Hexafluoroisopropanol (HFIP) as a multifunctional agent in gold-catalyzed cycloisomerizations and sequential transformations

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ABSTRACT: Despite the unique position of gold catalysis in contemporary organic synthesis, this area of research is notorious for requiring activators and/or additives that enable catalysis by generating cationic forms of gold catalysts. Cycloisomerization reactions occupy a significant portion of the gold-catalyzed reaction space, while they represent a diverse family of reactions which are frequently utilized in synthesis. Herein, hexafluoroisopropanol (HFIP) is shown to be a uniquely simple tool for gold-catalyzed cycloisomerizations, rendering the use of external activators obsolete, and leading to highly active catalytic systems with ppm levels of catalyst loading in certain cases. HFIP assumes a dual role as solvent and activator, operating *via* the dynamic activation of the Au-Cl bond through hydrogen bonding, which initiates the catalytic cycle. This special mode of catalysis can enable efficient and scalable cyclization reactions of propargylamides and ynoic acids with simple [AuCl(L)] complexes. A thorough screening of ancillary ligands and counter anions has been performed, establishing this methodology as an alternative to elaborate ligand/catalyst design and to the use of activators. Additionally, this concept is applied in C-C bond forming cycloisomerization reactions leading to 2*H*-chromenes and to the design of catalytic systems for sequential or one-pot transformations leading to activated ketoesters, a functionalized *N*-heterocyclic carbene (NHC) precursor salt, and a compound bearing the bioactive indole core, among others. Importantly, through mechanistic investigations including a "snapshot" of the species of interest in the solid state, we were able to unambiguously detect the key H-bonding interaction between HFIP and the gold catalyst, shedding light on the intermolecular mode of activation that enables catalysis. In the cases examined herein, HFIP is not only an excellent solvent, but also a potent activator and a valuable synthetic handle when incorporated into functional groups of products.

Introduction

Gold catalysis has become a vibrant field of chemistry during the last two decades and has remained a challenging, engaging, incredibly diverse, and innovation-oriented research topic for a long, uninterrupted period of time.[1] While the coordination chemistry of gold continues to occupy global research efforts and regularly offers new insights of fundamental importance,[2] the road towards establishing gold catalysis as a unique tool in contemporary organic synthesis has been paved with many discoveries regarding this metal's reactivity in the presence of various organic molecules.[3] The arguably unmatched ability of gold complexes for carbophilic activation of compounds bearing multiple bonds is frequently tuned by ancillary ligands such as *N*-heterocyclic carbenes (NHCs) and tertiary phosphines,[4,5] while the reaction-specific and intricate web of interactions between counter anions, additives and solvents is still being unraveled by detailed studies and recently developed models focusing on the topic of catalytic system design.[6,7] A fundamental concept in homogeneous gold catalysis, which continues to plague novice and experienced practitioners alike, is the activation of gold complexes. Specifically, this is the activation of the dormant site present in the vast majority of commercial and/or easily prepared, well-defined (pre-)catalysts: the Au-Cl bond.[8] With a high affinity towards gold, the chloride anion binds strongly to the metal center of linear two-coordinate Au(I) complexes and prevents the binding of substrates.[6,7b] The most widely practiced method for Au-Cl bond activation is the use of silver salts bearing weakly coordinating anions, which abstract the chloride ion, although not in a manner that can be considered exactly irreversible.[9] The hygroscopic and light-sensitive nature of silver salts, along with their interference in gold catalysis through activity and selectivity modulation, require the development of new methods to activate the Au-Cl bond in order to perform gold catalysis. The synthesis of well-defined gold complexes bearing weakly bound anions ("cationic" complexes in the broadest sense) has eliminated most problems associated with *in situ* silver activation, although this synthesis most often requires silver salts as well. The latter can persist in the final material, while the removal of silver *via* filtration through materials such as celite can also cause problems, stemming from basic impurities, and leading to less active or irregularly active catalysts.[10] A historically important method used to generate cationic gold

catalysts, either *in situ* or in a preparative manner, is the addition of acids to the Brønsted-basic gold complexes bearing hydrocarbyl, hydroxide or other reactive or sacrificial ligands.[11-15] However, this method requires installation of sacrificial ligands by pre-functionalizing [AuCl(L)] complexes (L = NHC or PR_3), therefore an additional step before catalysis and an acid additive are needed. Modern activation methods replace silver salts with copper salts or alkali metal borate salts, which can be advantageous.[16,17] However, we want to stress that no method is applicable to all, or even to most gold-catalyzed reactions, and importantly, modern or not, an additive remains an additive.

Ingenious approaches towards activating the Au-Cl bond have appeared in the last six years, focusing on dynamic modes of activation under which the chloride anion is reversibly removed. These can be broadly categorized as either intramolecular or intermolecular activation modes, depending on whether the activating interaction transpires because of a feature of the ancillary ligand or a feature of an external entity, which can be considered an additive, even though it operates in a different manner when compared to silver, copper or borate salts. More specific classification leads to three main categories: those that rely on ancillary ligand design to render complexes more electrophilic, those operating *via* halogen bonding, and those based on hydrogen bonding, be it intra- or intermolecular. Examples from the first category include the cobaltocene-containing NHC gold complexes and phosphaalkene/phosphinine-based gold complexes,[18,19] and also the recent gold complex bearing an ambiphilic phospine/xanthylium ligand reported by Gabbaï and co-workers.[20] The halogen bonding approach utilizes iodonium salts of various designs, used in stoichiometric amounts with respect to the gold chloride catalyst.[21] Hydrogen bonding between a functionality of the ancillary ligand and the Au-Cl moiety or between the latter, the ligand, and the solvent and/or substrate, has been the key concept upon which many unconventional catalytic systems have been based. In most cases these fall under the "intramolecular" category and the ligand design encompasses the seminal design of Gabbaï and co-workers with phosphines bearing fluorinated amide groups,[22] a phosphine bearing a phosphoric acid group,[23] NHCs with secondary amine-bearing *N*-substituents,[24] phosphanoxy-substituted phosphaalkenes,[25] and squaramide- or urea- functionalized phosphines.[26] We recently contributed to the area by carrying out ligand and counter-anion screening in gold-catalyzed reactions in hexafluoroisopropanol (HFIP), exploiting this solvent's exceptional hydrogen bond-donor character to develop the first intermolecular H-bonding activation regime.[27] More recently, during the preparation of this manuscript, a report using specially designed squaramides as intermolecular H-bonding activators has appeared.[28]

Being aware of the effects of hydrogen bonding on gold catalysis,[29,30] as well as the cases in which Au-Cl containing complexes have been used in catalysis owing to their ligand design rendering them highly electrophilic or enabling their interactions with water or deep eutectic solvents,[19,31-39] we extensively studied the HFIP-based activation mode in order to uncover its underlying mechanism and its true potential.[40,41] HFIP is a solvent that has received significant attention by the chemical community in recent years, because of its recyclability, and H-bonding donor property in combination with its low nucleophilicity, high acidity, and cation-stabilizing ability.[42,43] This solvent, along with trifluoroethanol (TFE), in some cases, leads to superior reaction systems for many classical organic transformations, can enable catalyst-free systems, and has proven to be exceptional in C-H activation reactions.[44,45] We chose to investigate its dual capabilities as a solvent and as an activating entity in gold-catalyzed cycloisomerization reactions, which have a central position in gold catalysis and diversity-oriented synthesis. [46,47] Three different reactions were selected for this purpose: the cycloisomerization of propargylic amides, which is a benchmark gold-catalyzed reaction, the lactonization of ynoic acids, and the C-C bond forming hydroarylation/propargyl-Claisen rearrangement of aryl propargyl ethers. During our studies, we discovered that HFIP has a hidden ability to act as a useful synthetic handle when added to an organic structure, and this ability is also explored.[48] Finally, we unambiguously uncover the intermolecular H-bonding interaction between HFIP and the Au-Cl bond, both theoretically and by directly observing it in the solid state.

Results and Discussion

The complexes depicted in Figure 1 were chosen for informative catalyst screening in the three different cycloisomerizations studied herein.[49]

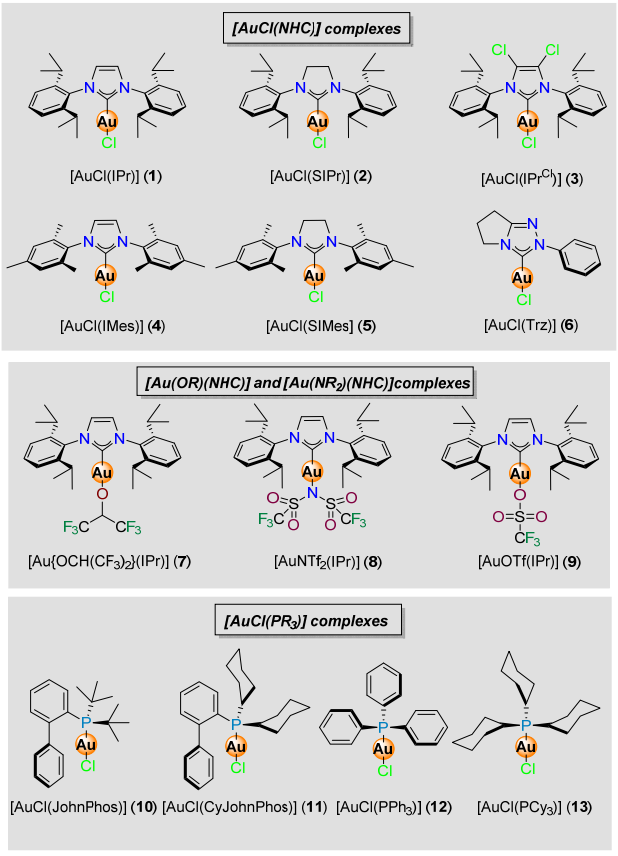


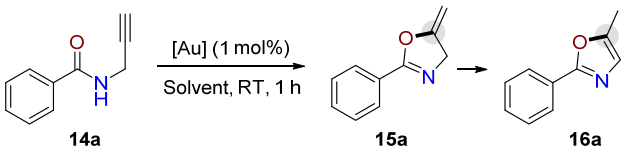
Figure 1. Selected gold complexes tested in this study.

Besides [AuCl(NHC] and [AuCl(PR_3)] complexes, which are the most interesting for practical reasons in these catalytic systems, the Brønsted-basic Au complex **7**, a stable and easily synthesized NHC-Au-polyfluoroalkoxide, allows us to probe the extent to which the acidic nature of HFIP, along with its associated hydrogen bonding network, are able to facilitate the binding of substrates and thus allow catalysis to occur for each of the three transformations. Comparing the catalytic activity of **7** to that of **1** and in turn to those of the already activated complexes **8** and **9** which bear weakly coordinating anions provides information relating to counterion effects in HFIP-assisted systems. In the case of *N*-propargyl benzamide cyclization,[7d,27,50] counterion effects were determined to be minimal, more so than in systems examined in other protic solvents;[51] therefore, it was deemed necessary to also conduct these experiments in other gold-catalyzed reactions in HFIP.

Having performed a thorough screening of ancillary ligands in the HFIP-assisted, gold-catalyzed cycloisomerization reaction of *N*-propargyl benzamide,[27] a more targeted approach was chosen in the present study. The superiority of phosphine ligands in this case, along with literature reports concluding that more electrophilic complexes display high catalytic activity in this reaction,[19] prompted us to examine whether appropriate changes in NHC design could improve the results obtained when using [AuCl(NHC)] catalysts. As shown in Table 1 (Entries 1, 2 and 3), a [AuCl(NHC)] catalyst with electron-withdrawing backbone substituents (**3**) and possessing a stereochemical profile very similar to IPr (IPr = *N,N′*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) led to higher yield of **15a** in 1 hour.[52] This stands in contrast to results obtained when using a catalyst with methyl substituents on the NHC backbone, which exhibited lower activity than **1**.[27] When the easily accessible 1,3,4-triazolylidene coordinated catalyst **6** was used,[17,18] the result was significantly closer to those obtained with [AuCl(PR_3] complexes (Table 1, Entry 4). This is in line with the observations reported in the literature regarding this catalytic reaction and showcases that appropriate ligand design can significantly improve catalyst performance in this system. Finally, an important test was carried out to examine the potential of another widely used fluorinated alcohol solvent in H-bonding-assisted gold catalysis: trifluoroethanol (TFE). As expected, based on our hypothesis that it is the exceptional H-bonding donor ability of HFIP that allows activation of the dormant Au-Cl bond, the use of TFE led to only a 47% yield of **15a** in one hour, which corresponds to half the turnover number obtained when HFIP is used (Table 1, Entries 2 and 5). Although it is notable that TFE can also act as a useful solvent for activator-free gold catalysis, HFIP is clearly a superior solvent in this case, considering its lower toxicity and easier recyclability.

The transformation of **14a** into oxazoline **15a** is the most widely studied gold-catalyzed reaction exploring novel Au-Cl activation manifolds.[19-27] To thoroughly compare our simple system to others of similar nature, representative propargylic amides were subjected to these conditions (Scheme 1). Although many of these innovative catalytic systems employ 2 mol% [Au] or higher,[19-25,28] we purposefully do not exceed 1 mol% loading throughout our studies, since the circumvention of expensive additives and

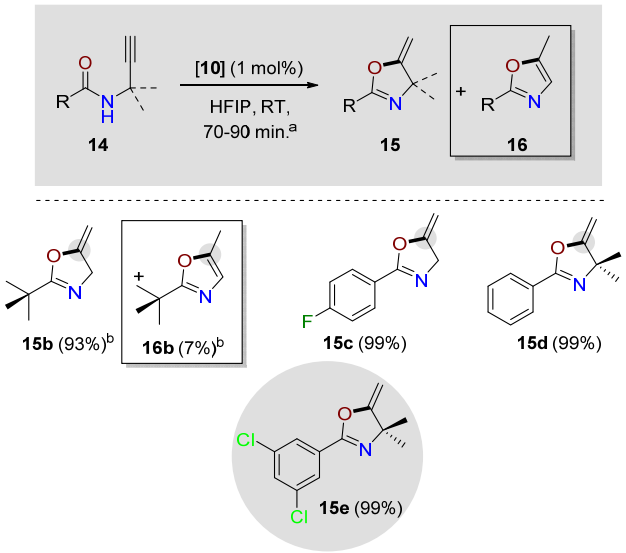
Table 1. Informative screening in *N*-propargyl benzamide (14a) cyclization.



Entry[a]	[Au]	Solvent	15a[b] (%)	16a[b] (%)
1[c]	**1**	HFIP	50	-
2[c]	**10**	HFIP	95[d]	<1
3	**3**	HFIP	61	<1
4	**6**	HFIP	85	<1
5	**10**	TFE	47	<1

[a] Reaction conditions: 0.5 mmol of **14a**, 0.005 mmol (1 mol%) catalyst, 0.250 mL of HFIP, 20-25 °C, 1 hour. [b] Percentages correspond to the yields as determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene internal standard and are the average of two runs. [c] From reference 27. [d] 99% when reaction time is 70 minutes.

Scheme 1. Scope of the HFIP-assisted, [AuCl(L)]-catalyzed propargylic amide cyclization.



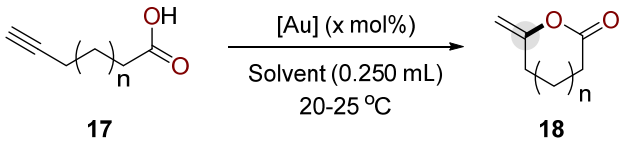
[a] Reaction conditions unless otherwise noted: 0.5 mmol of **14**, 0.005 mmol (1 mol%) **10**, 0.250 mL of HFIP, 20-25 °C, 70 minutes for **14b** and **14c**, 90 minutes for **14d** and **14e**. Isolated yields are shown in parentheses. [b] Volatile product, yields determined by ^{1}H-NMR after full conversion of **14b.**

activators should not come at the cost of additional quantities of precious gold complexes in order to perform efficient catalysis. Thus, our system is competitive with the state-of-the-art catalytic systems, already having the advantage of lower than average catalyst loading.[19] The electron rich, alkyl-substituted propargylic amide **14b** was efficiently converted to the cyclized products **15b** and **16b** without deviating from the optimal conditions, including the reaction time of 70 minutes, which is less than that of most related systems regardless of catalyst loading; however, the percentage of the oxazole product was relatively high in this

case. The comparatively electron deficient propargylic amide **14c** led to the desired product **15c** in quantitative yield in 70 minutes. Usually, this product is obtained after longer reaction times (4-8 hours).[17,24,26] A substrate which also usually requires longer reaction times to be fully converted, because of the steric hindrance imparted by the two propargylic methyl substituents (**14d**),[24] only required 90 minutes to quantitatively lead to **15d** under these conditions. Encouraged by this result, suggesting a robust and reliable catalytic system, we applied this cycloisomerization method to the commercial herbicide propyzamide (**14e**),[53] obtaining the corresponding methylidene oxazoline product **15e** in quantitative yield after 90 minutes. Of note, under the conditions reported here, this transformation takes place cleanly for all examined substrates, without exclusion of air or moisture. Moreover, isolation of the product is simply a matter of removing **10** by evaporating HFIP and filtering the mixture through a short (*ca*. 2 cm) silica plug, using pentane as the eluent.

Continuing with the exploration of the potential of this system, a targeted screening was performed in the case of the HFIP-assisted, gold-catalyzed intramolecular hydroacyloxylation of alkynoic acids (Table 2).[27] The high activity of **1** (0.01 mol%) in the cyclization of 5-hexynoic acid (**17a**) was confirmed by the isolation of the corresponding alkylidene lactone **18a** in quantitative yield after ten minutes of reaction time (Table 2, Entry 1). Complex **3** displayed high catalytic activity in these transformations as well (Table 2, Entry 2). It is established that the (2,3-diisopropyl)phenyl- group on the NHC ligand is the key feature in catalyst design for reactions of this type.[5,27,46,54,55] The Brønsted-basic Au complex **7** also displayed notable activity in HFIP, with 65% conversion/yield in ten minutes (Table 2, Entry 3). Brønsted-basic Au complexes are known to be active in transformations involving the addition of carboxylic acids to alkynes; however, the activity we observe in HFIP is remarkably higher than that observed in toluene or under neat (solventless) conditions.[54,56] Still, the activity of this complex lags **1** and is in contrast with our observations in the case of propargylic amide cyclization. It is expected however that different factors will influence alkynoic acid cyclization, another one being for example the superiority of the IPr ligand in the latter case. The activated complex **9**, even at 1 mol% loading, only led to 30% yield of the desired product in ten minutes, while side-products and mostly starting material could be detected in the mixture (Table 2, Entry 4). Performing the reaction in TFE under otherwise optimal conditions only led to 12% conversion/yield, which is significantly diminished, even though it still corresponds to a TOF value of 3600 h^{-1} and full conversion can be reached in TFE with 0.1 mol% catalyst loading and longer reaction time (Table 2, Entries 5 and 6). In HFIP, 10 ppm of **1** are sufficient to achieve full conversion of **17a** to **18a** in 16 hours, while 1 ppm still leads to 83% conversion after the same time (Table 2, Entries 7 and 8). With 10 ppm catalyst loading of **1**, a conversion/yield of 39% was obtained in 1 hour, which corresponds to a TOF value of 39000 h^{-1} (Table 2, Entry 9). It is noteworthy that stock solutions of **1**, **7**, and **10** in HFIP with a concentration of 0.0025 M or lower, were stable and retained their activity for more than six months. However, this remarkable catalytic activity does not continue to apply when a seven-membered lactone is targeted, and 1 mol% of **1** and prolonged reaction time are required to reach full conversion to **18b** (Table 2, Entries 10 and 11). This transformation also enables the clear establishment of the IPr ligand's superiority over IPr^{Cl} and JohnPhos, with the latter leading to a significantly lower yield than its NHC counterparts (Table 2, Entries 12 and 13). Notably, the construction of the seven-membered ring in **18b** proceeded in a straightforward manner in all cases, without the need to lower concentration as no side products were observed. This is an important factor to consider, even for otherwise highly active catalysts.[56,57]

Table 2. Informative screening in alkynoic acid cyclization.



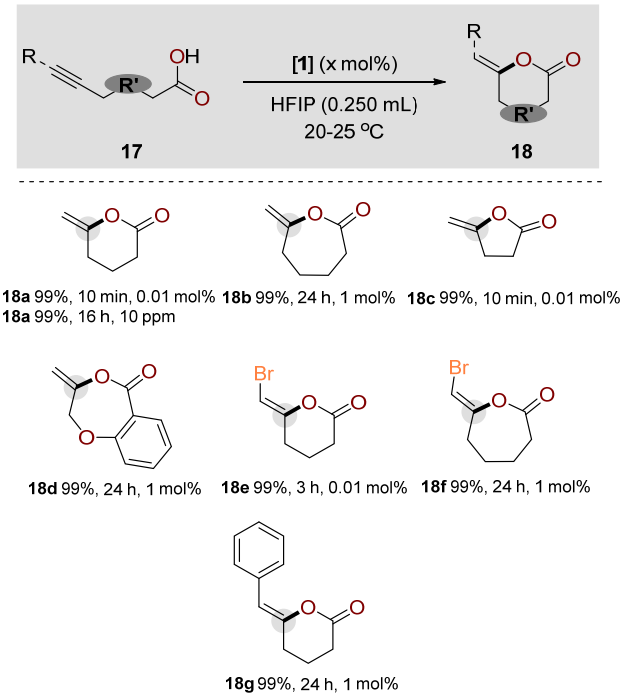
17 **18**

Entry[a]	[Au]	Solvent	Time	Yield[b](%)
1[c]	**1**	HFIP	10 min	99[d]
2[c]	**3**	HFIP	10 min	99
3[c]	**7**	HFIP	10 min	65
4[ce]	**9**	HFIP	10 min	30
5[c]	**1**	TFE	10 min	12
6[c,f]	**1**	TFE	16 h	99
7[cg]	**1**	HFIP	16 h	99
8[ch]	**1**	HFIP	16 h	83
9[cg]	**1**	HFIP	1 h	39
10[e,i,j]	**1**	HFIP	16 h	88
11[e,i]	**1**	HFIP	24 h	99[d]
12[e,i]	**3**	HFIP	16 h	79
13[e,i]	**10**	HFIP	16 h	32

[a]Reaction conditions unless otherwise noted: 0.5 mmol of **17**, 0.01 mol% of catalyst (from stock solutions in HFIP or TFE), 0.250 mL of HFIP, 20-25 °C, 1 hour. [b] The percentages correspond to the yields as determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene internal standard unless otherwise noted. [c] n = 1. [d] Isolated yield. [e] 1 mol%. [f] 0.1 mol%. [g] 10 ppm. [h] 1 ppm. [i] n = 2. [j] From reference 27.

Having optimized the reaction parameters to obtain lactones **18a** and **18b** (Scheme 2), further exploration of the scope was in order. The five-membered lactone **18c** was obtained under identical conditions to those used in the case of **18a**, which was anticipated. A more complex seven-membered lactone bearing an allylic ether functionality and an aromatic, carboxylic enol ester functionality (**18d**) was obtained under the conditions required for **18b**. Substrates bearing internal alkyne groups, including 6-bromo- and 6-phenyl-substituted alkynoic acids, were also subjected to our conditions, with certain modifications that were required for full conversion to products. Thus, lactones **18e**, **18f** and **18g** were obtained in quantitative yields after some substrate-specific screening of conditions for their convenient synthesis in HFIP. Of note, column chromatography was unnecessary in all cases and the products were obtained

Scheme 2. Scope of the HFIP-assisted, [AuCl(L)]-catalyzed ynoic acid cyclization.



[a] Reaction conditions unless otherwise noted: 0.5 mmol of **17**, 0.01 or 1 mol% of catalyst (from stock solutions in HFIP), 0.250 mL of HFIP, 20-25 °C for the indicated time. Isolated yields are shown.

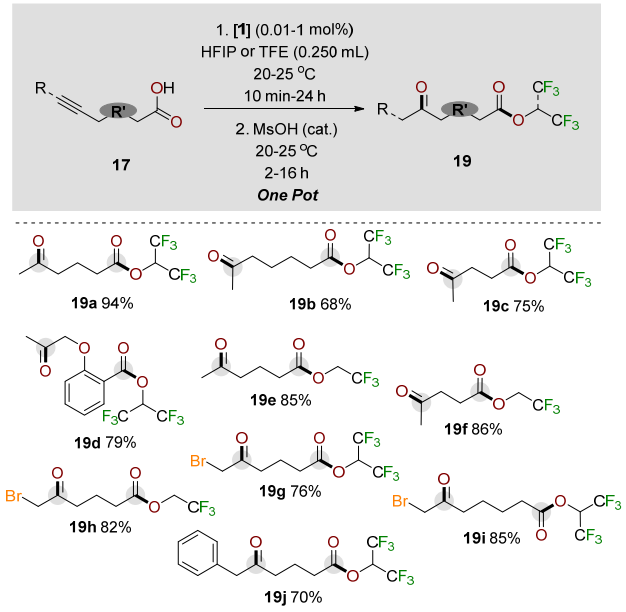
after evaporation of HFIP and filtration through short (*ca.* 2 cm) silica plugs with suitable solvents. As for comparison with state-of-the-art systems, this simple system not only circumvents the use of activators or additives or more complex catalysts, it also proved to be highly efficient in some cases, reliable in all cases, and chemo-, regio-, and stereoselective, considering the quantitative conversion to the desired lactones, without exclusion of air or moisture to avoid the competitive alkyne hydration reaction.[31-36,55] Low catalyst loading, high selectivity while operating under air and at room temperature, short to moderate reaction times and generally the synthetic ease that accompanies these features, along with the recyclable HFIP solvent, establish this system as one among the state-of-the-art.[55]

Despite the low nucleophilicity of HFIP and its ability to stabilize cationic species,[43] there are several cases in which the hexafluoroisopropoxy- moiety is incorporated, not always intentionally, into the structure of organic molecules acting as substrates or products.[41,48,58] This non-innocent behavior of HFIP is anything but a disadvantage when occurring in a controllable fashion, as we showcase here, given that the moiety in question may serve as an additional functionalization handle. This has been shown in an early example examining the spontaneous acetalization of enol ethers in HFIP,[58a] as well as more recently in the generation of the corresponding HFIP-derived *N,O*-acetals.[41,48,] Based on these precedents, as well as the recently reported Rh-catalyzed C-H activation/base-assisted solvolysis of enol esters with TFE,[58f] we next explored a sequential transformation.

After subjecting the ynoic acids to the optimized lactonization protocol in HFIP or TFE, methanesulfonic acid (MsOH) was added as a catalyst, triggering the reaction between the solvent and the enol lactones (Scheme 3). MsOH was chosen as it is a non-aqueous and easily handled/removable acid on this scale and on larger scale (*vide infra*). The result was the formal hydration of the alkyne functionality, generating an ω-ketone group along with the formation of a hexafluoroisopropyl- ester group. This is reminiscent of the acyl group transfer methodology developed by Kita and coworkers, which has found numerous applications in organic synthesis, only in this case the vinyl ester is part of a ring and the nucleophile is the solvent itself.[59] Gold-catalyzed cycloisomerization followed by Brønsted acid-mediated rearrangements can be a powerful sequence of reactions, with recent application in total synthesis.[60] In this fashion, the library of hexafluoroisopropyl ω-ketoesters derived from the lactones of Scheme 2 and HFIP or TFE was rapidly generated without the need for tedious purification procedures (Scheme 3). A simple extraction with diethyl ether and water was sufficient in removing MsOH, while evaporating the organic phase and removing the residual gold catalyst by filtration through short (*ca.* 2 cm) silica plugs with suitable solvents gave the desired products in high yields. The only case in which purification by column chromatography was required was for product **19d**, as the procedure also led to partial dealkylation of the aryl ether functionality. The corresponding phenol was detected by GC/MS and a pure sample was isolated from the chromatographic purification, which was enough for characterization by ^{1}H-NMR spectroscopy. Changing the number of equivalents of MsOH, adding it while the reaction is at 0 °C (ice bath), and reducing the reaction time, did not lead to a more selective reaction in this case. Thus, with this sequential, controllable, one-pot procedure, we obtained linear ketoesters of varying lengths and two different fluorinated groups (**19a**, **19b**, **19c**, **19e**, **19f**), α-bromoketones **19g**, **19h**, and **19i**, which are compounds with a particular reactivity under basic conditions in TFE or HFIP,[61] and a product with a benzylic ketone functionality (**19j**). Some optimization was performed for this step: such products could not be efficiently and selectively obtained if the mixture was heated in the absence of MsOH, and the acid had to be added after full conversion to the lactone was reached. The reaction time required for complete solvolysis was significantly less than 16 hours (*vide infra*); however, we determined that since the products did not undergo decomposition, it was simpler to let reactions stir for a longer time as a general protocol. It should be noted that hexafluoroisopropyl esters have been shown to be useful synthons.[43d,62-64] Aside from their activated nature which enables them to undergo nucleophilic addition by compounds bearing hydroxyl groups or by various amines without the presence of coupling agents, they also lead to higher enantioselectivities in the asymmetric Kulinkovich cyclopropanation.[64]

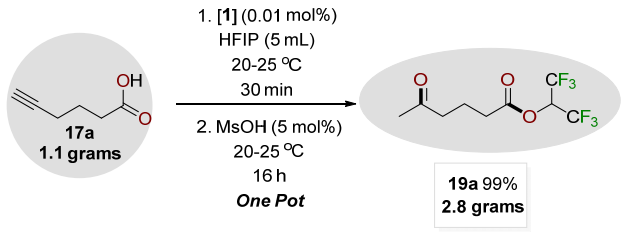
As a testament to the practical value of this system, the synthesis of **19a** was performed on a 10 mmol scale (Scheme 4). Because of the larger scale, more time than necessary was purposefully allocated to each step. The first step is slightly exothermic, which was not noticeable on smaller scale, while for the second step, a water bath had to be added to avoid overheating of the reaction. Using *less*

Scheme 3. Scope of the HFIP- or TFE-assisted, [AuCl(L)]-catalyzed ynoic acid cyclization and the one pot, MsOH-catalyzed enol lactone solvolysis.



[a] Reaction conditions unless otherwise noted: 0.5 mmol of **17**, 0.01 or 1 mol% of catalyst (from stock solutions in HFIP or TFE), 0.250 mL of HFIP or TFE, 20-25 °C for the time indicated for each substrate in Scheme 2. For **19e**, **19f** and **19h**, 0.1 mol% of **1** was used and the reaction was stirred for 16 h before addition of MsOH (see the Supplementary Information for details). Isolated yields are shown.

Scheme 4. Large-scale synthesis of 19a.

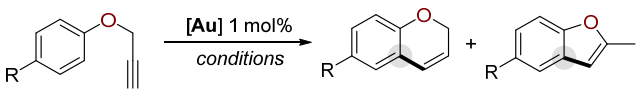


[a] Conditions: 10 mmol of **17a**, 0.01 mol% of catalyst (0.6 mg, from stock solution in HFIP), 5.0 mL of HFIP, 20-25 °C for 30 minutes, then MsOH (0.5 mmol, 32 µL), 16 hours.

*than 1 mg of [AuCl(IPr)] (**1**)* and only 32 µL of MsOH, quantitative yield amounting to *2.8 grams of product* (**19a**) was obtained after a simple work-up procedure.

Having explored the HFIP-assisted, gold-catalyzed cyclization reactions of propargylic amides and ynoic acids, the logical next step was to probe the generality of HFIP as an agent with this dual role of solvent and activator. The use of gold catalysis by the organic synthesis community is largely based on powerful protocols for cyclization reactions involving C-C bond formation. Therefore, it is important to explore this side of gold chemistry using HFIP as a tool. A reaction which is known not to occur in the presence of [AuCl(L)] complexes unless there are silver salts present is the formal intramolecular hydroarylation of *O*-tethered alkynes in aryl propargyl ethers (also classified as a propargyl-Claisen rearrangement) to generate primarily 2*H*-chromenes.[65-67] This transformation can occur at very high temperatures (>200 °C) in *N*,*N*-diethylaniline; however, cationic gold catalysts (typically 1-5 mol%) lead to excellent yields in short reaction times at room temperature. The reaction rate and the regio- and chemo-selectivity depend heavily on the exact composition of the catalyst, as well as on the substituents on the aromatic part of the substrate, among other factors, as shown by the Banwell, Stratakis, Kanan and other research groups in detailed studies.[66-73] An intermediate in the synthesis of substrate **17d** is such an aryl propargyl ether with a methyl ester group (an electron-withdrawing group) adjacent to the propargyl ether functionality. As a proof-of-concept, we subjected this compound to our cyclization protocol using 1 mol% of **1** in 300 µL HFIP for 20 hours, obtaining only 10% yield of the desired product (see the Supplementary Information for details). At 60 °C, the yield was increased to 50%; however, these are rather harsh conditions compared to those described herein for other reactions, therefore a change of substrate was in order. As shown in Table 3, substrates **20a** and **20b**, bearing electron-rich and neutral arene cores respectively, were chosen for further tests. In the absence of gold, no conversion of the substrate was observed, while at 60 °C only 23% yield of the desired product **21a** was obtained along with 8% of the benzofuran co-product **22a** (Table 3, Entries 1 and 2). The formation of benzofurans as products of this rearrangement under gold catalysis is a known process,[66-73] while the formation of free phenol and unidentified side-products account for the remaining amount of starting material when full conversion was achieved throughout this work.[74] At room temperature, however, 70% yield of **21a** was obtained, along with 10% of **22a** (Table 3, Entry 3). This result is a proof-of-concept that C-C bond-forming cycloisomerization reactions can be achieved effectively under our conditions, while it appears that the formation of non-trivial amounts of the benzofuran and other side-products is a characteristic of this system regardless of substrate or catalyst, possibly stemming from the protic/acidic nature of HFIP. A screening of complexes ensued (Table 3, Entries 4-13), suggesting that complex **10** is the most selective among the catalysts that were capable of leading to full conversion. Complexes bearing smaller ancillary ligands did not lead to full conversion, presumably because of decomposition in the reaction mixture (Table 3, Entries 6-8, 11 and 12), which was visibly evident by intense colour changes, attributable to generation of gold nanoparticles. Contrary to the other two catalytic reactions studied so far, complex **7** was not a competent catalyst in this case (Table 3, Entry 13). Although the 20-hour mark was the standard so far as a means to allow all reactions to reach completion, the reaction was allowed to proceed for only 1 hour, so that catalysts can be compared. **1** and **10** led to high conversions and appreciable yields of the desired product, while TFE proved to be an inferior solvent in this case as well (Table 3, Entries 14-16). Activated complexes **8** and **9** led to violently exothermic reactions in HFIP, full conversion as expected, and good yields of **21a**; however, increased amounts of the benzofuran **22a** were also produced, presumably because of the uncontrolled temperature increase upon catalyst addition (Table 3,

Table 3. Conditions screening in alkyne hydroarylation/propargyl-Claisen.



20a R = OMe
20b R = H

21a R = OMe
21b R = H

22a R = OMe
22b R = H

Entry[a]	Substrate	[Au]	Solvent	Temperature (°C)	Time (h)	Conversion[b] (%)	21[b] (%)	22[b] (%)
1	**20a**	-	HFIP	RT	20	0	0	0
2	**20a**	**1**	HFIP	60	20	100	23	8
3	**20a**	**1**	HFIP	RT	20	100	70	10
4	**20a**	**10**	HFIP	RT	20	100	81	9
5	**20a**	**11**	HFIP	RT	20	100	76	7
6	**20a**	**12**	HFIP	RT	20	96	68	-
7	**20a**	**13**	HFIP	RT	20	92	62	-
8	**20a**	**6**	HFIP	RT	20	96	68	-
9	**20a**	**2**	HFIP	RT	20	100	75	15
10	**20a**	**3**	HFIP	RT	20	100	72	11
11	**20a**	**4**	HFIP	RT	20	81	9	5
12	**20a**	**5**	HFIP	RT	20	80	11	4
13	**20a**	**7**	HFIP	RT	20	18	15	3
14	**20a**	**1**	HFIP	RT	1	92	65	10
15	**20a**	**10**	HFIP	RT	1	80	65	9
16	**20a**	**10**	TFE	RT	1	28	10	10
17	**20a**	**8**	HFIP	RT	1	100	68	23
18	**20a**	**9**	HFIP	RT	1	100	65	22
19	**20a**	**10**	HFIP	RT	2	100	71[c]	9[c]
20	**20b**	**10**	HFIP	RT	2	89	63	10
21	**20b**	**10**	HFIP	RT	3	100	59[c]	11[c]

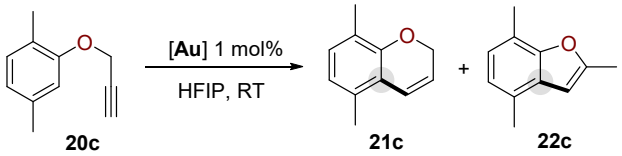
[a] Reaction conditions unless otherwise noted: 0.5 mmol of **20**, 0.005 mmol (1 mol%) catalyst, 0.3 mL of HFIP or TFE, 20-25 °C. [b] The percentages correspond to the yields as determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene internal standard. [c] Isolated yield.

Entries 17 and 18). After 2 hours, full conversion was reached with **10** as the catalyst, leading to isolated yields of **21a** (71%) and **22a** (9%) as a mixture (Table 3, Entry 19). When a neutral substrate was used, the time required to reach full conversion was increased, as expected, and a total of 70% isolated yield was obtained (Table 3, Entries 20 and 21). The percentage corresponding to side-products is higher in this case, even though these isolated yields are in line with the values obtained by Banwell and co-workers using a cationic, JohnPhos-based catalyst.[69]

When a sterically demanding substrate was used, no difference was observed in the outcomes of using **1** or **10** as catalysts (Table 4). In fact, the reaction was completed in less than 1 hour, presumably because of inductive electron donation from the two methyl groups. The isolated yield was

higher in this case as well, with a slightly increased percentage of the benzofuran product (Table 4, Entry 5).

Table 4. Conditions screening in alkyne hydroarylation/propargyl-Claisen of a sterically demanding substrate.



20c **21c** **22c**

Entry[a]	[Au]	Time (h)	Conversion (%)	21[b] (%)	22[b] (%)
1	**1**	20	100	73	13
2	**1**	2	100	73	13
3	**10**	2	100	72	13
4	**10**	1	100	71	13
5	**1**	1	100	77[c]	14[c]

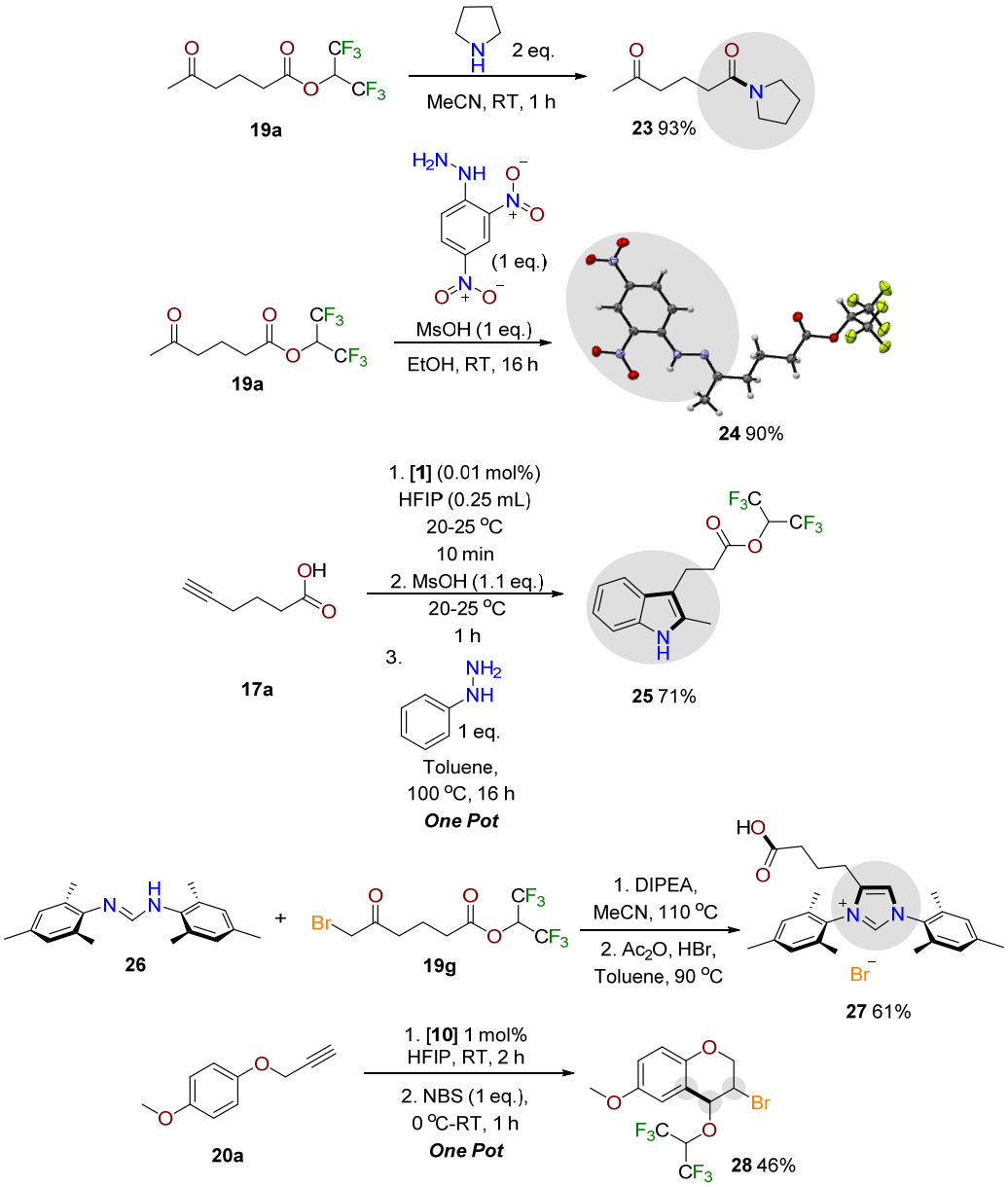
[a] Reaction conditions unless otherwise noted: 0.5 mmol of **20c**, 0.005 mmol (1 mol%) catalyst, 0.3 mL of HFIP, 20-25 °C. [b] The percentages correspond to the yields as determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene internal standard. [c] Isolated yield.

The utility of HFIP-assisted gold catalysis in C-O and C-C bond forming cycloisomerizations has been established. To place this simple and synthetically valuable concept within the context of organic synthesis, we performed reactions that would exemplify the utility of the products or the methodology itself as parts of broader synthetic sequences (Scheme 5). Taking advantage of the activated character of hexafluoroisopropyl esters, an amide bond can be constructed by simply adding pyrrolidine to **19a** at room temperature and without any coupling agents commonly used to construct such bonds. Product **23** has been previously synthesized *via* a remote C-H oxidation protocol in moderate yield.[75] To unambiguously determine the atom connectivity of the ketoester products and to gauge the reactivity of the ketone group in the presence of the hexafluoroisopropyl ester, the hydrazone product **24** was synthesized in EtOH, using 1 equivalent of MsOH. This sequence (from **17a** to **24**) can be performed in one-pot, in the absence of ethanol (*vide infra*), while this experiment confirms the compatibility of the hexafluoroisopropyl ester group with alcohols under acidic conditions. Single crystals of **24** were obtained as orange needles after vapor diffusion of pentane into a chloroform solution of **24** and the X-ray molecular structure was determined. After confirming the synthesis of **24**, the potential for a four-step, one-pot sequence of gold-catalyzed lactonization, MsOH-catalyzed solvolysis, hydrazone formation, and Fischer indole synthesis was apparent.[76] In this manner, phenylhydrazine and toluene were added to the vial after the formation of **19a** was completed and the mixture was heated overnight to efficiently produce compound **25** bearing the indole core and the valuable hexafluoroisopropyl ester group.

The products bearing the α-haloketone functionality along with the hexafluoroisopropyl ester group are particularly interesting, given that the functionality in question has been utilized as a building block for imidazolium salts with substituted backbones.[77] These NHC precursors have additional potential in transition metal chemistry and organocatalysis, while also presenting the opportunity for heterogenization or tethering by exploiting the backbone substituents.[78] By subjecting **19g** to the reported conditions, the imidazolium salt **27** was generated in 61% isolated yield on small scale after chromatographic purification. The hexafluoroisopropyl moiety did not withstand the procedure, as the ester was likely hydrolyzed during the first step; however, this is only a minor inconvenience from a synthetic perspective. We were able to identify the bromide anion of this salt by ESI-MS, also observing the corresponding anionic carbene (with a deprotonated carboxylic acid group), while HRMS and NMR confirmed the structure of the imidazolium cation. To our surprise, this structure is rather rare, with only few examples of smaller, *N*-alkyl-substituted imidazolium salts having been prepared via an entirely different route.[79] Finally, being aware of the enhancing effects of HFIP on electrophilic bromination with N-bromosuccinimide (NBS),[80] we designed a second reaction sequence, which would controllably lead to grafting of the hexafluoroisopropoxy moiety onto the scaffold of a gold-catalyzed reaction product. Therefore, after the HFIP-assisted, gold-catalyzed hydroarylation/propargyl-Claisen reaction was complete, 1 equivalent of NBS was added to the solution, affording **28** as the primary product. This compound is a highly functionalized chroman, reminiscent of a halohydrin in terms of structure and method of preparation.[81] The addition of NBS must be performed while the reaction is in an ice bath, given that it is violently exothermic. Also, while this is not an optimized procedure, the reaction time should not exceed 1 hour, as unidentified side-products are generated in the mixture if left stirring at room temperature. Overall, a synthetically useful yield of 46% over two steps was obtained under non-optimized conditions and purification procedures. The structure of **28** was confirmed by MS and NMR, with the characteristic fluorine-coupled signal of the proton nucleus of the hexafluoroisopropoxy moiety corelating with that of the only H nucleus whose signal can be a singlet, as suggested by the corresponding cross-peak in 2D-NOESY. Interestingly, the ^{1}H-decoupled, ^{19}F-NMR spectrum shows two signals as quadruplets, suggesting the inequivalence of the two trifluoromethyl groups, which arises presumably because of conformational/rotational restrictions. With this example, along with the variety of compounds shown in Scheme 3, one might envision the development of more synthetic sequences exploiting the robust features of HFIP-assisted gold catalysis and the reactive nature of the hexafluoroisopropoxy appendage.

The entirety of our catalytic experiments is predicated on the hypothesis that HFIP operates as an activator of Au-Cl bonds in the presence of π-nucleophilic substrates and that the mode of activation is hydrogen bonding between the hydroxyl group of HFIP and the chloride ligand. Catalysis is possible in HFIP with [AuCl(L)] complexes, as we have demonstrated, and it can be highly efficient in certain cases, with this system rivaling even those based on the most active cationic catalysts. It is therefore a plausible hypothesis.

Scheme 5. Synthetic utility and sequential transformations



[a] Reactions performed under air, on a 0.5 mmol or smaller scale (see the Supplementary Information for details). The X-ray molecular structure of hydrazone **24** is depicted, showing thermal displacement ellipsoids at the 50% probability level (CCDC = 2244746). Selected bond lengths (Å) and angles (°): C=N = 1.389(2), O-CH$(CF_3)_2$ = 1.414(3), OC-OCH$(CF_3)_2$ = 1.381(2), dihedral angle O=C-O-C$(CF_3)_2$-H = 16.68.

However, it is also imperative here to determine how HFIP interacts with these gold complexes. The ^{1}H- and ^{13}C{^{1}H} NMR spectra of both [AuCl(IPr)] (**1**) and [AuCl(JohnPhos)] (**10**) in the presence of 8-10 equivalents of HFIP exhibit changes for certain key signals, such as the C2 carbon of IPr and the proton nuclei of the backbone which are now located slightly upfield and the ^{31}P-NMR signal located slightly downfield. These are slight changes pointing towards the formation of species which are more "cationic" in nature;[8,14] however, combined with the complete picture of the spectra, which involves a significantly different aromatic region in the case of JohnPhos and differences in the relative chemical shifts of the diisopropyl groups of IPr, there is evidence of a different environment in the close vicinity of the ancillary ligands, attributed to HFIP (see the Supplementary Information for spectra). Up to this point there was no clear evidence of hydrogen bonding, and combined with the lack of hard evidence in most cases of intermolecular, dynamic activation of Au-Cl bonds, be it through halogen bonding or a case of intermolecular hydrogen

bonding that appeared after our first report on HFIP and during the preparation of this manuscript,[28] the probability of obtaining such evidence seemed low.[82] However, inspired by the work of Gabbaï and co-workers on Au---H-O hydrogen bonds and their data on intermolecular Au-Cl---H-O hydrogen bonding between two molecules of their hydroxyl group-containing complex,[83] we attempted to co-crystallize **1** and **10** with HFIP. It should be noted at this point, that recent reports by others and by us have shown evidence in the solid state for intermolecular hydrogen and halogen bonding in gold fluoride or gold bifluoride complexes; however, these cases involve fluoride and activating molecules which are not volatile solvents such as HFIP.[30, 84] After numerous attempts including slow vapor diffusion of solvents, such as pentane and diethyl ether into concentrated solutions of **1** and **10** in HFIP or in dichloromethane/HFIP mixtures, the complexes either precipitated, remained in solution, or crystallized without HFIP being present in the asymmetric unit. Slow evaporation of HFIP from a solution of **1** (10 mg in 0.6 mL) at 4 °C in a controlled manner, gave single crystals of suitable quality for X-ray diffraction analysis. Remarkably, the molecular structure features an HFIP molecule clearly engaging in hydrogen bonding through the O-H moiety with the chloride anion bound to gold (Figure 2). This structure represents a "snapshot" of the activating role of HFIP and strongly supports our working activation hypothesis.

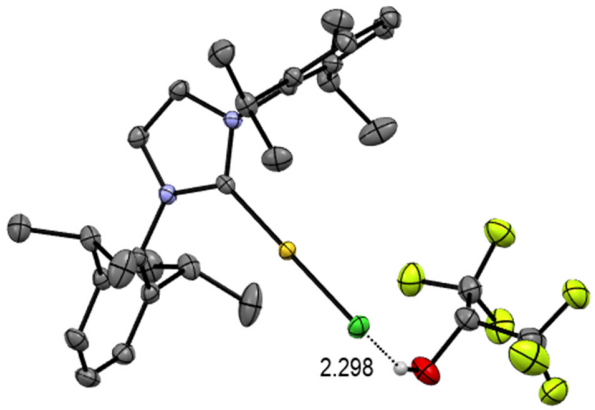


Figure 2. Hydrogen bonding interaction between **1** and HFIP in the solid state. The X-ray molecular structure is depicted, showing thermal displacement ellipsoids at the 50% probability level and most hydrogen atoms are omitted for clarity (CCDC = 2244745). Selected bond lengths (Å) and angles (°): C_{NHC}-Au = 1.981(3), Au-Cl = 2.2895(8), O-H = 0.840, C_{NHC}-Au-Cl = 179.68(9). Selected bond lengths (Å) and angles (°) for **1**: C_{NHC}-Au = 1.942(3), Au-Cl = 2.2698(11), C_{NHC}-Au-Cl = 177.0(4).

A closer look at this molecular structure of IPrAuCl---H-OCH$(CF_3)_2$ reveals interesting information in comparison to the molecular structure of **1**.[85] The Au-Cl bond is elongated in the former case (Figure 2), while the same is true for the Au-C_{IPr} bond. The degree of linearity of IPr-Au-Cl is unexpectedly increased when HFIP is present. The O-H and Au-Cl bond lengths are in line with the data reported by Gabbaï and co-workers for their dimeric structure where a phosphine ligand is present. Of note, even though this information supports our hypothesis, the effects of hydrogen bonding on the Au-Cl bond are expected to be enhanced in solution, as there will be a network of hydrogen bonds with a Au-Cl terminus. Of course, it would be impossible to crystallize such species under standard laboratory conditions, therefore we turned to computational methods as a means to gain more insights into the hydrogen bonding-assisted initiation step of catalytic cycles.

DFT calculations were carried to further probe the origin of these effects (Figure 3). The initiation step of any catalytic cycle would be the H-bonding assisted displacement of the chloride ligand by the alkyne, and this is the focus of the computational study. All calculations were carried out at the MN15-L/6-31+G(d,p)+SDD level of theory,[86] with implicit solvation provided by the SMD model.[87] Energies quoted are free energies relative to [AuCl(IPr)] (**1**) and include a +1.89 kcal/mol correction to reflect a 1 mol/L rather than 1 atm state.[88] Propyne was selected a model alkyne. The direct displacement of the chloride ligand with propyne was examined first. A transition state (TS1) was obtained in which this process takes place in an interchange manner, in both DCM and TFE. These transition states are feasible (G_{rel} = 17.2 kcal/mol in TFE, 18.5 kcal/mol in DCM). The reaction has a slightly lower barrier in TFE than in DCM and is overall more thermodynamically favorable in TFE ($\Delta G°$ = +11.5 kcal/mol in TFE, +16.8 kcal/mol in DCM). The η^2-complex **B** is likely to undergo rapid reaction with the nucleophile present in solution, once it is formed, especially if the nucleophile is tethered to the alkyne.

However, given the experimental evidence for interactions between the chloride ligand and the fluorinated alcohol solvent, further investigations examined how such interactions might facilitate catalyst activation. Optimized structures were obtained for **1** with one, two, or three TFE molecules (G_{rel} = 0.3, 2.7, and 0.2 kcal/mol, respectively). A transition state was identified that allowed TFE to displace the chloride ligand (TS2), leading to [Au(IPr)(TFE)]Cl (**D**); the substrate might then subsequently displace TFE. However, the energy of this transition state was like that of TS1 (17.5 *vs* 17.2 kcal/mol, respectively) and so this does not fully explain experimental observations. The former calculation was performed in order to examine all possible pathways; however, HFIP is much less nucleophilic than TFE, and such a pathway would be less likely under the experimental conditions. A third pathway was considered in which TFE coordination to **1** facilitates a single step displacement of chloride by propyne. Transition state TS3 was identified (G_{rel} = 15.1 kcal/mol) in which TFE coordination decreases the barrier to catalyst activation by 2.1 kcal/mol.

Overall, these DFT calculations support the facilitation of chloride displacement by the substrate, both from electric field effects (as captured by implicit solvation) and from specific interactions between the solvent and the chloride ligand in TS3.

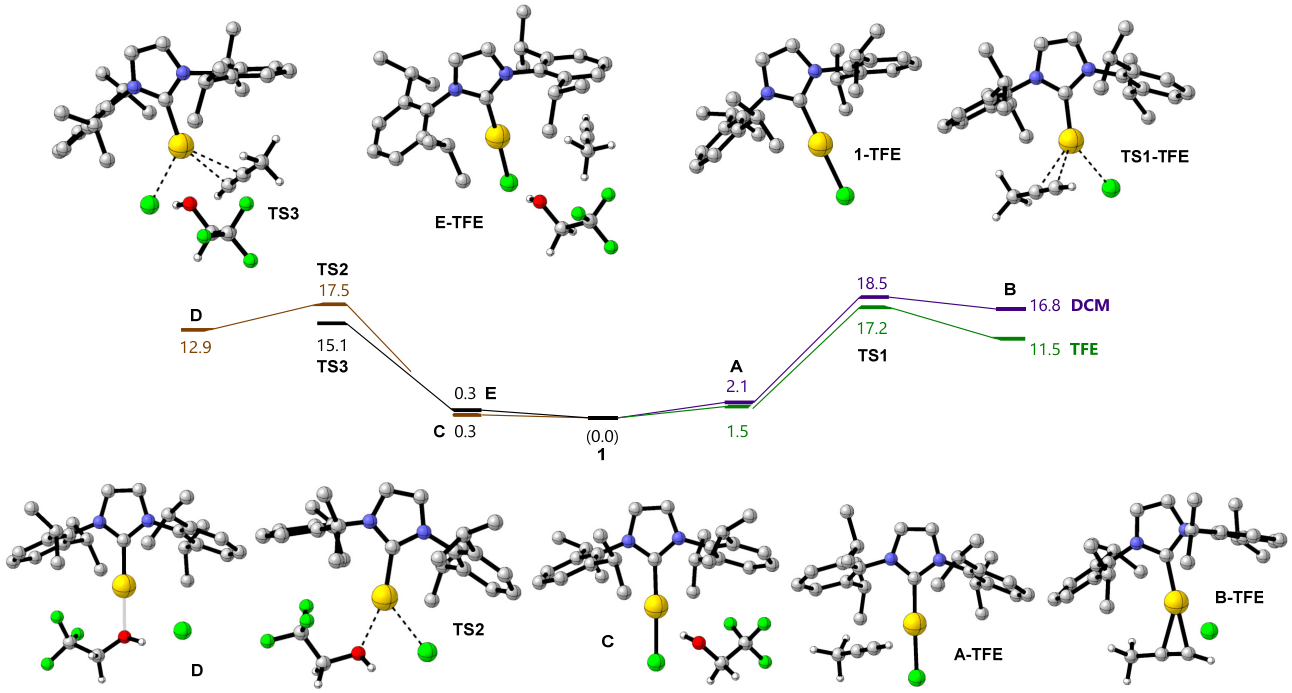


Figure 3. Free energy profiles (kcal/mol) for the reactions of [AuCl(IPr)] (**1**) at the MN15-L/6-31+G(d,p)+SDD/SMD level theory. Most hydrogen atoms are omitted from structures for clarity.

Conclusions

Gold-catalyzed cycloisomerization reactions can benefit from the use of HFIP. This recyclable solvent not only solubilizes a wide range of organic and organometallic compounds, but also serves as a suitable solvent for catalyst stock solution preparation. However, it is also more than a solvent. It is commonly known among gold catalysis practitioners that discovering novel ways to activate the Au-Cl bonds of commercial or easily accessed and widely used complexes is a worthwhile pursuit, as this tackles one of the fundamental issues related to applying gold chemistry in organic synthesis. No solution to this ubiquitous problem can be applicable to all gold-catalyzed reactions; however, a simple solution is required as an effective alternative (or complementary) method to the use of activators, especially silver salts. HFIP serves as this simple solution as a dynamic activator in the cases of two C-O bond-forming and so far one C-C bond-forming cycloisomerization reactions, which have received wide attention during the last decade. Importantly, these catalytic systems are robust, practical and in certain cases remarkably efficient. We will continue to explore the potential of the HFIP system, since, given the vast number of gold-catalyzed cyclization reactions, its impact may be significant. The potential role of HFIP as a controllably installed synthetic auxiliary is also an added and attractive feature as we demonstrated herein. By determining the hydrogen bonding interaction between HFIP and the chloride ligand, we have established this as a "well-defined" system to use in catalysis and hope to see its utilization as a standard test in optimization tables present in future studies.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, additional optimization experiments, mechanistic experiments, computational information, compound characterization data and copies of spectra. This material is available free of charge via the Internet at http://xxxxx.org.

CCDC 2244745 (**1**) and 2244745 (**24**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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Notes

The authors declare no competing financial interest.

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