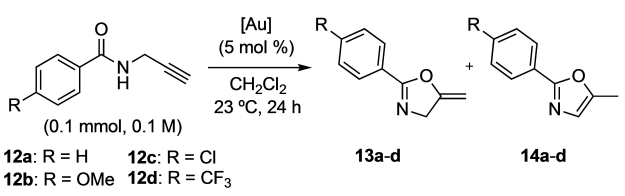


Scheme 1. Bifunctional Au(I) complexes (**1**–**9**) and reference compounds (**10** and **11**). A) Synthetic route. B) Library. X-ray structures of representative complexes **1**, **4**, **6**, **8b** and **9b** visualized using CYLview, selected solvent molecules omitted for clarity. For the sake of simplicity, phosphinothiourea complexes **4** and **6** are drawn as classical Au(I) chloride complexes (see Supporting Information, Section 3 for a discussion on their structure).

crystallization solvent. In phosphinourea complexes **5**, **8a** and **9a**, the Au–Cl distance falls in the 2.275(2)–2.283(1) Å range, and the urea moiety engages in intermolecular H-bonds with another urea. Instead, in the crystal structures of phosphinourea complexes **7a**, **7b**, **8b** and **9b**, the urea establishes H-bonds with the chloride ligand of another [LAuCl] unit, causing weakening of the Au–Cl bond, as attested by its elongation to 2.297(2)–2.326(1) Å. Complex **8b** adopts a dimeric structure very similar to the one described by Gabbaï for complex **A**,[11] held together also by aurophilic interactions, as evidenced by the short Au–Au distance (3.077(1) Å) and smaller P–Au–Cl angle (169.67(3)°). Finally, the X-ray structures of phosphinothiourea complexes **4** and **6** show a dimeric core (with a Au–Au distance of 3.416(9) Å for **6**), where the thiourea of one molecule coordinates via S to the Au atom of another unit. The displaced chloride ligands are stabilized by H-bonds with the thiourea NH groups and with polar solvent molecules ($CHCl_3$ and adventitious water, for details see Supporting Information, Section 9).

Having prepared a library of complexes, some of which were found to H-bond with the chloride ligand (**7a**, **7b**, **8b**, **9b**) or the chloride anion (**4**, **6**) in the solid state, we performed catalytical tests without silver additives to see whether such H-bonding interactions would prove strong enough in solution to render the metal center catalytically active. The cyclization of *N*-propargyl benzamide **12a** was chosen as benchmark reaction, as it is a model transformation for silver-free Au(I) catalysis,[4b,6,8–11,13] and, to further aid comparison, the same conditions employed by Gabbaï were used (Scheme 2).[11] Importantly, this reaction under Au(I) catalysis affords exclusively methylene oxazoline **13a**,[25] whereas isomerized oxazole **14a** is obtained in the presence of Au(III) or acidic additives,[26,27] being thus ideally suited to discriminate a pure Au(I) manifold from catalytic activity due to impurities or degradation/disproportionation products.

Complex **1**, bearing a pendant squaramide, as well as complexes **8b** and **9b**, incorporating electron-poor aromatic ureas, provide excellent yields of oxazoline **13a** in 24 h at 23 °C (96–99%, Table 1, entries 1, 10 and 12). Their activity greatly outperforms the one shown by complex **A** (36% yield under the same conditions, Table 1, entry 13),[11] thus highlighting the importance of ligand design to achieve catalytic efficiency. By comparing the performances of homologous phosphinosquaramide complexes **1**–**3**, a significant drop in activity is observed with increasing linker length (Table 1, entries 1–3). Thus, the tether between the P and N atoms has to possess an optimal length (3 C atoms), which presumably reduces the entropic cost



Scheme 2. Cycloisomerization of amide **12** to oxazoline **13** and/or oxazole **14**.

Table 1. Catalyst screening and control experiments for the cyclization of **12a**.

Entry	[Au]	**13a** [**14a**] Yield [%][a]	Entry	[Au]	**13a** [**14a**] Yield [%][a]
1	**1**	98	13[b]	**A**	36
2	**2**	57	14	[(Me_2S)AuCl]	<5 [72]
3	**3**	<5 [5]	15	[(Ph_3P)AuCl] (**E**)	<5
4	**4**	6	16[c]	**E** + **10** or **E** + **11**	<5
5	**5**	23	17[c]	**E** + $AgSbF_6$	95 [5]
6	**6**	<5	18[c]	**E** + $AgNTf_2$	95 [5]
7	**7a**	23	19[c]	**E** + AgOTf	81
8	**7b**	76	20[c]	**E** + $NaBAr^F_4$	99
9	**8a**	65	21[c]	**L1**, **L8a**, **L9a**	<5
10	**8b**	96	22[c]	Diphenylurea	<5
11	**9a**	64	23[c]	Diphenylthiourea	<5
12	**9b**	99	24[c]	**1** + TBACl	18

[a] Yields for **13a** and **14a** (indicated in brackets only if ≥5%) were determined by ^{1}H NMR analysis using *n*-dodecane or tetraethoxysilane as internal standard; average of at least 2 independent repeats. An error margin of ca. 5% is assumed. The remaining mass is unreacted **12a**. [b] Data taken from ref. 11. [c] Using 5 mol% additive.

of placing the H-bond donor in close proximity to the Au-bound chloride. Comparison between phosphinosquaramide complex **1** and analogous phosphino(thio)urea complexes **4** and **5**, which have the same optimal linker but provide much lower conversions (Table 1, entries 4–5), reveals that also the nature of the H-bond donor group is important. Stronger H-bond donor groups on the ligand induce higher reactivity, a fact that can be rationalized by the greater stabilization offered to the abstracted chloride ion via H-bonds. This trend between reactivity and H-bonding ability can be inferred also from the following two observations: (i) complexes **7b**–**9b** possessing electron-poor urea rings systematically outperform their non-fluorinated counterparts **7a**–**9a** (Table 1, entries 7–12), and (ii) within each a/b series, the activity of catalysts **8** and **9**, bearing an additional trifluoromethyl substituent on the internal aryl ring, surpasses that of **7**. The greater acidity of these groups might also speed up the protodeauration step, thought to be turnover-limiting in this transformation at least in some cases.[13,27] It is worth specifying that all complexes except **7a** are soluble in CH_2Cl_2 under the reaction conditions, so the difference in activity cannot be attributed to solubility profiles.

Phosphinothiourea complexes **4** and **6** were not active (Table 1, entries 4 and 6), likely because the thiourea moiety, even if able to stabilize a displaced chloride ion by H-bonding interactions, coordinates too strongly to the metal center, preventing ligand exchange with the substrate. This hypothesis is supported by the known thiophilicity of Au[28] and the P–Au–S coordination motif observed in the solid-state structures of **4** and **6**.

The use of [(Me_2S)AuCl] (a precursor employed in the preparation of most [LAuCl] complexes, including **1**–**9**) leads to the exclusive formation of isomerized oxazole **14a** (Table 1, entry 14), accompanied by decomposition of the complex as judged by visual inspection of the reaction mixture (dark suspension). This result indirectly attests the purity of complexes **1**–**9**, as their use did not result in the formation of

significant amounts of oxazole **14a**, and is in line with the common notion that strongly coordinating ligands, such as phosphines[11] or carbenes,[13] are required to impart sufficient stability to the Au(I) center during catalysis. On the other hand, [(Ph_3P)AuCl], alone or in combination with urea **10** and squaramide **11**, does not promote the reaction, indicating that the H-bond donor has to be tethered on the ligand backbone in order for this strategy to be viable (Table 1, entries 15 and 16). As expected, intermolecular chloride scavenging from [(Ph_3P)AuCl] using common additives such as $AgSbF_6$, $AgNTf_2$, AgOTf and $NaBAr^F_4$ affords high yields of product **13a** (Table 1, entries 17–20), and the reaction cannot be catalyzed by squaramides or (thio)ureas on their own (Table 1, entries 21–23). When complex **1** is mixed with tetrabutylammonium chloride in equimolar ratio, the yield for product **13a** decreases from 98% to 18% (Table 1, entry 1 vs. 24), as the metal center is saturated by exogenous chloride ions.

Monitoring the reaction profile by ^{1}H NMR confirmed the correlation between catalytic activity and H-bonding ability for complexes **7**–**9** (Figure 2). The activity of the bifunctional complexes spans the range between [(Ph_3P)AuCl]/$AgSbF_6$, which gives rise to a very fast catalytic system (grey line), and [(Ph_3P)AuCl], which is barely active (black line).

Employing the most active phosphinosquaramide Au(I) chloride complex **1**, the cyclization of *N*-propargyl benzamides **12b**–**d**, bearing respectively *p*-methoxy, *p*-chloro and *p*-trifluoromethyl substituents on the aromatic ring, was studied (Figure 3). The reaction was found to be faster for more electron-rich substrates, while it required more than 24 h to reach completion with electron-poor amides **12c** and **12d**. Whereas electronic variations on the standard substrate **12** were tolerated, complexes **1**–**5**, **8b** and **9b** did not to catalyze the silver-free cyclizations of *N*-(but-3-yn-1-yl)benzamide, bearing a homopropargylic substituent, and of the less reactive[13,25] *N*-(3-phenylprop-2-yn-1-yl)benzamide possessing an internal alkyne.[29]

The new complexes were tested also in a range of other intra- and intermolecular reactions of alkynes in the absence of external activators (for a complete overview, see Supporting Information, Section 5). Complexes **1**, **8b** and **9b** display moderate activity at room temperature in the cycloisomerization of benzene-tethered enyne **15** (Scheme 3A).[30] Interestingly, although the conversion was only partial, diene **16** was observed as the sole product, in stark contrast with the formation of dimers **17** and **18** as major products when the

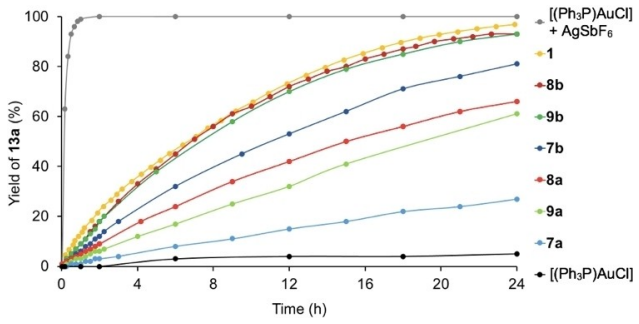


Figure 2. Formation of product **13a** in the reaction of **12a** (0.1 M in CD_2Cl_2, 25 °C) catalyzed by [Au] (5 mol%), monitored by ^{1}H NMR against internal standard.

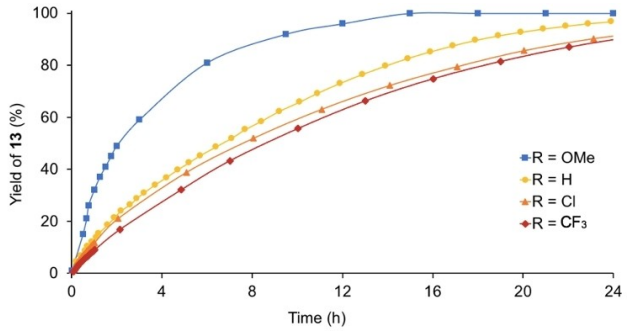
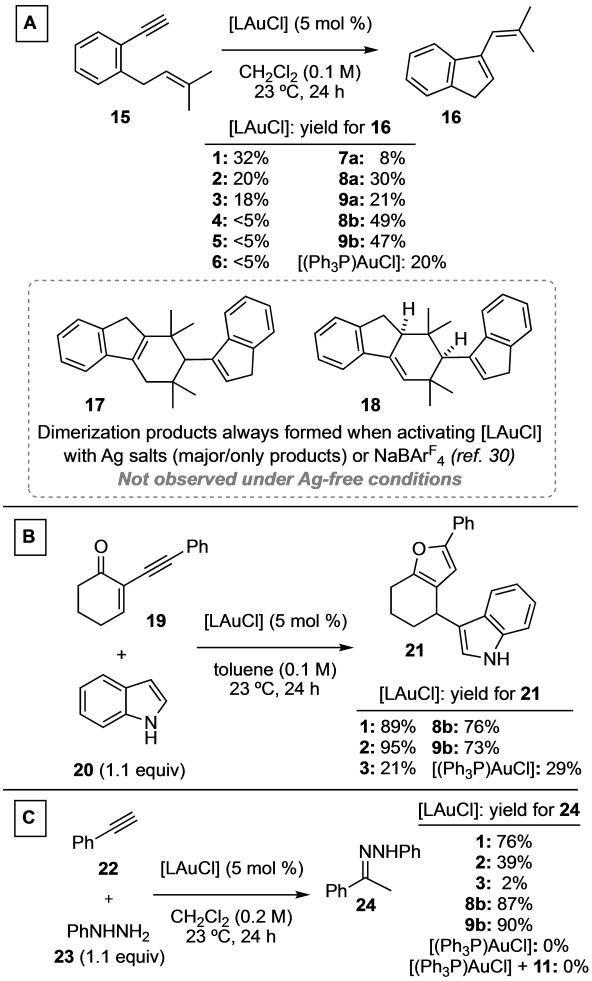


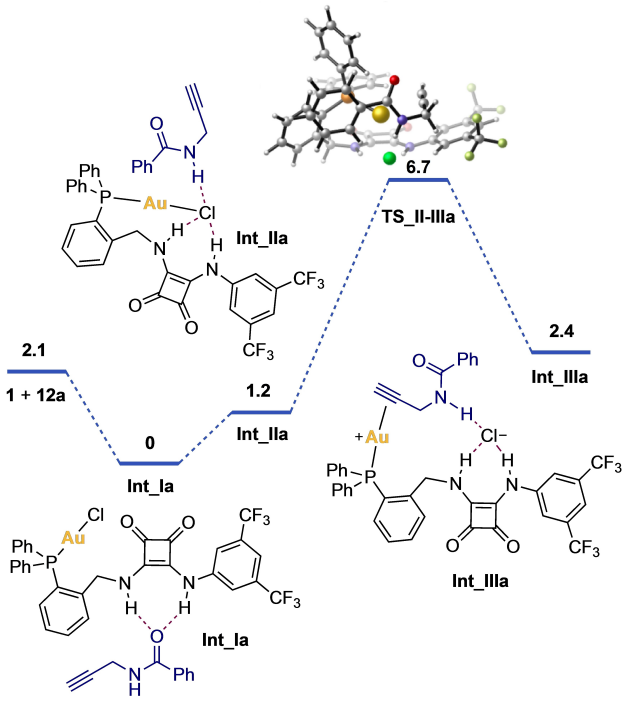
Figure 3. Formation of product **13** in the reaction of **12** (0.1 M in CD_2Cl_2, 25 °C) catalyzed by **1** (5 mol%), monitored by ^{1}H NMR against internal standard.



Scheme 3. Additional intra- and intermolecular silver-free reactions catalyzed by complexes **1**–**9**. Yields determined by ^{1}H NMR analysis against internal standard. A) Cycloisomerization of 1,6-enyne **15**. B) Tandem cycloisomerization-indole addition reaction of 2-alkynylenone **19**. C) Hydrohydrazination of phenylacetylene.

activation of standard Au(I) chloride complexes is performed using silver salts and $NaBAr^F_4$.[30] Complexes **1**, **2**, **8b** and **9b** were also catalytically competent in the tandem cycloisomerization-indole addition reaction of 2-alkynylenone **19**,[12,31] affording good yields of furan **21** and outperforming simple [(Ph_3P)AuCl] on its own (Scheme 3B). Finally, very good activity was observed in the hydrohydrazination of phenylacetylene (Scheme 3C).[32] These results allow once again to appreciate the dependence of catalytic activity on tether length and H-bond donor strength, thus painting a consistent picture across different transformations.

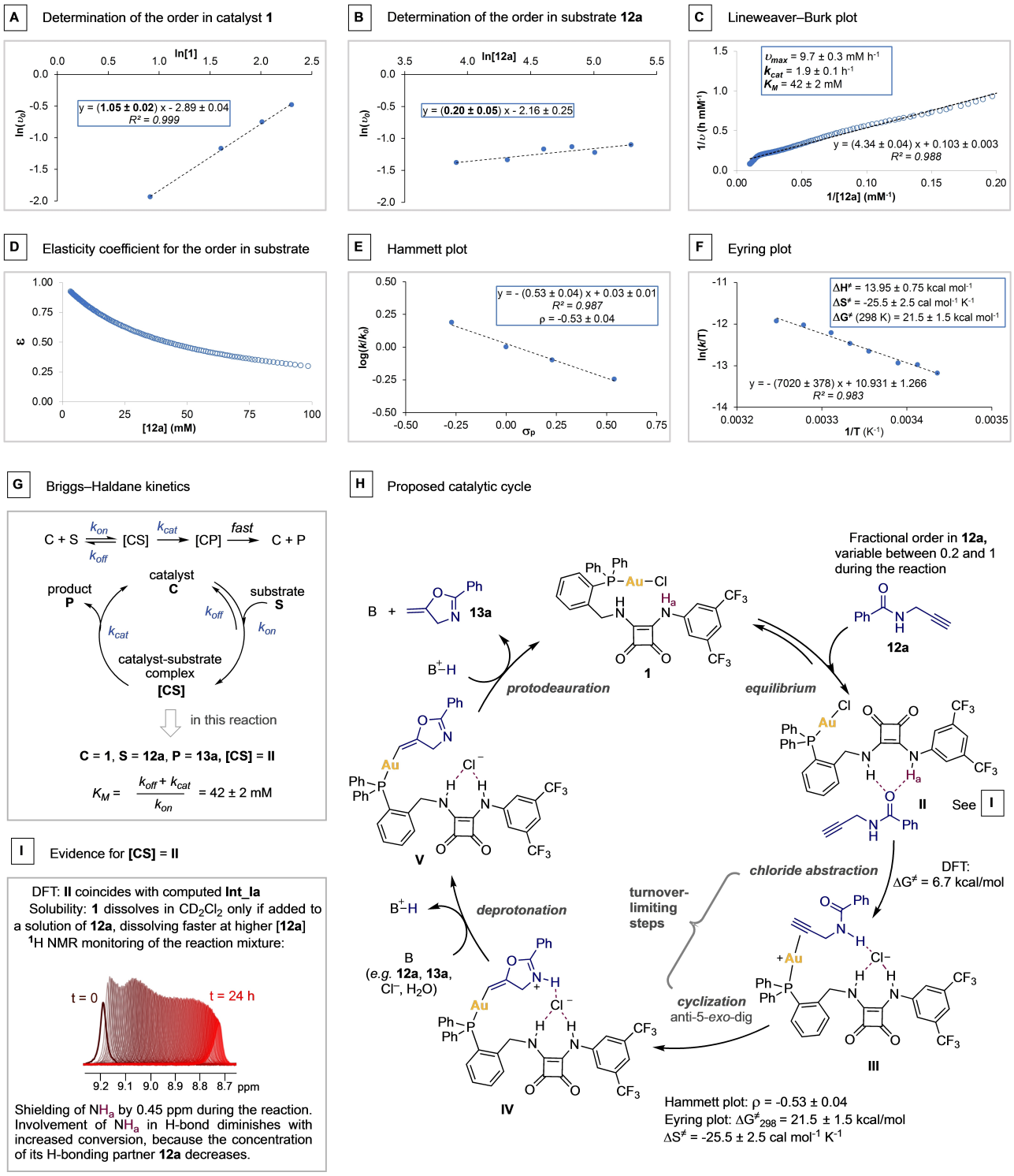
The chloride abstraction step is generally overlooked when performing mechanistic studies on Au-catalyzed transformations, under the assumption that chloride scavenging from [LAuCl] complexes using Ag salts is fast, quantitative and irreversible, which is not correct.[2,4,33] In order to shed light on this often neglected step, DFT calculations for the Au–Cl bond activation were conducted considering both associative and dissociative mechanisms (Scheme 4, for details see Supporting Information, Section 10). It was found that chloride abstraction occurs with a remarkable low barrier of 6.7 kcal/mol, via an associative ligand exchange mechanism, wherein the displaced chloride ion is stabilized by a triple H-bond established with the two NH groups of the squaramide and the NH functionality of amide **12a**. Helaja and coworkers computed a very similar mechanism for the Au–Cl bond activation of a NHC–Au(I) chloride complex possessing a pendant tosylamide, finding a 13.2 kcal/mol barrier with their system.[13] Therefore, computations suggest that the bidentate HBD on complex **1** facilitates the chloride abstraction step. Moreover, the rather low energy barrier found for this step indicates that Au–Cl bond activation on its own cannot be turnover-limiting, since the reaction requires several hours at room temperature to go to completion.



Scheme 4. DFT calculations for the Au–Cl bond activation by associative ligand exchange with substrate **12a**. Energies in kcal/mol; PCM (dichloromethane)-B3LYP-D3/6-31G(d,p) (H, C, N, O, F, P, Cl) + SDD (Au)//6-311G(d,p) (H, C, N, O, F, P, Cl) + SDD (Au).

To shed light on the nature of the turnover-limiting step, kinetic studies on the cyclization of **12a** catalyzed by phosphinosquaramide Au(I) chloride complex **1** in CD_2Cl_2 at 25 °C were undertaken (Scheme 5).[34] With the initial-rate method, the reaction was determined to be first order in catalyst (1.05 ± 0.02, Scheme 5A) and approximately zeroth order in substrate (0.20 ± 0.05, Scheme 5B); no appreciable induction period was observed. We note that a first order in catalyst is common to most catalyzed transformations, as long as the catalyst does not form oligomers. Similarly, a zeroth order in substrate can be expected for unimolecular catalyzed transformations that follow Briggs-Haldane kinetics[35] (of which the well-known Michaelis-Menten regime[36] is regarded as a special case), provided that the Michaelis-Menten constant of the reaction (K_M) is much smaller than substrate concentration ([S]) (Scheme 5G). If instead K_M was much larger than [S], a first order in substrate would be observed. To understand which was the case for the transformation under study, the reaction progress kinetic analysis (RPKA) popularized by Blackmond[37] was applied to the entire reaction profile and the double reciprocal Lineweaver-Burk plot was constructed (Scheme 5C).[38] From it, a Michaelis-Menten constant (K_M) of 42 ± 2 mM was obtained. Given this value, and considering the 0–100 mM substrate concentration present during the reaction, it indeed appears that the current transformation lies in an intermediate scenario between the two limit cases described above (zeroth and first order in substrate), thus justifying a fractional order in substrate included between 0 and 1. Furthermore, since the concentration of **12a** changes during the reaction, the order in substrate is also expected to vary, a phenomenon that can be quantified by the elasticity coefficient ε introduced by Burés.[39] Thus, applying the formula for deriving ε from K_M in Briggs-Haldane kinetic regimes,[39] the order in substrate was calculated to be closer to 0 at the beginning of the reaction (0.3, in good agreement with the 0.2 order determined by initial-rate kinetics) and to approach 1 towards the end of the reaction (Scheme 5D). An intermediate order in substrate of 0.4 was determined for the entire reaction profile using the variable-time normalization analysis (VTNA) described by Burés.[40]

Next, we conducted a Hammett analysis comparing the initial rate of the reactions of substrates **12a–d** (Scheme 5E). A very good correlation in the Hammett plot was found using the standard σ values for para substituents.[41] The rather small, negative sensitivity constant ρ (-0.53 ± 0.04) is indicative of a slight build-up of positive charge in the transition state. While the negative sign of ρ would be consistent with nucleophilic addition of the amide to the Au(I)-activated alkyne being turnover limiting, as in this elementary step a significant build-up of positive charge occurs on the amide functionality conjugated with the aromatic ring, the low magnitude of ρ makes it very unlikely. We thus propose that the energetic span



Scheme 5. Mechanistic studies. A) Determination of the order in catalyst (initial-rate method). B) Determination of the order in substrate (initial-rate method). C) Lineweaver-Burk plot. D) Determination of the elasticity coefficient for the order in substrate. E) Hammett analysis. F) Eyring analysis. G) Generic Briggs-Haldane scenario applied to the present reaction. H) Proposed catalytic cycle. I) Computational and experimental evidences for the catalyst-substrate complex **II**; overlay of ^{1}H NMR spectra acquired over 24 h for the cyclization of **12a** (0.1 M in CD_2Cl_2) catalyzed by **1** (5 mol%) at 25 °C, in the 8.7–9.2 ppm window (NH_a resonance).

of the reaction be accounted by both the chloride abstraction step (with a barrier of 6.7 kcal/mol as calculated by DFT, Scheme 4) and the subsequent amide cyclization step. This would also be in line with DFT calculations for the entire reaction profile carried out by Helaja and coworkers on the

cyclization of **12a** catalyzed by an NHC–Au(I) chloride complex of type **C**.[13]

Finally, the thermodynamic activation parameters were obtained via Eyring analysis.[42] The excellent linear correlation in the 18–35 °C range suggests that only one mechanism is operative (Scheme 5F). The calculated $\Delta G^{\neq}$ at 25 °C (21.5 ± 1.5 kcal/mol) is in agreement with the experimental observation that the reaction proceeds relatively slowly at room temperature. The negative entropy of activation ($\Delta S^{\neq} = -25.5 \pm 2.5$ cal mol^{-1} K^{-1}) supports a scenario in which the energetic span of the catalytic cycle is composed of the chloride abstraction step, proceeding *via* associative ligand exchange, and the subsequent amide cyclization, since a negative entropy of activation is expected also for the cyclization. The contribution of the cyclization step to the overall barrier might explain why **1** catalyzes the 5-*exo*-dig cyclization of terminal benzamides **12**, but not the energetically more demanding cyclizations of less reactive[25] substrates *N*-(but-3-yn-1-yl)benzamide and *N*-(3-phenylprop-2-yn-1-yl)benzamide (the same lack of reactivity with these substrates was observed employing complexes **C**).[13]

On the basis of the kinetic and computational data, we thus propose the catalytic cycle depicted in Scheme 5H. Initially, complex **1** interacts with substrate **12a** forming intermediate **II**, where NH groups of the squaramide establish H-bonds with the carbonyl functionality of the amide. Intermediate **II** corresponds to the so-called catalyst-substrate complex **[CS]** (Scheme 5I), the putative resting state of the catalytic cycle. Computationally, intermediate **II** coincides with the calculated **Int_Ia** (see Scheme 4), which is indeed the lowest energy species located considering several combinations of **12a** and **1**, being 2.1 kcal/mol more stable than **1** and **12a** separately. Experimentally, at the onset of kinetic experiments it was observed that complex **1** (on its own insoluble in CD_2Cl_2) readily dissolves when added to a solution of **12a**, and at higher concentration of **12a** dissolves faster (1–5 s). A possible interpretation for this observation is that, upon mixing **12a** and **1**, the soluble **[CS]** forms, where the carbonyl group of the substrate H-bonds with the squaramide, breaking intermolecular H-bonds between squaramide units which would otherwise make **1** by itself insoluble. Additional evidence comes from ^{1}H NMR monitoring of the reaction mixture in CD_2Cl_2. The signal for the most acidic squaramide NH (NH_a) moves upfield by 0.45 ppm during the reaction, indicating increased shielding. This can be rationalized considering that the involvement of NH_a in H-bonding interactions diminishes with increased conversion, because the concentration of its H-bonding partner **12a** decreases. From the catalyst-substrate complex, chloride abstraction occurs with a 6.7 kcal/mol barrier as calculated by DFT (Scheme 4). Next, the 5-*exo*-dig cyclization takes place, contributing to the total energetic span of the catalytic cycle, as indicated by Hammett and Eyring analysis. Deprotonation of intermediate **IV** by a basic species present in the reaction mixture (such as **12a**, **13a**, adventitious water, or the chloride anion) is expected to occur readily, affording vinyl gold(I) species **V**. Protodeauration of the latter would then liberate product **13a** and regenerate catalyst **1**. We note that this mechanistic picture, while rationalizing all kinetic, computational and experimental results for the cyclization of **12a** catalyzed by **1**, is in contrast to previous investigations on the same Au(I)-catalyzed reaction *in the presence of silver salts*.[27] Those studies rather point towards a turnover-limiting protodeauration step, based on the ^{1}H NMR observation[27a] and isolation[27a,b] of vinyl gold(I/III) complexes in the reaction of **12a** (and analogous substrates possessing an internal alkyne), as well as on ligand effects.[27c] This interesting dichotomy highlights that the chloride abstraction step is far from obvious: the choice of a different chloride scavenging system (e.g. **1** as opposed to Ag salts) can have implications not only for the Au–Cl bond activation, but also for the following steps of the catalytic cycle. Furthermore, in this case the tethered H-bond donor group on the ligand can not only aid chloride scavenging, but potentially also speed up protodeauration by virtue of its Brønsted acidity.

Conclusion

A library of Au(I) chloride complexes with bifunctional phosphine ligands that incorporate classical bidentate H-bond donors, structurally characterized by X-ray diffraction, have been employed as self-activating Au(I) catalysts in both intra- and intermolecular reactions of alkynes, in the absence of silver or acidic additives. A correlation between H-bonding ability and activity was found, suggesting that H-bonding interactions indeed aid chloride abstraction from the Au(I) center, as confirmed computationally. The uncovered design principles regarding linker length and H-bond donor strength, together with other recent advances in this field,[11,12,13] should aid the development of more effective (intermolecular and/or chiral) chloride scavengers based on H-bonds for the activation of M–Cl bonds. In this sense, detailed kinetic studies offer solid ground for further mechanism-based developments, and give new insights into the reactivity of Au(I) complexes in the absence of silver scavengers. The synthetic efforts presented herein could also inspire the implementation of Au(I)-catalyzed transformations that take advantage of the presence of a tethered HBD moiety on the ligand.

Acknowledgements

We acknowledge the European Union (Horizon 2020 Marie Skłodowska-Curie COFUND postdoctoral fellowship to A.F., No. 754510), the European Research Council (Advanced Grant No. 835080), Ministerio de Ciencia e Innovación (PID2019-104815GB–I00), Severo Ochoa Excellence Accreditation2020-2023 (CEX2019-000925-S), the AGAUR (2017 SGR 1257), and CERCA Program/Generalitat de Catalunya for financial support. We also thank Dr Eduardo Escudero for useful discussion, and ICIQ X-ray diffraction, NMR and mass spectrometry units.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: chloride abstraction · hydrogen bond · gold · kinetics · phosphine ligands

[1] M. Jia, M. Bandini, *ACS Catal.* **2015**, *5*, 1638–1652.

[2] a) D. Weber, M. R. Gagné, *Org. Lett.* **2009**, *11*, 4962–4965; b) D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen, X. Shi, *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019; c) A. Zhdanko, M. E. Maier, *ACS Catal.* **2015**, *5*, 5994–6004; d) Z. Lu, J. Han, G. B. Hammond, B. Xu, *Org. Lett.* **2015**, *17*, 4534–4537; e) M.-A. Abadie, X. Trivelli, F. Medina, N. Duhal, M. Kouach, B. Linden, E. Génin, M. Vandewalle, F. Capet, P. Roussel, I. Del Rosal, L. Maron, F. Agbossou-Niedercorn, C. Michon, *Chem. Eur. J.* **2017**, *23*, 10777–10788; f) M. Veguillas, G. M. Rosair, M. W. P. Bebbington, A.-L. Lee, *ACS Catal.* **2019**, *9*, 2552–2557.

[3] a) U B. Kim, D. J. Jung, H. J. Jeon, K. Rathwell, S. Lee, *Chem. Rev.* **2020**, *120*, 13382–13433; b) C. Han, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2021**, *60*, 10637–10642; *Angew. Chem.* **2021**, *133*, 10731–10737.

[4] a) H. Schimdbaur, A. Schier, *Z. Naturforsch.* **2011**, *66b*, 329–350; b) A. Franchino, M. Montesinos-Magraner, A. M. Echavarren, *Bull. Chem. Soc. Jpn.* **2021**, *94*, 1099–1117.

[5] A. Guérinot, W. Fang, M. Sircoglou, C. Bour, S. Bezzenine-Lafollée, V. Gandon, *Angew. Chem. Int. Ed.* **2013**, *52*, 5848–5852; *Angew. Chem.* **2013**, *125*, 5960–5964.

[6] J. Wolf, F. Huber, N. Erochok, F. Heinen, V. Guérin, C. Y. Legault, S. F. Kirsch, S. M. Huber, *Angew. Chem. Int. Ed.* **2020**, *59*, 16496–16500; *Angew. Chem.* **2020**, *132*, 16638–16643.

[7] M. Freytag, S. Ito, M. Yoshifuji, *Chem. Asian J.* **2006**, *1*, 693–700.

[8] a) M. Rigo, L. Hettmanczyk, F. J. L. Heutz, S. Hohloch, M. Lutz, B. Sarkar, C. Müller, *Dalton Trans.* **2017**, *46*, 86–95; b) M. Rigo, E. R. M. Habraken, K. Bhattacharyya, M. Weber, A. W. Ehlers, N. Mézailles, J. C. Slootweg, C. Müller, *Chem. Eur. J.* **2019**, *25*, 8769–8779.

[9] a) D. Schweinfurth, L. Hettmanczyk, L. Suntrup, B. Sarkar, *Z. Anorg. Allg. Chem.* **2017**, *643*, 554–584; b) S. Vanicek, M. Podewitz, J. Stubbe, D. Schulze, H. Kopacka, K. Wurst, T. Müller, P. Lippmann, S. Haslinger, H. Schottenberger, K. R. Liedl, I. Ott, B. Sarkar, B. Bildstein, *Chem. Eur. J.* **2018**, *24*, 3742–3753; c) P. Veit, C. Volkert, C. Förster, V. Ksenofontov, S. Schlicher, M. Bauer, K. Heinze, *Chem. Commun.* **2019**, *55*, 4615–4618; d) A. Straube, P. Coburger, L. Dütsch, E. Hey-Hawkins, *Chem. Sci.* **2020**, *11*, 10657–10668.

[10] a) J. S. Jones, F. P. Gabbaï, *Chem. Eur. J.* **2017**, *23*, 1136–1144; b) L. C. Wilkins, Y. Kim, E. D. Litle, F. P. Gabbaï, *Angew. Chem. Int. Ed.* **2019**, *58*, 18266–18270; *Angew. Chem.* **2019**, *131*, 18434–18438.

[11] S. Sen, F. P. Gabbaï, *Chem. Commun.* **2017**, *53*, 13356–13358.

[12] Z. Zhang, V. Smal, P. Retailleau, A. Voituriez, G. Frison, A. Marinetti, X. Guinchard, *J. Am. Chem. Soc.* **2020**, *142*, 3797–3805.

[13] O. Seppänen, S. Aikonen, M. Muuronen, C. Alamillo-Ferrer, J. Burés, J. Helaja, *Chem. Commun.* **2020**, *56*, 14697–14700.

[14] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743.

[15] G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner, *Org. Lett.* **2012**, *14*, 1724–1727.

[16] X. Ni, X. Li, Z. Wang, J.-P. Cheng, *Org. Lett.* **2014**, *16*, 1786–1789.

[17] R. R. Walvoord, P. N. H. Huynh, M. C. Kozlowski, *J. Am. Chem. Soc.* **2014**, *136*, 16055–16065.

[18] a) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199; b) D. D. Ford, D. Lehnherr, C. R. Kennedy, E. N. Jacobsen, *ACS Catal.* **2016**, *6*, 4616–4620.

[19] B. W. Gung, S. C. Schlitzer, *Tetrahedron Lett.* **2015**, *56*, 5043–5047.

[20] Chiral phosphinourea Au(I) complexes with a *trans*-1-diphenylphosphino-2-aminocyclohexane scaffold, activated using Ag salts: M. J. Campbell, F. D. Toste, *Chem. Sci.* **2011**, *2*, 1369–1378.

[21] Cooperative organo-gold catalysis employing Au(I) triflimide complexes with non-tethered chiral squaramides: G. Dong, M. Bao, X. Xie, S. Jia, W. Hu, X. Xu, *Angew. Chem. Int. Ed.* **2021**, *60*, 1992–1999; *Angew. Chem.* **2021**, *133*, 2020–2027.

[22] a) C. M. McGuirk, C. L. Stern, C. A. Mirkin, *J. Am. Chem. Soc.* **2014**, *136*, 4689–4696; b) C. M. McGuirk, J. Mendez-Arroyo, A. M. Lifschitz, C. A. Mirkin, *J. Am. Chem. Soc.* **2014**, *136*, 16594–16601.

[23] For seminal work on bifunctional ligands in Au(I) catalysis, see: X. Cheng, L. Zhang, *CCS Chem.* **2020**, *2*, 1989–2002.

[24] Deposition numbers for complexes **1**–**9b** (CCDC numbers 2072784–2072795) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[25] A. S. K. Hashmi, A. M. Schuster, F. Rominger, *Angew. Chem. Int. Ed.* **2009**, *48*, 8247–8249; *Angew. Chem.* **2009**, *121*, 8396–8398.

[26] a) M. D. Milton, Y. Inada, Y. Nishibayashi, S. Uemura, *Chem. Commun.* **2004**, 2712–2713; b) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391–4394; c) A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus, W. Frey, *Eur. J. Org. Chem.* **2006**, 4905–4909; d) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzic, J. Visus, F. Rominger, W. Frey, J. W. Bats, *Chem. Eur. J.* **2010**, *16*, 956–963; e) M. Teci, D. Hueber, P. Pale, L. Toupet, A. Blanc, E. Brenner, D. Matt, *Chem. Eur. J.* **2017**, *23*, 7809–7818.

[27] Selection of mechanistic studies: a) Ref. 25; b) O. A. Egorova, H. Seo, Y. Kim, D. Moon, Y. M. Rhee, K. H. Ahn, *Angew. Chem. Int. Ed.* **2011**, *50*, 11446–11450; *Angew. Chem.* **2011**, *123*, 11648–11652; Correction: *Angew. Chem. Int. Ed.* **2012**, *51*, 4511–4511; *Angew. Chem.* **2012**, *124*, 4589–4589; c) W. Wang, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2012**, *134*, 5697–5705; d) H. Peng, N. G. Akhmedov, Y.-F. Liang, N. Jiao, X. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8912–8915; e) Ref. 21.

[28] a) K. P. Kepp, *Inorg. Chem.* **2016**, *55*, 9461–9470; b) R. Visbal, R. P. Herrera, M. C. Gimeno, *Chem. Eur. J.* **2019**, *25*, 15837–15845.

[29] A. S. K. Hashmi, A. M. Schuster, M. Schmuck, F. Rominger, *Eur. J. Org. Chem.* **2011**, 4595–4602.

[30] M. Álvarez-Pérez, M. Frutos, A. Viso, R. Fernández de la Pradilla, M. C. de la Torre, M. A. Sierra, H. Gornitzka, C. Hemmert, *J. Org. Chem.* **2017**, *82*, 7546–7554.

[31] T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165.

[32] Catalytic activity remains inferior to that of state-of-the-art Au(I) catalysts specifically tailored for this transformation: a) R. Manzano, T. Wurm, F. Rominger, A. S. K. Hashmi, *Chem. Eur. J.* **2014**, *20*, 6844–6848; b) X. Hu, D. Martin, G. Bertrand, *New J. Chem.* **2016**, *40*, 5993–5996; c) N. L. Rotta-Loria, A. J. Chrisholm, P. M. MacQueen, R. McDonald, M. J. Ferguson, M. Stradiotto, *Organometallics* **2017**, *36*, 2470–2475.

[33] a) S. G. Weber, F. Rominger, B. F. Straub, *Eur. J. Inorg. Chem.* **2012**, 2863–2867; b) A. Homs, I. Escofet, A. M. Echavarren, *Org. Lett.* **2013**, *15*, 5782–5785; c) Y. Zhu, C. S. Day, L. Zhang, K. J. Hauser, A. C. Jones, *Chem. Eur. J.* **2013**, *19*, 12264–12271; d) D. Canseco-Gonzalez, A. Petronilho, H. Mueller-Bunz, K. Ohmatsu, T. Ooi, M. Albrecht, *J. Am. Chem.* **2013**, *135*, 13193–13203; e) J.-E. Siewert, A. Schumann, M. Fischer, C. Schmidt, T. Taufer, C. Hering-Junghans, *Dalton Trans.* **2020**, *49*, 12354–12364.

[34] For raw data, additional graphs, comments and analysis including VTNA kinetics and catalyst degradation studies, see Supporting Information, Section 6.

[35] G. E. Briggs, J. B. S. Haldane, *Biochem. J.* **1925**, *19*, 338–339. Application of this model rests on a series of underlying assumptions that are all satisfied in the present case (see Supporting Information, Section 6.2).

[36] a) L. Michaelis, M. L. Menten, *Biochem. Z.* **1913**, *49*, 333–369; b) K. A. Johnson, R. S. Goody, *Biochemistry* **2011**, *50*, 8264–8269; c) L. Michaelis, M. L. Menten, *FEBS Lett.* **2013**, *587*, 2712–2720.

[37] D. G. Blackmond, *Angew. Chem. Int. Ed.* **2005**, *44*, 4302–4320; *Angew. Chem.* **2005**, *117*, 4374–4393; Correction: *Angew. Chem. Int. Ed.* **2006**, *45*, 2162–2162; *Angew. Chem.* **2006**, *118*, 2218–2218.

[38] H. Lineweaver, D. Burk, *J. Am. Chem. Soc.* **1934**, *56*, 658–666.

[39] J. Burés, *Top. Catal.* **2017**, *60*, 631–633.

[40] a) J. Burés, *Angew. Chem. Int. Ed.* **2016**, *55*, 2028–2031; *Angew. Chem.* **2016**, *128*, 2068–2071; b) J. Burés, *Angew. Chem. Int. Ed.* **2016**, *55*, 16084–16087; *Angew. Chem.* **2016**, *128*, 16318–16321; c) C. D.-T. Nielsen, J. Burés, *Chem. Sci.* **2019**, *10*, 348–353.

[41] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.

[42] a) H. Eyring, *J. Chem. Phys.* **1935**, *3*, 107–115; b) M. G. Evans, M. Polanyi, *Trans. Faraday Soc.* **1935**, *31*, 875–894; c) K. J. Laidler, M. C. King, *J. Phys. Chem.* **1983**, *87*, 2657–2664.

Manuscript received: May 17, 2021
Accepted manuscript online: May 21, 2021
Version of record online: June 28, 2021

