Investigation and Application of Perfluorinated Au(III) Complexes

By

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Acknowledgements

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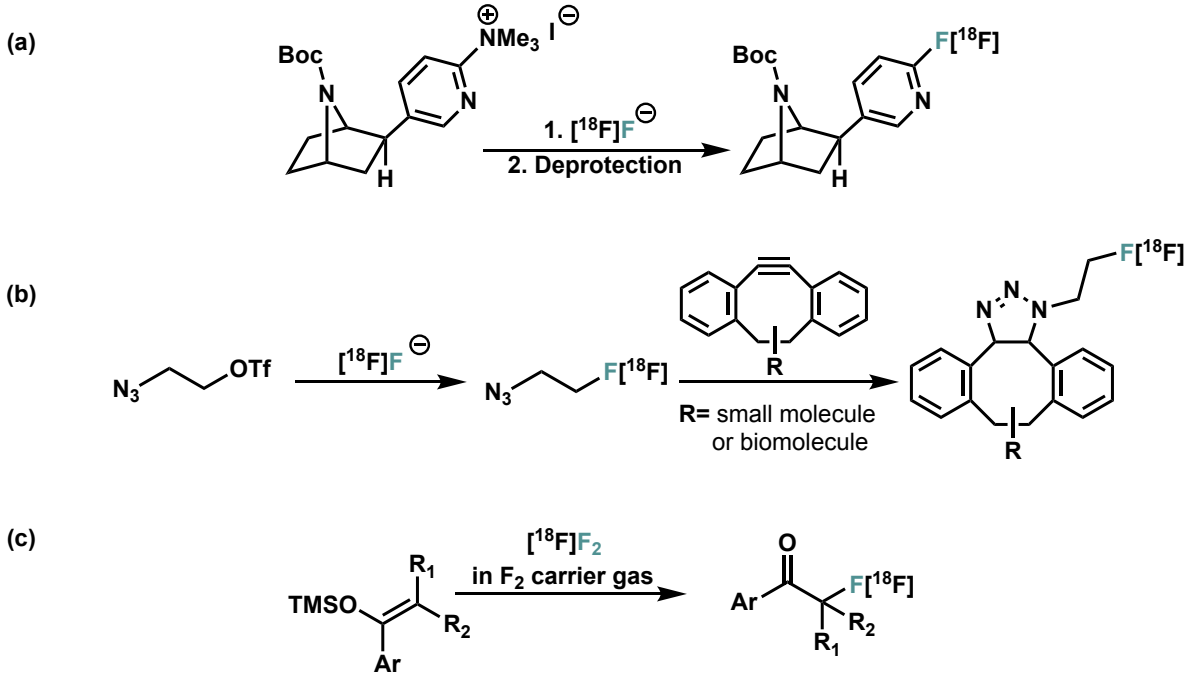
Because I'm running out of space, I'd lastly like to thank Greg Veber. The past few years have been amazing, mainly because I have you in my life. Thank you for always encouraging me to just have fun, relax, and put my own happiness first. You are such an incredibly kind person that has a palpable love of chemistry, beer, and life in general that is contagious to everyone around you. I'm so excited for this next adventure we've chosen to go on together. Love you.

Introduction

While the development of fluorination chemistry began more than 100 years ago, there still remains challenges in the scope and predictability of late stage C-F bond formation.[1] However, the relevance of fluorination in the world of drug design and discovery cannot be understated. In particular, fluorination of a molecule of biological interest can promote a multitude of pharmacological properties, including increased lipophilicity,[2] enhanced metabolic stability towards cytochrome P450,[3] and greater conformational control.[4]

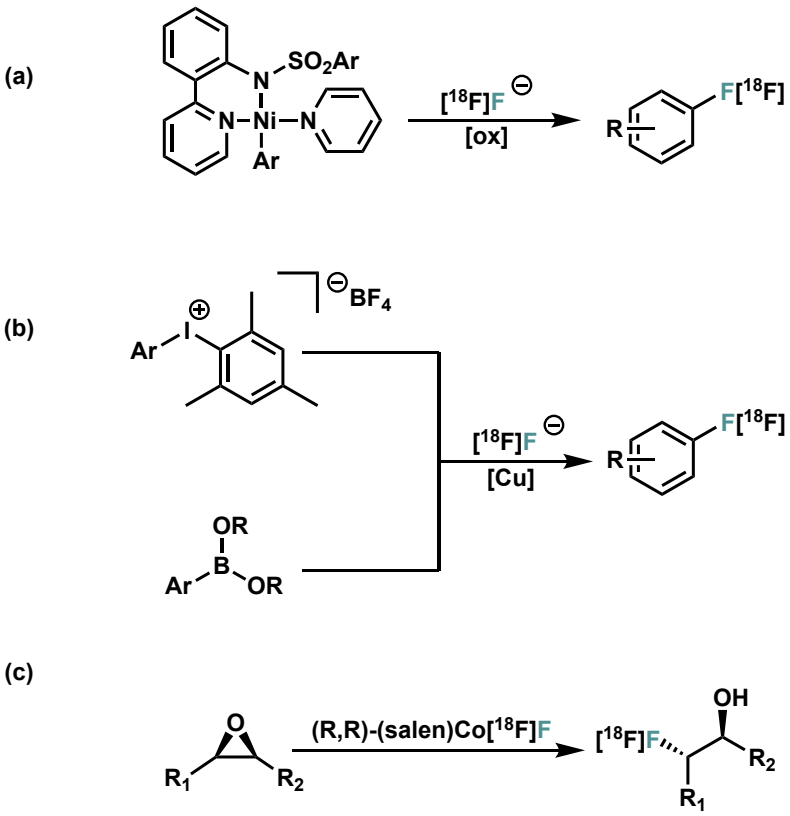
An additional benefit of late stage C-F bond formation is the potential to synthesize positron emission tomography (PET) radiotracers, where the radioactive fluorine atom, ^{18}F, is introduced into the probe as late in the synthesis as possible in order to preserve the maximum amount of radioactivity. The radiolabeled tracers can then be employed to monitor interactions between a particular compound and its physiological target for the purposes of either medical diagnostics or drug discovery.[5] Due to its accessibility and optimal half-life (109.8 min), ^{18}F is one of the most widely used nuclides in radiopharmaceuticals.[6]



Scheme 1. (a) Fluorination of a nicotinic acetylchlorine receptor radioligand through an S_NAr type reaction.[7] (b) Secondary labeling of a "clickable" prosthetic group.[8] (c) Labeling of a nucleophilic substrate using radioactive elemental fluorine.[9]

The most common methods used in ^{18}F-labeled PET tracer synthesis typically involve either S_N2 or S_NAr type reactions (Scheme 1a and 1b).[10] Small molecules or biomolecules that cannot be selectively labeled directly can be subjected to a secondary labeling method, in which a radiolabeled fragment is incorporated into the product via modern bioorthogonal chemistry (Scheme 1b).[11] The electrophilic attack of radioactive elemental fluorine, $^{18}F_2$ can also be used, though the reactive gas is difficult to handle and thus not commonly utilized (Scheme 1c).[12] For a compound to be a good candidate for radiolabeling, it must contain functionality that facilitates incorporation of a labeled atom. Furthermore, the incorporation must be done selectively as to not

interrupt the carefully designed molecular structure pertinent for biological activity.[13] While use of prosthetic groups can provided alternatives when a radionuclide cannot be added directly,[14] the synthetic challenges associated with [^{18}F]-fluorination could benefit from a concerted push by chemists to develop new methods of late-stage isotope incorporation, broadening the scope of compounds that can be radiolabeled and used in PET.[15]

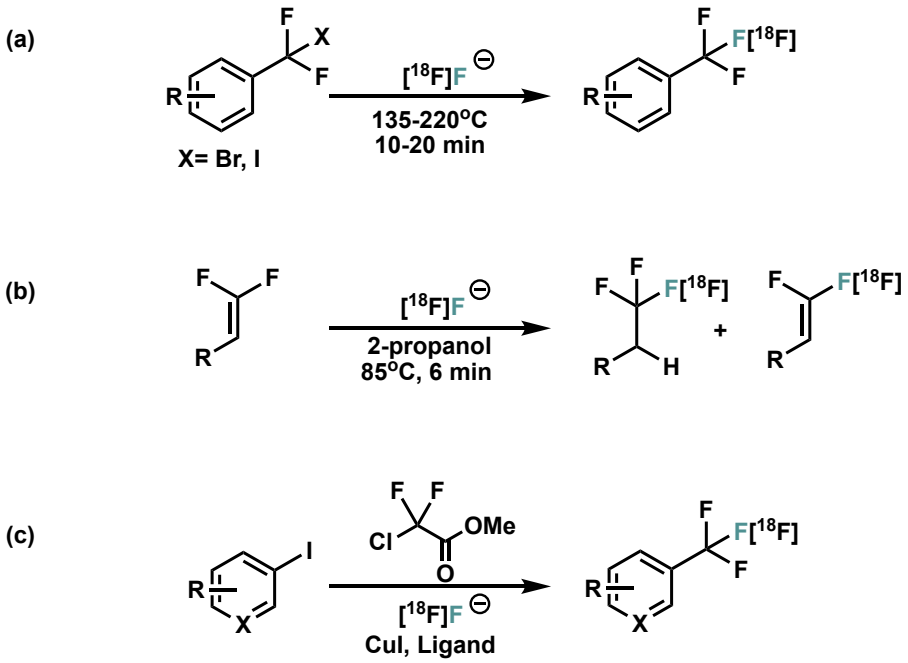


Scheme 2. (a) Aryl radiofluorination via an organonickel complex. (b) Copper coupling of [^{18}F]-fluoride with diaryliodonium salts, boronic acids or esters. (c) Enantioselective epoxide ring opening with a cobalt-salen complex.

Due to the recent application of transition-metal complexes to facilitate transformations challenging using traditional organic methods, such reactions have been developed to promote key C-[^{18}F]F bond forming step in radiosynthesis as well.[16] Successful examples include the oxidative fluorination of arylnickel complexes developed by Hooker and Ritter (Scheme 2a),[17] the copper coupling of diaryliodonium salts, aryl boronic acids and esters (Scheme 2b),[18] and enantioselective epoxide ring opening using a cobalt-salen complex (Scheme 2c).[19] Despite these advances, radioligands synthesized using transition-metal mediated methods must demonstrate high purity and radiochemical yield, as well as low levels of toxic metal side products before being used in a clinical setting.[20]

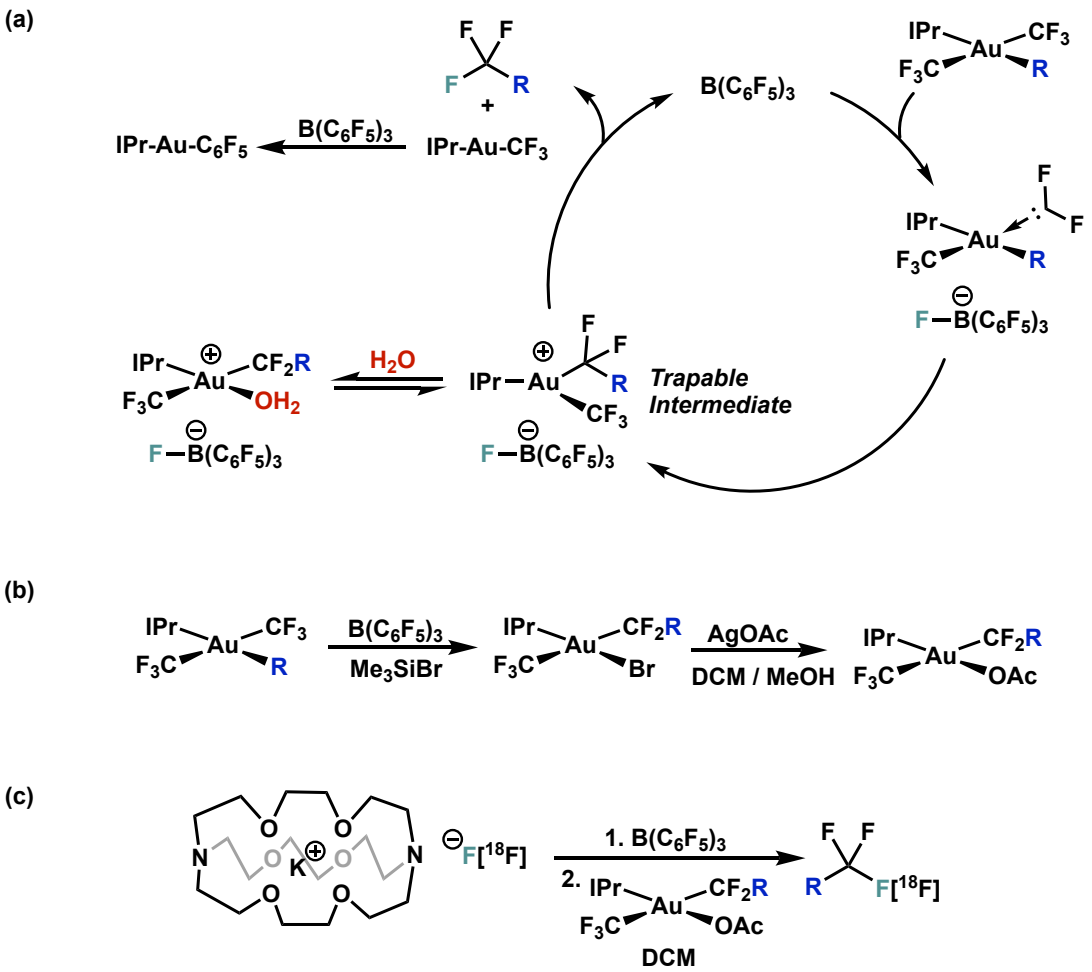
In addition to the synthetic challenges present in existing fluorination reactions, there also remains a deficiency in [^{18}F]-trifluoromethylation strategies despite the increasing number of medicinal compounds that possess these groups.[21] This is largely due to the inability to introduce [^{18}F]-fluorine into trifluoromethyl groups through the nucleophilic methods typically used in radiofluroination given the low reactivity of leaving groups in difluoromethylene precursors

(Scheme 3a).[22] The formal addition of HF[^{18}F] across gem-difluoro olefins provides a path towards alkyl [^{18}F]-trifluoromethylated products, though an undesired side product is often present in high yields via [^{18}F]fluoride exchange (Scheme 3b).[23] The most promising method to date involves *in situ* formation of [^{18}F]$CuCF_3$ as a means to couple [^{18}F]-trifluoromethyl groups to aryl and heteroaryl iodides (Scheme 3c).[24] However, the specific activities (SA), or the amount of radioactivity per mass of the compounds, of the labeled products were low due to release of ^{19}F upon degradation of ethyl chlorodifluoroacetate.[25]



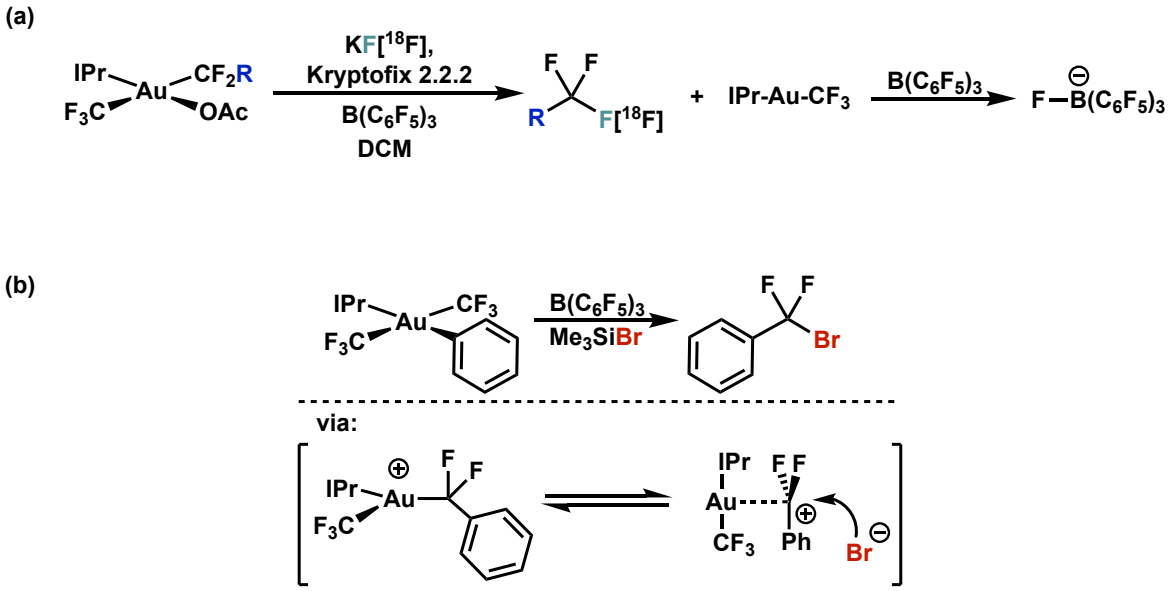
Scheme 3. (a) Formation of [^{18}F]-trifluoromethylated products via halide exchange. (b) Formal addition of HF[^{18}F] across gem-difluoro olefins. (c) *In situ* formation of [^{18}F]$CuCF_3$ in the radiolabeling of aryl and heteroaryl iodides.

The recent discovery of a boron-catalyzed, formal C(sp^3)-CF_3 reductive elimination from bis(trifluoromethyl)Au(III) complexes by our group provides an innovative path to accessing aliphatic [^{18}F]-trifluoromethyl groups, which proceeds through fluoride-abstraction and subsequent migratory insertion of the R group ligand. Without the presence of a strongly Lewis basic substrate, the boron-bound fluoride is reincorporated into the molecule, yielding the reductive elimination of trifluromethylated aliphatic species (Scheme 4a). However, the three-coordinate, cationic Au center can also be trapped by nucleophilic attack (Scheme 4b), allowing for a radioactive [^{18}F]-fluorine surrogate to be incorporated into the trifluoromethylated product (Scheme 4c).[26]



Scheme 4. (a) Proposed mechanism of fluoride-rebounding C-CF_3 reductive elimination from bis(trifluoromethyl)Au(III) complexes. (b) Nucleophilic trapping of the cationic Au-center. (c) Protocol for the [^{18}F]-trifluromethylation via the trapped gold intermediate.[26]

Despite the wide scope and functional group tolerance of this novel discovery, several issues were encountered in the process of making the radiochemical protocol ready for use in a clinical setting.[27] The SA of the [^{18}F]-trifluoromethylated products were low due to the presence of ^{19}F-$B(C_6F_5)_3$ in the reaction mixture, likely resulting from fluoride-abstraction of the (trifluoromethyl)Au(I) reduction product (Scheme 5a). Another issue our group encountered when attempting to subject Au(III) aryl complexes to the same trapping conditions used for their aliphatic counterparts in Scheme 4b, is that nucleophilic attack occurred exclusively on the aryl-CF_2 ligand, indicating that formation of trapped intermediates is highly dependent on the localization of charge (Scheme 5b).[26]



Scheme 5. Subsequent fluoride-abstraction from the Au(I) reduction product is proposed to lower the radiochemical specific activity. (b) Nucleophilic trapping agents prefer to add to the difluoromethyl ligand due to the localization of positive charge.

The ways in which I attempted to solve these shortcomings are laid out in the next three sections. Sections on complex synthesis via CF_3I oxidative addition and cyclometalated Au(III) complexes contain efforts to favor nucleophilic trapping onto the Au metal center over outer sphere reductive elimination of (bromodifluoromethyl)benzene by modulating the ligand sphere. The third section aims to bypass the fluoride-abstraction and migratory insertion events altogether by introduction of CF_2R type ligands onto gold directly. The final section of this thesis describes the investigation into reactive gold difluorocarbene complexes.

Results and Discussion

I. Accessing Au(III) Aryl Complexes via CF_3I Oxidative Addition

My initial work was in synthesizing a new class of Au(III) complexes that are similarly capable of undergoing fluoride-rebound carbon-CF_3 bond formation, but with improved specific activity and substrate scope.

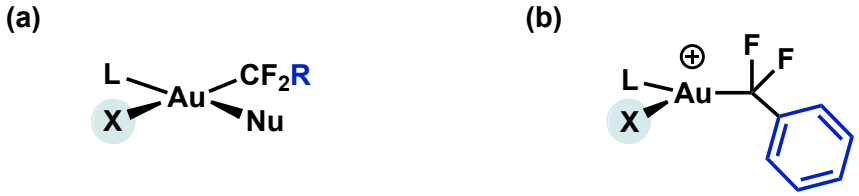
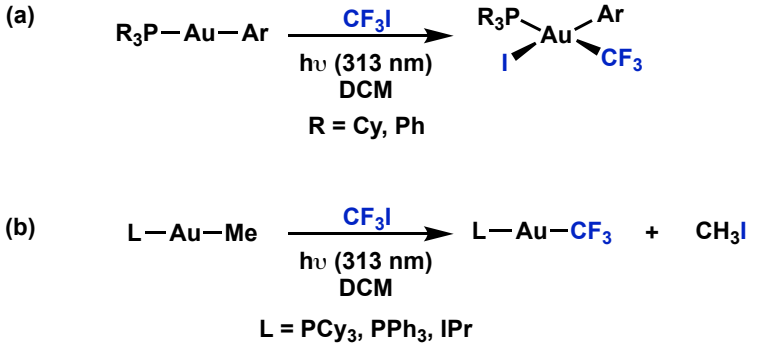


Figure 1. (a) Proposed changes to improve SA of radiolabeled products. (b) Proposed changes to accommodate aromatic substituents.

I hypothesized that the SA of the radiofluorination might be improved by changing the X-type spectator ligand that will be present on the Au(I) reduction product following the formation of the radiolabeled product. My second goal was the expansion of the reaction scope to include aryl-CF_3 bond formation by making the X-type ligands on the Au(III) complex more amenable to electronic tuning in order to direct nucleophilic trapping of the cationic intermediate to the gold center (Figure 1b).

Formation of Mono-Trifluoromethylated Gold Complexes

One major synthetic challenge in the formation of this new class of compounds is the limited precedent of mono-trifluoromethyl gold complexes. Of the methods available to make Au-CF_3 bonds, transfer agents such as $Cd(CF_3)_2(DME)$ and TMS-CF_3/CsF can give mixtures of Au(I) and Au(III) trifluoromethylated products,[28] and more reliable agents, such as the reaction of Au atoms with gaseous •CF_3, are dangerous and difficult to perform.[29] While Menjón and coworkers reported synthesizing mono-trifluoromethylated gold complexes through BF_3-assisted hydrolysis of $[Au(CF_3)_2]^-$ to form $[Au(CF_3)(CO)]$ and CO substitution by L-type ligands, the carbonyl intermediate was moisture-sensitive and unstable.[30] Vicente and coworkers have made $[Au(CF_3)(L)]$ complexes from the chlorinated precursor; however the reaction equilibria were dominated by thermodynamic stability, involved long reaction times, and necessitated the vigorous drying of uncommon solvents.[31] I discovered improved conditions to this reaction, which will be discussed later on in section III.

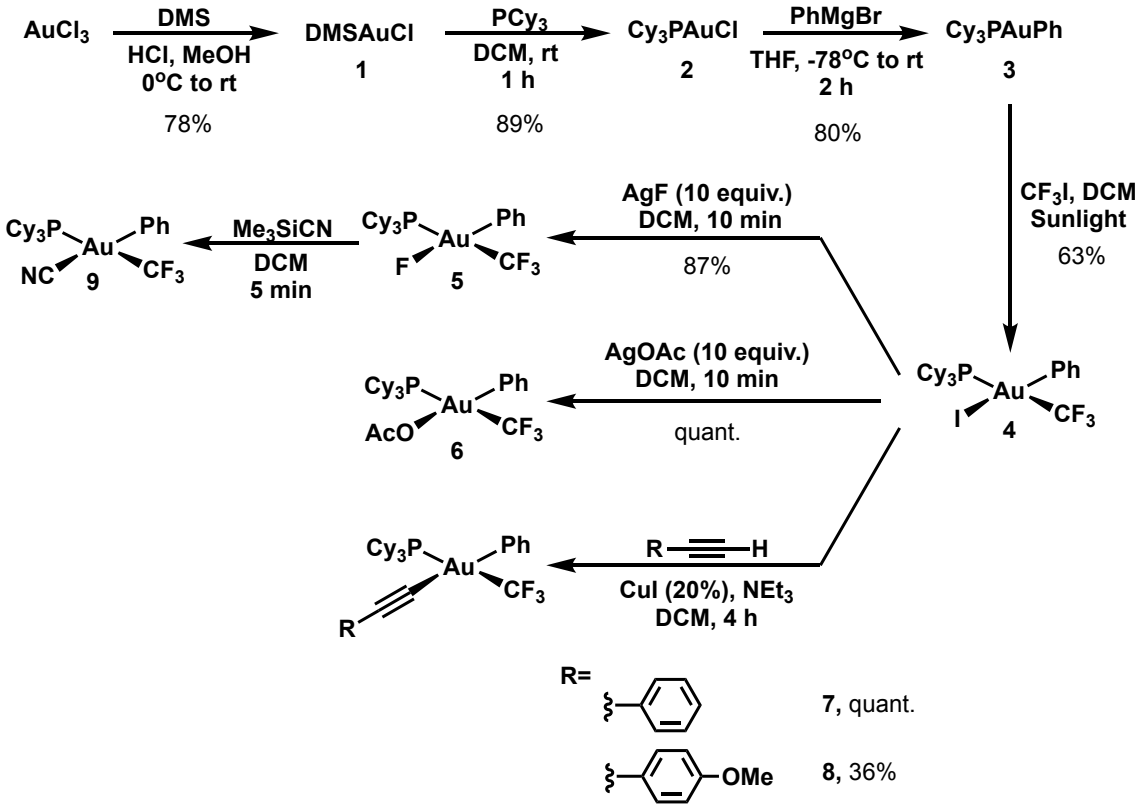


Scheme 6. (a) Oxidative addition of CF_3I to Au(I). (b) Ligand exchange to Au(I) from CF_3I.

In 2014, our group discovered an easily reproducible method to mono-trifluoromethylated gold complexes with CF_3I. Oxidative addition to a family of [Au(Ar)(PR_3)] was found to form [(CF_3)(Ar)AuI(PR_3)] (Scheme 6a). When [Au(L)(Me)] was subjected to the same conditions, the resulting trifluoromethylated analogue was formed through a photoinitiated ligand exchange with $\bullet CF_3$ (Scheme 6b).[32] These facile methods were chosen as the basis for the initial introduction of the Au-CF_3 moiety in the following synthesis.

Synthesis of Au(III) Aryl Complexes

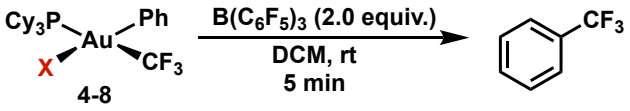
Synthesis of the gold (III) aryl complexes began with the formation of [AuCl(SMe_2)] from $AuCl_3$, followed by addition of the tricyclohexylphosphine ligand. Transmetalation to the Au(I) species was possible from both phenylboronic acid and MgBrPh, though the latter gave higher yields and cleaner oxidative addition in the following reaction. With complex **4** in hand, I was able to subject a new class of Au(III) trifluoromethyl compounds to the reductive elimination conditions used in Scheme 3a, as well as screen a number of X-type ligands and evaluate their potential electronic effects. In order to test these effects, I synthesized five different Au(III) species using the various conditions shown in Scheme 7.



Scheme 7. Multistep synthesis used to access (trifluoromethyl)Au(III) derivatives.

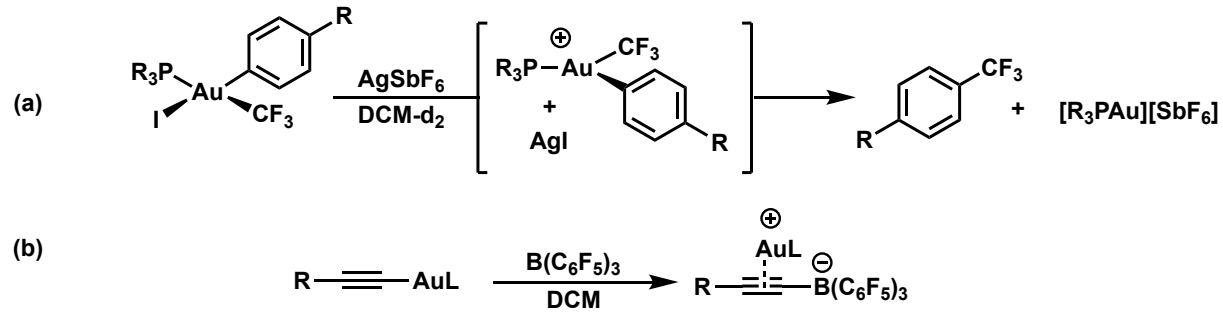
Complexes **4** through **8** all showed full consumption of starting material by ^{19}F-NMR and produced trifluorotoluene as the major product (Scheme 8). (Cyano)Au(III) complex **9** was the only derivative that was found inert in the presence of the Lewis acid and formed no new

trifluoromethylated species. This is likely due to the fact that the strong electron withdrawing effects of the ligand prohibit the gold from activating the C-F bond to fluoride abstraction by BCF.



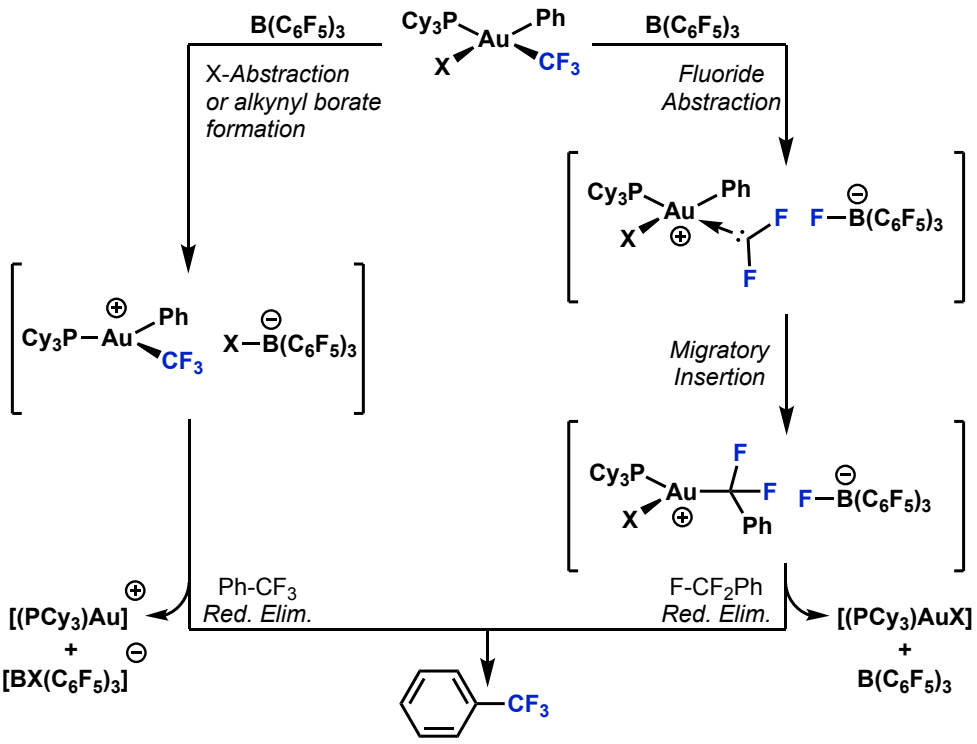
Scheme 8. Reductive elimination of selected Au(III) complexes.

While formation of trifluorotoluene from five of the selected Au(III) complexes was promising, there were still mechanistic discrepancies to be resolved. If the trifluoromethyated products are to be amenable to [^{18}F]-fluorination, they must undergo a fluoride-rebounding mechanism where a nucleophilic [^{18}F]-fluoride surrogate is capable of being reincorporated into the trifluoromethylated product.[26] However, alternative mechanisms could be conceived given the precedented reactivity of similar gold complexes. Our group previously found that these same (trifluoromethyl)Au(III) complexes underwent rapid Ar-CF_3 reductive elimination from a three-coordinate, cationic gold intermediate upon halogen-abstraction by silver salts (Scheme 9a).[32]



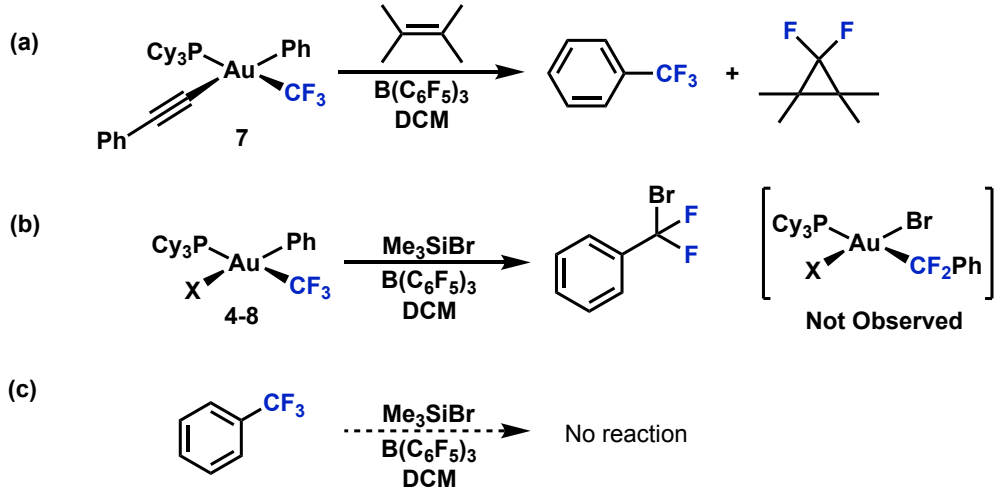
Scheme 9. C-CF_3 reductive elimination through a three-coordinate Au(III) intermediate.[32] (b) Formation of an alkynyl borate species from a Au(I) alkyne.[33]

Additionally, Hashmi and coworkers discovered that the reaction of Au(I) acetylides with $B(C_6F_5)_3$ yielded alkynyl borate species with the alkyne π-bound to the cationic gold center (Scheme 9b).[33] It could be envisioned that compounds **4** though **8** undergo Ph-CF_3 reductive elimination from a three-coordinate, cationic Au(III) intermediate resulting from either the X-type ligand abstraction from the metal center or the formation of a alkynyl borate species rather than a fluoride-rebounding mechanism (Scheme 10). I preformed several mechanistic experiments in order to probe the occurrence of fluoride-abstraction from the CF_3 ligand and subsequent phenyl migration.



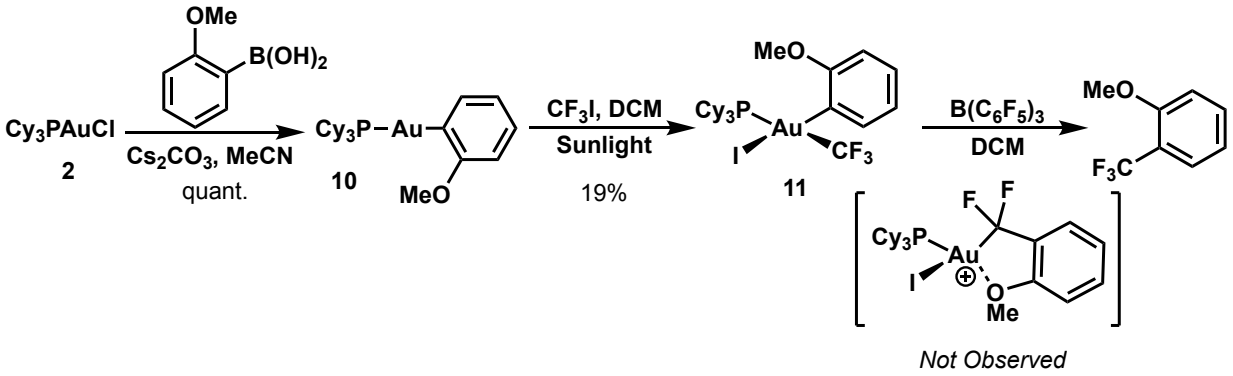
Scheme 10. Possible mechanisms for the formation of trifluorotoluene.

The first experiment was designed to trap any carbene intermediates present in the reaction using tetramethylethylene. Compound **7** was subjected to the given conditions and was found to give both the trifluorotoluene reductive elimination product as well as the cyclopropanated product of the alkene trap (Scheme 11a). A second trap was targeted at intercepting the cationic intermediate following the migratory insertion event. All gold compounds tested were shown to give (bromodifluoromethyl)benzene as the sole product of the reaction (Scheme 11b). It should also be noted that when trifluorotoluene is treated with BCF and bromotrimethylsilane, no starting material is consumed within 24 hours and no (bromodifluoromethyl)benzene is formed (Scheme 11c).



Scheme 11. (a) Carbene trapping experiment with tetramethylethylene. (b) Attempted trap of the Au cationic intermediate. (c) Trifluorotoluene is inert to the presence of BCF and Me_3SiBr.

Thus, formation of product is likely due to phenyl migration and nucleophilic trapping onto the difluorobenzyl ligand. Unfortunately, this renders **4** though **8** similarly incapable of being trapped at the gold center, as is depicted in Scheme 5b.

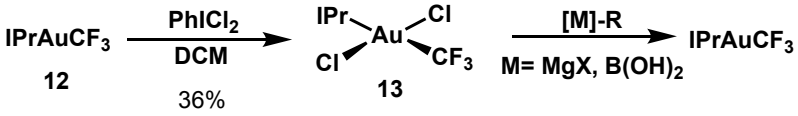


Scheme 12. Synthetic route used to attempt an intramolecular trap.

I imagined it possible that an intermolecular trap could be capable of forming an observable intermediate. Thus, compound **11** was synthesized using a parallel procedure to that of **4** in hope that the nucelophilic *ortho*-methoxy group would be capable of coordinating to the cationic gold center. However, no intermediate was detected and the reaction gave 1-methoxy-2-(trifluoromethyl)-benzene as the sole product (Scheme 12).

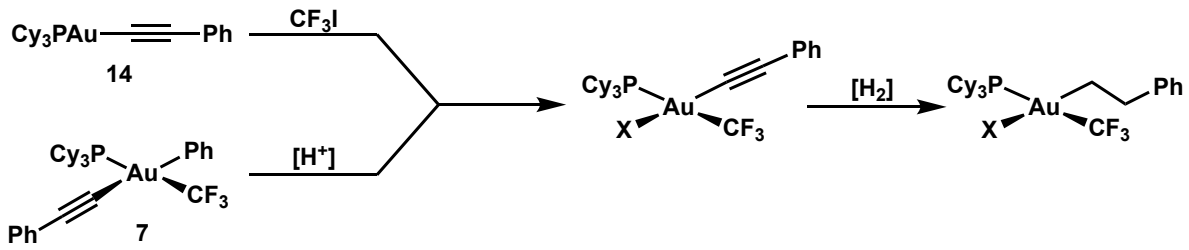
Synthesis of Au(III) Alkyl Complexes

Concurrent the work above, I also attempted to synthesize complexes similar to those seen in figure 1a, in which the gold (III) alkyl complex possesses an X-type spectator ligand inert to the Lewis acidic reaction conditions. As mentioned above, when treated with the photoinitiated oxidative addition conditions used to form Au(III) aryl complex **4**, alkyl Au(I) species instead undergo a formal ligand exchange to yield [Au(L)(CF_3)] and the corresponding alkyl iodide.[32] Thus, an alternative route must be used to introduce the Au-CF_3 moiety in alkylated gold (III) complexes.



Scheme 13. Attempted multistep synthesis for the formatin of (trifluoromethyl)Au(III) alkyl complexes.

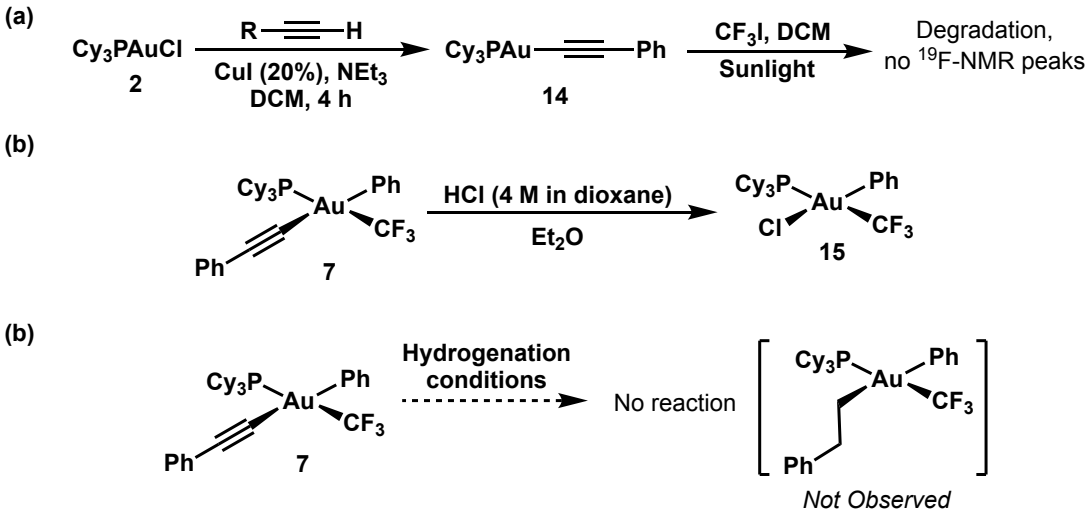
Using the light mediated ligand exchange reaction described above, [Au(IPr)(CF_3)] could easily be formed from its methylated counterpart. Oxidative addition with $PhICl_2$ then gives the trans-dichloro Au(III) complex **13**. However, all attempts to transmetalate result only in reductive elimination to the Au(I) precursor, likely accompanied by R-R homocoupling (Scheme 13).



Scheme 14. Proposed synthetic routes for formation of mono-trifluoromethylated alkyl gold (III) complex.

I then imagined it possible to access the alkyl Au(III) species by hydrogenation of an alkynyl gold complex, formed either through CF_3I oxidative addition to Au(I) alkynyl complex **14** or protonolysis of **7** (Scheme 14). However, protonolysis formed only the chlorinated Au(III) aryl species **15** (Scheme 15a). Photoexcitation of **14** in the presence of CF_3I resulted in degradation to and unrecognizable species with no fluorinated species detectable by ^{19}F-NMR (Scheme 15b).

Given the difficulties in accessing the monoalkylated species shown in scheme 14, I turned my attention to direct hydrogenation of compound **7**. Unfortunately, the alkynyl complex was found to be inert to a myriad of hydrogenation conditions (Scheme 15c). It should be noted, however, that no reactions with high pressure of H_2 were attempted and this could potentially be an avenue in accessing the desired alkyl compound.



Catalyst	H_2 Source	Solvent
Pd/C	1 atm H_2	EtOAc/MeOH (1:1)
Pd/C	1 atm H_2	EtOAc
Pd/C	1 atm H_2	MeOH
Pd/C	$NH_4[H_2NCO_2]$	EtOAc/MeOH (1:2)
PtO_2	1 atm H_2	EtOAc
Rh/C	1 atm H_2	EtOAc

Scheme 15. (a) Synthesis of alkynyl Au(I) compound. Attempted CF_3I oxidation addition resulted in degradation. (b) Protonolysis conditions instead result in the chlorinated aryl gold product. (c) Listed hydrogenation conditions resulted in no reaction.

II. (L,X) Tethered Au(III) Complexes

Despite the successful synthesis of mono-trifluoromethylated Au(III) aryl complexes, the goals of the previous section remained insurmountable given that nucleophilic trapping of the difluorobenzyl ligand was favored despite modification of spectator ligand. Furthermore, no monotrifluoromethylated alkyl gold complex could be successfully formed from [Au(IPr)(CF_3)] using the conditions above.

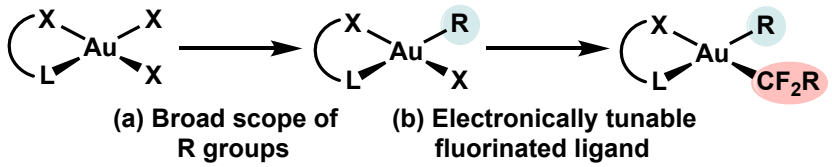


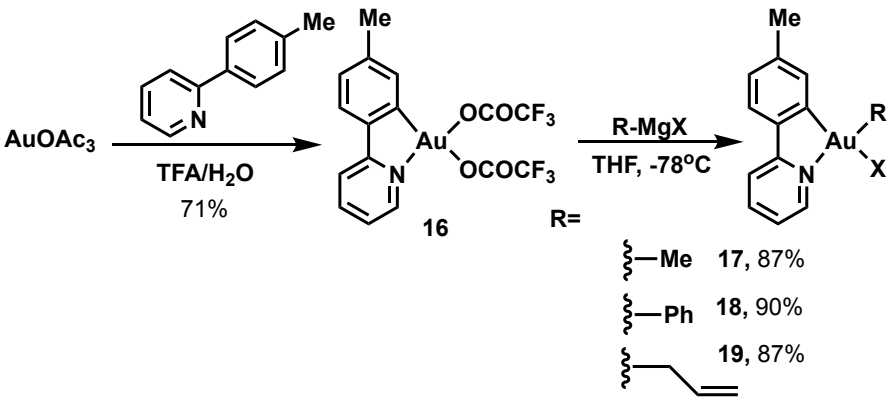
Figure 2. A synthetically versatile route towards (L,X) tethered Au(III) complexes.

This being the case, an alternative approach began to seem more advantageous. A synthetically versatile route that could accommodate a broad scope of both fluorinated ligands and R-group coupling partners could provide access to both the electron poor gold center required for nucleophilic trapping and increased product diversity (Figure 2). I envisioned that gold complexes with tethered (L,X) ligands could be an excellent platform to access such systems given the following reasons:

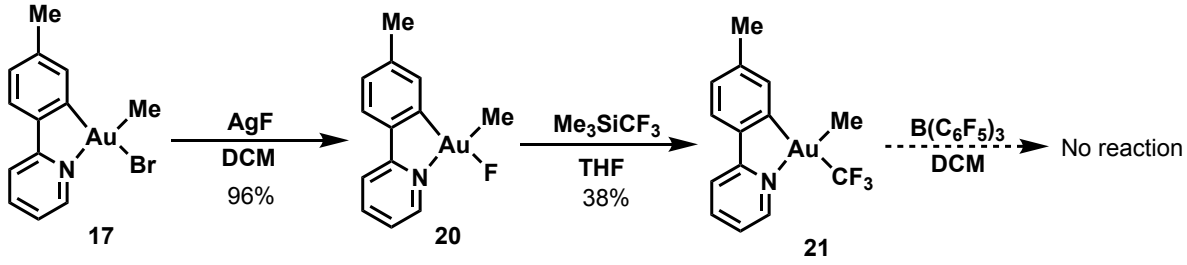
1. The tethered system provides facile formation of Au(III) using relatively mild conditions, without the need for harsh oxidants.[34]
2. The (L,X) ligand geometry necessitates a stereochemistry at the metal center in which the R-group and fluorinated ligand are situated cis to each other, as is necessary for migratory insertion.
3. The complex syntheses can accommodate a broader scope of R-groups, both aromatic and aliphatic (Figure 2a).[35]
4. Late-stage installation of the fluorinated ligand permits electronic and structural diversity of the complex (Figure 2b).

Synthesis of (N,C) Gold (III) Complexes

The initial synthesis of such a complex began with the cyclometalation of the 2-phenylpyridine ligand via microwave heating in TFA to form (N,C) gold (III) complex **16**. Tilset *et al.* has previously found that the monoalkylated or monoarylated derivatives can be selectively obtained using the respective Grignard reagent.[35] I additionally found this to be true in the case using allylmagnesium chloride. It was imagined that trifluoromethylation could be feasible by treatment with silver fluoride followed by Ruppert-Prakash reagent. Surprising, given the previously mentioned difficulty of Au(I) trifluoromethylation, full conversion to product **21** was achieved.

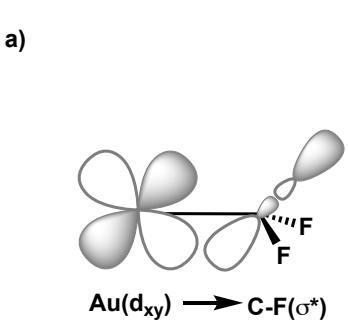


Scheme 16. Synthesis used to access 2-phenylpyridine cyclometalated gold compounds.



Scheme 17. Synthetic route used to access trifluoromethylated Au(III) complex. Compound is inert to reductive elimination conditions.

With the trifluoromethylated compound **21** in hand, I attempted formation of trifluoroethane via treatment with BCF. Unfortunately, no sign of the reductive elimination product was visible by ^{19}F-NMR. Furthermore, no major products were seen over a period of 24 hours and the starting complex appeared to undergo nonspecific degradation to Au(0). The lack of any new fluorinated species indicates that its likely no initial fluoride abstraction by the borane occurred.



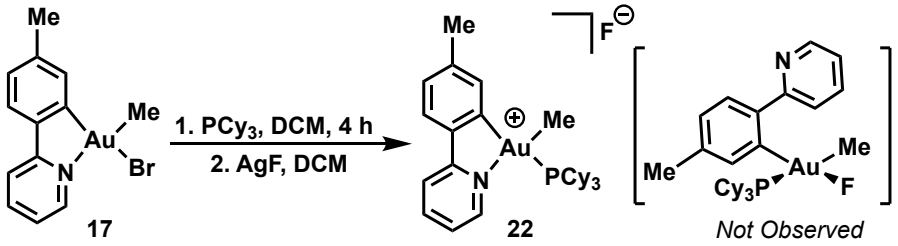
b)

Ligand	ν_{CO}(cm^{-1})
ICy	2049.8
IPr	2051.5
PCy_3	2056.5
$P(i\text{-}Pr)_3$	2059.2
PPh_3	2067.5
Pyridine	2070.5

Figure 3. (a) Molecular orbitals involved in electron donation of metal d orbital into C-F antibonding orbital of the ligand. (b) Tolman electronic parameters (TEPs) of select ligand.[37]

This result can be understood by recognizing the electronic requirements for fluoride abstraction from metal-CF_3 complexes. Formation of M-CF_2 complexes rely on the lability of the

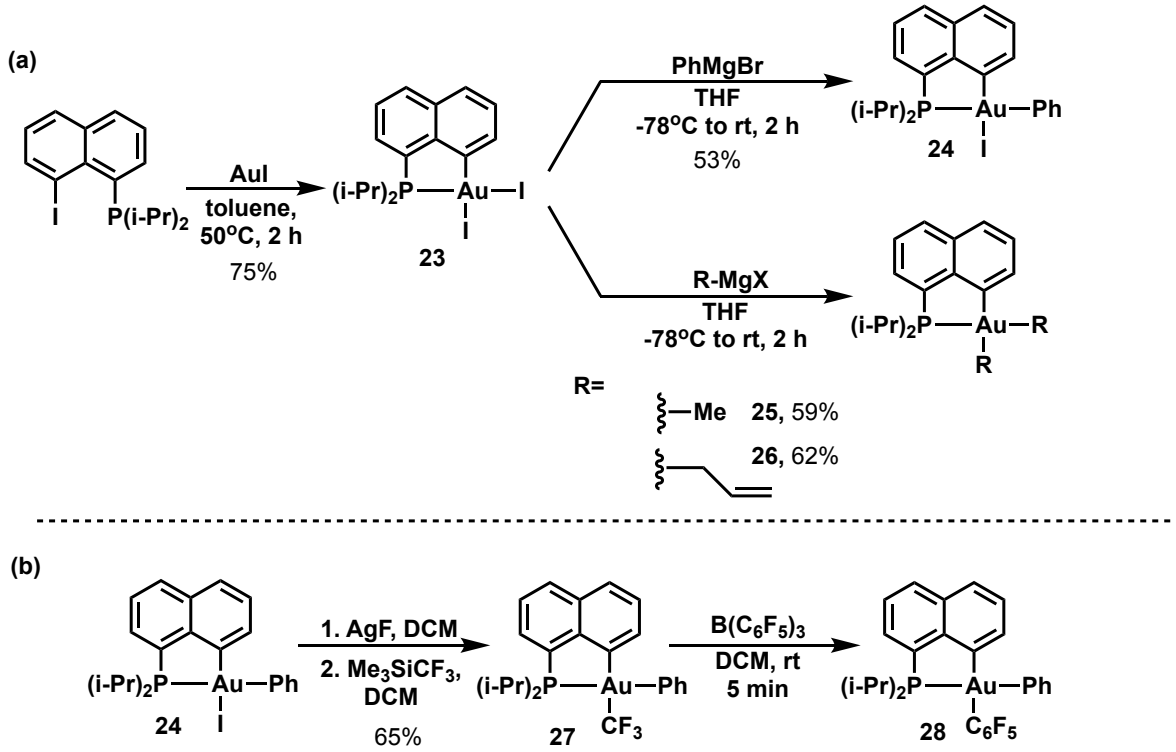
C-F bond imparted by electron donation of the metal d orbital into the antibonding orbital of the carbon-fluorine bond (Figure 3a).[36] It's possible that the pyridine L-type ligand in compound **21** is not sufficiently donating to activate the C-F bond for abstraction. Indeed, Tolman electronic parameters (TEPs), which measure the stretching frequency of the A1 C-O vibrational mode (ν(CO)) of $Ni(CO)_3L$, show that the donating ability of pyridine ligands are much less than that of either N-heterocyclic carbenes or alkyl phosphines, both of which were previously used in cases were fluoride abstraction occurred from [Au(III)CF_3] complexes (Figure 3b).[37]



Scheme 18. Attempted ligand exchange using tricyclohexylphosphine.

Initial attempts to probe this hypothesis were done *via* ligand exchange between the pyridine-based ligand with the more donating PCy_3 resulted only in substitution of the bromide and formation of cationic Au(III) complex **22** (Scheme 18).

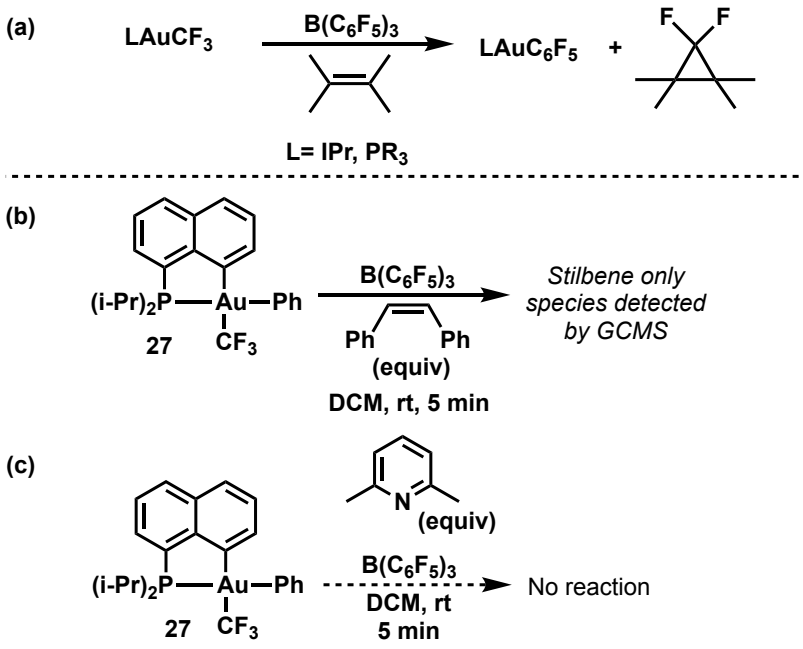
Synthesis of (P,C) Gold (III) Complexes



Scheme 19. (a) Synthetic route used to make (P,C) cyclometalated gold complexes. (b) Synthesis of trifluoromethyl Au(III) complex, which forms an aryl transfer product in the presence of BCF.

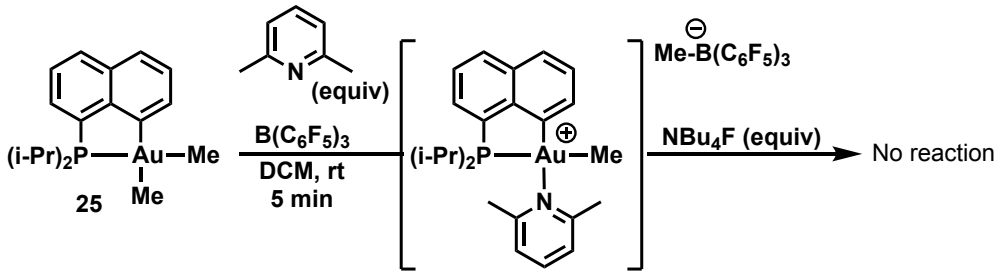
To form a cyclometalated species with a more donating L-type ligand, (P,C) gold (III) complex **23** was synthesized by treating AuI with a naphthalene-based phosphine ligand. Only the monoarylated complex could be selectively formed *via* PhMgBr and treatment of **23** with both methyl and allyl Grignard reagents resulting in large quantities of dialkylation (Scheme 19a). Pushing forward monoarylated compound **24**, trifluomethylated **27** can be formed using AgF and Me_3SiCF_3 (Scheme 19b).

Reductive elimination from **27** was attempted using stoichiometric BCF. As in the case of compound **21**, no C-CF_3 reductive elimination product was observed. However, the starting material was consumed within 5 minutes and new ^{19}F-NMR peaks observed in the aromatic region of the spectrum were identified as belonging to aryl transfer product **28** (Scheme 19b). Such perfluoroaryl products have previously been observed upon treatment of [(CF_3)AuL] complexes with BCF.[26,38] Introduction of a carbene trap in those instances gave an additional difluorocyclopropanated side product, indicating initial formation of a gold difluorocarbene species (Scheme 20a). Subjecting compound **27** to BCF in the presence of cis-stilbene formed **28** without producing any difluorocyclopropane, as indicated by both ^{19}F-NMR or GCMS (Scheme 20b). Attempts to promote migratory insertion by addition of weakly coordinating lutidine instead resulted in no reaction, likely due to formation of a Lewis acid-base pair between the lutidine and borane (Scheme 20c).



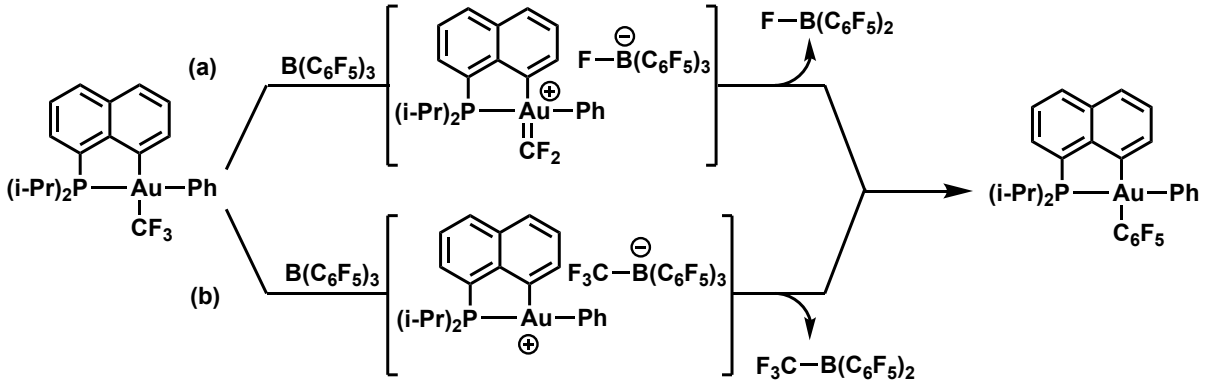
Scheme 20. (a) Previous work on fluoride abstraction from [(CF_3)AuL].[26,38] (b) Attempted carbene trap of a difluorocarbene species resulted in no observable cyclopropanated species. (c) Attempt to promote migratory insertion by inclusion of weakly coordinating lutidine resulted in no reaction.

While no aryl migration occurred from compound **27**, the possibility of outer-sphere reductive elimination from a cationic gold (III) center was probed *via* an alternative route. Dimethyl compound **25** was treated with BCF to form a lutidine trapped cationic intermediate. Upon treatment with a fluoride source, no new products are formed however (Scheme 21).



Scheme 21. Attempt to reductively eliminate fluoromethane resulted in no reaction.

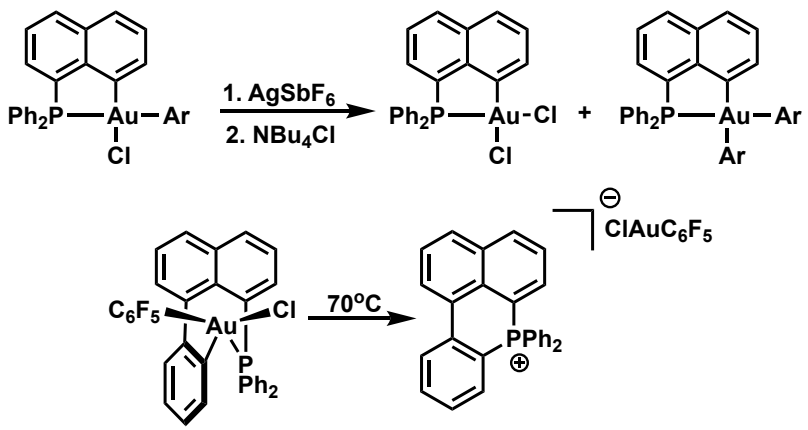
At this time, it appears that either (a) the difluorocarbene is forming, but the rigid geometry of the naphthalene backbone on the (P,C) ligand prevents access to the geometry necessary for aryl migration; or (b) the difluorocarbene is not forming and instead the trifluoromethyl ligand is abstracted by the borane (Scheme 22). If mechanism (a) is occurring, it seems plausible that use of a less rigid (P,C) ligand may allow migratory insertion to occur.



Scheme 22. Possible mechanisms for formation of the aryl transfer product. (a) Fluoride-abstraction is occurring to form a difluorocarbene intermediate or (b) CF_3-abstraction is occurring.

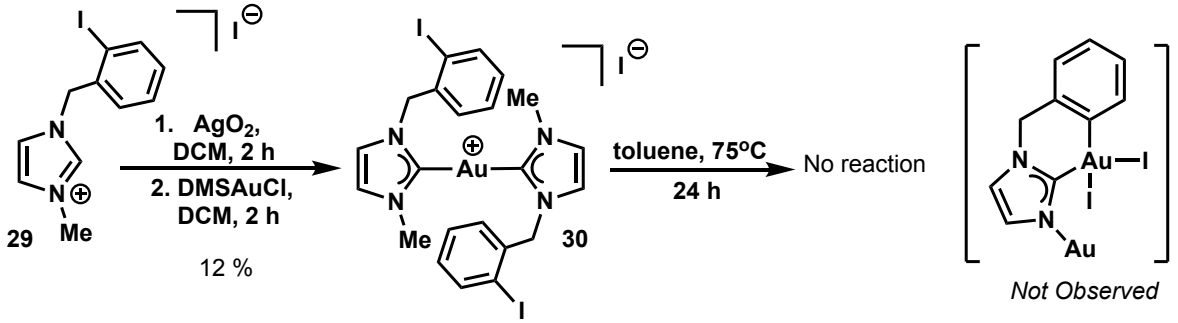
Unfortunately, it has already been reported by our group that P-C reductive elimination is favored in cases where the bite angle of the ligand allows for a stable reduction product (Scheme 23).[39] Thus, migratory insertion and C-CF_3 reductive elimination would have to be competitive with phosphonium formation.

More evidence is needed to probe the mechanism of Au-perfluoroaryl complex, including detection of the borane side product and modulation of the Lewis acid. Treatment of compound **28** with Me_3SiOTf is examined later in section IV.



Scheme 23. Phosphonium formation occurs in cases where the bidentate phosphines ligand is less sterically constrained.[39]

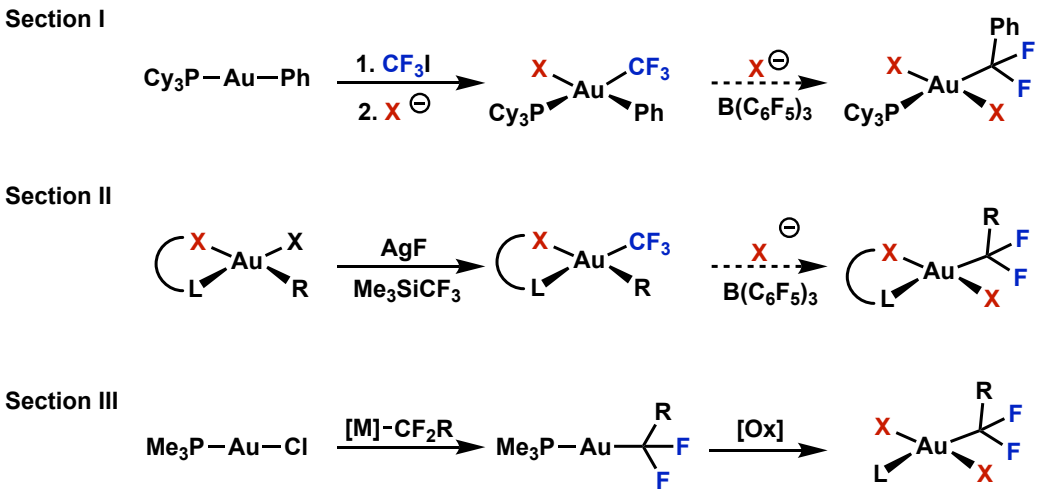
It should be noted that I also attempted to synthesize an NHC-based (L,X) tethered gold complex in order to access an electron rich complex without competitive phosphonium formation. While imidazolium **29** was successfully synthesized and ligated to Au(I), oxidative addition by heating complex **30** in toluene for 24 hours resulted in no reaction. It's likely that the barrier for oxidative addition to Au(III) is such that C-X activation of the freely rotating aryl iodide could not be accessed by simple heating. Indeed, Ribas et al. have previously found that C_{Ar}-I oxidative addition is not possible without fixed rotation of the chelating ligand.[40]



Scheme 24. Attempted formation of an NHC-based (L,X) tethered gold complex.

III. Formation of Au(III)-CF_2R Complexes *via* Direct Transmetallation

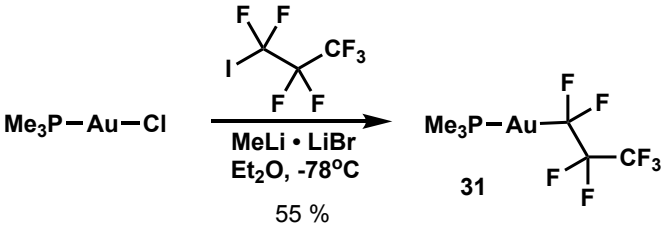
After complexes described in sections I and II both failed to form gold difluoroaryl complexes *via* nucleophilic trapping of the gold center, an alternative synthesis that omits the necessity of fluoride abstraction and migratory insertion became more appealing. Rather than forming a radiosynthetic precursor via treatment with a Lewis acid and nucleophilic trapping agent, this section describes the direct transmetallation of CF_2R groups onto gold (Scheme 25).



Scheme 25. The syntheses done in this section aims to circumvent the use of fluoride-abstraction and migratory insertion reactions.

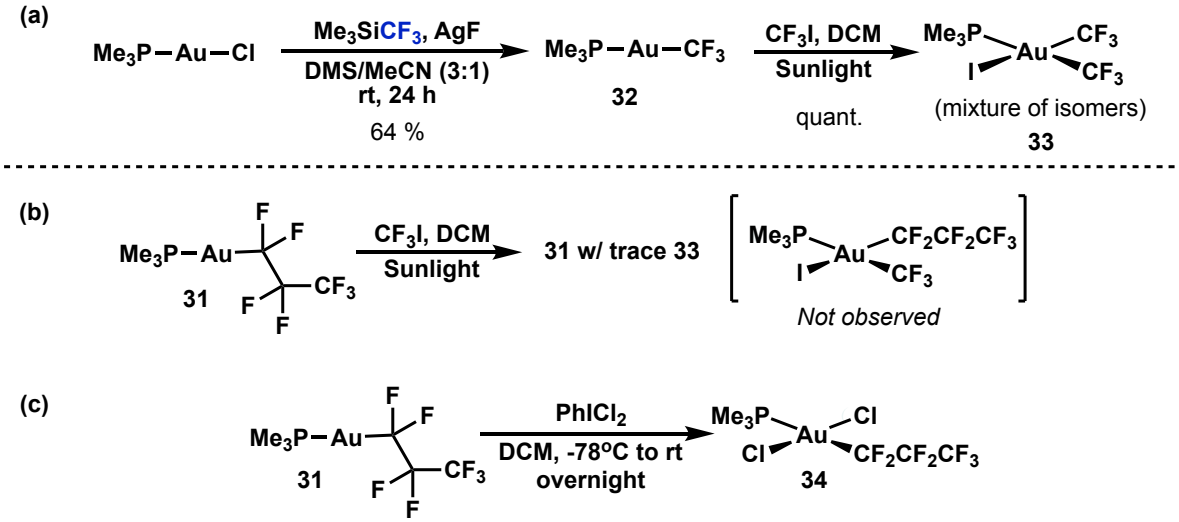
Formation of perfluoroalkyl- or 1,1-difluoroalkylmetal species from which to transmetalate is difficult due the fact that reactive fluorinated organometallic reagents can be prone to α-elimination and subsequent rearrangement or degradation.[41] Less reactive species, such as organozinc, copper and indium complexes, often suffer from low nucleophilicity that prevents efficient transmetalation.[42] For these reasons, I assumed formation of a [$AuCF_2R$] complex would be synthetically challenging.

Perfluoroalkylmetal species, which are less inclined to undergo α-elimination, have a resultingly higher stability and seemed like a promising place to begin probing the possibility of this synthetic route.[43] Indeed, perfluoroalkylated gold species **31** was formed in the presence of 1-iodoperfluoropropane and methyllitium lithium bromide complex at -78°C (Scheme 26).



Scheme 26. Synthesis of perfluoroalkylated gold species.

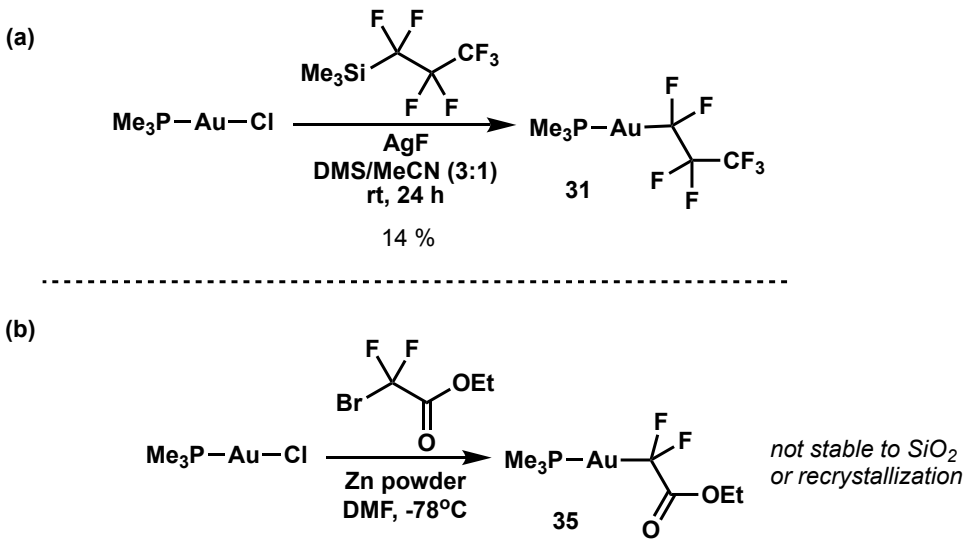
With the compound in hand, I began attempts to oxidize **31**. Previous report of the ligand effects on the reaction of [(Me)AuL] with CF_3I showed that while L = PPh_3 and PCy_3 both undergo ligand exchange to form [(CF_3)AuL], L = PMe_3 instead gives the oxidative addition product [$(CF_3)_2AuI(PMe_3)$].[44] I reproduced these results via formation of **32** from a modified procedure in which a solvent mixture of 1:3 acetonitrile, dichloromethane is used (Scheme 27a).



Scheme 27. (a) Synthetic route to access Au(I) trifluoromethyl species and CF_3I oxidative addition to Au(III). (b) Unsuccessful attempt at CF_3I oxidative addition to gold perfluoropropyl species. (c) Oxidative addition to dichlorinated gold (III) perfluoropropyl complex.

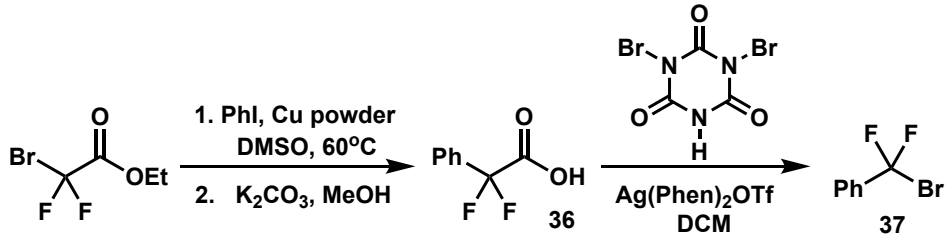
It was my hope that gold perfluoropropyl complex **31** would similarly undergo oxidative addition with CF_3I. Unfortunately, when treated to the conditions seen in scheme 27b the only product formed was trace amounts of **33** along with unreacted starting material (Scheme 27b). Contents of the reaction flask failed to turn pale yellow upon irradiation, as related gold complexes do when efficient photoexcitation is achieved.[32] Formation of **33** suggests whatever amount of Au(II) intermediate formed is exchanging the trifluoromethyl and perfluoropropyl ligands to favor the Au(III) product with greater thermodynamic stability. When treated with $PhICl_2$, the corresponding Au(III) dichloride complex **34** is formed (Scheme 27c). However, alkylation and arylation of similar compounds have already been shown to result in reduction to Au(I) (Scheme 13). Thus, **34** cannot be further derivatized via transmetalation.

It should also be noted that compound **31** was also accessed using the corresponding trimethylsilyl reagent using similar conditions as trifluoromethylated compound **32** (Scheme 28a). In addition, ethyl difluoroacetate compound **35** was formed using Barbier-type reaction conditions. However, the product was unstable in atmosphere at room temperature. Isolation by either column chromatography or recrystallization resulted in significant degradation (Scheme 28b).



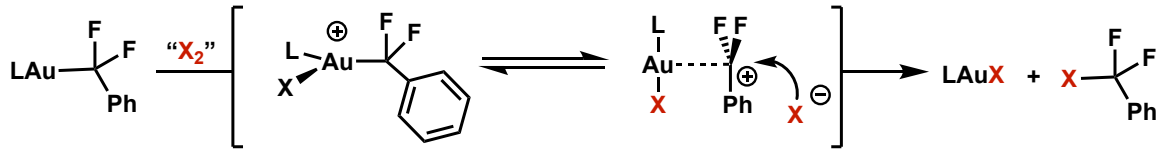
Scheme 28. (a) Synthesis of perfluoroalkylated gold species using trimethylsilyl reagent. (b) A gold (I) ethyl difluoroacetate complex could be made, but was unstable to purification conditions.

The ultimate goal of this section was to access difluorobenzyl Au(III) complexes via direct transmetalation of the fluorinated ligand. $PhCF_2Br$, made from silver mediated decarboxylation of **36** in the presence of a brominating agent, could be subjected to transmetalation to [(L)AuX] (Scheme 29).



Scheme 29. Synthesis of $PhCF_2Br$ via silver mediated decarboxylation.

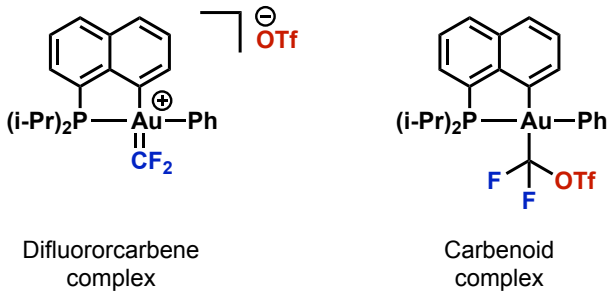
However, even with Au(I) compound precursor accessible, oxidation using CF_3I will likely be unsuccessful given the apparent reversibility of fluorinated ligand addition in forming the Au(II) intermediate. Furthermore, treatment with formal X_2 oxidants, such as $PhICl_2$ will yield three-coordinate cationic intermediates as shown in scheme 30. As discussed in section I, such a complex will undergo outer-sphere reductive elimination in the presence of a nucleophile. Thus, this route cannot give the desired Au(III)-CF_2Ph complex.



Scheme 30. Treatment of difluorobenzyl gold complex will likely result in reductive elimination.

IV. Investigation of Observable Au-CF_2 Species

Following the formation of aryl transfer compound **28**, I was interested to see whether a weaker Lewis acid could yield the desired migratory insertion product or otherwise provide more insight into whether fluoride-abstraction occurs.



Difluororcarbene complex

Carbenoid complex

Figure 4. Structures of the gold-difluorocarbene complex and carbenoid complex potentially resulting from treatment of compound **27** with Me_3SiOTf.

If a gold difluorocarbene complex is being formed, it's possible that a weakly coordinating anion could stabilize the complex, making it observable either as the free difluorocarbene or carbenoid complex (Figure 4). The treatment of **27** with Me_3SiOTf at room temperature was monitored by ^{19}F-NMR and ^{31}P-NMR. A multiplet corresponding to Me_3SiF indicates the occurrence of a C-F bond breaking event (δ -157.77 – -158.01, m). Additionally, several doublets appear in the [AuCF] region of the spectrum suggestive of key products or reaction intermediates (Figure 5).

Variable Temperature NMR was used to further investigate the reaction and better understand the nature of the products being formed. In this case, the reaction was set up in the glovebox using water and air free solvents and reagent. Upon slowly warming the sample from -78°C (150 K) revealed formation of several key species. A singlet forming at 250 K later disappears at 290 K and thus was not seen in the spectrum of the reaction at room temperature. A doublet (δ = -33.95, J = 66.8 Hz) appears in the [AuCF] region of the spectrum at 270 K, concurrent to formation of Me_3SiF. Lastly, a singlet appears at 290 K. (Figure 6)

Inspection of the ^{31}P-NMR at room temperature shows a quartet with an identical coupling constant to that of the doublet in the ^{19}F-NMR (Figure 7). This splitting pattern is indicative of neither a difluorocarbene complex nor a carbenoid. Instead, the magnitude of the coupling constant suggests possible isomerization to the trans complex.[45] Due to low reaction conversion, the nature of singlets appearing at 260 K (δ -15.61) and 290 K (δ -91.89) are still unknown.

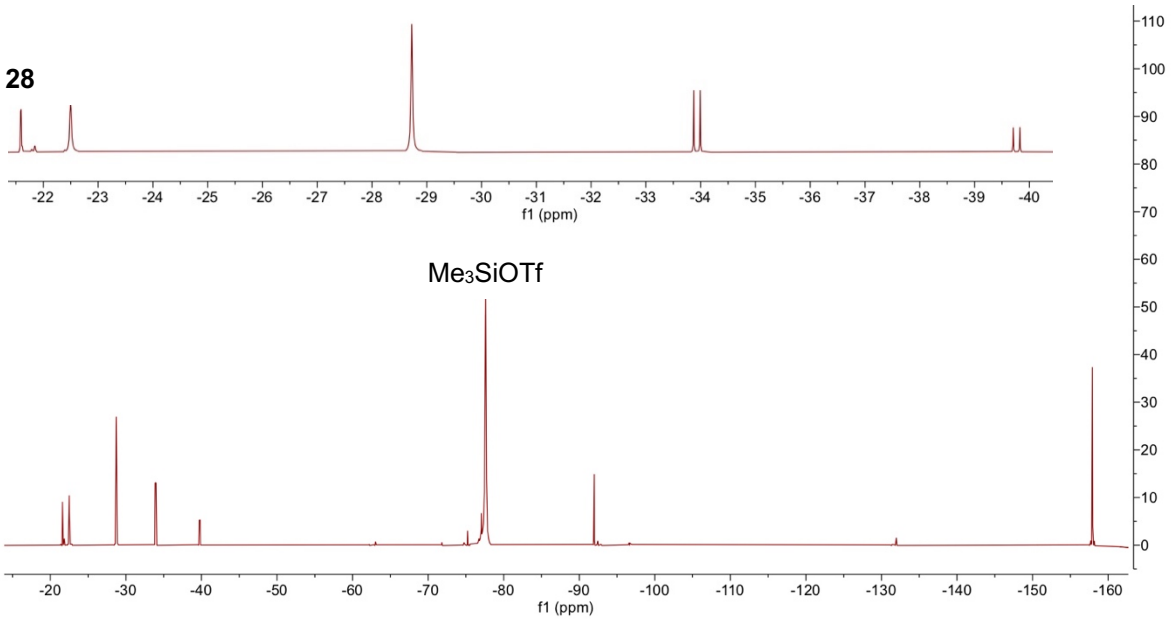


Figure 5. ^{19}F-NMR spectrum of the reaction of compound **27** with Me_3SiOTf at room temperature.

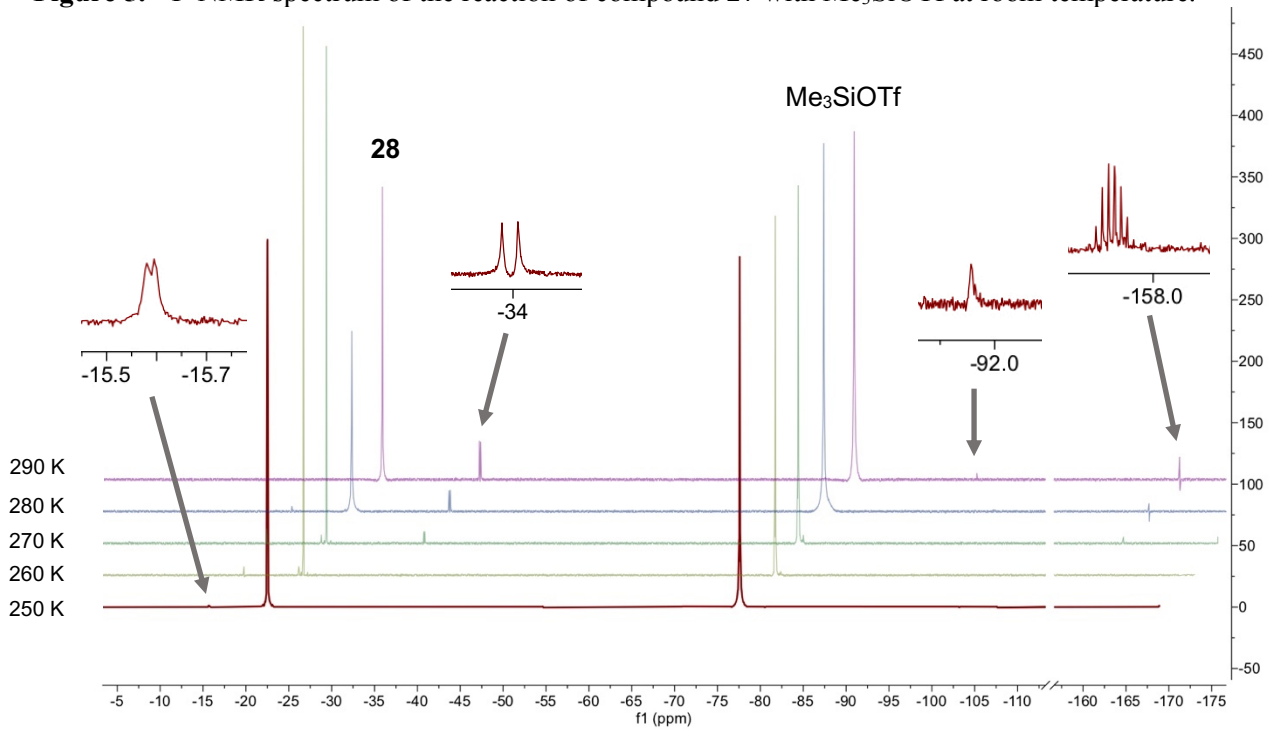


Figure 6. Variable temperature ^{19}F-NMR spectra of the reaction of **27** with Me_3SiOTf.

Confirmation of the isomerized product could provide substantial insight into novel reactivity of trifluoromethyl complexes and Lewis acids. Such a complex is likely formed through a three-coordinate cationic intermediate. There are few operative mechanisms involving fluoride-abstraction that could support this. However, abstraction of the trifluoromethyl ligand can account for both isomerization as well as the unusual reactivity mentioned in section II (Scheme 31). Contradictory formation of Me_3SiF refutes this idea however, unless its formation is not through

the breaking of the $AuCF_2$-F bond. As of now, there are no known complexes from which trifluoromethyl-abstraction occurs.

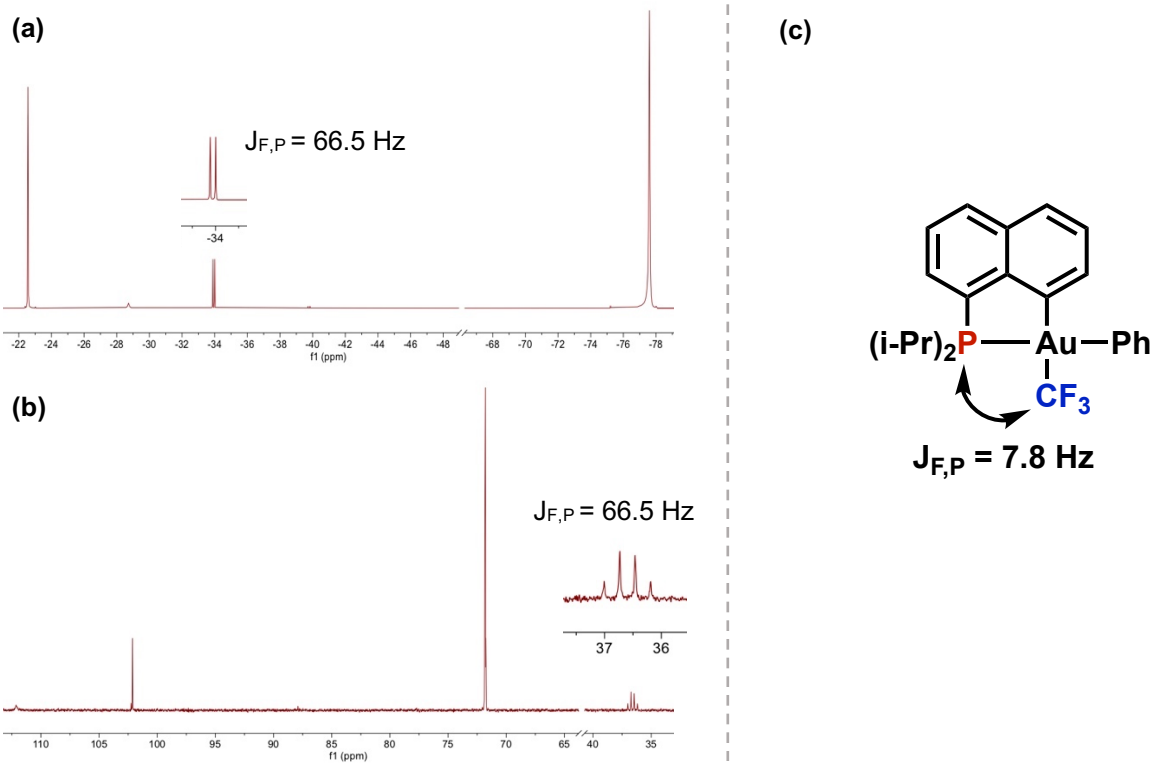
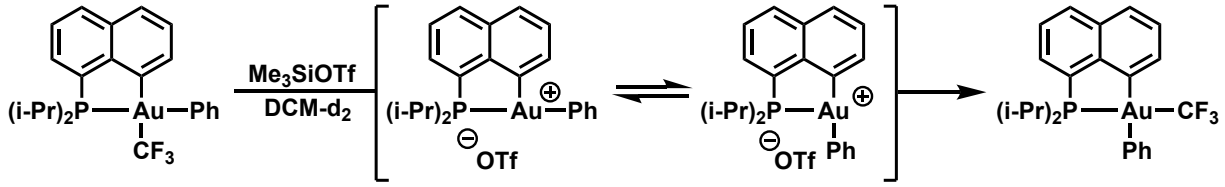


Figure 7. (a) ^{19}F-NMR spectrum of the reaction of compound **27** with Me_3SiOTf at room temperature. (b) ^{31}P-NMR spectrum of the reaction of compound **27** with Me_3SiOTf at room temperature. (c) Coupling constants of compound **27**.

To further confirm the presence of the isomerized product and identify the reaction mechanism, it will be necessary optimize the reaction so that product conversion is high enough to isolate individual the components seen in the NMR.



Scheme 31. Proposed trifluoromethyl-abstraction and isomerization.

Conclusions and Future Work

In conclusion, I successfully synthesized several new classes of gold complexes in order to expand the scope and SA of Au(III) mediated incorporation of ^{18}F into fluorinated and perfluorinated reductive elimination product. Unfortunately, due to the difficulties disclosed in sections I, II, and III this goal was never achieved.

Promising work towards the investigation of observable transient gold intermediates was featured in section IV. While the identity of the species observed by NMR were never definitively determined, this work provides an auspicious avenue into potentially novel Au(III) reactivity in the presence of Lewis acids.

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Methods and Materials

General Considerations

Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware. All glassware was cleaned using aqua regia to remove metal impurities. NMR tubes used for reductive elimination studies with $B(C_6F_5)_3$ were additionally silylated with hexamethdisilazane at 100°C prior to use. Reaction vessels were sealed with rubber septa under a nitrogen atmosphere and solutions were stirred with Teflon-coated magnetic stir bars. Dry tetrahydrofuran (THF), toluene (Tol), acetonitrile (MeCN), triethylamine, and dichloromethane (DCM) were obtained by passing these previously degassed solvents through activated alumina columns.
All other reagents were used as received, with the following exceptions: Tris(pentafluorophenyl) borane was purchased from Strem Chemical and purified by hot filtration and recrystallization from hexanes, followed by vacuum sublimation at 100°C. For all reactions conducted in a glovebox, reagents were thoroughly dried and degassed prior to use.

Reactions were monitored by thin layer chromatography (TLC) on Silicycle SiliaplateTM glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized by UV irradiation. Volatile solvents were removed under reduced pressure with a rotary evaporator and additional volatiles were removed at high vacuum on a Schlenk line. ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and ^{31}P NMR spectra were taken with spectrometers operating at 300, 400, 500, or 600 MHz for ^{1}H. Chemical shifts are reported relative to the residual solvent signal (^{1}H NMR: $\delta = 5.32$; ^{13}C NMR: $\delta = 53.84$ for DCM-d_2). NMR data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet. Elemental Analyses and HRMS were performed by the Microanalytical Facility at the University of California, Berkeley.

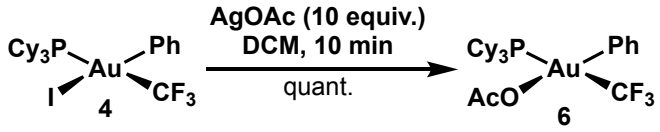
Most of the gold complexes reported herein are moderately light sensitive, so reactions, work up procedures, and purifications were conducted with exclusion of light.

Previously Reported Compounds

[(Me_3P)Au(Cl)][9] and compounds **1**,[1] **2**,[9] **3**, **4**,[2] **5**,[3] **12**,[1] **13**,[9] **16**, **17**, **18**,[5] **23**,[6] **24**,[7] **25**,[6] and **29**[8] were all prepared according to previously reported conditions and the resulting spectra corresponded to those published.

Synthetic Procedures

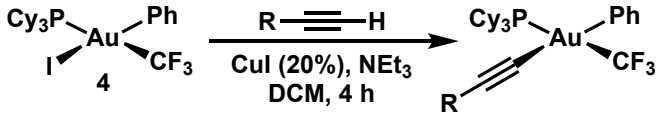
[(Cy_3P)Au(Ph)(CF_3)(OAc)], **6**



Compound **4** (7.4 mg, 0.01 mmol, 1.0 equiv.) was dissolved in DCM (1 mL) in a vial. AgOAc (5.0 mmol) was added and the reaction mixture was capped and sonicated for 5 min in the dark, followed by a second addition of AgOAc (5.0 mmol) and further sonication for 5 min. The suspension was filtered through a bed of Celite and concentrated to dryness under reduced pressure. The solid was then dissolved in minimal DCM and precipitated out of solution by the gradual addition of pentane. The solid was removed by filtration and washed with excess pentane to afford **6** as a white solid (8.9 mg, quant. yield).

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.33 (d, *J* = 7.0 Hz, 1H), 7.16 (d, *J* = 6.9 Hz, 1H), 2.12 – 1.98 (m, 4H), 1.87 (d, *J* = 14.2 Hz, 4H), 1.82 (d, *J* = 12.1 Hz, 3H), 1.70 (d, *J* = 13.8 Hz, 2H), 1.56 (q, *J* = 12.8 Hz, 3H), 1.29 (dq, *J* = 21.8, 12.9, 11.6 Hz, 3H), 1.09 (q, *J* = 13.1 Hz, 3H).
^{13}C NMR (151 MHz, CD_2Cl_2) δ 175.44, 132.54, 128.81, 126.02, 53.70, 53.52, 53.34, 53.16, 52.98, 32.94, 32.78, 28.95, 28.93, 27.41, 27.33, 25.83, 23.40.
^{19}F NMR (376 MHz, CD_2Cl_2) δ -36.13 (d, *J* = 63.6 Hz).
^{31}P NMR (162 MHz, CD_2Cl_2) δ 29.29 (q, *J* = 63.6 Hz).
EA: Calculated: C, 47.51; H, 6.05; Found: C, 46.30; H, 6.12

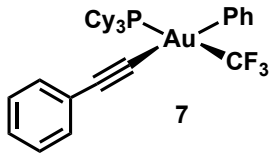
General procedure for the formation of Au(III)-alkynes



A solution of **4** (35.5 mg, 0.05 mmol, 1.0 equiv.) in DCM (5 mL) was added to the reaction flask followed by addition of the substituted acetylene (0.15 mmol, 3.0 equiv.). The solution was allowed to stir for 10 min before the addition of CuI (1.9 mg, 20 mol%), then the rapid addition of triethylamine (35 mL, 1.75 mmol, 35 equiv.). The reaction mixture was allowed to stir for 4 hours before being quenched by water, turning the solution a bright yellow. The layers were separated and the aqueous layer was extracted three times with additional DCM. The organic layer was then washed three times with water until the solution became colorless. The liquid was then dried over

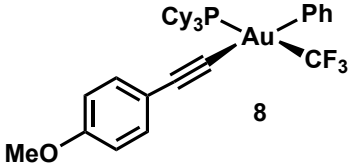
sodium sulfate and filtered to dryness. Further purification was achieved *via* preparatory TLC with compounds eluding in DCM/hexane (1:1).

Compound **7**



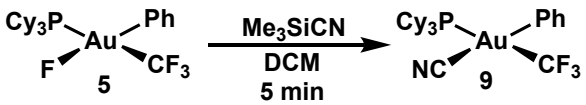
White solid (17.8 mg, quant. yield)
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.52 – 7.13 (m, 9H), 7.13 – 7.01 (m, 1H), 2.36 (q, *J* = 12.1 Hz, 2H), 2.10 – 1.56 (m, 20H), 1.45 – 1.19 (m, 4H), 1.15 – 0.97 (m, 4H).
^{13}C NMR (151 MHz, CD_2Cl_2) δ 134.66, 131.05, 128.60, 128.10, 53.74, 53.56, 53.38, 53.20, 53.02, 33.79, 33.62, 29.39, 29.37, 27.35, 27.28, 25.90.
^{19}F NMR (376 MHz, CD_2Cl_2) δ -27.50 (d, *J* = 63.1 Hz).
^{31}P NMR (162 MHz, CD_2Cl_2) δ 25.86 (q, *J* = 62.2 Hz).
EA: Calculated: C, 54.70; H, 5.98; Found: C, 54.32; H, 6.04

Compound **8**



Pale yellow solid (13.5 mg, 36.2% yield)
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.32 (dd, *J* = 8.5, 2.9 Hz, 4H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 2.36 (q, *J* = 12.5, 12.1 Hz, 1H), 2.10 – 1.50 (m, 9H), 1.42 – 0.89 (m, 4H).
^{13}C NMR (151 MHz, CD_2Cl_2) δ 158.50, 134.70, 132.30, 128.57, 124.88, 118.54, 113.67, 106.97, 55.15, 33.77, 33.60, 29.38, 29.36, 27.36, 27.29, 25.90.
^{19}F NMR (376 MHz, CD_2Cl_2) δ -27.50 (d, *J* = 62.9 Hz).
^{31}P NMR (162 MHz, CD_2Cl_2) δ 25.91 (q, *J* = 63.5 Hz).
EA: Calculated: C, 54.11; H, 6.01; Found: C, 63.91; H, 6.21

[(Cy_3P)Au(Ph)(CF_3)(CN)], **9**

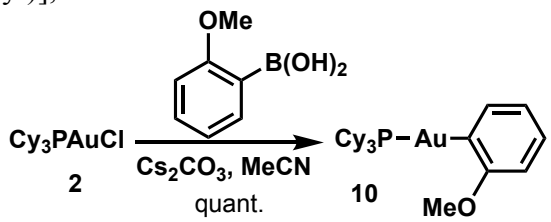


Compound **5** (16.1 mg, 0.025 mmol) was dissolved in DCM and cooled to -78°C. Me_3SiCN was then added slowly and the reaction mixture was allowed to warm to room temperature. After stirring for 10 min, the solution was concentrated to dryness under reduced pressure and placed under high vacuum overnight to ensure the evaporation of TMS-F and excess TMS-CN. The solid

was then dissolved in minimal DCM and precipitated out of solution by the gradual addition of pentane. The solid was removed by filtration and washed with excess pentane to afford **9** as a white solid (9.8 mg, 60% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.28 – 7.18 (m, 4H), 7.18 – 7.07 (m, 1H), 2.33 – 2.17 (m, 3H), 2.01 – 1.75 (m, 11H), 1.70 (d, *J* = 12.6 Hz, 3H), 1.54 (s, 2H), 1.26 (s, 12H), 1.12 (t, *J* = 12.8 Hz, 6H), 0.95 – 0.77 (m, 2H).
^{19}F NMR (376 MHz, CD_2Cl_2) δ -26.51 (d, *J* = 63.8 Hz).
^{31}P NMR (162 MHz, CD_2Cl_2) δ 29.43 (q, *J* = 63.6 Hz).

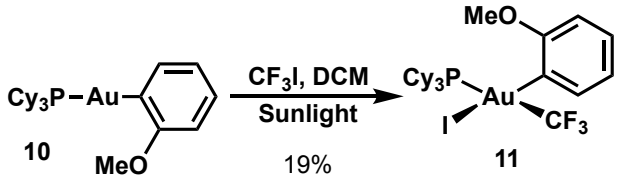
[(Cy_3P)Au(2-methoxyphenyl)], **10**



Complex **2** (25.6 mg, 0.05 mmol, 1.0 equiv.), the 2-methoxyphenylboronic acid (26.6 mg, 0.175 mmol, 3.5 equiv.) and cesium carbonate (26.6 mg, 0.175 mmol, 3.5 equiv.) were dissolved in acetonitrile (2.5 mL) and heated to 65°C for 1 hour. After being allowed to cool to room temperature, the reaction mixture was concentrated to dryness under reduced pressure, dissolved in benzene and filtered through a pad of Celite. Upon concentration, the filtrate was washed with pentane and minimal methanol to afford **10** as a white solid (36.4 mg, quantitative yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.34 (t, *J* = 6.7 Hz, 1H), 7.01 (s, 1H), 6.89 – 6.78 (m, 1H), 6.10 (s, 1H), 5.33 (s, 1H), 3.91 (d, *J* = 11.1 Hz, 1H), 3.73 (d, *J* = 14.4 Hz, 2H), 2.13 – 2.02 (m, 4H), 1.96 (s, 15H), 1.91 – 1.83 (m, 4H), 1.74 (s, 2H), 1.41 – 1.34 (m, 1H), 1.29 (dd, *J* = 17.7, 10.8 Hz, 4H).
^{31}P NMR (162 MHz, CD_2Cl_2) δ 57.67 (s).

[(Cy_3P)Au(2-methoxyphenyl)(CF_3)(Cl)], **11**



Compound **10** (34.6 mg, 0.06 mmol, 1.0 equiv.) was dissolved in DCM (0.5 mL) and transferred to a Schlenk tube. The vessel was sealed with a Teflon cap and subjected to 3x freeze-pump-thaw cycles before introducing CF_3I (1 atm). The vessel was placed in direct sunlight and the solution turned pale-yellow. After 30 minutes volatiles were removed *in vacuo* to give a crude solid which was purified *via* preparatory TLC eluting in 1:1 hexane / benzene to afford **11** as a white solid (8.7 mg, 19% yield).

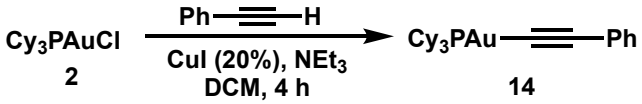
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.21 (t, *J* = 7.7 Hz, 1H), 7.09 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.85 (t, *J*

= 7.4 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 3.78 (s, 3H), 2.42 (q, *J* = 12.1 Hz, 3H), 1.93 (s, 10H), 1.88 – 1.71 (m, 6H), 1.70 – 1.59 (m, 7H), 1.54 (s, 4H), 1.26 (s, 2H), 1.25 – 1.09 (m, 6H), 1.01 (d, *J* = 12.7 Hz, 3H).

^{19}F NMR (376 MHz, CD_2Cl_2) δ -22.71 (d, *J* = 62.7 Hz).

^{31}P NMR (162 MHz, CD_2Cl_2) δ 27.04 (q, *J* = 61.2 Hz).

[(Cy_3P)Au(phenylacetylene)], **14**

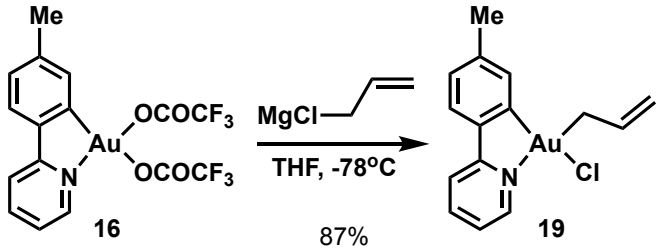


A solution of **2** (38.1 mg, 0.07 mmol, 1.0 equiv.) in DCM (10 mL) was added to the reaction flask followed by addition of phenylacetylene (0.02 mL, 0.2 mmol, 3.0 equiv.). The solution was allowed to stir for 10 min before the addition of CuI (2.6 mg, 0.014, 20 mol%), then the rapid addition of triethylamine (0.3 mL, 2.45 mmol, 35 equiv.). The reaction mixture was allowed to stir for 4 hours before being quenched by water, turning the solution a bright yellow. The layers were separated and the aqueous layer was extracted three times with additional DCM. The organic layer was then washed three times with water until the solution became colorless. The liquid was then dried over sodium sulfate and filtered to dryness to afford **14** as a yellow solid (22.5 mg, 56% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.28 – 6.99 (m, 3H), 2.13 – 1.95 (m, 9H), 1.86 (d, *J* = 11.0 Hz, 5H), 1.78 – 1.68 (m, 2H), 1.49 (d, *J* = 12.6 Hz, 6H), 1.40 – 1.20 (m, 8H).

^{31}P NMR (162 MHz, CD_2Cl_2) δ 56.43 (s).

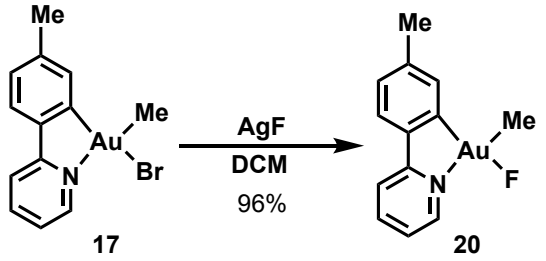
[(tpy)Au(allyl)(Cl)], **19**



A solution of compound **16** (53.2 mg, 0.09 mmol, 1.0 equiv.) in THF (10 mL) was cooled in a dry ice/acetone bath, and allylmagnesium chloride (2 M, 0.22 mmol, 2.0 equiv) was added. The solution formed a milky suspension shortly after addition. The reaction mixture was stirred for 1 hour at −78 °C and then at room temperature for 1 h. While warming to ambient temperature, the reaction mixture cleared up to a light-yellow solution. The reaction mixture was quenched with water and diluted with DCM. The solution was further extracted 3x with DCM and the resulting organic phase was washed 3x with water before being dried over $MgSO_4$ and filtered through Celite to give a light yellow solution. Solvent was removed *in vacuo* to afford **19** as a yellow solid (42.0 mg, 87% yield). The product was slightly light sensitive and the solid turned slightly purple upon prolonged storage under atmosphere.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 9.31 (dd, *J* = 5.8, 1.7 Hz, 1H), 8.06 – 7.97 (m, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.55 (s, 1H), 7.50 – 7.43 (m, 1H), 7.23 (s, 1H), 6.35 – 6.21 (m, 1H), 5.52 – 5.44 (m, 1H), 5.11 – 4.98 (m, 1H), 3.25 (d, *J* = 8.2 Hz, 2H), 2.49 (s, 3H).

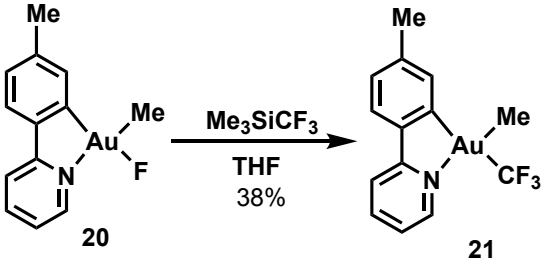
[(tpy)Au(Me)(F)], **20**



To a solution of **17** (35.8 mg, 0.078 mmol, 1.0 equiv.) in DCM (8 mL) was added silver fluoride (78.7 mg, 0.62 mmol, 8.0 equiv.). The reaction flask was covered in foil and suspension was stirred for 24 hours at room temperature. The mixture was then filtered through a pad of Celite and the volatiles were removed in vacuo to afford **19** as a grey solid (29.9 mg, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.01 (t, *J* = 7.9 Hz, 1H), 7.90 (dd, *J* = 16.7, 8.0 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.1 Hz, 1H), 7.22 (s, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 2.40 (s, 3H), 1.30 (s, 3H).
^{19}F NMR (470 MHz, THF) δ -221.27 (s).

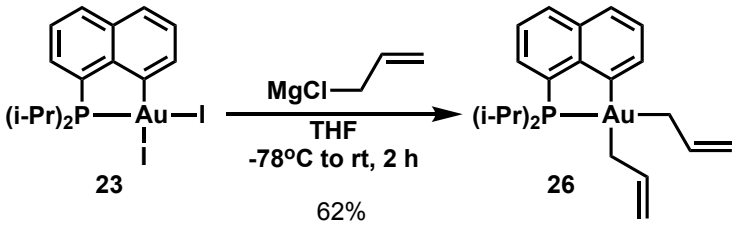
[(tpy)Au(Me)(CF_3)], **21**



To a solution of **20** (29.9 mg, 0.075 mmol, 1.0 equiv.) in THF (1.5 mL) was added Me_3SiCF_3 (0.02 mL, 0.15 mmol, 2.0 equiv.), upon which the solution immediately turned pale yellow. The reaction mixture was filtered through a pad of neutral alumina and volatiles were evaporated in vacuo to afford **21** as a white solid (13.4 mg, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 5.6 Hz, 1H), 8.02 – 7.91 (m, 2H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.42 (s, 2H), 7.16 (d, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 0.37 – -0.10 (m, 3H).
^{19}F NMR (470 MHz, THF) δ -38.38 (s).

[(P,C)Au(allyl)$_2$], **26**

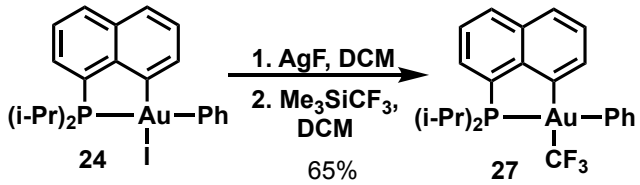


A solution of compound **23** (74.3 mg, 0.106 mmol, 1.0 equiv.) in THF (10 mL) was cooled in a dry ice/acetone bath, and a 2 M solution of allylmagnesium chloride in THF (0.16, 0.24 mmol, 2.2 equiv) was added. The solution formed a milky suspension shortly after addition. The reaction mixture was stirred for 1 hour at −78 °C and then at room temperature for 1 h. While warming to ambient temperature, the reaction mixture cleared up to a light-yellow solution. The reaction mixture was quenched with water and diluted with DCM. The solution was further extracted 3x with DCM and the resulting organic phase was washed 3x with water before being dried over $MgSO_4$ to give a light-yellow solution. Solvent was then removed in vacuo to afford **26** as a yellow solid (34.3 mg, 62% yield).

When 1.0 equivalent of allylmagnesium chloride wass used a mixture of starting material, mono- and diallylated product was formed.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.30 (d, J = 6.9 Hz, 1H), 8.01 (dt, J = 8.1, 1.5 Hz, 1H), 7.89 – 7.70 (m, 2H), 7.63 (t, J = 7.5 Hz, 1H), 6.49 – 6.11 (m, 2H), 5.16 (dd, J = 16.8, 1.4 Hz, 1H), 5.02 – 4.98 (m, 1H), 4.68 (d, J = 9.8 Hz, 1H), 3.02 – 2.94 (m, 2H), 2.88 – 2.78 (m, 2H), 2.50 (t, J = 7.9 Hz, 2H), 1.22 (m, 12H).
^{31}P NMR (162 MHz, CD_2Cl_2) δ 71.35 (s).

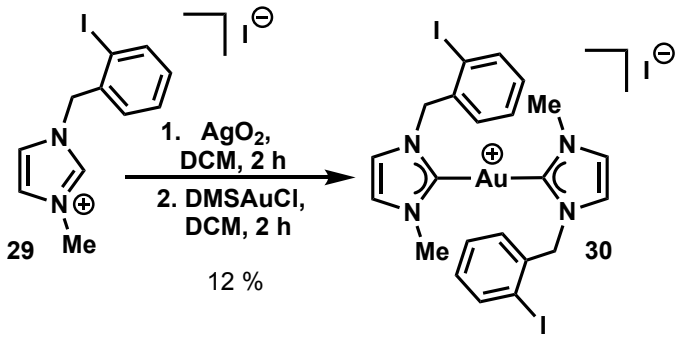
[(P,C)Au(Ph)(CF_3)], **27**



To a solution of **24** (34.8 mg, 0.05 mmol, 1.0 equiv.) in DCM (6 mL) was added silver fluoride (68.5 mg, 0.54 mmol, 10.0 equiv.). The reaction flask was covered in foil and the suspension was allowed to stir for 2 hours, after which Me_3SiCF_3 (0.04 mL, 0.25 mmol, 5.0 equiv.) was added and the reaction mixture immediately turned pale yellow. After 2 hours, the mixture was filtered through a pad of Celite and volatiles were evaporated *in vacuo*. The crude solid was then purified using column chromatography (3:7 DCM / pentane) to give **27** as a white solid (19.1 mg, 65 % yield).

^{19}F NMR (565 MHz, CD_2Cl_2) δ -22.61 (d, J = 7.8 Hz).
^{31}P NMR (243 MHz, CD_2Cl_2) δ 71.81 (q, J = 7.8 Hz).

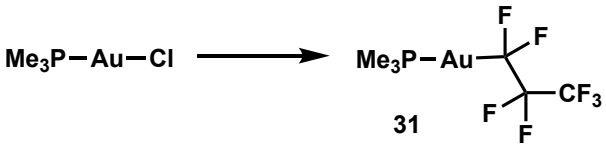
[Au(bis(1-(2-iodobenzyl)-3-methyl-2,3-dihydro-1H-imidazol-2-yl)$_2$]I, **30**



To a solution of **29** (41.7 mg, 0.18 mmol, 1.0 equiv.) in DCM (6 mL) was added silver oxide (50 mg, 0.12 mmol, 1.5 equiv.). The reaction flask was wrapped in foil and the suspension was stirred for 2 hours. The mixture was then filtered through a pad of Celite and the volatiles were evaporated *in vacuo*. The silver salt was precipitated out of a minimum amount of DCM via the gradual addition of Et_2O before being dissolved in DCM (6 mL). DMSAuCl (21.8 mg, 0.074 mmol, 1.0 equiv), was then added to the solution and the mixture was allowed to stir for 2 hours. The solvent was evaporated *in vacuo* and the product was recrystallized *via* layering of pentane over a solution of the gold adduct in minimal DCM to afford compound **30** as colorless crystals (13.3 mg, 12% yield over two steps).

^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.27 (d, J = 1.7 Hz, 1H), 7.20 (dt, J = 7.8, 1.9 Hz, 1H), 7.15 – 7.04 (m, 1H), 7.00 (t, J = 2.0 Hz, 1H), 5.41 (d, J = 1.9 Hz, 1H), 5.37 (d, J = 1.9 Hz, 1H), 3.90 (s, 3H).
HRMS (EI) m/z: calculated for $[C_{22}H_{22}N_4I_2Au_1]^+$ 792.96, found 792.9598.

[(PMe_3)Au($CF_2CF_2CF_3$)], **31**



Method 1:

To a solution of Me_3PAuCl (154.3 mg, 0.5 mmol, 1.0 equiv.) in 3:1 DCM/MeCN (4.5 mL / 1.5 mL) was added silver fluoride (317.2 mg, 2.5 mmol, 5.0 equiv.) and $Me_3SiCF_2CF_2CF_3$ (0.18 mL, 1.0 mmol, 2.0 equiv.). The reaction flask was covered in foil and the suspension was allowed to stir for 24 hours before being filtered through a pad of Celite and volatiles concentrated *in vacuo*. The resulting crude solid was purified using column chromatography (1:1, DCM/pentane) to afford **31** as a white solid (30.9 mg, 14% yield).

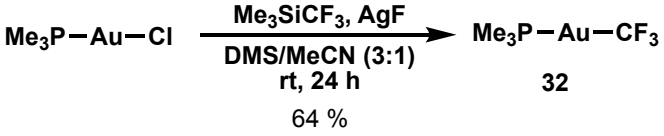
Method 2:

A solution of Me_3PAuCl (154.25 mg, 0.5 mmol, 1.0 equiv.) dissolved in Et_2O (7 mL) was cooled in a dry ice/acetone bath and heptafluoro-3-iodopropane (0.36 mL, 2.5 mmol, 5.0 equiv.) was added, followed by the dropwise addition of a 2.2 M solution of methyl lithium•lithium bromide

complex in Et_2O (1.2 mL, 2.5 mmol, 5.0 equiv.). The reaction mixture was allowed to stir for 1 hour at −78 °C and then at room temperature for 1 h. The reaction mixture was quenched with water and diluted with Et_2O. The solution was further extracted 3x with Et_2O and the resulting organic phase was washed 3x with water before being dried over $MgSO_4$. Solvent was then removed *in vacuo* to afford **31** as a white solid (121.6 mg, 55% yield).

^{19}F NMR (565 MHz, CD_2Cl_2) δ -79.81 (t, J = 11.0 Hz, 3H), -105.55 (dd, J = 25.2, 10.9 Hz, 2H), -124.11 (s, 2H).
^{31}P NMR (243 MHz, CD_2Cl_2) δ 0.67 (t, J = 24.3 Hz).

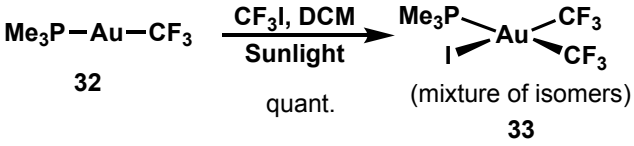
[$(PMe_3)Au(CF_3)$], **32**



The following was altered from previous procedures by Menjón and coworkers and Fürstner and coworkers.[9,10] To a solution of Me_3PAuCl (400 mg, 1.3 mmol, 1.0 equiv.) in 3:1 DCM/MeCN (37 mL / 12 mL) was added silver fluoride (824.7 mg, 6.5 mmol, 5.0 equiv.) and Me_3SiCF_3 (0.38 mL, 2.6 mmol, 2.0 equiv.). The reaction flask was covered in foil and the suspension was allowed to stir for 24 hours before being filtered through a pad of Celite and volatiles concentrated *in vacuo*. The resulting crude solid was purified using column chromatography (1:1, DCM/pentane) to afford **32** as a white solid (284.6 mg, 64% yield).

^1H and ^{19}F NMR match those of previously reported spectra. [9,10]

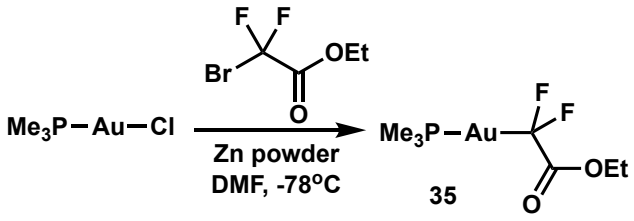
[$(PMe_3)Au(I)(CF_3)_2$], **33**



The following was altered from a previous procedure by Droege and coworkers.[11] Compound **32** (28.2 mg, 0.082 mmol, 1.0 equiv.) was dissolved in DCM (2.5 mL) and transferred to a Schlenk tube. The vessel was sealed with a Teflon cap and subjected to 3x freeze-pump-thaw cycles before introducing CF_3I (1 atm). The vessel was placed in direct sunlight and the solution turned pale-yellow. After 30 minutes volatiles were removed *in vacuo* to afford **33** as a mixture of isomers (43.7 mg, quantitative yield).

^1H and ^{19}F NMR match those of previously reported spectra.[11]

[(Me_3P)Au(ethyl difluoroacetate)], **35**



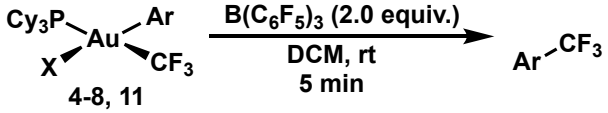
Zinc powder was activated by washing with 1 M aqueous HCl, water, acetone and Et_2O. The reaction flask was then charged with the zinc solid (10 mg, 0.14 mmol, 1.4 equiv.) and put under vacuum. The flask containing the activated zinc and stir bar was then flame dried and allowed to cool.

To the reaction flask was then added DMF (10 mL) and the flask was cooked using a dry ice/acetone bath. Ethyl 2-bromo-2,2-difluoroacetate (0.02 mL, 0.14 mmol, 1.4 equiv.) was then added dropwise and the reaction was allowed to stir for 10 minutes. A solution of [(Me3P)Au(Cl)] (30.6 mg, 0.1 mmol, 1.0 equiv.) in DMF (10 mL) was then added slowly and the reaction mixture was allowed to stir for 3 hours at −78 °C before being quenched with water and diluted with Et_2O. The solution was further extracted 3x with Et_2O and the resulting organic phase was washed 3x with water and 3x with a concentrated aqueous LiCl solution before being dried over $MgSO_4$. Solvent was then removed in vacuo to afford **35** as a white solid (23.3 mg crude, no isolated yield obtained due to decomposition at room temperature).

^{19}F NMR (471 MHz, CD_2Cl_2) δ -99.42 (d, J = 26.5 Hz).
^{31}P NMR (202 MHz, CD_2Cl_2) δ 1.23 (t, J = 26.1 Hz).

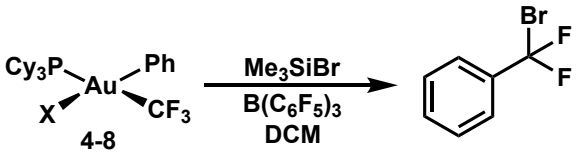
Non-Preparative Reactions

General Procedure for BCF Reductive Elimination of **4-8** and **11**



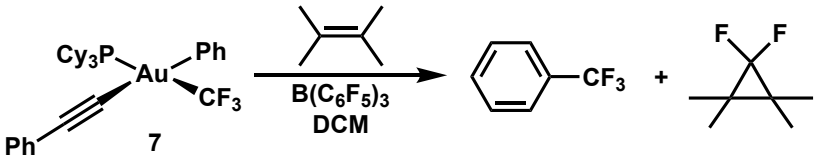
In a nitrogen-filled glovebox, a solution of the gold(III) complex (0.01 mmol, 1.0 equiv.) in DCM (0.3 mL) was added to a silylated NMR tube, followed by a solution of tris(pentafluorophenylborane) in DCM (10.2 mg, 0.02 mmol, in 0.3 mL). The mixture was capped with an NMR-tube septum and sealed with electrical tape. For all compounds, analysis by ^{19}F-NMR after 5 min showed the complete consumption of starting material and formation of Ph-CF_3 as the major product.

General Procedure for TMS-Br Trap of **4-8**



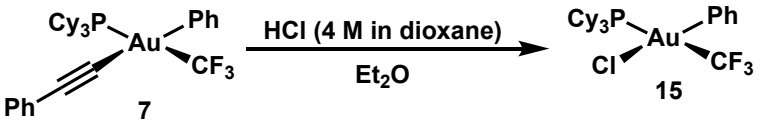
In a nitrogen-filled glovebox, to a solution of the gold(III) complex (0.01 mmol, 1.0 equiv.) in DCM (0.3 mL) in a silylated NMR tube was added TMS-Br (0.01 mL) followed by a solution of tris(pentafluorophenylborane) in DCM (0.5 mg, 0.001 mmol, 0.3 mL). The mixture was capped with an NMR-tube septum and sealed with electrical tape. Analysis by ^{19}F-NMR after 1 hour showed partial conversion to afford a mixture of $PhCF_2Br$ and TMS-F.

General Procedure for Olefin-Carbene Trap of **7**

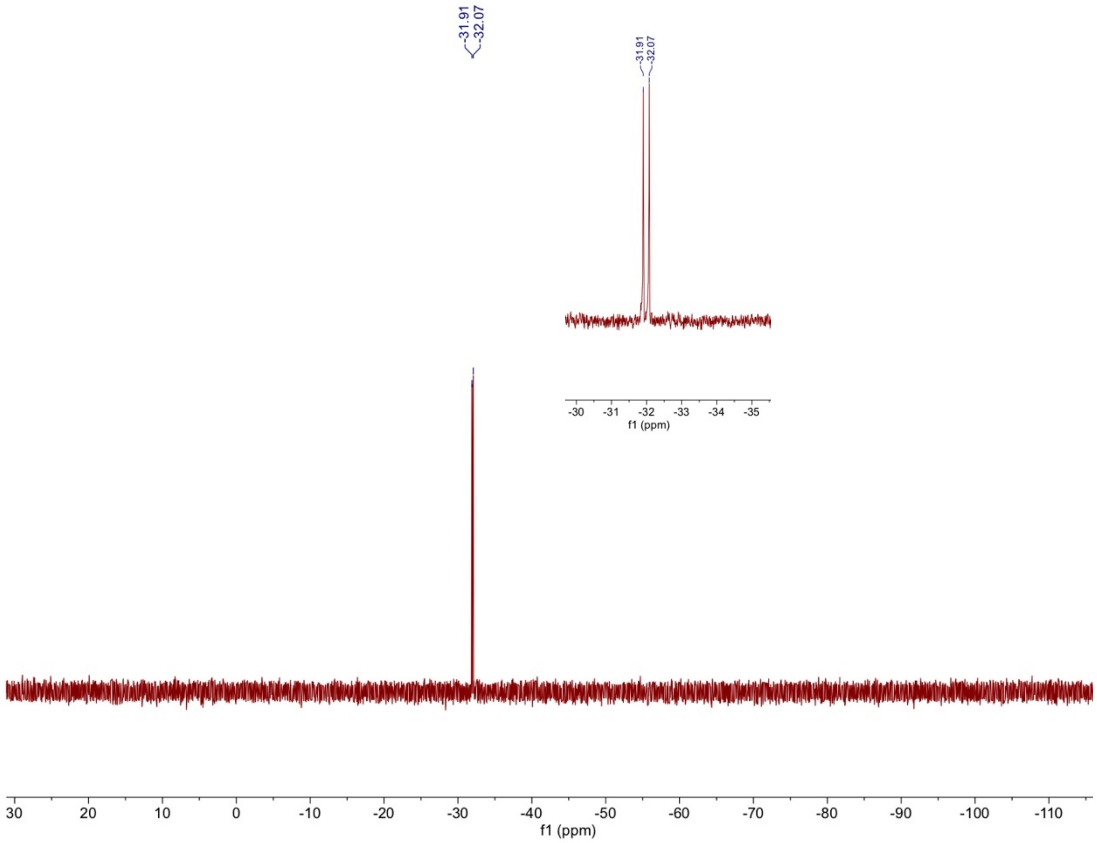


In a nitrogen-filled glovebox, to a solution of **7** (7.4 mg, 0.01 mmol) and tetramethylethylene (1.6 mg, 0.02 mmol, prepared as a stock solution) in DCM-d_2 (0.3 mL) in a silylated NMR tube was added a solution of tris(pentafluorophenylborane) in DCM (10.2 mg, 0.02 mmol, in 0.3 mL). The mixture was capped with an NMR-tube septum and sealed with electrical tape. Analysis by ^{19}F-NMR after 5 minutes showed the complete consumption of 1, formation of Me-CF_3 as the major product, along with C_6F_5H, 1,1,2,2-dimethyl-3,3-difluorocyclopropane, and IPr-Au-C_6F_5 as the exclusive Au-containing product.

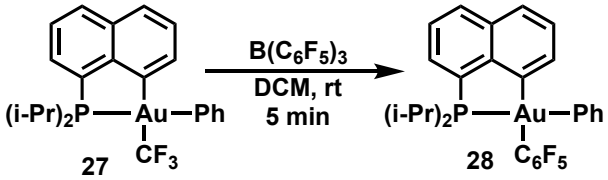
Protonolysis of **7**



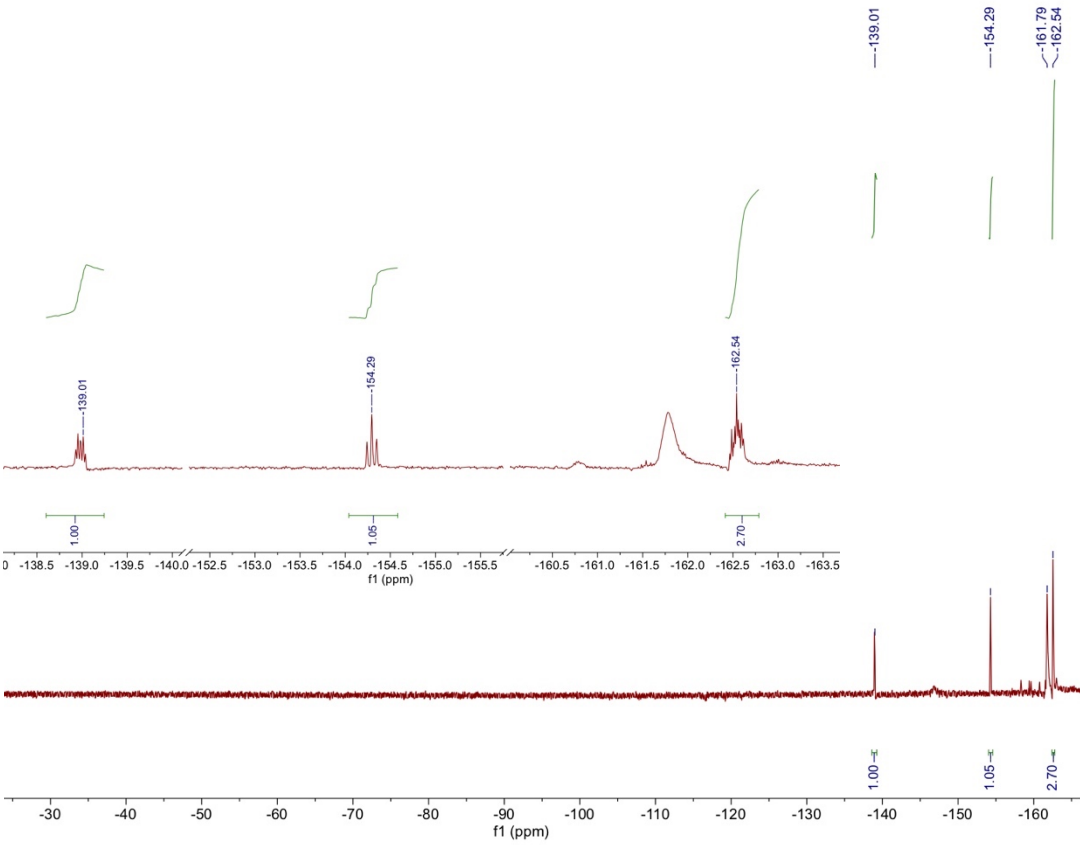
To a solution of compound **7** (7.24 mg, 0.01 mmol, 1.0 equiv.) dissolved in Et_2O (1 mL) was added a 4 M solution of HCL in dioxane (0.01 mL, 0.01 mmol, 1.0 equiv.). After 30 minutes, aliquot of the solution was taken and ^{19}F NMR revealed the complete consumption of starting material and **15** to be the sole reaction product.



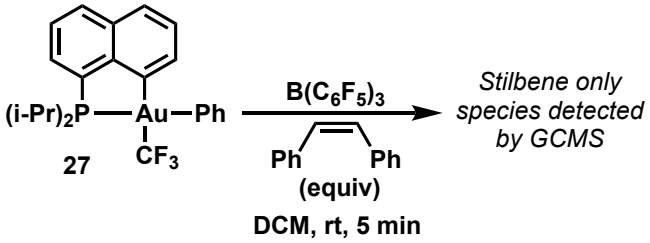
Aryl Transfer of **27**



In a nitrogen-filled glovebox, a solution of **27** (0.008 mmol, 1.0 equiv.) in DCM (0.3 mL) was added to a silylated NMR tube, followed by a solution of tris(pentafluorophenylborane) in DCM (8.5 mg, 0.016 mmol, in 0.3 mL). The mixture was capped with an NMR-tube septum and sealed with electrical tape. Analysis by ^{19}F-NMR after 5 min showed the complete consumption of starting material and formation of aryl-transfer product **28**.

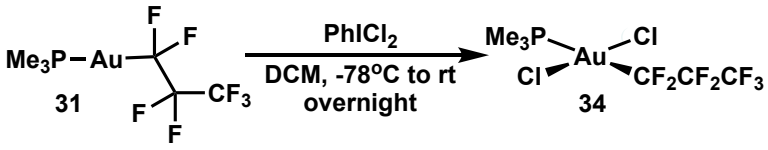


General Procedure for Olefin-Carbene Trap of **27**

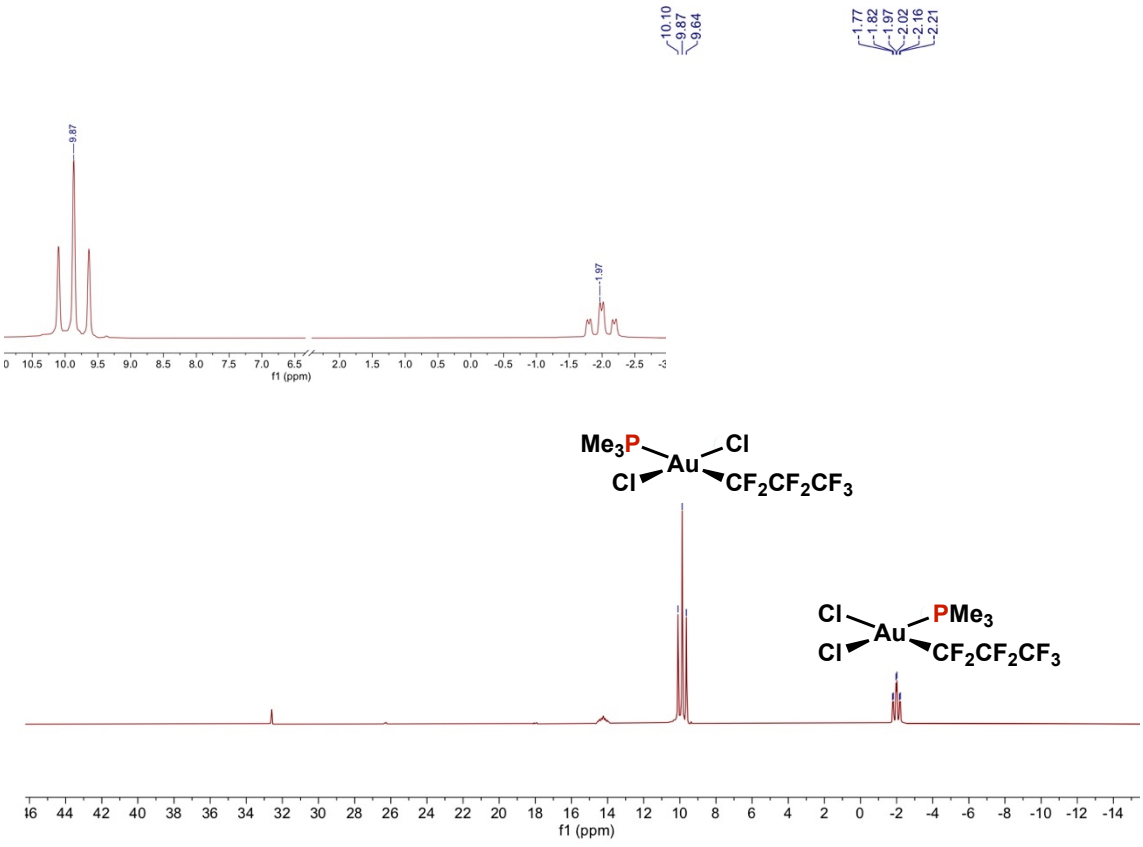


In a nitrogen-filled glovebox, to a solution of **27** (7.4 mg, 0.01 mmol) and cis-stilbene (0.01 mL, 0.065 mmol, 5.0 equiv.) in DCM (0.3 mL) in a silylated NMR tube was added a solution of tris(pentafluorophenylborane) in DCM (10.2 mg, 0.02 mmol, in 0.3 mL). The mixture was capped with an NMR-tube septum and sealed with electrical tape. Analysis by ^{19}F-NMR after 5 minutes showed formation of aryl transfer product 28 (see above). GC-MS detected cis-stilbene as the sole species.

Oxidative Addition to **31**



A solution of 31 (122.1 mg, 0.28 mmol, 1.0 equiv.) in DCM (6 mL) was cooled in a dry ice/acetone bath after which freshly prepared iodobenzene dichloride (75.9 mg, 0.28 mmol, 1.0 equiv.) was added. The reaction was allowed to warm to room temperature before volatiles were evaporated *in vacuo*. An NMR of the resulting crude solid showed complete consumption of starting material and formation of **34** as a mixture of isomers.



Procedure for Variable Temperature NMR Studies

In a nitrogen-filled glovebox, a solution of **27** (0.012 mmol, 1.0 equiv.) in DCM-d_2 (0.3 mL) was added to an NMR tube. The mixture was capped with an NMR-tube septum, sealed with electrical tape. In a separate vial was added Me_3SiOTf in DCM-d_2 which was sealed with a septum cap. Both were then removed from the box and the NMR tube was cooled in a dry ice/acetone bath. The Me_3SiOTf solution in DCM-d_2 was then added slowly. The reaction was kept at -78°C until it was put in a 500 MHz NMR and slowly warmed from -78°C to room temperature.

Experimental References:

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