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Drastic fluorine effect: complete reversal of the selectivity in the Au-catalyzed hydroalkoxylation reaction of fluorinated haloalkynes†

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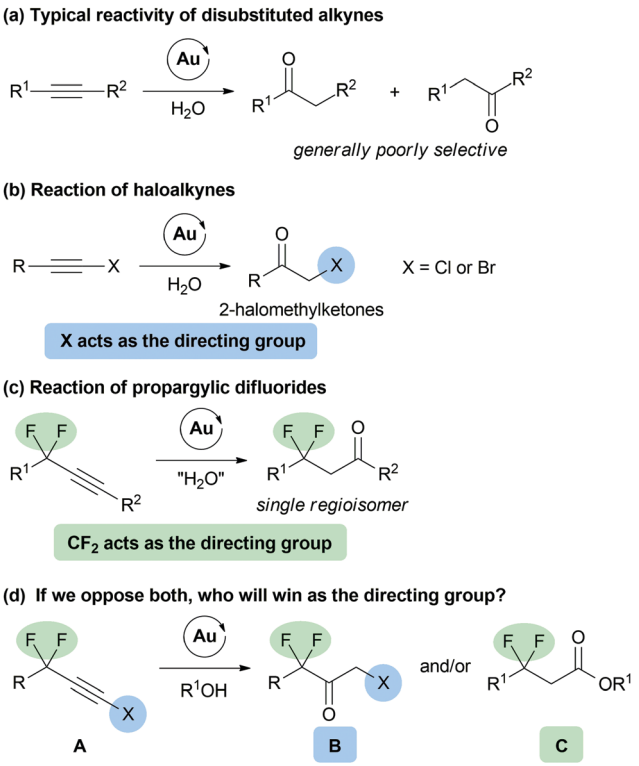
The gold-catalyzed hydration reaction of haloalkynes is highly regioselective producing 2-halomethylketones as the sole products. Herein, we document a drastic fluorine effect where the reaction of 1-halo-3,3-difluoroalkynes as substrates leads to a complete reversal of selectivity and produces 3,3-difluoroesters as the unique products.

The gold-catalyzed hydration and hydroalkoxylation of alkynes are powerful and versatile reactions.[1] However, the control of the regioselectivity in those transformations still represents a challenge (Scheme 1a).[1,2] Indeed, reaction of internal alkynes will generally provide a mixture of regioisomers with a low to moderate selectivity at best. The use of biased substrates is one strategy to compensate for the inherent lack of discrimination between the two sp carbon atoms.[2,3] In pioneer work, Xiang, He and coworkers have shown that the hydration reaction of haloalkynes (X = Cl or Br) under gold catalysis could produce selectively the corresponding 2-halomethylketones as the sole product, in which case the halogen atom acted as a powerful directing group (Scheme 1b).[4–6]

Through its unique properties,[7] the fluorine atom is known to influence dramatically the physicochemical properties of fluorinated compounds, a feature abundantly used in medicinal chemistry[8] and agrochemistry.[9] The fluorine atom can also greatly impact the reactivity of organic molecules,[10] though its use as a competent directing group in transition-metal catalyzed reaction is scarce.[11] Recently, we disclosed the potential of the difluoromethylene unit to direct the regioselectivity in the Au-catalyzed formal hydration of propargylic *gem*-difluorides.[12–15] We showed that the addition occurred distal to the CF_2 group producing 3,3-difluoroketones as single regioisomers (Scheme 1c). In that case, the CF_2 acted as the directing group and could impose a strong bias, to otherwise, non-selective disubstituted alkynes.



Scheme 1 Selectivity in Au-catalyzed hydration reaction of alkynes.

Given the precedents discussed above, we wondered what would happen if we were to oppose two directing groups on a disubstituted alkyne, in this case, a halogen atom and a difluoromethylene-containing substituent (Scheme 1d). In other words, would the reaction of 1-halo-3,3-difluoroalkynes (**A**) in the presence of a gold catalyst and an oxygen-based nucleophile (R^1 = H or alkyl) produce 1-halomethyl-3,3-difluoroketones (**B**), 3,3-difluorocarbonyl compounds (**C**) or a mixture of both? From a more general perspective, independent of the selectivity observed, this method would offer a new approach to difluoromethylene-containing molecules,[16] a motif found in numerous bioactive

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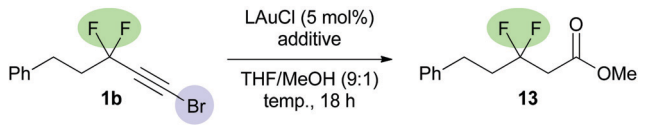
molecules,[8,9] but also used as a conformational tool in organic/medicinal chemistry.[17]

Herein, we report that the Au-catalyzed hydroalkoxylation of 1-halo-3,3-difluoroalkynes (**A**) using methanol (R^1 = Me) is highly regioselective and produces 3,3-difluoroesters (**C**; R^1 = Me) as the sole products. This transformation is noteworthy on a number of grounds. First, it represents a rare case of a highly regioselective gold-catalyzed hydroalkoxylation of disubstituted alkynes,[2] while showcasing a drastic fluorine effect that leads to a unique and complete reversal of selectivity. Also, this study unveils the use of a difluoromethylene unit as an effective directing group in transition-metal catalyzed reactions. Finally, it provides functionalized 3,3-difluoroesters, a valuable aspect, since only a limited number of methods for their synthesis (or the related carboxylic acids) has been described and none of them provide complex molecules because of the conditions used.[18]

We began the exploration using 1-bromo-3,3-difluoroalkyne **1b**.[19] Though early studies focused on the hydration reaction using water as a co-solvent, the corresponding 3,3-difluorocarboxylic acid was never observed (results not shown). We then switched to the conditions previously developed for propargylic *gem*-difluorides which used MeOH as the co-solvent[12] and selected results are shown in Table 1. Initially, this resulted in the absence of conversion both at 21 or 40 °C (Table 1, entries 1 and 2), while running the reaction at 70 °C provided a mere 9% conversion (Table 1, entry 3). At this point, albeit the conversion was low, we were pleased to note a complete selectivity in favour of the 3,3-difluoroester. Switching Au complexes from Ph_3PAuCl to (JohnPhos)AuCl improved slightly the conversion to 17% (Table 1, entry 4). We hypothesized that the low conversion was due to the poisoning of the gold-catalyst by the bromide ion released as the reaction proceeded. As such, we increased the amount of AgOTf. Gratifyingly, going from 10 mol% to 105 mol% (Table 1, entries 5–7) of AgOTf, a steady improvement of the conversion was noted. Hence, when 105 mol% of AgOTf was employed, a full conversion was observed and the desired methyl ester **13** was isolated in 74% yield (Table 1, entry 7). At this point, efforts to replace AgOTf with either $Cu(OTf)_2$ or LiOTf were unsuccessful as significantly lower conversions were observed (Table 1, entries 8 and 9).[20] Other silver salts ($AgNO_3$, AgOAc, $AgBF_4$) were also evaluated, but none proved superior to AgOTf (Table 1, entries 10–12). Overall, the conditions reported in entry 7 were found to be the optimal ones. It is important to note that, in all cases, the reaction was highly regioselective and the corresponding 1-bromomethyl-3,3-difluoroketone, *i.e.*, the other regioisomer, was never observed by NMR analysis of the crude reaction mixture. Some control experiments were performed. In the absence of silver triflate, no conversion was observed indicating that the cationic gold species is essential for the reaction (Table 1, entry 13). Only trace amounts of ester **13** were observed without (JohnPhos)AuCl, but in the presence of AgOTf (105 mol%), demonstrating that the reaction is truly gold-catalyzed and that the silver additive is only there to capture the halide ions (Table 1, entry 14). Finally, we evaluated the potential role of *in situ* generated triflic acid.[21] No conversion was observed when using 5 or 105 mol% of TfOH, thus discarding a Brønsted acid-catalyzed pathway (Table 1, entry 15).

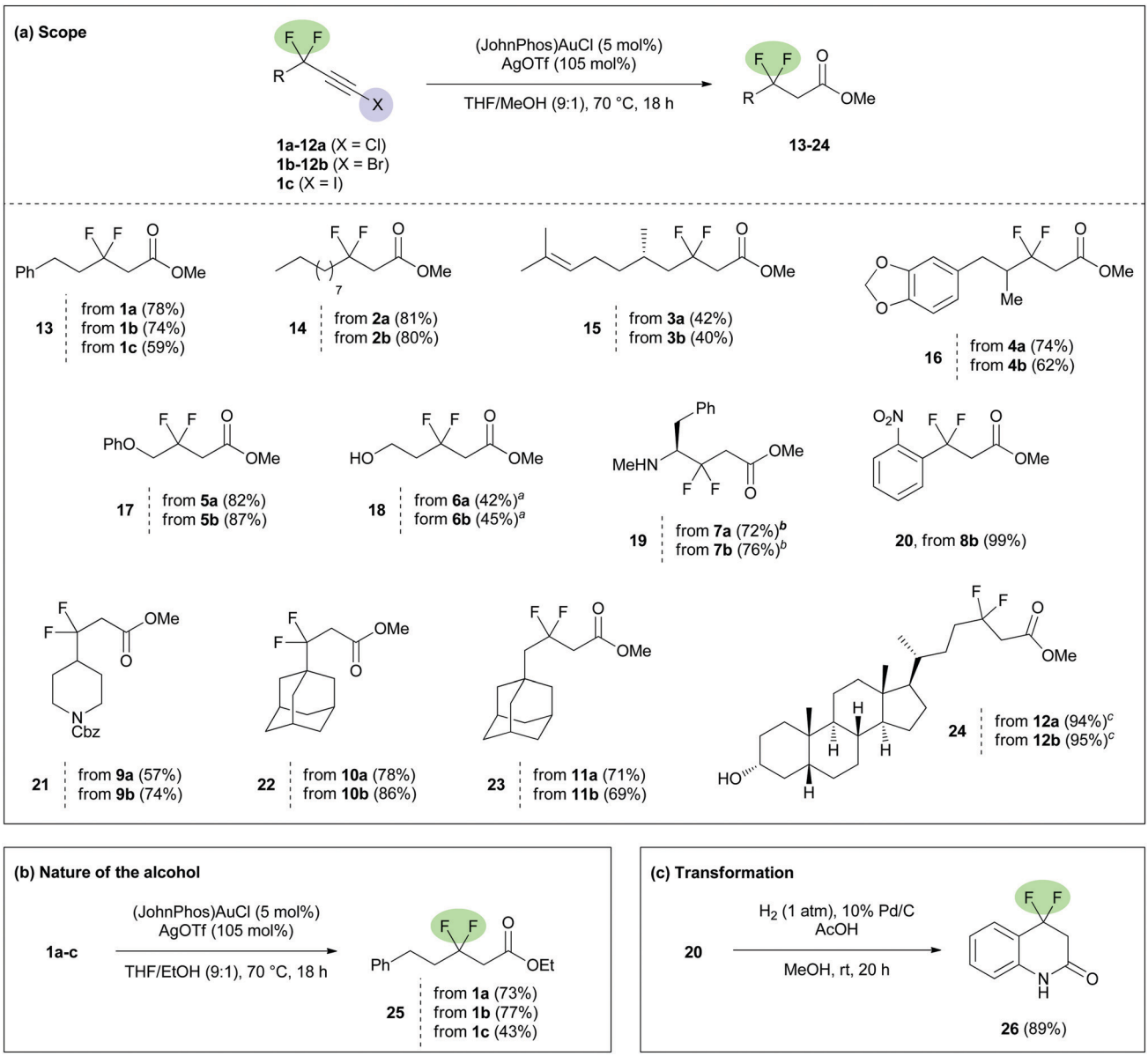
Table 1 Selected optimization data using 1-bromo-3,3-difluoroalkyne **1b**[a]



Entry	L	Additive (mol%)	Temp. (°C)	Conv.[bc] (%)
1	PPh_3	AgOTf (5)	21	0
2	PPh_3	AgOTf (5)	40	0
3	PPh_3	AgOTf (5)	70	9
4	JohnPhos	AgOTf (5)	70	17
5	JohnPhos	AgOTf (10)	70	33
6	JohnPhos	AgOTf (50)	70	71 (59)
7	**JohnPhos**	**AgOTf (105)**	**70**	**100 (74)**
8	JohnPhos	$Cu(OTf)_2$ (105)	70	17
9	JohnPhos	LiOTf (105)	70	9
10	JohnPhos	$AgNO_3$ (105)	70	100 (64)
11	JohnPhos	AgOAc (105)	70	75 (31)
12	JohnPhos	$AgBF_4$ (105)	70	100 (66)
13[d]	JohnPhos	—	70	0
14[e]	—	AgOTf (105)	70	<3
15[f]	—	TfOH (5 or 105)	70	0

[a] See ESI for the detailed experimental procedure. The optimized conditions are shown in bold. [b] Conversion estimated by ^{19}F NMR analysis of the crude mixture after an aqueous workup (sat. aq. $NaHCO_3$) and using 2-fluoro-4-nitrotoluene as the internal standard. [c] Isolated yield of **13** after column chromatography in parentheses. [d] The reaction was performed without AgOTf. [e] The reaction was performed without (JohnPhos)AuCl. [f] The reaction was performed replacing (JohnPhos)AuCl/AgOTf with TfOH (5 or 105 mol%).

The scope of the reaction was next evaluated (Scheme 2a). First, the effect of the nature of the halogen was studied. While the use of a chloroalkyne (**1a**) and a bromoalkyne (**1b**) provided the methyl ester **13** in similar yields (78% and 74% respectively), the use of the iodoalkyne (**1c**) gave only a moderate yield of 59%. Based on those results, only chloroalkynes and bromoalkynes were used for the rest of the study, and with few exceptions, they were found to provide similar results. A wide range of substrates bearing various functional groups were subjected to the reaction conditions and the respective products were isolated in moderate to excellent yields (40–99%). When the substrate presented another insaturation (*i.e.*, **3a** and **b**), moderate yields of the ester were obtained (40–42%). We hypothesized that a slow, yet competitive, reaction at the alkene was occurring,[1a] as supported by the multiple products observed by NMR in the crude mixtures. While various functional groups such as ethers and a nitro group were tolerated, deprotection was observed in a few cases, likely because of the acid generated during the reaction. For instance, the THP and acetate protected alcohols from **6a–b** and **12a–b** were lost during the reaction. Nonetheless, the corresponding products (**18** and **24**) could be isolated in moderate (42–45%) and excellent (94–95%) yields respectively. A Cbz-protected amine was intact for the reaction of **9a–b** while its deprotection was observed on the phenylalanine-derived haloalkynes **7a–b**. Notably, ethanol can also be used instead of methanol (Scheme 2b). In this case, the



Scheme 2 Au-Catalyzed hydroalkoxylation reaction of haloalkynes. See ESI† for the detailed experimental procedure. Isolated yield after column chromatography. [a] The alcohol in **6a–b** was originally protected as a THP. [b] The amine in **7a–b** was originally protected as a Cbz. [c] The alcohol in **12a–b** was originally protected as a Ac.

corresponding ethyl ester **25** was obtained in similar yields for the chloro- and bromoalkynes **1a–b** (73–77%) and in a lower one for the iodoalkyne **1c** (43%). Other alcohols (i-PrOH, *n*-BuOH, *s*-BuOH, *t*-BuOH) provided the corresponding esters in much lower yields (<39%). Finally, a one-step protocol involving hydrogenation of **20** in the presence of AcOH afforded the difluorinated dihydroquinolin-2-one **26** in 89% yield (Scheme 2c). This result further showcases the utility of the 3,3-difluoroesters generated through the Au-catalyzed hydroalkoxylation reaction of fluorinated haloalkynes.

In conclusion, we have reported on the Au-catalyzed hydroalkoxylation of 1-halo-3,3-difluoroalkynes which results in 3,3-difluoroesters as the sole regioisomers. The significant electronic bias imposed by the two fluorine atoms leads to a drastic fluorine effect with a unique and complete reversal of selectivity compared to non-fluorinated haloalkynes. In addition, this transformation represents a rare case of a highly regioselective gold-catalyzed hydroalkoxylation of disubstituted alkynes.[2] Finally, this study unveils the CF_2 group as an effective directing group, which may prove useful in other catalytic systems.

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Conflicts of interest

There are no conflicts to declare.

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