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

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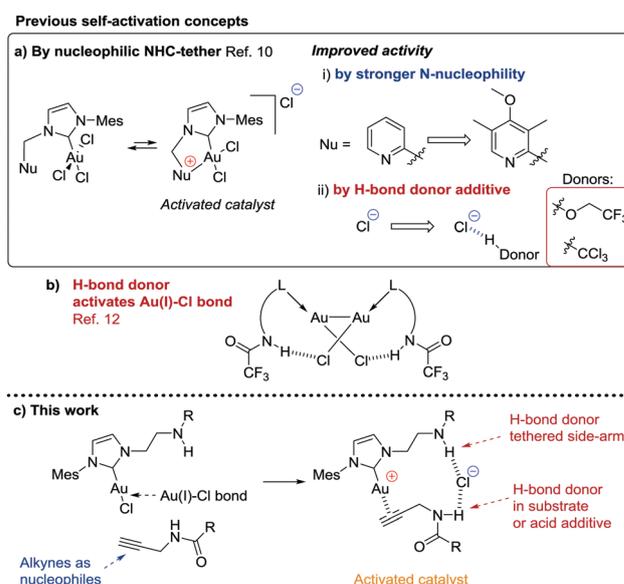
Novel approach with amide-tethered H-bond donor NHC ligands enabled Au(I)-catalysis via H-bonding. The plain NHC–Au(I)–Cl complex catalysed conversions of terminal N-propynamides to oxazolines, and enyne cycloisomerization with an acid additive, in DCM at RT. DFT calculations enlightened the function 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 π -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[−] 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],⁷ 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 NHCOCF₃ tethered ligand proved to be catalytically active for cyclization of propargylamides, while under same conditions bare PPh₃AuCl with PhNHCOCF₃ 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.

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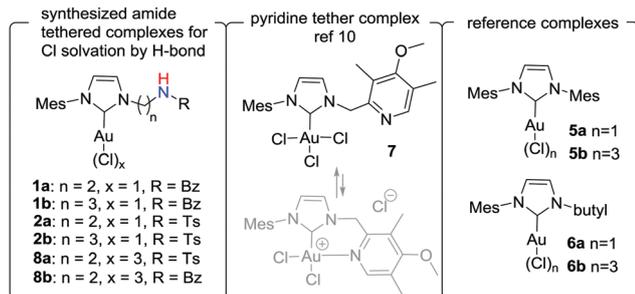
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Scheme 2 Studied complexes for catalysis. (Mes = mesityl).

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) NHC complexes **1a–2b** with benzoyl and tosyl amide tethers bridged with ethyl and propyl linkers (Scheme 2). We selected the cycloisomerization of *N*-(prop-2-yn-1-yl)benzamide **3a** to oxazoline **4a** as a test reaction to investigate the catalytic efficiency due to its popularity in gold catalysis studies.¹³

In catalysts screening (Table 1), the ethyl amide tethered NHC–Au(I) complex **1a** yielded a clean 73% conversion of **3a** to **4a**, while the corresponding tosyl 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 NHC–Au(I) catalysts, respectively.

The NHC 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 **7**¹⁰ 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 ESI†). The solvent screening (Table S2, ESI†) exposed that chlorinated solvents CD₂Cl₂ and CDCl₃ favour the catalysis, while the performance was sluggish in acetone-*d*₆, CD₃CN and CD₃OD.

Table 1 Catalysts screening

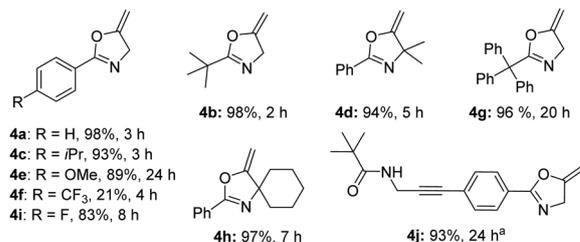
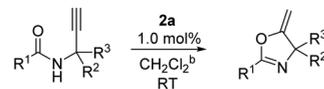
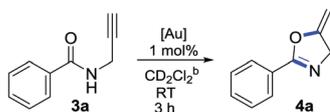
| Entry | [Au] | Yield ^a [%] of 4a | Entry | [Au] | Yield ^a [%] of 4a |
|-------|-----------|-------------------------------------|-------|-----------------------|-------------------------------------|
| 1 | 1a | 73 | 7 | 6a | 0 (68) ^c |
| 2 | 2a | 95 | 8 | 6b | 0 (30) ^c |
| 3 | 1b | 58 | 9 | 7 | Trace |
| 4 | 2b | 67 | 10 | 8a | 20 |
| 5 | 5a | 0 (55) ^c | 11 | 8b | 5 |
| 6 | 5b | 0 (8) ^c | 12 | IPrAuNTf ₂ | 58 |

^a Determined by ¹H 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 IPrAuNTf₂ (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, ESI†).

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; ^tBu (**3b**), electroneutral 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 **4e**. Curiously electron deficient 4-CF₃-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 R¹ substituent (**4g**) and spirocyclohexyl as R² 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 terminally functionalised alkynes **3k** and **3l**, see ESI,† 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 (ESI†). 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, ESI†).

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 ¹H 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 ESI†) up to 200 ppm increased the rate and the yield of the reaction, but a higher water content of 250

Scheme 3 Substrate scope in oxazoline synthesis with isolated yields. ^aCatalyst loading 3.0 mol%. ^bWater content in all reactions 150 ppm.

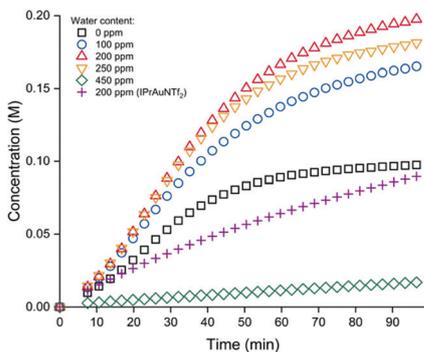


Fig. 1 Kinetic monitoring of **2a** catalysed conversion of **3a** to **4a** conversion in various water contents. [**3a**] = 0.226 M, and [**2a**]/IPrAuNTf₂] = 0.0023 M, in CD₂Cl₂ at 25 °C.

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 (**TS2s** 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 ΔG 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** → **10** + **11**, Table 2) and observed no reactivity with bare [PPh₃AuCl] complex, but exchange of coordinative chloride counterion to SbF₆[−] or BF₄[−] 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 mono- and dichloroacetic acid additive gave selectively isomer **10** with

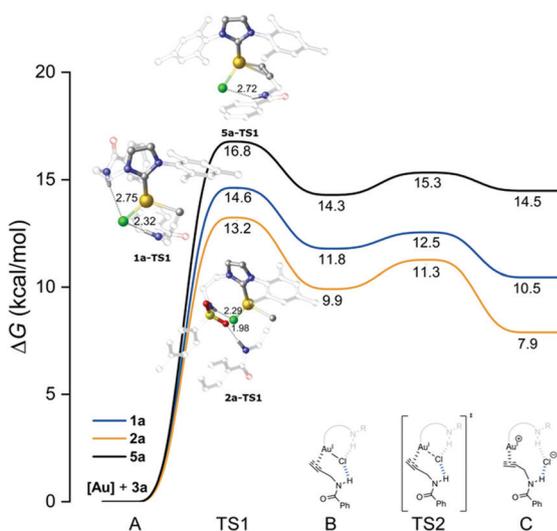


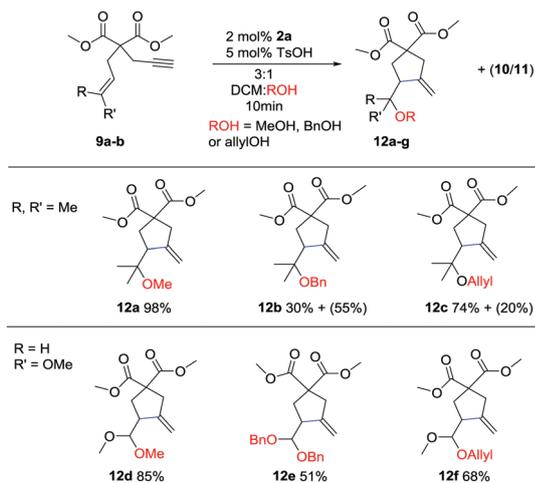
Fig. 2 Free energy profiles for Au–Cl bond activation with catalysts **1a** (blue line), **2a** (yellow line), and **5a** (black line). Full computational details are in ESI[†].

Table 2 Screening of additives for enyne cycloisomerization

| Entry | Additive | pK _a ^a | ΔG(Au–X) ^b | t | Yield ^c 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 | ClCH ₂ COOH | 54.5 | 4.2 | 1 h | 50 : 0 |
| 5 | Cl ₂ CHCOOH | 50.7 | 7.2 | 1 h | 99 : 0 |
| 6 | Cl ₃ CCOOH | 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 | <i>p</i> -TsOH | 41.3 | 14.1 | 10 min | 66 : 33 |
| 10 | <i>p</i> -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 ¹H NMR using trimethoxybenzene as an internal standard.





Scheme 4 Substrate scope in enyne cycloisomerization, with isolated yields. Yield in parenthesis is the combined yield of products **10** and **11**.

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 higher²⁰ 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 $pK_a(\text{DCE}) = 45.2$,²¹ chloride anion exchange takes place forming an active catalyst for enyne **9** 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 acid-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.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351.
- W. Wang, G. B. Hammond and B. Xu, *J. Am. Chem. Soc.*, 2012, **134**, 5697.
- M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638.
- A. Zhdanko and M. E. Maie, *ACS Catal.*, 2015, **5**, 5994.
- (a) M. Jia and M. Bandini, *ACS Catal.*, 2015, **5**, 1638; (b) B. Ranieri, I. Escofeta and A. M. Echavarren, *Org. Biomol. Chem.*, 2015, **13**, 7103; (c) D. Zuccaccia, A. Del Zotto and W. Baratta, *Coord. Chem. Rev.*, 2019, **396**, 103.
- T. Zhou, L. Xu and Y. Xia, *Org. Lett.*, 2013, **15**, 6074.
- M. Wegener, F. Huber, C. Bolli, C. Jenne and S. F. Kirsch, *Chem. – Eur. J.*, 2015, **21**, 1328.
- C. Nevado and A. M. Echavarren, *Chem. – Eur. J.*, 2005, **11**, 3155.
- E. Peris, *Chem. Rev.*, 2018, **118**, 9988.
- (a) M. Muuronen, J. E. Perea-Buceta, M. Nieger, M. Patzschke and J. Helaja, *Organometallics*, 2012, **31**, 4320; (b) M. Muuronen, PhD thesis, University of Helsinki, 2015.
- (a) E. Mendivil-Tomás, P. Y. Toullec, J. Díez, S. Conejero, V. Michelet and V. Cadierno, *Org. Lett.*, 2012, **14**, 2520; (b) E. Tomás-Mendivil, P. Y. Toullec, J. Borge, S. Conejero, V. Michelet and V. Cadierno, *ACS Catal.*, 2013, **3**, 3086.
- S. Sen and F. P. Gabbai, *Chem. Commun.*, 2017, **53**, 13356.
- Key references: (a) A. S. K. Hashmi, J. P. Weyrauch, W. Frey and J. W. Bats, *Org. Lett.*, 2004, **6**, 4391; (b) G. Verniest and A. Padwa, *Org. Lett.*, 2008, **10**, 4379; (c) D. Aguilar, M. Contel, R. Navarro, T. Soler and P. E. Urriolabeitia, *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. Hamzic, 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.
- A. S. K. Hashmi, A. M. Schuster, M. Schmuck and F. Rominger, *Eur. J. Org. Chem.*, 2011, 4595.
- R. BabaAhmadi, P. Ghanbari, N. A. Rajabi, A. S. K. Hashmi, B. F. Yates and A. Ariaferd, *Organometallics*, 2015, **34**, 3186.
- M. Chiarucci and M. Bandini, *Beilstein J. Org. Chem.*, 2013, **9**, 2586.
- C. M. Krauter, A. S. K. Hashmi and M. Pernpointner, *Chem Cat Chem*, 2010, **2**, 1226.
- C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2004, **43**, 2402.
- Previously, an acid additive (HSbF_6) 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.
- 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.
- E. Paenurk, K. Kaupmees, D. Himmel, A. Kütt, I. Kaljurand, I. A. Koppel, I. Krossing and I. Leito, *Chem. Sci.*, 2017, **8**, 6964.
- Y. Tang, I. Benaissa, M. Huynh, L. Vendier, N. Lugan, S. Bastin, P. Belmont, V. César and V. Michelet, *Angew. Chem., Int. Ed.*, 2019, **58**, 7977.

