Dual H-bond activation of NHC–Au(i)–Cl complexes with amide functionalized side-arms assisted by H-bond donor substrates or acid additives†

Otto Seppänen,‡ Santeri Aikonen,‡ Mikko Muuronen,§ Carla Alamillo-Ferrer, Jordi Burés and Juho Helaja*

Novel approach with amide-tethered H-bond donor NHC ligands enabled Au(i)-catalysis via H-bonding. The plain NHC–Au(i)–Cl complex catalysed conversions of terminal N-propynamides to oxazolines, and enyne cycloisomerization with an acid additive, in DCM at RT. DFT calculations enlightened the function of the side-arm in the activation.

Phosphine and N-heterocyclic carbene (NHC) ligands (L) have brought about adjustable stability, activity, and selectivity for homogeneous gold-catalysed carbon–carbon bond activations.1,2 To access the active cationic gold catalyst from ligated gold–chloride salt (LAuCl), the precatalyst is usually activated with AgX salts by exchanging the Cl⁻/CO counterion to a non- or weakly coordinating one, e.g., BF₄⁻, OTf⁻, NTF₂, PF₆⁻, SbF₆⁻.3 Many of the activated LAuX catalysts are also commercially available, but these salts are often hygroscopic. In situ activation, on the other hand, brings an extra step of removing the precipitate or alternatively carrying out the reaction in the presence of AgCl. The precipitating AgCl residues are non-innocent in gold-catalysis4 and multiple roles have been assigned for the counter ions.5,6 Silver-free activations of LAuCl have been reported with sodium salts, e.g., Na[BARF₄]⁻, and with strong acid, HBF₄.8 Multifunctional NHC-ligands have shown to be capable to deliver additional designed functions for homogeneous TM catalysis.9 Recently, ambiphilic ligand Au(i/iii) activation strategies have been developed to generate active catalyst without the need of ion exchange. We10 and others11 have utilised a pyridine side-arm to replace one chloride ion from the Au(III) centre with a hemilabile N–Au σ-coordination (Scheme 1a). Additionally, we noted that higher activity was achieved with a more nucleophilic pyridine moiety and in the presence of H-bond donor solvent or additive,10 which helped to stabilise the cleaved chloride. Previously, Sen and Gabbai integrated the H-bond donor moiety into a phosphine ligand and observed N–H...Cl interactions in the dimer together with aurophilic interaction (Scheme 1b).12 The dimer equipped with NHCOOCF₃ tethered ligand proved to be catalytically active for cyclization of propargylamides, while under same conditions bare PPh₃AuCl with PhNHCOOCF₃ additive was inactive.12

Inspired by these findings, we hypothesised that amide-based H-bond donor tethers in NHC ligands would help to activate the Au(i)–Cl bond directly with alkynes via N–H...Cl interactions, see Scheme 1c. The approach would circumvent

Scheme 1 Ambiphilic ligand Au-catalyst activation modes.
the need to create the vacant site with a hemilabile ligand, thus offering a straightforward approach to activated gold(I)-catalysts. To probe this hypothesis, we synthesized Au(I) NH$_2$ complexes 1a–2b with benzoyl and tosyl amide tethers bridged with ethyl and propyl linkers (Scheme 2). We selected the cycloisomerization of 1a–2b with benzoyl and tosyl amide tethers bridged with ethyl and propyl linkers (Scheme 2). We selected the cycloisomerization of 1a–2b with benzoyl and tosyl amide tethers bridged with ethyl and propyl linkers (Scheme 2). We selected the cycloisomerization of 1a–2b with benzoyl and tosyl amide tethers bridged with ethyl and propyl linkers (Scheme 2). We selected the cycloisomerization of 1a–2b with benzoyl and tosyl amide tethers bridged with ethyl and propyl linkers (Scheme 2).

Scheme 2 Studied complexes for catalysis. (Mes = mesityl).

In catalysts screening (Table 1), the ethyl amide tethered NH$_2$-Au(I) complex 1a yielded a clean 73% conversion of 3a to 4a, while the corresponding trosyl functionalized amide 2a gave an excellent 95% yield after 3 h monitoring period. Elongating the ethyl arms to propyls lowered the yields to 58% and 67% for Bz (1b) and Ts (2b) functionalized NH$_2$-Au(I) catalysts, respectively.

The NH$_2$ gold complexes without H-bond donors (5a–6b) proved to be inactive, while the same complexes gave modest (8%) to decent (68%) yields of 4a with AgOTs (entries 5–8). Surprisingly, our previously developed self-activated Au(III) complex 8a showed only negligible activity for the reaction, as well as the gold(III)-catalysts 8a and 8b (entries 9–11). Although AgOTs or TsOH additives promoted the reaction with 8a and 8b, the catalysts were gradually reduced to the respective Au(I)-complexes (see 8b + TsOH the reaction NMR monitoring in ESIF). The solvent screening (Table S2, ESIF) exposed that chlorinated solvents CD$_2$Cl$_2$ and CDCl$_3$ favour the catalysis, while the performance was sluggish in acetone-$d_6$, CD$_3$CN and CD$_3$OD.

Table 1 Catalysts screening

| Entry | [Au] | Yield$^d$ [%] of 4a | Entry | [Au] | Yield$^d$ [%] of 4a |
|-------|------|---------------------|-------|------|---------------------|
| 1     | 1a   | 73                  | 7     | 6a   | 0 [68]$^e$          |
| 2     | 2a   | 95                  | 8     | 6b   | 0 [30]$^e$          |
| 3     | 1b   | 58                  | 9     | 7    | Trace               |
| 4     | 2b   | 67                  | 10    | 8a   | 20                  |
| 5     | 5a   | 0 [55]$^f$          | 11    | 8b   | 5                   |
| 6     | 3b   | 0 [8]$^f$           | 12    | 1PrAuNTf$_2$ | 58     |

$^a$ Determined by $^1$H NMR using trimethoxybenzene as internal standard. $^b$ Water content 150 ppm. $^c$ With 1 mol% of AgOTs.

Importantly, the complexes 1a–2b showed comparable or superior activity in comparison to the 58% yield of 4a with commercially available IPrAuNTf$_2$ (entry 12). The performance of catalysts 1a–2b was also better than what has been reported for other NHC or P ligands in homogeneous gold-catalytic conversion with weakly or non-coordinative counter ions (Table S1, ESIF).

Next, we studied the substrate scope for the catalytic alkynyl amide oxazoline conversion (Scheme 3) with 1 mol% loading of 2a in DCM at RT. Several propynamides; $^1$Bu (3b), electronneutral and rich aryls (3a, c–e) provided excellent yields of oxazolines 4a–e, though an extended reaction time of 24 h was necessary for 4-methoxy-phenyl oxazoline 4c. Curiously electron deficient 4-Cl$_2$F-phenyl amide (3f) provided an unclear reaction and a poor yield of product 4f, while the 4-F-phenyl oxazoline 4i was isolated in high 83% yield. Interestingly, bulky functional groups such as triphenylmethyl as R$^1$ substituent (4g) and spirocyclohexyl as R$^2$ substituent (4h) were well tolerated and excellent yields of 96% and 97%, respectively, were received after longer reaction times. Unlike complexes without functional group tethers,$^{14}$ the catalyst 2a proved to be chemoselective towards terminal alkynes as terminal functionalised alkynes 3k and 3l, see ESIF, were unreactive. Similarly, in the case of substrate 3j that is equipped with both types of alkynes, the terminal alkynylamide cyclised selectively producing 4j with 93% yield. Additionally, the catalyst was not active for 6-exo-dig cyclisation in oxazoline 4m synthesis (ESIF). In the case of terminally substituted alkynes 3j, 3k, and 3l, the computational study indicated that steric hindrance between the ligand and the alkynes’ terminal substituent limited the reactivity (see Fig. S5, ESIF).

The effect of the concentration of water in DCM for the activation of the catalyst (2a) became a relevant issue, since aqueous media was previously found necessary for Brønsted acid self-activated ligands (Scheme 1a).$^{11}$ We studied the effect of small amounts of water in the solution for the catalytic activity of 2a in the conversion of 3a to 4a in $^1$H NMR, see Fig. 1. The results clearly show that even in the absence of water (0 ppm), the catalyst 2a is activated. The gradual increase of the water content (Fig. 1 and ESIF) up to 200 ppm increased the rate and the yield of the reaction, but a higher water content of 250
and 450 ppm decreased the rate or even inhibited the reaction, respectively. A plausible explanation for the behaviour is that the small amount of water could assist in the anion solvation (see ESI) or in the proton transfer, 15–17 meanwhile higher amount of water lowers the proton’s acidity. 15 An alternative interpretation is that H-bonding interactions between the amide tether and chloride anion are weakened by the water content above 200 ppm thus inhibiting the activation step.

To understand the side-arm’s mechanistic role in the Au–Cl bond activation, we compared the computational free energy profiles for catalysts 1a, 2a, and 5a (Fig. 2). Noteworthy, both benzoyl and tosyl amide side-arms lowered the activation free energy barrier in the alkyne addition to the gold, TS1, by 2.2 and 3.6 kcal mol$^{-1}$, respectively, compared to 5a (Fig. 2). The chloride was hydrogen bonded to the side-arm’s NH with both 1a and 2a while the NH of the substrate coordinated side-arm’s sulfonyl oxygen with 2a (Fig. 2) and the chloride with 1a. Similar bidentate coordination to chloride in 2a-TS1$^+$ (ESI$^+$) was close in energy to 1a-TS1: 14.0 kcal mol$^{-1}$, whereas the barrier was 18.2 kcal mol$^{-1}$ in the absence of substrate’s hydrogen bond coordination in 2a-TS1$^+$ (see ESI$^+$).

All catalysts then converged to a tricoordinate complex B, from which the chloride spontaneously cleaves (TS2$^-$ in Fig. 2). The chloride anion hydrogen bonded with NH of the substrate, and with the side-arm’s NH if the catalyst was 1a or 2a (Cs in Fig. 2). The bidentate hydrogen bond donation from the NHs of substrate and side-arm to chloride stabilised B, TS2, and C, over the monodentate hydrogen bonding with 5a and the stabilisation was stronger with a better H-bond donor, tosyl amide (Fig. 2). Importantly, bidentate H-bonding with 1a and 2a favoured the bicoordinate gold-complex over tricoordinate by 1.3 and 2.0 kcal mol$^{-1}$, respectively, whereas the $\Delta G$ was thermoneutral between B and C for 5a.

The rate limiting step of the reaction can either be the C–O bond formation or the protodeauration step for the catalyst 2a. This will depend on whether the chloride anion is bound to the catalytic complex by hydrogen bonds or solvated by small water cluster. In the former case, the rate-determining step is the protodeauration with 21.3 kcal mol$^{-1}$ activation free energy barrier. In the latter case, the rate-determining step is significantly faster with an activation free energy barrier of 17.2 kcal mol$^{-1}$ for the C–O bond formation (ESI$^+$). This agrees with the observed water effect in Fig. 1. The barriers for 5a are systematically higher, see ESI.$^+$

Beyond the oxazoline synthesis, we investigated how 2a performed in other classic catalytic L-Au(I) transformations. Echavarren and co-workers have originally reported L-Au(I) catalysed cycloisomerization of enynes ($9 \rightarrow 10 + 11$, Table 2) and observed no reactivity with bare [PPh$_3$AuCl] complex, but exchange of coordinative chloride counterion to SbF$_6^-$ or BF$_4^-$ allowed smooth catalytic cycloisomerization at RT. 18 In our case, the enyne $9$ was unreactive with 2 mol% loading of 2a alone (entry 1 in Table 2). However, a 5 mol% addition of monodichloroacetic acid additive gave selectively isomer 10 with

| Entry | Additive | $pK_a$ | $\Delta G$[Au–X]$^+$ | $t$ | Yield $10:11$ (%) |
|-------|----------|--------|-----------------------|----|-----------------|
| 1     | —        | —      | —                     | 1 h| Trace : 0       |
| 2     | TFE      | 73.2   | —                     | 1 h| Trace : 0       |
| 3     | AcOH     | 59.3   | -0.5                  | 1 h| Trace : 0       |
| 4     | ClC$_2$H$_4$COOH | 54.5 | 4.2                  | 1 h| 50 : 0         |
| 5     | Cl$_2$CHCOOH | 56.7 | 7.2                  | 1 h| 99 : 0         |
| 6     | Cl$_2$COOH | 48.4 | 9.3                 | 40 min | 99 : 0 |
| 7     | TFA      | 46.2   | 9.4                  | 15 min | 99 : 0 |
| 8     | MsOH     | 41.4   | 12.0                 | 15 min | 45 : 54 |
| 9     | $p$-TsOH | 41.3   | 14.1                 | 10 min | 66 : 33 |
| 10    | $p$-TsOH + 5a | 41.3 | 14.1                 | 1 h | Trace : 0 |

$^a$ Computed $pK_a$ values in DCM, see ESI for details. $^b$ Au–X bond strength with the conjugate base relative to Au–Cl in kcal mol$^{-1}$, see ESI for details. $^c$ Determined by $^1$H NMR using trimethoxybenzene as an internal standard.
50% and 99% yields, respectively. When TsOH was used as an additive a complete conversion to mixture of isomers 10 and 11 took place in 10 min.\(^{19}\) The acid additive was unable to activate the non-functionalized complex 5a in similar efficiency and only traces of product was observed after 1 h (entry 10).

Because chloride's gold-affinity is higher\(^{20}\) compared to all of the tested acid-additives (Table 2), we reason that the acidity of the additive is important. Inspection of Table 2 reveals that as the acidity of the additive approaches HCl's pK\(_a\) of 45.2,\(^{21}\) chloride anion exchange takes place forming an active catalyst for enyne cycloisomerization. Based on the activation mechanism of 2a in Fig. 2 and in ESI,\(^{†}\) we reason that the activation of Au–Cl bond with enyne 9 is too high in energy since the enyne substrate has no H-bond donors. Therefore, an acid-additive is needed to help in the activation via H-bonding, subsequent protonation and release of HCl, and generation of a loosely coordinating counterion (RCO\(_2^-\) or RSO\(_3^-\)).

The developed acidd-assisted activation mechanism was then utilised in enyne cycloisomerization and nucleophilic alcohol (ROH) addition cascade reaction, following previous L-Au(i) catalysis reports (Scheme 4 and Table S3, ESI).\(^{18,22}\) Full conversion was achieved for each case, and MeOH delivered the best yield of 98% for 12a while allyl and benzyl alcohols gave lower yields. Similarly, good yields were obtained for OMe-substituted vinyl enyne substrates (9d–9f), but benzyl alcohol nucleophile substituted the methoxy group in the product 12e.

In conclusion, we have developed H-bond donor tethered NHC-ligands for in situ activated L-Au(i)Cl catalysis. Ethyl tosyl amide functionalised Au(i) complex 2a catalysed the oxazole synthesis selectively from terminal alkynes, and successful enyne cycloisomerization was accomplished with an acid additive. Computational analysis supports the dual H-bond donor assisted Au–Cl bond activation mechanism.

Financial support from Academy of Finland [project no. 129062 [J. H.]], Emil Aaltonen foundation [grant number 180234 [O. S.]] and EPSRC funding [EP/S005315/1 (C. A.-F and J. B.)] is acknowledged. The Finnish National Centre for Scientific Computing (CSC) is recognized for computational resources. M. Sc. Karina Moslova is acknowledged for measuring elemental analysis.

Conflicts of interest
There are no conflicts to declare.

Notes and references
1 D. J. Gorin, B. D. Sherry and F. D. Toste, Chem. Rev., 2008, 108, 3351.
2 W. Wang, G. B. Hammond and B. Xu, J. Am. Chem. Soc., 2012, 134, 5697.
3 M. Jia and M. Bandini, ACS Catal., 2015, 5, 1638.
4 A. Zh danko and M. E. Maie, ACS Catal., 2015, 5, 5994.
5 (a) M. Jia and M. Bandini, ACS Catal., 2015, 5, 1638; (b) R. Ranieri, I. Escofeta and A. M. Echavarren, Org. Biomol. Chem., 2015, 13, 7103; (c) D. Zucaccia, A. Del Zotto and W. Baratta, Coord. Chem. Rev., 2019, 396, 103.
6 T. Zlot, I. Xu and Y. Xia, Org. Lett., 2013, 15, 6074.
7 M. Wegener, F. Huber, C. Bolli, C. Jenne and S. F. Kirsch, Chem. – Eur. J., 2015, 21, 1328.
8 C. Nevado and A. M. Echavarren, Chem. – Eur. J., 2005, 11, 3155.
9 E. Peris, Chem. Rev., 2018, 118, 9988.
10 (a) M. Muuronen, J. E. Perea-Buceta, M. Neyer, M. Patschke and J. Helaja, Organometallics, 2012, 31, 4320; (b) M. Muuronen, PhD thesis, University of Helsinki, 2015.
11 (a) E. Mendivil-Tomás, P. Y. Toulliec, J. Diez, S. Conejero, V. Michele and V. Cadierno, Org. Lett., 2012, 14, 2520; (b) E. Tomás-Mendivil, P. Y. Toulliec, J. Borge, S. Conejero, V. Michele and V. Cadierno, ACS Catal., 2013, 3, 3086.
12 S. Sen and F. P. Gbabai, Chem. Commun., 2017, 53, 13356.
13 Key references: (a) A. S. K. Hashmi, J. P. Weyrauch, W. Frey and J. W. Bats, Org. Lett., 2004, 6, 4391; (b) G. Vermiest and A. Padwa, Org. Lett., 2008, 10, 4379; (c) D. Aguilar, M. Contel, R. Navarro, T. Soler and P. E. Urrildalbeita, J. Organomet. Chem., 2009, 694, 486; (d) J. P. Weyrauch, A. S. K. Hashmi, A. Schuster, T. Hengst, S. Schetter, A. Littmann, M. Rudolph, M. Hamzie, J. Visus, F. Rominger, W. Frey and J. W. Bats, Chem. – Eur. J., 2010, 16, 956; (e) O. A. Egorova, H. Seo, Y. Kim, D. Moon, Y. M. Rhee and K. H. Ahn, Angew. Chem., Int. Ed., 2011, 50, 11446.
14 A. S. K. Hashmi, A. M. Schuster, M. Schmuck and F. Rominger, Eur. J. Org. Chem., 2011, 4595.
15 R. Baba-Ahmadi, P. Ghanbari, N. A. Rajabi, A. S. K. Hashmi, B. F. Yates and A. Ariaifar, Organometallics, 2015, 34, 3186.
16 M. Chiarucci and M. Bandini, Beilstein J. Org. Chem., 2013, 9, 2586.
17 C. Krauter, A. S. K. Hashmi and M. Perpnounier, Chem Cat, Organometallics, 2010, 2, 1226.
18 C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas and A. M. Echavarren, Angew. Chem., Int. Ed., 2004, 43, 2402.
19 Previously, an acid additive (H3BF4) has been reported to cause similar mixture of isomers in the NHC–Au(i) catalysis: S. Ferrer and A. M. Echavarren, Organometallics, 2018, 37, 781.
20 Z. Lu, J. Han, O. E. Okoromoba, N. Shimizu, H. Amii, C. F. Tormena, G. B. Hammond and B. Xu, Org. Lett., 2017, 19, 5848.
21 E. Paenurk, K. Kaupmees, D. Himmel, A. Kütt, I. Kaljurand, I. A. Koppel, I. Escofeta and A. M. Echavarren, Chem. Sci., 2017, 8, 6964.
22 Y. Tang, I. Benaiissa, M. Huynh, L. Vendier, N. Lukan, S. Bastin, P. Belmont, V. César and V. Michele, Angew. Chem., Int. Ed., 2019, 58, 7977.