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Hydrogen bonding-enabled gold catalysis: ligand effects in gold-catalyzed cycloisomerization of 1,6-enynes in hexafluoroisopropanol (HFIP)

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Hydrogen bonding has recently emerged as a powerful yet under-explored tool to enable gold(I) catalysis. Here, we demonstrate that HFIP can directly activate [Au(L)Cl] complexes through hydrogen bonding, in the cycloisomerization of 1,6-enynes under mild conditions without the need for external activators. The influence of ancillary ligands on the catalytic efficiency was systematically examined, revealing that ligand–HFIP interactions play a key role in the activation process. This study provides new insight into hydrogen-bond-assisted gold catalysis and offers a simple strategy for activator-free transformations.

Over the past two decades, gold catalysis has undergone remarkable development and is now regarded as one of most powerful and versatile tools in organic synthesis.^{1–3} Among gold-based catalysts, gold(I) chloride complexes [Au(L)Cl] are particularly attractive due to their stability and commercial availability. However, because of the inherent inertness of the Au–Cl bond, activation is typically required to initiate catalysis. Silver salts bearing weakly coordinating anions have long served as standard activators for gold(I) chloride complexes. However, their hygroscopic nature, light sensitivity, and the so-called “silver effect” in catalysis often present significant drawbacks and limitations.^{4–7}

Several strategies have been developed to overcome these specific issues in gold catalysis.⁸ Including the use of alternative alkali metal borates⁹ and copper salts,¹⁰ Brønsted acid activation of basic gold precursors¹¹ and the self-activation of gold(I) chloride complexes bearing specially designed ancillary ligands,⁸ as well as the use of halogen-bonding donors to activate the Au–Cl bond and generate catalytically active species.^{12,13} Despite their effectiveness, these strategies share a common limitation: the need for external reagents to promote the Au–Cl bond activation.

Hydrogen bonding can exert a profound influence on gold catalysis.¹⁴ In this regard, hexafluoroisopropanol (HFIP) is emerging as a particularly promising medium. Its unique combination of properties—including strong hydrogen bond-donating ability, low nucleophilicity, efficient cation stabilization, enhanced acidity, and conveniently low boiling point (59 °C)—makes it a broadly applicable and easily recyclable solvent for catalytic applications.^{15–17} For its unique properties, the use of HFIP has exponentially increased in the past decade and has become a solvent of choice in some areas, such as in C–H functionalization chemistry.¹⁵ This evolving area encouraged us to explore its use further in gold(I) catalysis. Our group has recently shown that HFIP can promote two distinct cyclization reactions, namely the *N*-propargyl benzamide cyclization and the alkynoic acid cyclization, without requiring external activators.^{18,19} In these systems, HFIP plays a dual role by dynamically activating the Au–Cl bond through hydrogen bonding, thereby initiating the catalytic cycle and acting as solvent.

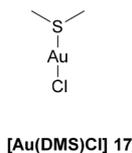
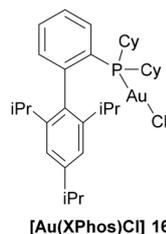
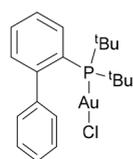
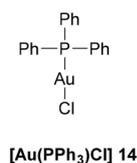
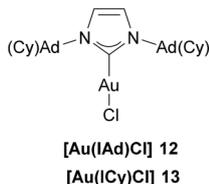
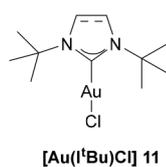
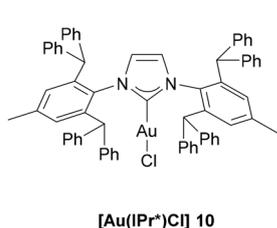
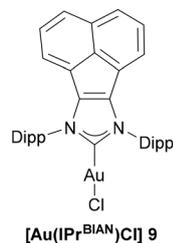
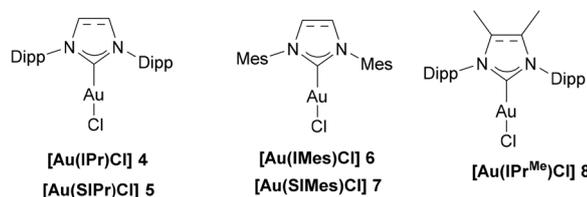
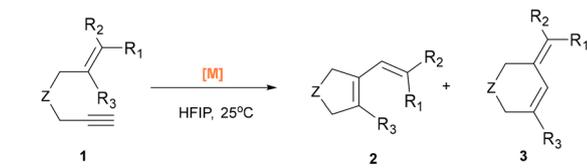
Building on these findings and driven by our ongoing interest in the potential of HFIP in gold catalysis, we sought to explore its broader applicability and performance across a range of gold-catalyzed transformations. The cycloisomerization of 1,6-enynes is a well-established reaction widely employed to evaluate the activity of gold catalysts and the efficiency of activators in homogeneous gold catalysis.^{20–22} In addition to catalyst performance, this transformation also presents a challenge in terms of controlling product distribution, as it often involves competing rearrangement pathways.^{23,24} In recent years, various improvements in catalyst design and activator use have been made to the cycloisomerization of 1,6-enynes.^{12,25–28} However, despite extensive efforts, silver salts remain the most effective activators for this reaction, with no suitable alternatives having been identified to date.

In this context, we report our study on the cycloisomerization of 1,6-enynes in the presence of HFIP, with a focus on the role of ligands in modulating reactivity and selectivity. The representative [Au(NHC)Cl] and [Au(PR₃)Cl] complexes employed in this study are illustrated in Scheme 1. Our aim

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Scheme 1 Model reaction and ligand based-catalyst library. Ph = phenyl, Dipp = (2,3-diisopropyl) phenyl, Ad = 1-adamantyl, Cy = cyclohexyl, ^tBu = *tert*-butyl.

was to explore commonly used ligands in gold catalysis,²⁹ in the hope of enhancing selectivity and provide an alternative to silver-based activation in the cycloisomerization of 1,6-enynes.

We began our catalytic investigations with the benchmark cycloisomerization of *N*-Tosyl-1,6-enyne **1a**. To our delight, the reaction proceeded smoothly when complex **4** was used, reaching full conversion within 4 hours and affording five-membered lactone **2a** and six-membered product **3a** with 14.5 : 1 selectivity in favor of **2a** (Table 1, entry 1). A focused screening of [Au(L)Cl] complexes was then conducted (Table 1). Entries 2–6 show that increasing the steric bulk on the NHC ligand generally leads to diminished reactivity and selectivity. However, complex **10** exhibited good performance, providing high conversion but only moderate selectivity (entry 7). Bulky ligands such as I^tBu and IAd resulted in only moderate conversion and poor

Table 1 Screening in the gold-catalyzed cycloisomerizations of **1a**^a

Entry	[M]	Combined yield (%)	Selectivity ratio (2a : 3a)
1	[Au(IPr)Cl] 4	99	14.5 : 1
2	[Au(SIPr)Cl] 5	80	9 : 1
3	[Au(IMes)Cl] 6	82	3 : 1
4	[Au(SIMes)Cl] 7	89	2.5 : 1
5	[Au(IPr ^{Me})Cl] 8	70	10 : 1
6	[Au(IPr ^{BIAN})Cl] 9	71	10 : 1
7	[Au(IPr*)Cl] 10	99	6 : 1
8	[Au(I ^t Bu)Cl] 11	72	1 : 1
9	[Au(IAd)Cl] 12	76	1 : 1.5
10	[Au(ICy)Cl] 13	39	—
11	[Au(PPh ₃)Cl] 14	99	1 : 15
12	[Au(JohnPhos)Cl] 15	99	1 : 11
13	[Au(XPhos)Cl] 16	85	1 : 10
14	[Au(DMS)Cl] 17	13	—
15	[Ag(IPr)Cl]	0	—
16	[Cu(IPr)Cl]	0	—
17	[Au(IPr)(Cbz)]	31	—
18	[Au(IPr)(OH)]	56	—
19	[Au(IPr)(OAc)]	47	—
20	[Au(IPr)(OC(CF ₃) ₂)]	50	—
21	[Au(IPr)(NTf ₂)]	39	—
22	[Au(IPr)(OTf)]	65	—
23 ^b	4	0	—
24 ^c	4	0	—
25 ^d	4	20	—
26 ^e	4	0	—

^a Unless otherwise noted, the reaction was conducted with **1a** (0.2 mmol) and [M] (0.002 mmol, 1 mol%) in HFIP (0.2 mL) in 4 h, 25 °C; the yield and selectivity determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^b DCM instead of HFIP. ^c Mixture of DCM and HFIP (9 : 1) instead of HFIP. ^d Trifluoroethanol (TFE) instead of HFIP. ^e 0.5 mmol of phenol instead of HFIP.

selectivity (1 : 1 ratio, entries 8 and 9). In contrast, the catalyst bearing the small ICy ligand, complex **13**, gave only 39% conversion of **1a** (entry 10). Overall, the IPr ligand remains the most effective and reliable among the NHC series.³⁰ Notably, phosphine-based catalysts exhibited reversed selectivity. For example, **14** favored the formation of **3a** over **2a** in a 1 : 15 ratio. Other common phosphine ligands, including **15** and **16**, displayed slightly reduced activity and selectivity (entries 12 and 13). Interestingly, silver and copper congener complexes of **4** were catalytically inactive under the same conditions (entries 14 and 15), as was **17** (entry 16). Several Brønsted-basic gold complexes, such as [Au(IPr)(Cbz)] (Cbz = carbazolyl), [Au(IPr)(OH)], and [Au(IPr)(OAc)], gave moderate conversions (31–56%, entries 17–19).

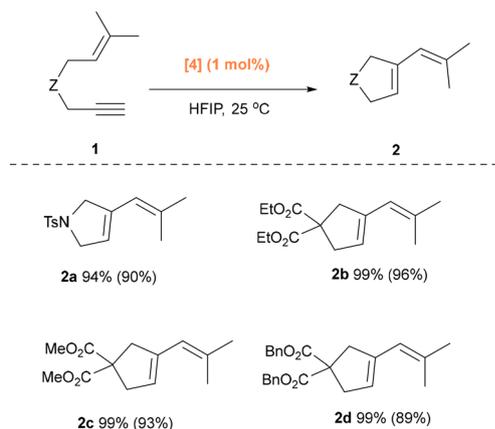
Comparing the catalytic activity of [Au(IPr)(OC(CF₃)₂)] to that of **4** and to those of the already activated complexes [Au(IPr)(NTf₂)] and [Au(IPr)(OTf)], which bear weakly coordinating anions, provides information relating to counterion effects in HFIP assisted systems (entries 20–22). Complex **4** showed no catalytic activity either in neat DCM or in a DCM/HFIP (9 : 1) mixture (entries 23 and 24). Finally, trifluoroethanol (TFE),



which is a widely used fluorinated alcohol solvent in H-bonding-assisted gold catalysis, was also tested and led to only a 20% yield of the product (entry 25). Replacing HFIP with phenol as an activator also failed to activate the reaction (entry 26). Compared with previously reported systems,^{22,32} using precatalyst **14** in the HFIP-activated protocol enables cyclization with an efficiency nearly equivalent to that of silver salt-activated reactions for producing the six-membered ring **3a**, although requiring slightly longer reaction times. Notably, using simple precatalyst **4** alone enables highly selective formation of the five-membered ring **2a**, a result rarely achieved in studies involving silver additives. This highlights the unique effectiveness of HFIP as a hydrogen-bonding solvent in promoting gold-catalyzed cycloisomerization under mild and practical conditions.

Having performed a thorough screening of ancillary ligands in the HFIP-assisted, gold-catalyzed cycloisomerization reaction of *N*-Tosyl-1,6-enyne **1a**. Next, the selectivity towards the formation of the 5-membered cycle seen with substrate **1a** under [Au(IPr)Cl] was also observed with propargylmalonates **1b–1d** (Scheme 2). Due to the Thorpe–Ingold effect,³¹ the reaction times were correspondingly shortened. The reactions of 1,6-enynes **1b** and **1c** proceeded smoothly to afford the corresponding vinyl cyclopentene derivatives **2b** and **2c** in quantitative yields within 1 hour. Substrate **1d** required 1.5 hours to reach full conversion. It is worth noting that when a phosphine-based catalyst is used in this case, no six-membered ring product was observed. When 1,6-enyne bearing a phenyl substituent on the alkyne was used as the substrate (See SI), no conversion was observed under the standard conditions. This observation is consistent with previous results,¹⁹ showcasing that the presence of steric hindrance near the alkyne bond prevents effective binding to a bulky gold catalyst.

We next examined the reactivity of variously substituted 1,6-enynes under the Au/HFIP catalytic system (Tables 2 and 3).



Scheme 2 Product selectivity in the cycloisomerization of various propargylmalonates **1a–1d**.^a Unless otherwise noted, the reaction was conducted with **1** (0.20 mmol) and **4** (0.002 mmol, 1 mol %) in HFIP (0.2 mL), the yield and selectivity determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard; Isolated yields are given in parentheses; reaction time: 4 h for **1a**, 1 h for **1b**, **1c**, 1.5 h for **1d**.

Table 2 The selectivity in the cycloisomerizations of diethyl propargylmalonates **1e**^a

Entry	Substrate	[Au]	Combined yield (%)	Selectivity ratio (2e : 3e)
1	1e	4	99 (95)	1 : 0
2		14	99	1 : 0

^a Unless otherwise noted, the reaction was conducted with **1e** (0.2 mmol) and [M] (0.002 mmol, 1 mol%) in HFIP (0.2 mL), 25 °C; the conversion and selectivity determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses; reaction time: 1 h.

Table 3 The selectivity in the cycloisomerizations of diethyl propargylmalonates **1f** and **1g**^a

Entry	Substrate	[Au]	Combined yield (%)	Selectivity ratio (2 : 3)
1	1f	4	85 (71%)	1 : 1.7
2		15	46	1.3 : 1
3		14	54	1 : 3.3
4	1g	4	28	13 : 1
5		15	80 (77%)	28 : 1
6		14	71	10 : 1

^a Unless otherwise noted, the reaction was conducted with **1** (0.2 mmol) and [M] (0.002 mmol, 1 mol%) in HFIP (0.2 mL), 25 °C, 2.5 h. Conversion and selectivity determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields are given in parentheses.

1e, bearing a methyl group, proceeded smoothly to afford the corresponding vinyl cyclopentene **2e** in 1 hour, regardless of whether **4** or **14** were used as catalyst.

Using the 1,6-enyne **1f** without any substituted group, gave a mixture of five-membered lactone **2f** and six-membered product **3f**, with a selectivity of 1 : 1.7 when complex **4** was used. Changing the catalyst to complexes **14** or **15** did not improve the yield or selectivity. Substrate **1g** afforded a mixture of **2g** and **3g** in 80% yield with excellent selectivity (28 : 1) when complex **15** was used as the catalyst, whereas only 28% yield and 13 : 1 selectivity was observed when **4** was employed. However, when a 1,7-enyne was subjected to the reaction conditions, only trace amounts of product were observed, indicating that the longer tether likely weakens the cooperative interaction between the reactive sites and thus severely reduces the reactivity (see SI).

In conclusion, we have developed a Au/HFIP catalytic system that enables the activation of [Au(L)Cl] complexes for the



cycloisomerization of 1,6-enynes under external activator-free conditions, providing a silver-free and efficient synthetic strategy. Moreover, in this protocol the simple precatalysts [Au(IPr)Cl] (**4**), [Au(PPh₃)Cl] (**14**) and [Au(JohnPhos)Cl] (**15**) exhibit excellent catalytic performance and afford outstanding yields and selectivity. Ongoing studies in our group aim to further explore the broader potential of HFIP in related catalytic transformations.

All authors contributed to the writing and revision of the manuscript. The final version of the manuscript has been approved by all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its supplementary information (SI). Supplementary information: experimental details and NMR spectra for all compounds. See DOI: <https://doi.org/10.1039/d5cc07022h>.

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References

- R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028–9072.
- A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211.
- A. S. K. Hashmi, *Chem. Rev.*, 2021, **121**, 8309–8310.
- Z. Lu, J. Han, G. B. Hammond and B. Xu, *Org. Lett.*, 2015, **17**, 4534–4537.
- D. Wang, R. Cai, S. Sharma, J. Jirak, S. K. Thummanapelli, N. G. Akhmedov, H. Zhang, X. Liu, J. L. Petersen and X. Shi, *J. Am. Chem. Soc.*, 2012, **134**, 9012–9019.
- D. Weber and M. R. Gagné, *Org. Lett.*, 2009, **11**, 4962–4965.
- A. Zhdanko and M. E. Maier, *ACS Catal.*, 2015, **5**, 5994–6004.
- A. Franchino, M. Montesinos-Magraner and A. M. Echavarren, *Bull. Chem. Soc. Jpn.*, 2021, **94**, 1099–1117.
- M. Wegener, F. Huber, C. Bolli, C. Jenne and S. F. Kirsch, *Chem. – Eur. J.*, 2015, **21**, 1328–1336.
- A. Guérinot, W. Fang, M. Sircoglou, C. Bour, S. Bezzenine-Lafollée and V. Gandon, *Angew. Chem., Int. Ed.*, 2013, **52**, 5848–5852.
- P. Nun, S. Dupuy, S. Gaillard, A. Poater, L. Cavallo and S. P. Nolan, *Catal. Sci. Technol.*, 2011, **1**, 58–61.
- J. Wolf, F. Huber, N. Erochok, F. Heinen, V. Guérin, C. Y. Legault, S. F. Kirsch and S. M. Huber, *Angew. Chem., Int. Ed.*, 2020, **59**, 16496–16500.
- H. F. Jónsson, D. Sethio, J. Wolf, S. M. Huber, A. Fiksdahl and M. Erdelyi, *ACS Catal.*, 2022, **12**, 7210–7220.
- R. Gauthier, N. V. Tzouras, Z. Zhang, S. Bédard, M. Saab, L. Falivene, K. Van Hecke, L. Cavallo, S. P. Nolan and J.-F. Paquin, *Chem. – Eur. J.*, 2022, **28**, e202103886.
- H. F. Motiwala, A. M. Armaly, J. G. Cacioppo, T. C. Coombs, K. R. K. Koehn, V. M. I. Norwood and J. Aubé, *Chem. Rev.*, 2022, **122**, 12544–12747.
- F. Caporaletti, L. Gunkel, M. Á. Fernández-Ibáñez, J. Hunger and S. Woutersen, *Angew. Chem., Int. Ed.*, 2024, **63**, e202416091.
- M. Piejko, J. Moran and D. Lebcœuf, *ACS Org. Inorg. Au*, 2024, **4**, 287–300.
- N. V. Tzouras, L. P. Zorba, E. Kaplanai, N. Tsoureas, D. J. Nelson, S. P. Nolan and G. C. Vougioukalakis, *ACS Catal.*, 2023, **13**, 8845–8860.
- N. V. Tzouras, A. Gobbo, N. B. Pozsoni, S. G. Chalkidis, S. Bhandary, K. V. Hecke, G. C. Vougioukalakis and S. P. Nolan, *Chem. Commun.*, 2022, **58**, 8516–8519.
- A. Munawar, L. T. Maltz, W.-C. Liu and F. P. Gabbaï, *Organometallics*, 2023, **42**, 2742–2746.
- S. G. Mahamulkar, I. Cisařová and U. Jahn, *Adv. Synth. Catal.*, 2018, **360**, 4215–4224.
- A. Cervantes-Reyes, F. Rominger, M. Rudolph and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2020, **362**, 2523–2533.
- C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan and A. M. Echavarren, *Chem. – Eur. J.*, 2006, **12**, 1677–1693.
- E. García-Padilla, F. Maseras and A. M. Echavarren, *ACS Org. Inorg. Au*, 2023, **3**, 312–320.
- S. Ito, M. Nanko and K. Mikami, *ChemCatChem*, 2014, **6**, 2292–2297.
- M. Freytag, S. Ito and M. Yoshifuji, *Chem. – Asian J.*, 2006, **1**, 693–700.
- S. Bastin, C. Barthes, N. Lugan, G. Lavigne and V. César, *Eur. J. Inorg. Chem.*, 2015, 2216–2221.
- K. Muratov and F. Gagosz, *Angew. Chem., Int. Ed.*, 2022, **61**, e202203452.
- A. Collado, D. J. Nelson and S. P. Nolan, *Chem. Rev.*, 2021, **121**, 8559–8612.
- V. A. Voloshkin, L. P. Zorba and S. P. Nolan, *Chem. Sci.*, 2025, **16**, 2062–2082.
- For the Thorpe-Ingold effect, see: R. M. Beesley, C. K. Ingold and J. F. Thorpe, *J. Chem. Soc. Trans.*, 1915, **107**, 1080–1106.
- C. Nieto-Oberhuber, M. P. Munoz, S. Lopez, E. Jimenez-Nunez, C. Nevado, E. Herrero-Gomez, M. Raducan and A. M. Echavarren, *Chem. – Eur. J.*, 2006, **12**, 1677–1693.

