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Library-friendly synthesis of fluorinated ketones through functionalized hydration of alkynes and investigation of the reaction mechanism

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ABSTRACT

A library-friendly synthesis of α-substituted-α-fluoroketones through functionalized hydration of alkynes in one pot under mild conditions is reported. The ready availability of alkynes and organoboronic acids makes this reaction quite attractive. We also studied the key intermediate—a fluorinated cationic gold species—using in situ NMR spectroscopy and ESI-high resolution mass spectrometry.

1. Introduction

Extensive research has established that the chemical reactivity of fluorinated organic compounds is distinctly different from other halide-containing analogues [1–7]. The small size of fluorine, its high electronegativity, and its strong bond with carbon, contribute to the fact that, once fluorine is introduced in an organic compound—either in place of a hydrogen atom or another organic functionality—it induces only minimal steric alterations but profound electronic changes in the resulting compound. Consequently, fluorine substitution can effectively modify the physicochemical properties of the molecule [1–7]. Until 1957, though, no F-containing drugs had been developed. These days, fluorinated drugs make up 20% of all pharmaceuticals sold worldwide, with even higher figures for agrochemicals. Compared to other heteroatoms, fluorine is not easy to introduce in an organic compound, especially in non-aromatic systems. Today, the synthesis of drugs and agrochemicals rely on commercially available stocks of fluorinated aromatic substrates (e.g. fluorine substituted benzaldehydes). Fluoroaromatics can be made by traditional methods like conversion of aromatic amines via the aryldiazonium salt (Balz–Schiemann reaction) [8] and the nucleophilic substitution of electron-poor bromo- or chloroarenes with KF (Halex reaction) [9] as well as the more recent transition-metal promoted Ar–F bond formation with electrophilic "F^+" reagents such as Selectfluor or N-fluoropyridinium salts [10–12]. A notable recent breakthrough has been reported by Buchwald and co-workers whereby palladium catalyzes the conversion of aryl triflates to aryl fluorides [13], although this is not yet an industrially feasible or medicinal chemistry-friendly process. Compared to other heteroatoms, the use of fluorine as a tool in organic synthesis has not come to full fruition because fluorine is not an easy atom to introduce in an organic compound, especially in an aliphatic system. By far, the most common method that medicinal chemists use to make aliphatic fluorinated compounds is through the conversion of alcohol, carbonyl compounds or alkyl halides to fluorinated compounds by fluorination (e.g., DAST) [3]. But this protocol is not library-friendly, each fluorinated product needs one specific starting material (Scheme 1, left). Because of this, fluorine is not a user-friendly substituent to introduce, especially when it comes to generate synthetic libraries using combinatorial tools, so it comes as no surprise that the number of drug candidates possessing aliphatic or cyclic fluorine substituent is so dismally low.

We sought a more efficient strategy to access aliphatic fluorocompounds: using fluorine-generated cationic metal species to mediate a tandem nucleophilic addition/coupling/fluorination reaction, starting from readily available alkynes (Scheme 1, right). One advantage of using alkynes is that they are ubiquitous in synthesis and many of them are readily available [14,15]. Their reaction with suitable coupling reagents (e.g. phenyl boronic acid) and suitable nucleophiles in the presence of fluorination reagents

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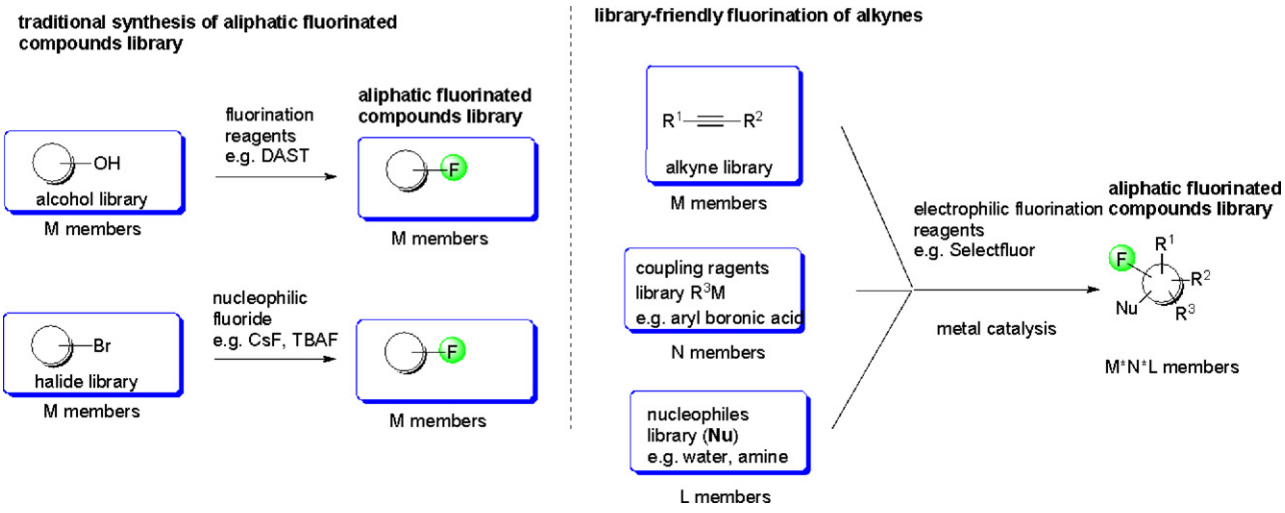


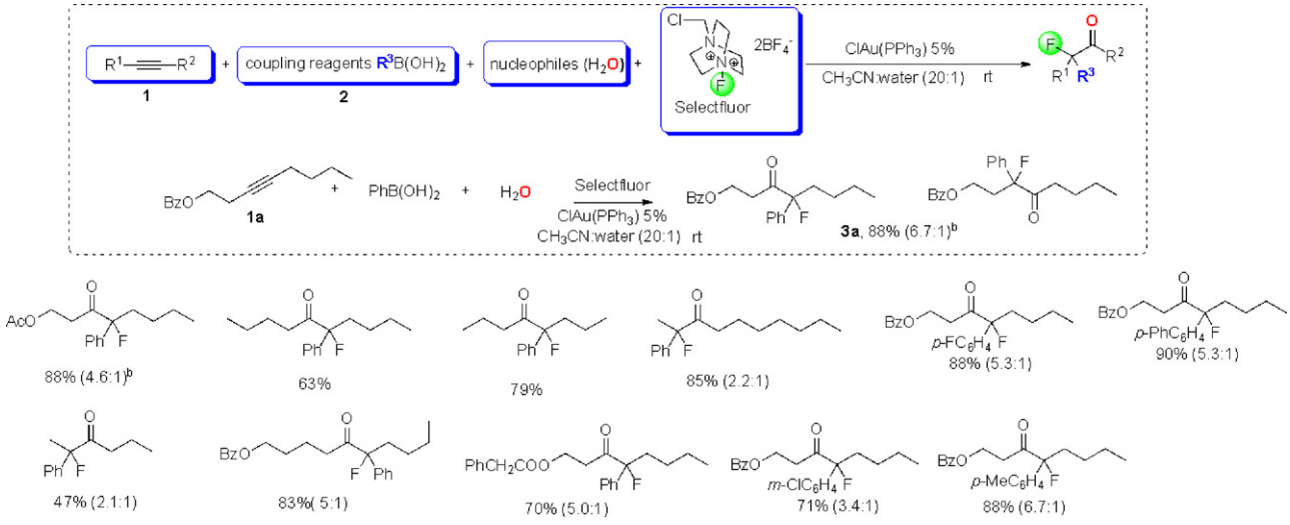
Scheme 1. Library-friendly synthesis of aliphatic fluorinated compounds library.

(e.g. Selectfluor) will generate a diversified library of aliphatic fluorinated compounds (M × N × L members, Scheme 1, right). An additional advantage is that alkynes are chemically inert to many reaction conditions (like acidic or basic conditions); this is especially important when using alkyne intermediates in late steps of target syntheses. A proof of principle is the synthesis of functionalized α-fluoroketones we recently discovered [16]. In this paper, we will describe this process in more detail, especially our mechanistic study of the key intermediate—fluorinated cationic gold species using in situ NMR and ESI-high resolution mass spectrometry.

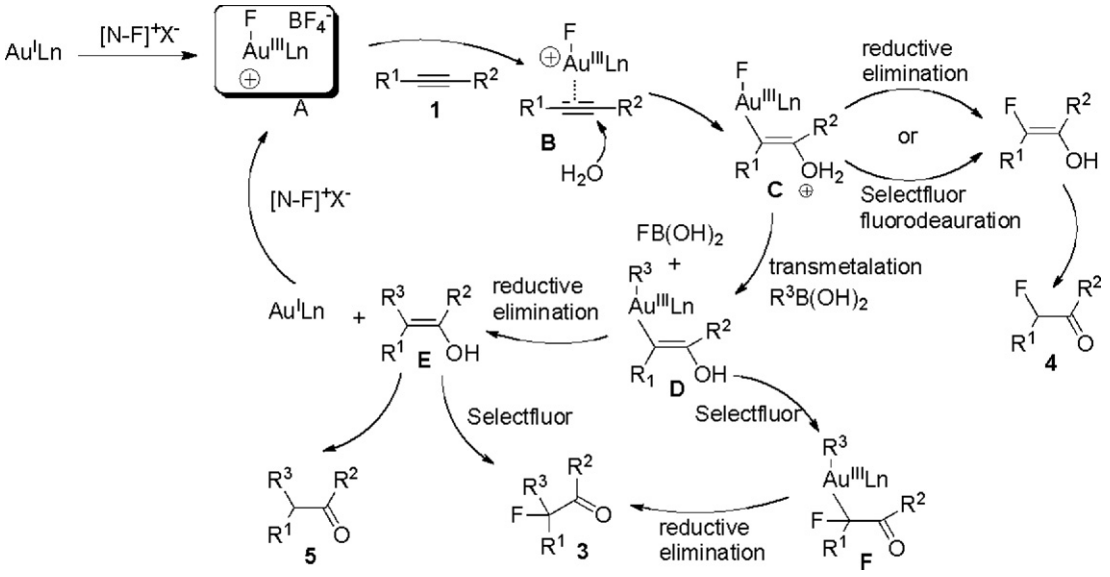
A major shortcoming of a transition metal catalyzed hydration is that it only adds the elements of H_2O to an alkyne [17–20]. We proposed that the vinyl metal complex hydration intermediate could react further during the hydration process to give an α, α-disubstituted ketone in a one-pot reaction. This process, that we coined 'functionalized hydration' allowed, for example, the synthesis of functionalized α-fluoroketones—well-known targets and important synthetic intermediates because they are effective mimics of α-hydroxy ketones, useful probes in various biological processes, and enzyme inhibitors [21,22]. They also provide configurationally stable substituents for molecules containing a tertiary chiral carbon atom next to a carbonyl group, an important structural motif in medicinal chemistry [22]. Our one-pot tandem addition/oxidative coupling/fluorination sequence—using readily available starting materials (alkyne, water, organoboronic acid and Selectfluor)—has clear advantages over literature methods, all of which require multiple synthetic steps [17–20].

2. Results and discussions

We examined the reaction of **1a** with phenyl boronic acid (Scheme 2). Ph_3PAuCl could not catalyze the reaction of **1** with phenyl boronic acid, but in combination with Selectfluor, we obtained good yields of **3**. Other gold(I) and gold(III) catalysts were less effective and other transition metals like copper, silver or palladium could not catalyze this transformation under similar conditions. On exploring the scope of this novel functionalized hydration, we found that functionalized and unfunctionalized internal alkynes reacted with aryl boronic acid, giving very good yields of α-substituted ketones, albeit with moderate regioselectivity (Scheme 2). Steric and electronic effects determine the



Scheme 2. Scope of the functionalized hydration[a]. [a]**1** (0.4 mmol), **2** (0.8 mmol), Selectfluor (1.0 mmol), $ClAuPPh_3$ (5%), 3 mL CH_3CN/water (20:1), rt, 18–24 h. [b]Numbers in parentheses correspond to the ratio of two regioisomers.



Scheme 3. Proposed mechanism for the functionalized hydration.

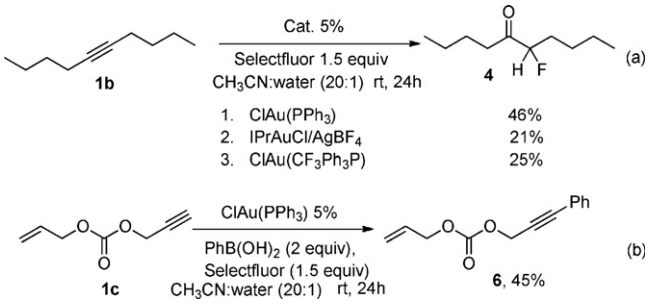
regioselectivity [23,24]. For internal alkynes possessing a nucleophilic site nearby (e.g. the ester group in **1a**), this site may influence the regioselectivity through neighboring group participation [23–25].

Our proposed mechanism is shown in Scheme 3. Initially, water attacks the gold-activated alkyne to form a vinyl gold complex **C** [26], which then reacts with a metal reagent RM (e.g., $PhB(OH)_2$) through a transmetalation process, to give intermediate **D** [27]. The transmetalation of Au(I)–Cl complex with boronic acid has been demonstrated by Hashmi and co-workers in a recent paper [28]. The transmetalation of Au–F with boronic acid has also been proposed by Zhang and co-workers in their gold catalyzed cross-coupling reaction of propargylic acetate [29]. We believe that the strong B–F bond and the weak Au–F bond are the driving forces behind this transmetalation. Reductive elimination of **D** gives **E**. The reaction does not stop at this stage; instead **E** can be fluorinated by Selectfluor to give the functionalized ketone **3** [30]. Because we had never isolated **5** in all cases, it is also possible that intermediate **D** reacts with Selectfluor first to give **F**, and, following reductive elimination, gives the final product **3**.

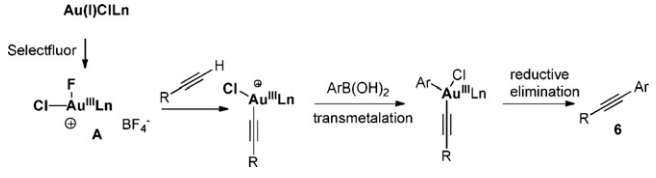
To probe the proposed mechanism in Scheme 3 we conducted two control experiments (Scheme 4). According to Scheme 3, fluoroketone **4** could be formed in the absence of a coupling partner R_3M, in which case, the vinyl metal complex **C** undergoes reductive elimination or fluorodemetalation [15] to give **4**. This was the case experimentally, although so far only moderate yields have been obtained (Scheme 4a). The reaction of terminal alkyne **1c** with phenylboronic acid gives the oxidative coupling product **6** [31]. The formation of **6** implies a tandem mechanism that involves fluorination of the gold complex, transmetalation with boronic acid or terminal alkyne, and reductive elimination, as shown in Scheme 3. We have not been able to isolate **5** (Scheme 3), possibly due to its fast conversion to **3**. It is interesting to note that gold catalysts undergo transmetalation and reductive elimination readily, although they are not able to undergo oxidative insertion—as Pd does in coupling reactions. A more detailed mechanism (Scheme 5) can be used to rationalize the formation of **6**.

The key step of this mechanism is the generation of cationic gold species **A** by fluorination or oxidation (Scheme 3). The oxidation state of gold changed from Au(I) to Au(III). Oxidation of Au(I) to Au(III) by Selectfluor, while postulated as a reasonable process [29,32,33], has never been confirmed experimentally. X-ray photoelectron spectroscopy (XPS) is a quantitative spectroscopic technique used to measure the chemical state of the elements [34]. For example, it can determine the chemical states of supported gold catalysts [35]. The binding energy (BE) of Au $4f_{7/2}$ electron of each gold oxidation states is usually different enough to be differentiated (for $ClAu^{I}PPh_3$, Au $4f_{7/2}$ = 85.7 eV, for $NaAu^{III}Cl_4$, Au $4f_{7/2}$ = 87.6 eV) [34]. We used this technique to investigate the valence change of gold in the reaction. First we tested our gold standard samples ($ClAu^{I}PPh_3$ and $NaAu^{III}Cl_4$), the Au $4f_{7/2}$ photoelectron peak is located at a BE value at 85.7 and 87.5 eV respectively, results that are quite consistent with the literature [34]. We investigated our Selectfluor treated Au(I) samples using the same conditions as for the standards. Our XPS measurements confirmed the existence of gold(III) (BE of Au $4f_{7/2}$ = 87.6 eV) in the reaction mixture of gold(I) catalyst and Selectfluor.

Our XPS measurements indicate the existence of gold(III) species, but XPS experiments can only be conducted in high



Scheme 4. Synthesis of fluoroketones and oxidative coupling of alkynes.



Scheme 5. Putative mechanism for the formation of **6**.

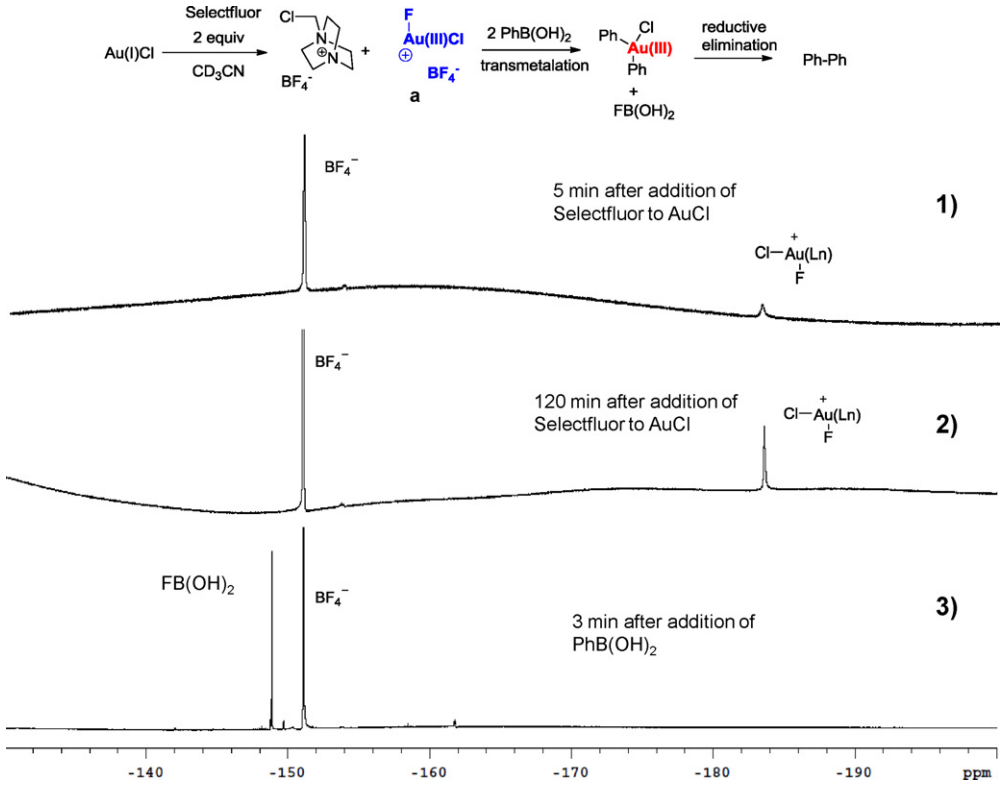
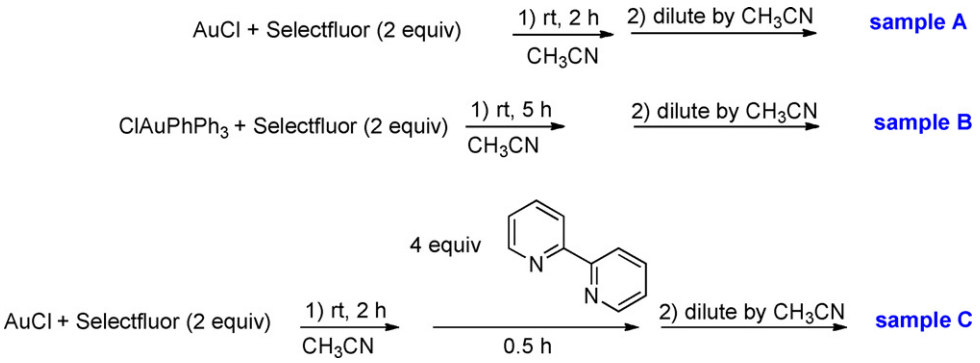


Fig. 1. Monitor of reaction of AuCl with Selectfluor using ^{19}F NMR (Ln = CH_3CN).

vacuum as solid state. In order to investigate the reaction in solution phase at room temperature, we monitored the progress of the reaction using ^{19}F NMR spectroscopy (Fig. 1). We mixed AuCl and Selectfluor in CD_3CN; after only 5 min (Figure 1a), a new peak appeared (6% conversion, using BF_4^- peak as reference); after 2 h, the new peak increased significantly (Fig. 1a, conversion 65%) and the N^+–F peak in Selectfluor decreased (δ +50 ppm, not shown in Fig. 1). We assigned this peak (bs, δ −184 ppm) to correspond to $Au(III)^+ClFLn$. And when we added $PhB(OH)_2$ to the system, and ran its ^{19}F NMR spectrum immediately after, the $Au(III)^+ClFLn$ had disappeared and a new peak appeared (δ −148 ppm, $FB(OH)_2$). After the addition of $PhB(OH)_2$, we also detected the formation of biphenyl (Ph–Ph, confirmed by flash chromatography of the reaction mixture). This result suggests that the new peak represents a reactive metal fluoride species, which we tentatively assigned as $[Au^{III}ClFLn]^+$ (Ln = CH_3CN). The formation of biphenyl can be rationalized by transmetalation with phenylboronic acid, followed by reductive elimination to give biphenyl (Fig. 1). This result indicates that $Au(III)^+ClFLn$ is a highly reactive species: it undergoes transmetalation with phenylboronic acid readily and its reductive elimination gives biphenyl. The high reactivity seems to rule out the possibility that it is a simple fluoride anion.

Literature reports on ^{19}F NMR of transition metal–fluorine complexes, especially Au–F complexes are rare. Gray, Sadighi and co-workers have reported a NHC-carbene-stabilized gold(I) fluoride; its ^{19}F NMR showed a single peak at δ −247.0 ppm [36]. Grushin and co-workers have reported a $PhPdF(Py)_2$ type complex (^{19}F NMR at δ −219.2 ppm). The fact that our Au–F signal appeared downfield may be due to the higher electron-withdrawing property of the cationic Au(III) metal center compared to Au(I) and Pd(II) complexes.

Electrospray ionization mass spectrometry (ESI-MS) has become an important tool in the identification of labile reaction



Scheme 6. Preparation of samples for ESI-MS study.

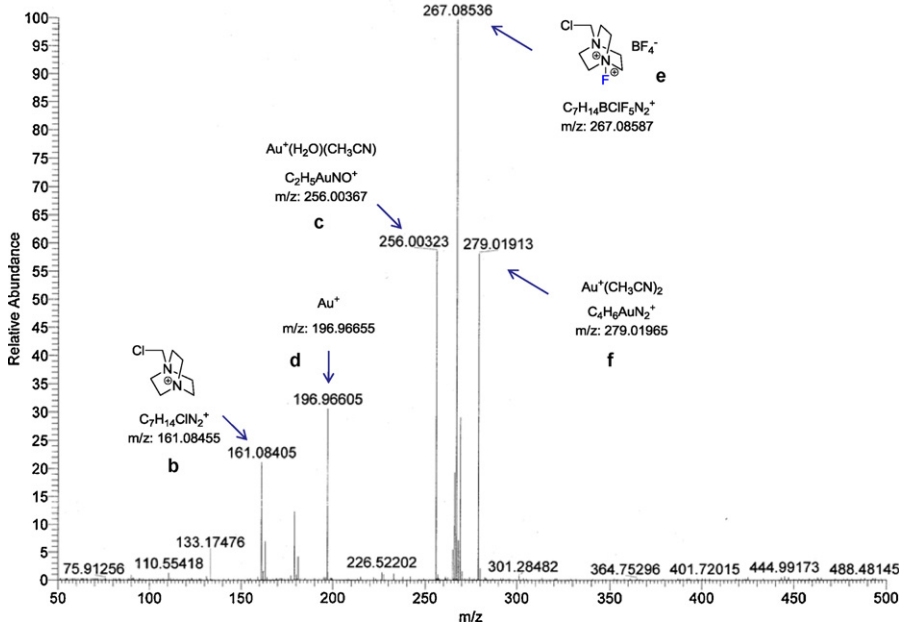


Fig. 2. ESI-MS of sample A.

intermediates. An advantage of ESI-MS is that it allows direct sampling from the reaction mixture, and because many of our gold intermediates are charged species, ESI-MS could help us to detect charged species. We conducted a high-resolution ESI-MS investigation of the cationic or anionic species in the catalytic system (Scheme 6). First, we checked the high-resolution ESI-MS spectra of samples A and B but only Au(I) species (peaks **c**, **d**, **f**) and reduced Selectfluor (peak **b**) were detected (Fig. 2). We speculated that a Au(III) species would be difficult to detect under our ESI-MS conditions due to possible multiple charge ($z > 1$) on the Au(III) cation. Because a Au(III) complex has a square-planar geometry, a bidentate ligand should greatly stabilize this Au(III) complex, which in turn, could be easier to detect by ESI-MS spectrometry. Hence, we added excess amounts of bipyridine to the reaction mixture (Scheme 6, sample C). The high-resolution ESI-MS spectrum is shown in Figs. 3 and 4.

In Fig. 3, various cationic Au(III) species were detected (peaks **i**, **k**, **l**, **m**), but $[Au(III)ClF]^+$ itself was not detected; this may be due to the fact that metal–fluorine bonds tend to be labile and reactive. Indeed, gold(I) fluoride, was once thought impossible to prepare. The fluoride ion, according to hard/soft acid–base theory, is mismatched with the cations formed by late transition metals especially gold [36]. Its π-donating ability, moreover, can lead to destabilizing interactions with filled *d* orbitals of gold [36]. Compared to many other metal–fluorine bonds, Au–F is a weaker bond. So, under the ESI-MS conditions (high temperature during the electrospray ionization), $[Au(III)ClF]^+$ (**a**) may lose fluorine and pick up chloride from other gold complexes or OH^- from trace

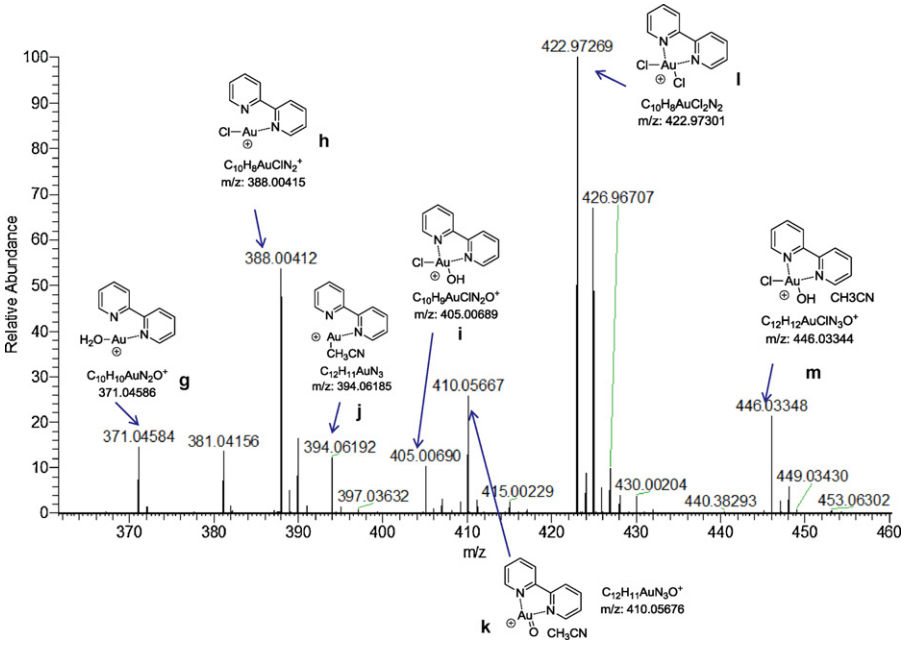


Fig. 3. ESI-MS of sample C (part 1, *m*/*z* 360–460).

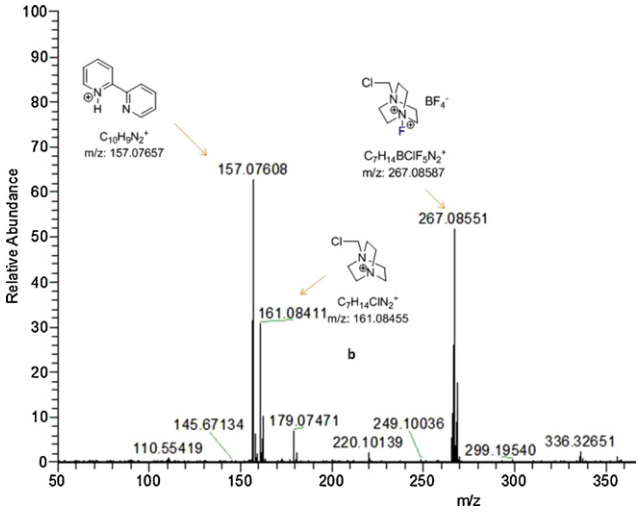


Fig. 4. ESI-MS of sample C (part 2, *m*/*z* from 50 to 360).

amounts of water in the system, because both chloride and hydroxyl have much stronger affinity to gold (Scheme 7).

The presence of Au(III)ClF$^+$ (**a**) was further confirmed by its conversion to Au(III)Br$_4^-$ through the reaction with a large excess of halide source (KBr). We prepared two samples (samples D and E) using ClAuPPh$_3$ and AuCl as starting materials, respectively (Scheme 8). Because samples D and E give very similar mass spectrum, only the spectrum for sample D is shown. The peak corresponding to Au(III)Br$_4^-$ was indeed detected by ESI-MS; the exact mass and distinct bromine isotope pattern matched theoretical calculations.

In summary, a potentially new role for fluorine in cationic gold catalysis is proposed, an example of which is the hydration of alkynes to give α-substituted-α-fluoroketones, in one pot and under mild conditions. The ready availability of alkynes and organoboronic acids, and the current interest in α-fluoroketones makes this reaction quite attractive. The broader implications of cationic metal species enabled by fluorine are underway in our laboratory.

Acknowledgements

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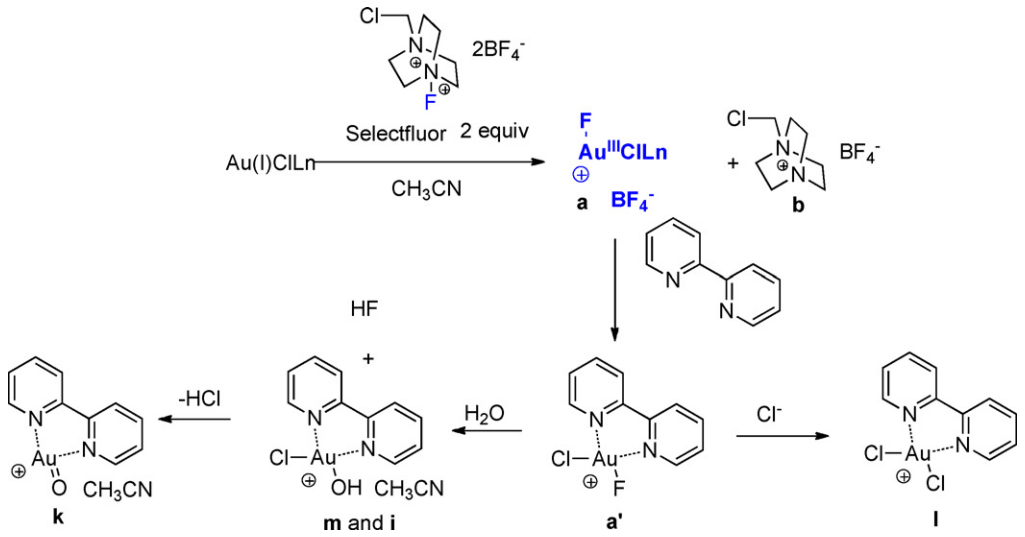
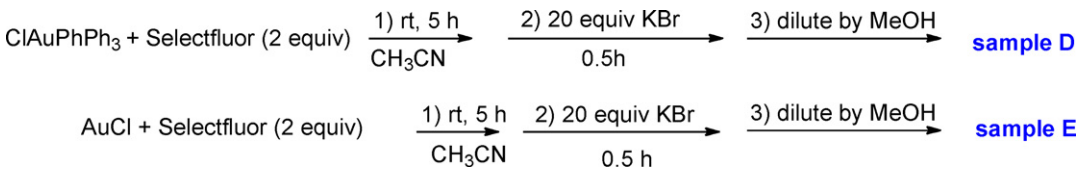


Scheme 7. Mechanism for the formation of gold(III) species in Fig. 3.



Scheme 8. Preparation of samples for ESI-MS study.

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