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Communication

Synthesis of L−Au(I)−CF_2H Complexes and Their Application as Transmetalation Shuttles to the Difluoromethylation of Aryl Iodides

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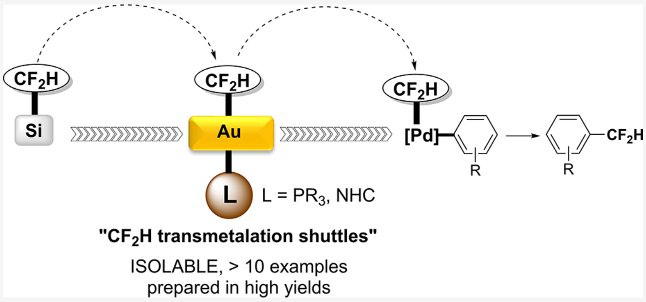
ABSTRACT: We describe herein two alternative protocols to efficiently prepare difluoromethylgold(I) complexes bearing ancillary ligands with different electronic and steric properties. LAu−OX (X = H and *t*-Bu) species, formed in the presence of base, have been identified as intermediate complexes involved in these transformations. The application of these compounds as "CF_2H transmetalation shuttles" from gold to palladium has been demonstrated in a Pd-catalyzed difluoromethylation reaction of aryl iodides, in which the Au-to-Pd transfer of "CF_2H" is feasible under stoichiometric conditions. These findings will pave the way for catalytic manifolds in gold chemistry.



CF_2H-containing compounds have found applications in several disciplines such as drug discovery,[1] agrochemistry,[2] and PET imaging technology.[3] In medicinal chemistry, the difluoromethyl group exhibits valuable properties, since it is a bioisostere of the hydroxyl and thiol groups and can act as a metabolically stable hydrogen bond donor. Consequently, in the past few years, an increasing number of synthesis methodologies aimed at incorporating these moieties in a direct and selective manner into structurally diverse carbon skeletons have been developed.[4] Transition metal promoted difluoromethylation has emerged as an alternative to overcome the challenging installation of a difluoromethyl group onto (hetero)aromatic rings.[5] Ideal strategies are represented by single-metal-catalyzed difluoromethylation reactions performed on easily accessible (hetero)aryl halides and/or with inexpensive industrial raw materials as "CF_2H" source, although these processes are scant.[6] Most often, nucleophilic organometallic M−CF_2H compounds have been used for this purpose. (NHC)Ag(CF_2H) complexes were among the first bench-stable organometallic compounds of this type to be prepared and broadly used.[5f,i,7] Later, Sanford and co-workers were able to isolate and characterize analogous (NHC)Cu(CF_2H) complexes, and they further explored their reactivity with aryl electrophiles, both in stoichiometric and catalytic fashions.[5d] Very recently, isolable [(L)Pd(CF_2H)X] complexes have also been synthesized, and the stoichiometric transfer of the CF_2H substituent to arenes was studied.[5l] Given the parallel reactivity exhibited by the coinage metals in many instances,[8] we wondered whether analogous L−Au−CF_2H complexes could be prepared by selecting the appropriate ancillary ligands on gold. Notably, gold-catalyzed photoredox reactions have been employed to form Csp^2−CF_2R bonds.[9]

In recent years, direct Si-to-Au(I) transmetalation has been achieved. A fluoride-free transmetalation of organic fragments from organosiloxanes to Au (I)[10] and the transmetalation of ethynyl groups from trimethylsilanes to gold complexes[11] have been reported. Furthermore, an early report from the beginning of this century described the preparation of trifluoromethylgold complexes by stoichiometric transmetalation with silanes.[12]

Difluoromethylgold(III) complex *cis*-[Au(PCy_3)(4-F-C_6H_4)(CF_2H)(Cl)] has been recently prepared; nevertheless, the use of (SIPr)Ag(CF_2H) complex as starting material is required for the synthesis.[13] Remarkably, Fürstner and co-workers have recently reported the challenging spectroscopic and chemical characterization of a highly reactive gold difluorocarbenoid complex.[14] Prompted by all these evidence we set out to explore the Si-to-Au(I) transmetalation process for the preparation of L−Au(I)−CF_2H complexes, employing the commercially available $TMSCF_2H$ as difluoromethylating agent. Herein we describe the synthesis and characterization of so far unknown L−Au(I)−CF_2H complexes and their applicability in the palladium-catalyzed difluoromethylation of aryl iodides.

We began our investigation with the synthesis of a series of Au(I) chloride complexes bearing a variety of ancillary ligands (L),[15] which are known to play a paramount role in modulating the reactivity of the complexes (Figure 1). Electron-poor, -rich, and -neutral phosphines (**1a**−**12a**), triphenyl phosphite (**8a**), and electron-rich *N*-heterocyclic carbene ligands (NHC) that

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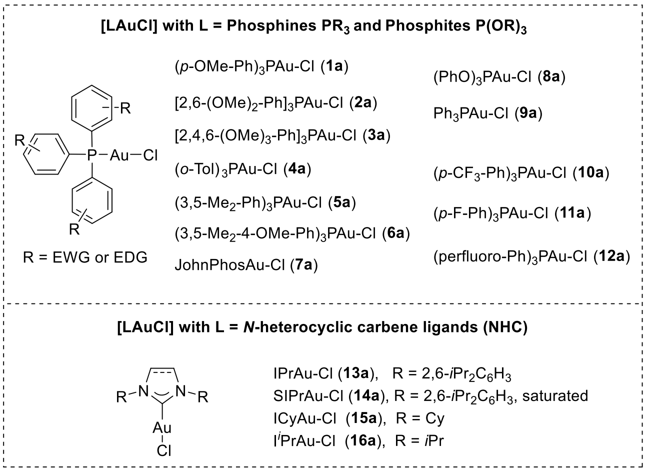
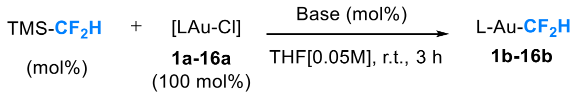


Figure 1. Starting [LAuCl] complexes.

could stabilize Au(I)–fluoroalkyl complexes (**13a–16a**)[16] were included in this study.

The Si-to-Au "transmetalation" experiments aimed to determine the "matching transmetalation couples" from the pool of gold(I) chloride derivatives and the commercially available TMSCF$_2$H. The optimization of the reaction conditions began with the treatment of all the starting gold(I) complexes with 200 mol % of the nucleophilic difluoromethylating agent in THF for 3 h without other additives. As expected, no formation of the product was observed for any of them (Table 1, entry 1). The use of bases such as acetates or fluorides did not allow to obtain the desired CF$_2$H–gold(I) complexes (Table 1, entry 2). Next, we focused our attention on NHC–Au(I) complex **14a** with the aim of investigating the effect of other bases in the reaction outcome. On the basis of the protocols employed in the synthesis of the analogous silver(I)[7b] and copper(I)[5d] complexes, NaO^{t}Bu was the first base selected. Unfortunately, the addition of 200 mol % of this additive led to the recovery of the starting complex (Table 1, entry 3). Nevertheless, when the same amount of NaOH was used, product **14b** was formed in trace amounts, as revealed by its diagnostic signals in the ^{1}H NMR and ^{19}F NMR spectra (Table 1, entry 4). Since the low yields obtained could be traced back to experimental errors during the addition of the base due to the small scale of the reaction, in the subsequent experiments the amount of both the base and TMSCF$_2$H were increased to 500 mol %. Fine-tuning of the experimental conditions for the workup and the handling of the gold complexes (see Supporting Information) led to almost full conversion to the product using IPrAuCl (**13a**) (Table 1, entry 6) and to full conversion for SIPrAuCl (**14a**) (Table 1, entry 5). Purification of both gold complexes by column chromatography, precipitation, or crystallization to give accurate isolated yields was not possible. Due to this drawback, we turned our attention to quantitative NMR for the determination of reaction yields with the addition of an internal standard. Dibromomethane was selected for this purpose and allowed to determine the yield for the IPrAu–CF$_2$H (**13b**) (92%) and SIPrAu–CF$_2$H (**14b**) (quantitative) gold complexes.

Table 1. Optimization of the Reaction Conditions for the Si-to-Au Transmetalation



entry	[LAu-Cl]	TMSCF$_2$H (mol %)	base (mol %)	yield[a,b]
1	**1a–16a**	200		
2	**1a–16a**	200	NaOAc, CsOAc, CsF,[c] NaF,[c] *n*-Bu$_4$NF (200)[c]	
3	**14a**	200	NaO^{t}Bu (200)	
4	**14a**	200	NaOH (200)	trace amounts
5	**14a**	500	NaOH (500)	quantitative (conditions A)[d]
6	**13a**	500	NaOH (500)	92% (conditions A)
7	**1a**	500	NaOH (500)	trace amounts
8	**1a**	500	NaO^{t}Bu (200)	94% (conditions B)

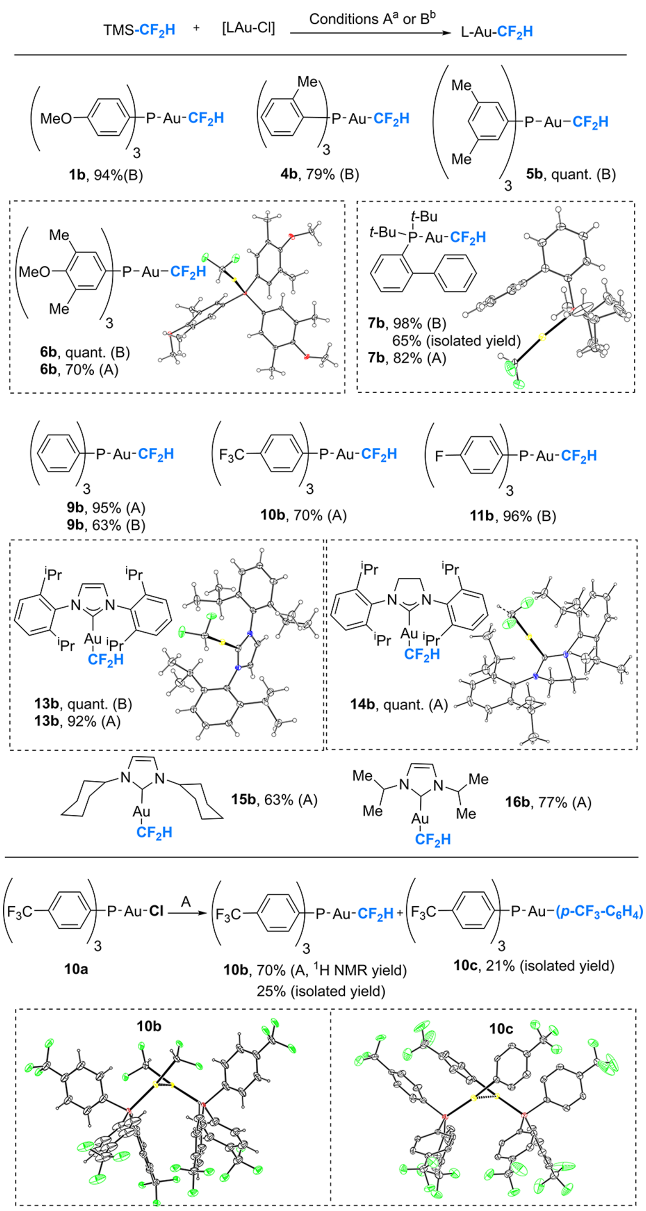
[a] Reaction scale: 0.030–0.040 mmol. [b] Yield calculated by ^{1}H NMR using CH_2Br_2 as internal standard. [c] Complex **1a** was used. MeOH or CH_3CN were used as cosolvents. [d] Concentration: [0.03M].

Next, we moved to the phosphine gold(I) complexes. Unfortunately, when the conditions developed for the preparation of (NHC)Au–CF$_2$H were tested on the electron-rich [tris(*p*-methoxyphenyl)phosphine]gold(I) chloride (**1a**), the desired product was obtained in trace amounts (Table 1, entry 7). Gratifyingly, the use of 200 mol % of NaO^{t}Bu and 500 mol % of TMSCF$_2$H delivered desired compound **1b** in excellent yield (Table 1, entry 8).

With two set of conditions in hand (conditions A and B) the full scope of this transformation was evaluated (Scheme 1). Additional gold(I) complexes bearing electron-rich phosphines could be converted into their corresponding Au–CF$_2$H complexes in yields ranging from very good to excellent (**4b**, **5b**, **6b**, and **7b**). The neutral triphenylphosphinegold(I) chloride (**9a**) was likewise a suitable substrate for this transformation, since corresponding Au–CF$_2$H complex **9b** could be generated in an excellent yield. To further expand the scope for NHC–Au complexes, analogues **15b** and **16b** were prepared following protocol A. To our delight, we were able to obtain suitable crystals for single-crystal X-ray diffraction analysis, which unambiguously confirmed the identity of compounds **6b**, **7b**, **13b**, and **14b**. Surprisingly, the more challenging electron-deficient (*p*-CF$_3$–Ph)$_3$PAu-CF$_2$H (**10b**) and (*p*-F-Ph)$_3$PAu-CF$_2$H (**11b**) complexes could be synthesized in good and excellent yields, respectively (for scope limitations, see the Supporting Information).[17]

Gold(I) complex **10c** was obtained as a byproduct in the formation of **10b**. To shed light on the origin of this compound and the general mechanism for the formation of the LAu–CF$_2$H complexes, the experiments outlined in Scheme 2 were performed. A TSMCF$_2$H-free experiment with JohnPhosAu–Cl **7a** in the presence of NaOH (eq 1, Scheme 2) revealed the partial conversion of the starting gold complex to gold(I) hydroxide **7c** and, very likely, to triaurated oxonium cation **7d**,[18] after 3 h of reaction. The fact that **7a**, **7c**, and **7d** were present in the crude mixture almost in the same ratio after 14 h of reaction seems to indicate the establishment of an equilibrium between the three species, which is eventually shifted to the right when the difluoromethylating agent is present in the reaction media to react with **7c** and furnish product **7b**. Similar results could be extrapolated to the NaO^{t}Bu base (see the Supporting Information for further details). The analogous control experiment with **10a** led to the isolation of **10c** in 75% yield (eq 2). Secondary phosphine oxide–gold(I) complex[19] **10d** and

Scheme 1. Scope for LAu−CF_2H Complexes

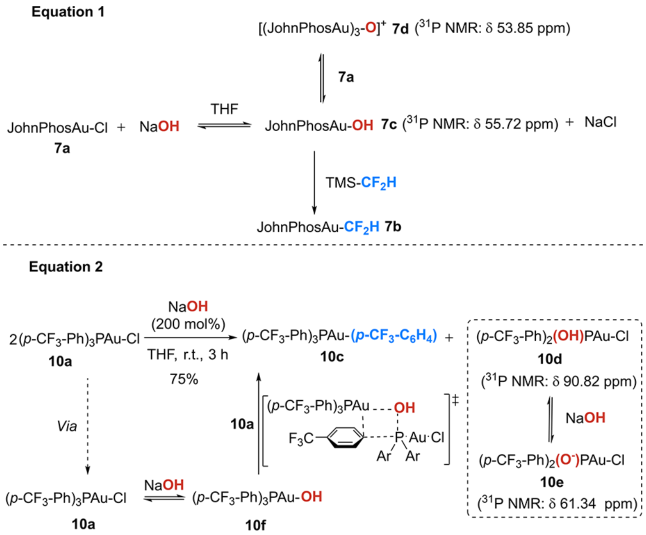


[a]Conditions A: $TMSCF_2H$ (500 mol %), NaOH (500 mol %), THF [0.05M], r.t., 3 h. [b]Conditions B: $TMSCF_2H$ (500 mol %), NaO^tBu (200 mol %), THF [0.05M], r.t., 3 h. Reaction scale: 0.030−0.040 mmol. Yield calculated by ^1H NMR using CH_2Br_2 as internal standard. The ORTEP diagrams are represented with the ellipsoids drawn at 30% probability level.

its anionic form, **10e**, were obtained as byproducts of this reaction, as confirmed by ^{31}P NMR and HR-ESI of the crude mixture. According to these results and the conclusions drawn from the previous control experiments, a metathesis reaction between starting gold(I) complex **10a** and gold(I) hydroxide species **10f** is proposed as a plausible pathway for this transformation, to our knowledge unreported in the literature. Very likely, this process occurs through a concerted transition state and might represent a potential catalyst decomposition pathway in gold-catalyzed reactions.

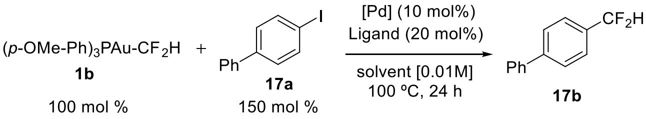
To evaluate the applicability of the synthesized gold complexes as difluoromethylating reagents, we set out to explore a Pd-catalyzed difluoromethylation of aryl iodides by means of a stoichiometric Au−Pd transmetalation[20] of the difluoromethyl moiety. Although this transformation has already been achieved with a single palladium[21] or copper[5d] catalysts or with a bimetallic Ag−Pd system,[7a] the results obtained in these studies will hopefully contribute to a better understanding of the unexploited Au−M bimetallic catalytic processes, since as demonstrated in previous reports in the literature, the transmetalation is a key step in the catalytic cycle.[22]

Scheme 2. Mechanistic Proposal for the LAu−CF_2H Formation (eq 1) and the Base-Promoted P-to-Au Transfer of an Aryl Ring (eq 2): Detection of Intermediate Species



4-Iodobiphenyl (**17a**) and (*p*-OMe-Ph)$_3$PAu-CF_2H (**1b**) were selected as model systems to study the desired transformation. Reactions were performed with freshly prepared Au-CF_2H crude mixtures; therefore, the yields were calculated over the two-step sequence. Starting from the general conditions depicted Table 2, palladium catalysts with different bidentate ligands were screened (for further details, see the Supporting Information). $Pd_2(dba)_3$ or $Pd(dba)_2$ in combination with Xantphos ligand turned out to be the most appropriate catalytic system, which afforded desired product **17b** in a 20% combined yield over 2 steps, after 24 h of reaction time in 1,4-dioxane at 100 °C (entry 1, Table 2). Lower temperatures or shorter

Table 2. Optimization of the Reaction Conditions for the Au−Pd Transmetalation[a]



entry	[Pd], ligand	solvent	yield (2 steps)[b]
1	$Pd_2(dba)_3$ or $Pd(dba)_2$ Xantphos	1,4-dioxane	20%
2	$Pd(dba)_2$, Xantphos	toluene	18%
3	$Pd(dba)_2$, Xantphos	MeOH/toluene(1:1)	3%
4	$Pd_2(dba)_3$ or $Pd(dba)_2$ Xantphos	1,4-dioxane/toluene (1:1)	30% (27%)

[a]Reaction scale: 0.030−0.040 mmol. [b]Yields calculated by ^{19}F NMR (200 mol % of 2-chloro-4-fluorotoluene as internal standard). Isolated yields are given in brackets. Each entry was repeated twice or three times; the highest yields obtained are shown.

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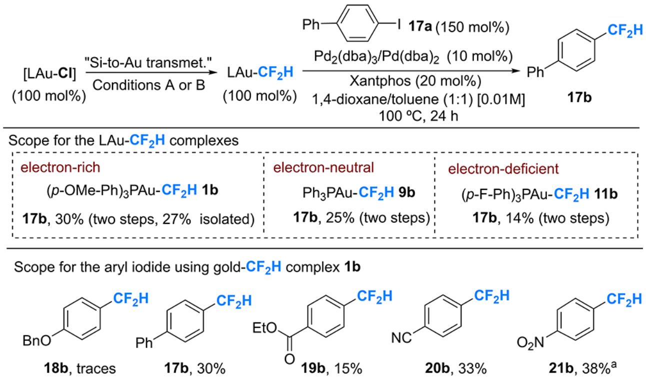
reaction times led to a decrease in the yield (data not shown). Likewise, the use of toluene or a binary mixture of MeOH and toluene as solvents did not improve the outcome of the reaction (entries 2 and 3). However, a 1:1 solvent mixture of 1,4-dioxane and toluene provided the product in 30% yield (entry 4).

To test whether these optimal conditions could be extrapolated to other gold(I)-CF_2H complexes, we examined the scope of the reaction on the entire series (Scheme 3).

Scheme 3. Scope for the Au–Pd Transmetalation



[a]Using a **1b/21a** ratio of 1.5:1 afforded the product in 35% yield.

NHC–Au–CF_2H complexes **13b**, **14b**, and **15b** were first assayed, but only traces of product were obtained. Despite the fact that (p-CF_3-Ph)Au–CF_2H (**10b**) afforded traces of the transmetalation product, the electron-poor (p-F-Ph)$_3$PAu–CF_2H (**11b**) furnished **17b** in 14% yield over the two steps. Gold complexes bearing electron-rich phosphines such as **4b**, **5b**, **6b**, and **7b** under the same reaction conditions delivered the desired product in yields ranging from 10 to 20%. Finally, the use of neutral $Ph_3PAu–CF_2H$ (**9b**) afforded the product in a significant 25% combined yield. Next, the scope on the aryl iodide was evaluated. Aryl iodides bearing electron-donating groups in the *para*-position were not suitable for this transformation, as shown by the detection of difluoromethylated product **18b** in trace amounts. However, the presence of electron-withdrawing groups was beneficial for the reaction as demonstrated by the preparation of the CF_2H-aryl derivatives **20b** and **21b** in 33 and 38% yield, respectively, which represent the best results achieved for this transformation. Given the low yields reported in the literature for the single-step Au–Pd transmetalation of alkyl groups,[23] we consider these yields calculated over the two-step sequence to be significant.

In summary, we have reported two efficient methods for the preparation of the first examples of difluoromethyl gold(I) complexes containing a variety of ancillary ligands. LAu–OX (X = H and *t*-Bu) species have been identified as intermediate complexes in these transformations. In addition, we have shown their application as a "CF_2H transmetalation shuttles"[24] in a Pd-catalyzed difluoromethylation reaction of aryl iodides, in which the Au-to-Pd transfer of "CF_2H" is possible in a stoichiometric manner. Meaningful yields for the overall Si-to-Au(I)-to-Pd process have been achieved with gold(I) complexes bound to phosphines with opposite electronic properties, which broadens the application of these transformations to substrates with different electronic demands. Given the versatility of gold(I) as a transmetalating partner,[24,25] these new Au(I)–CF_2H complexes represent potential candidates for further synthesis applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.1c00305.

Detailed experimental procedures and spectral data for all compounds (PDF)

Accession Codes

CCDC 2073749–2073754, 2073756, and 2073757 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The author declares no competing financial interest.

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