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Highly regioselective gold-catalyzed formal hydration of propargylic *gem*-difluorides†

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Herein, we report a highly regioselective gold-catalyzed formal hydration of propargylic *gem*-difluorides. Not only does this transformation provide access to versatile fluorinated building blocks that were difficult or hardly possible to access beforehand, but it also represents a rare case of a highly regioselective gold-catalyzed hydroalkoxylation of internal alkynes and puts forward the utility of the difluoromethylene unit as a directing group in catalysis.

Introduction

Gold catalysts[1] attracted a lot of attention in the past years for their propensity to selectively activate alkynes[2] over other functionalities towards nucleophilic attack under mild reaction conditions, and relativistic effects would be at the root of this preference for the activation of alkynes. Au(I) and Au(III) species both display such reactivity, and as such have been used in conjunction with a broad selection of O-, N- and C-based nucleophiles, for example. However, regarding intermolecular hydration and hydroalkoxylation reactions, caveats should be raised regarding the regioselectivity of the transformation. Indeed, while the Markovnikov product (*i.e.*, the ketone) is typically obtained upon performing the reaction on terminal alkynes (Scheme 1a), the use of internal alkynes generally leads to the formation of regioisomeric products (Scheme 1b).[3,4] This can be completely or partially solved using a neighboring nucleophile as a directing group (Scheme 1c).[5] Alternatively, the electronic nature of the substituents on the alkyne has also been shown to play a role in the regioselectivity in the Au-catalyzed hydrophenoxylation[6] or hydroalkoxylation[7] of 1,2-diarylalkynes, in the Au(I)-catalyzed hydration of propargylic alcohols[8] and in a Au(I)-catalyzed tandem intermolecular hydroalkoxylation/Claisen rearrangement of 1-aryl-2-alkylalkynes.[9] In these cases, nucleophilic attack was found to occur preferentially at the carbon distal to the electrowithdrawing fragment (Scheme 1d). In a few instances, ynamides and alkynyl ethers were also found to react regioselectively with *O*-nucleophiles.[10]

Parallel to this, owing to the distinctive properties of the fluorine atom,[11] organofluorine compounds have found wide applications in various fields including medicinal chemistry, agrochemistry and material sciences.[12–14] As such, the development of synthetic methods involving organofluorine compounds has been a stimulating research topic over the past years.[15] In that context and given the aforementioned impact of electron-withdrawing substituents onto the regioselectivity of the gold-catalyzed addition of O-based nucleophiles to alkynes, we set out to exploit the strong electrowithdrawing character of fluorine atoms to direct such a reaction. We hypothesized that the difluoromethylene unit intrinsic to propargylic *gem*-difluorides[16] would impose a significant-enough electronic bias to result in high regioselectivity,[17] thus favoring the formation of 3,3-difluoroketones in presence of a suitable nucleophile.

It is noteworthy that this new synthetic route to access 3,3-difluoroketones appears really attractive as it would circumvent issues associated with the deoxofluorination reaction. Indeed, the deoxofluorination of aldehydes or ketones is a classical approach for the preparation of *gem*-difluoro compounds, and this transformation can be performed using various reagents including sulfur tetrafluoride,[18] (diethylamino)sulfur trifluoride (DAST) or derivatives,[19] Deoxofluor,[20] XtalFluor[21] and Fluolead[22] (Scheme 1e). However, while this reaction can be applied to a wide range of substrates, its use with 1,3-diketones is known to be challenging (Scheme 1f). In the best cases, the desired 3,3-difluoroketone is obtained in low yield, while the presence of multiple side products, including tetrafluorinated products, fluoroalkenes, difluoroalkenes, as well as others, is generally observed.[23] The only exception is when a biased system (where one of the carbonyl groups is electronically deactivated in the form of an ester or an amide) is used,[24] although this may also be further complicated by the ketone/enol tautomerization leading to fluoroalkene derivatives.[25]

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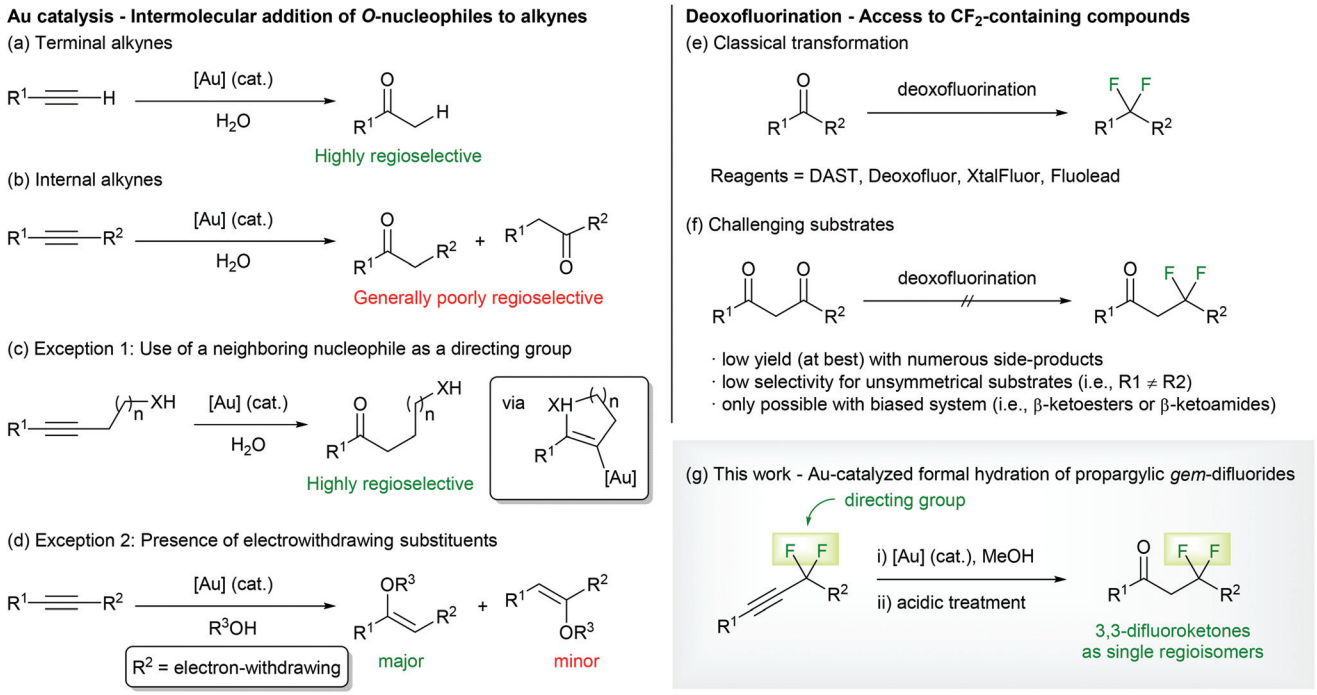


Scheme 1 Background for this study: (a–d) current status including regioselectivity issues in terms of Au-catalyzed addition of O-based nucleophiles to alkynes, (e–f) challenges associated with the installation of a difluoromethylene unit *via* a deoxofluorination reaction and (g) this work.

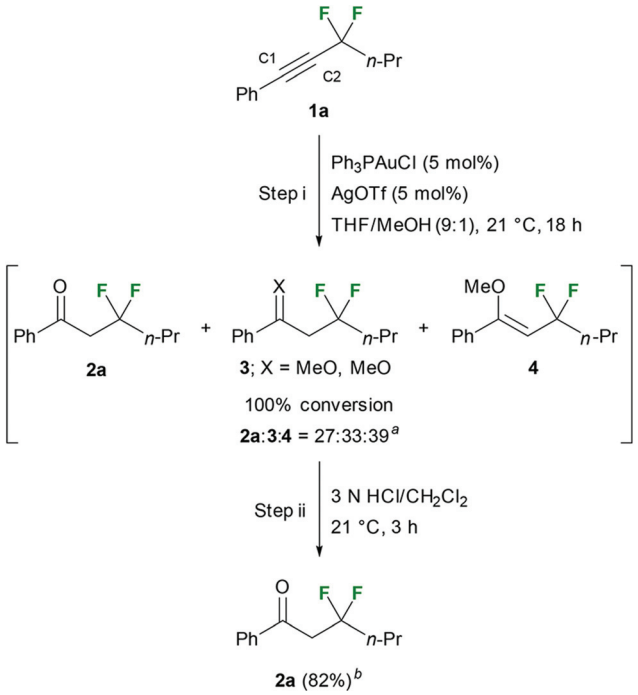
In that context and given the potential utility of 3,3-difluoroketones and their derivatives as versatile fluorinated building blocks or as bioactive compounds,[26] an alternative and more efficient approach for their synthesis is highly sought after.

Taking all this into account, we now wish to describe herein the development of a highly regioselective Au-catalyzed formal hydration of propargylic *gem*-difluorides (Scheme 1g). Notably, our report documents a rare occurence of a highly regioselective Au-catalyzed hydroalkoxylation of internal alkynes[3] and puts forward the utility of the difluoromethylene unit as a directing group. The current methodology also provides access to fluorinated compounds that were difficult or hardly possible to access beforehand.

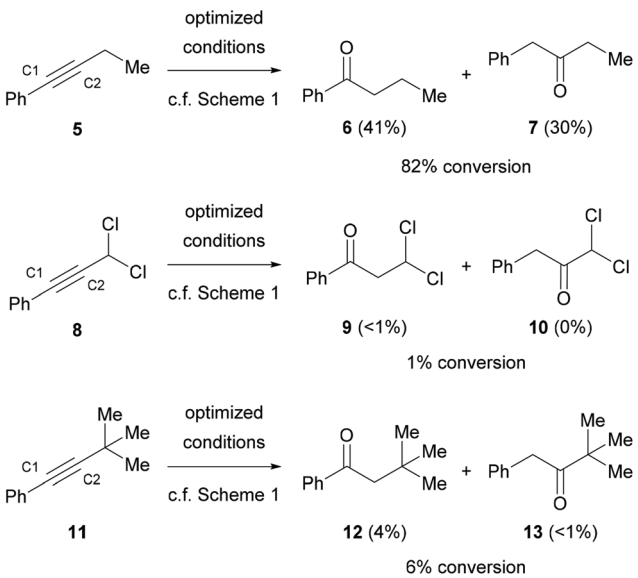
Results

While preliminary studies focused on the Au-catalyzed hydration of propargylic difluoride **1a**, the corresponding 3,3-difluoroketone (**2a**) was never observed (results not shown). We next explored the hydroalkoxylation of **1a** using MeOH, a slightly better nucleophile for such transformation,[27] and after some experiments (*cf.* Table S1†), optimized conditions were found (Scheme 2). Essentially, using a cationic gold complex derived from Ph_3PAuCl, generated *in situ* by the addition of 5 mol% of AgOTf in a THF/MeOH (9 : 1) mixture provided full conversion. Analysis of the crude mixture indicated a mixture of related products all originating from a regioselective attack of methanol at C1, and no products arising from attack at C2 were detected, thus representing a rare case of a highly regioselective Au-catalyzed hydroalkoxylation of internal alkynes. Under the reaction conditions, **4** would partially convert to ketone **2a** and acetal **3** through classical acid-catalyzed processes.[4d,28,29] Upon an acidic treatment after the reaction (3 N HCl/CH_2Cl_2 (1 : 1), 21 °C, 3 h), both **3** and **4** would convert to **2a**, which was isolated in 82% yield as the single regioisomer. When the reaction was repeated on 1 mmol scale, a 77% yield of **2a** was obtained, proving the applicability of the present methodology on a larger scale.

To compare this unprecedented effect of fluorine substitution on the reactivity and regioselectivity, the reaction was performed on related non-fluorinated substrates (Scheme 3). First, 1-phenyl-1-butyne (**5**) was reacted under our optimized conditions (*cf.* Scheme 2). An 82% conversion was observed and NMR analysis of the crude mixture indicated that both regioisomers **6** (produced by an attack at C1) and **7** (produced by an attack at C2) were formed in 41% and 30% NMR yields, respectively. In this case, without the strong electronic bias brought about by the two fluorine atoms, a modest selectivity is observed, where attack at the more electrophilic carbon is predominant. This result highlights the critical role played by the difluoromethylene unit in directing the addition at the C1 carbon, while, at the same time, increasing the reactivity of the alkyne towards addition. Surprisingly, using 3,3-dichloro-1-phenyl-1-propyne (**8**), almost no reaction was observed (*ca.* 1% conversion) even though related fluorinated substrates behaved normally (*vide infra*), suggesting that the strong electron-withdrawing ability of the fluorine atoms of the difluoromethylene unit is not the only factor at play and that a steric component may also be present. To probe this, 3,3-dimethyl-1-



Scheme 2 Optimized conditions using *gem*-difluoride **1a**. [a] NMR yield estimated by ^{19}F NMR analysis of the crude mixture after an aqueous work-up (sat. aq. $NaHCO_3$) using 2-fluoro-4-nitrotoluene as the internal standard. [b] Isolated yield of **2a**.

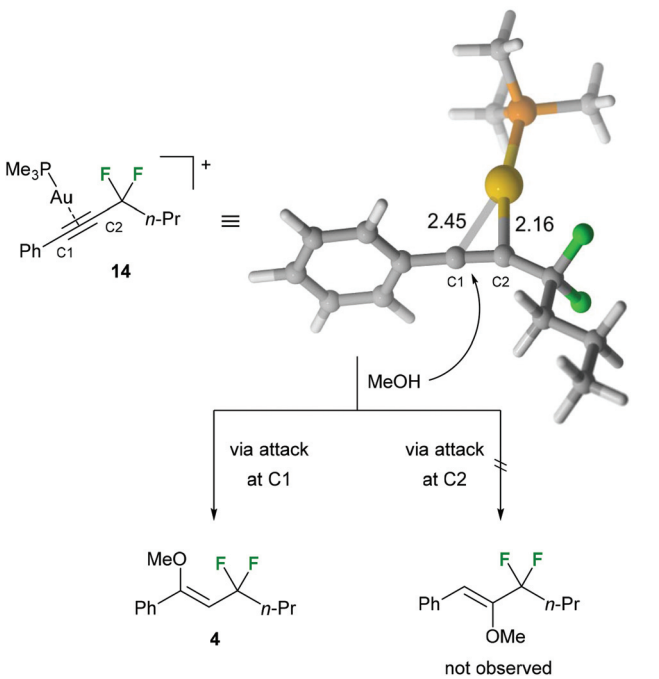


Scheme 3 Effect of fluorine atom replacement. Yields were determined by ^1H NMR analysis of the crude mixture using 1,4-dimethoxybenzene as the internal standard.

phenyl-1-butyne (**11**) was submitted to the optimized reaction conditions and a very low conversion was observed with both isomers **12** and **13** detected in the crude mixture (4% and <1% respectively). This suggests that the steric effect of the substituent at C2 is important and that a bulky substituent considerably slows down the reaction. Overall, these results demonstrate that the difluoromethylene unit offers a unique combination of a strong electron-withdrawing effect combined with a small steric impact, both of which seem essential for this transformation.

To gain a better understanding of the origin of the high regioselectivity observed for the addition of methanol to **1a**, we performed DFT calculations (BP86/def2-TZVP)[30] on intermediate π-complex **14** where the actual PPh_3 ligand was replaced with PMe_3.[31] Interestingly, a highly unsymmetrical π-complex is calculated. Indeed, while the C2–Au bond is 2.16 Å, the C1–Au bond is 2.45 Å (Scheme 4).[32] In comparison, Au–C bond distances in a H_3PAu/acetylene complex have been calculated to be 2.25 Å,[30] while a fully-relativistic calculation of the $AuCl_3$–propyne complex yielded Au–C distances of 2.162 and 2.197 Å.[33]

The profound difference in the calculated Au–C distances can be explained by the computed Mulliken charges and the structure of the HOMO for the π-complex **14**. The computed charges for the gold atom, C1, and C2 are +0.47, +0.06, and −0.21; favorable interactions between oppositely-charged Au and C2 result in a shorter Au–C2 distance from electrostatic attraction, while unfavorable interactions between similarly-charged Au and C1 would yield a greater Au–C distance from electrostatic repulsion. In the HOMO orbital density of π-complex **14**, there is a small contribution from Au, consistent with data reported previously.[33] Between the alkyne carbon atoms, however, the largest coefficients are found on C2, while there is little contribution from C1. By contrast, the LUMO density is much greater at C1, and there is some interaction

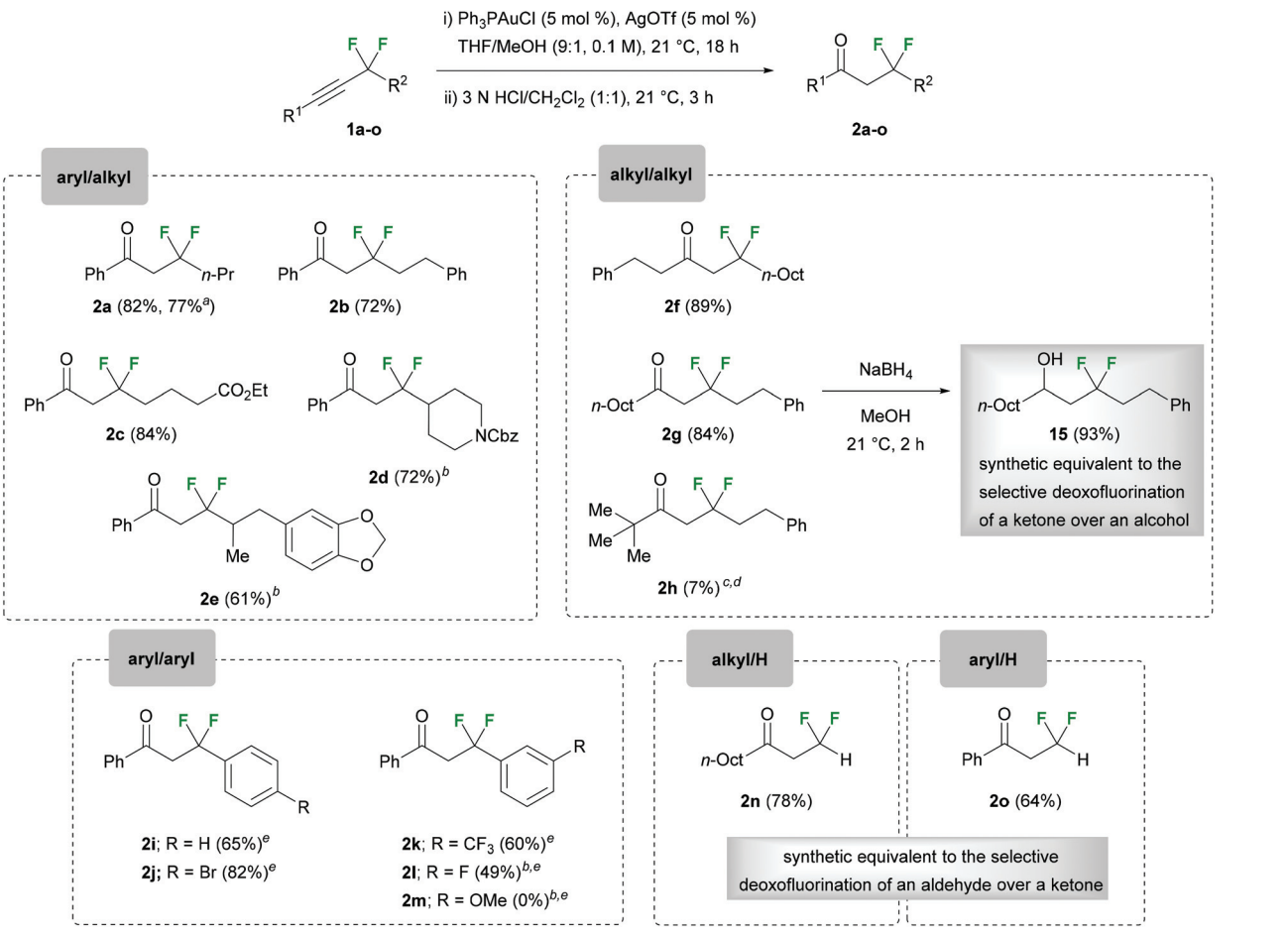


Scheme 4 Calculated structure for intermediate **14**. Distances are reported in Å.

between C1 and the *ipso* carbon of the adjacent phenyl ring, which would also preclude C1–Au interactions.

Other calculations had us find a 6.1 kcal mol^{-1} energy difference between attack on C1 *vs.* attack on C2 (see ESI†). Together, the Mulliken charge, orbital density, and energy data explain why addition of methanol at C1 is preferred over C2, and supports our initial hypothesis that the difluoromethylene unit would impose a significant electronic bias.

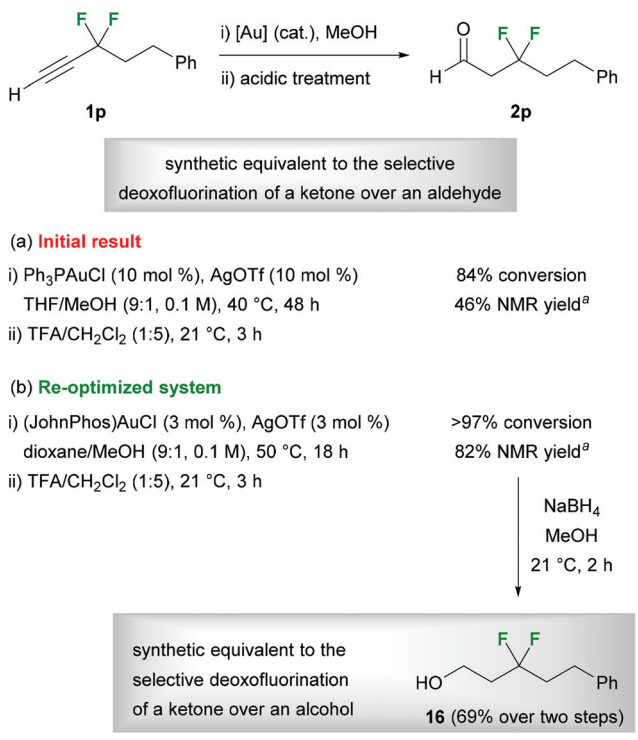
After establishing the unique directing ability of the difluoromethylene unit, the scope of this transformation was next explored. The results are classified according to the nature of both the R^1 and R^2 groups and are shown in Scheme 5. Hence, substrates bearing aryl/alkyl groups reacted well to provide the desired 3,3-difluoroketones **2a–e** in good yields (61–84%). Gratifyingly, the preparation of **2a** could be performed on a 1 mmol scale without any substantial loss of yield. The presence of an ester group did not influence the regiochemistry of the addition[5a] and as such, **2c** was isolated as the sole regioisomer. Substrates bearing a Cbz-protected amine or a 1,3-benzodioxole were well tolerated as products **2d** and **2e** were isolated in 72% and 61% yields, respectively. In both cases, a slight heating (40 °C) along with a prolonged reaction time was required for complete conversion. We attribute this lower reactivity to a steric effect caused by the presence of a secondary carbon at the R^2 position. For substrates bearing R^1/R^2 = alkyl/alkyl, high yields were obtained for the formation of 3,3-difluoroketones **2f** and **2g** (84–89%), those two compounds having the R^1 and R^2 substituents inverted from one another. This illustrates well the versatility of the method as this is equivalent to performing the deoxofluorination of the same 1,3-diketone, but with predictable and perfect regioselectivity towards the desired carbonyl moiety. It was noted that the size of the substituent at R^1 had an important influence on the yield as a *tert*-butyl group hindered the reaction even under more forcing conditions (7% NMR yield of **2h** at 70 °C for 18 h). 3,3-Difluoroketone **2g** was also reduced to the alcohol **15** in 93% yield under standard conditions. This two-step sequence (from the corresponding propargylic difluoride) demonstrates the utility of the products generated as it represents a synthetic equivalent to the selective deoxo-



Scheme 5 Substrate scope of the formal hydration of propargylic *gem*-difluorides. See ESI† for the detailed experimental procedure. Isolated yield of **2** after column chromatography. [a] The reaction was performed on a 1 mmol scale. [b] The reaction (step i) was performed at 40 °C for 48 h. [c] The reaction (step i) was performed at 70 °C for 18 h. [d] NMR yield estimated by ^{19}F NMR analysis using 2-fluoro-4-nitrotoluene as the internal standard. [e] Step ii was stirred for 24 h.

fluorination of a ketone over an alcohol, an unprecedented transformation.[34] A number of substrates with R^1/R^2 = aryl/aryl were also subjected to the reaction conditions and the products **2i–l** were isolated in moderate to good yields (49–82%). Surprisingly, the substrate bearing a 3-methoxyphenyl at the R^2 position did not react. This result hints that the presence of an electron-donating group may interfere with the reaction. Further investigations will aim at understanding this phenomenon. Substrates of the class alkyl/H or aryl/H both reacted under the standard conditions to provide the 3,3-difluoroketones **2n** and **2o** in 78% and 64% yields, respectively. Interestingly, these compounds pose as synthetic equivalents to the selective deoxofluorination of an aldehyde over a ketone. Overall, these results show that the selectivity observed is independent of the substrate type, hence alkynes bearing various R^1/R^2 groups all successfully reacted to provide the desired 3,3-difluoroketones as the unique regioisomer.

A substrate with a terminal alkyne was reacted under slightly modified reaction conditions, but showed lower reactivity (Scheme 6a). Partial conversion was observed even upon increasing catalyst loading, temperature and time (84% conversion, 46% NMR yield). This might come as a surprise when only taking steric factors into consideration. However, we attribute the lower reactivity of this substrate to the possibility for the intermediate π-complex to undergo rearrangement to the vinylidene, which might be an off-cycle resting state.[35] Re-optimization of the system revealed (JohnPhos)AuCl to be a more potent precatalyst, and full conversion was achieved within 18 hours at 50 °C, with formation of the expected 3,3-difluoroaldehyde **2p** in 82% NMR yield (Scheme 6b). As the aldehyde was slightly unstable to purification by column chromatography on silica gel, it was reduced to the corresponding alcohol **16** prior to isolation, which was finally obtained in 69% yield over two steps.



Scheme 6 Formal hydration of a propargylic *gem*-difluoride featuring a terminal alkyne. [a] NMR yield estimated by ^{19}F NMR analysis using fluorobenzene as the internal standard.

Conclusions

In conclusion, we have reported a highly regioselective Au-catalyzed formal hydration of propargylic *gem*-difluorides. This transformation results in 3,3-difluoroketones, versatile fluorinated building-blocks that were difficult or hardly possible to access beforehand, as single regioisomers. As such, this work represents a rare case of a highly regioselective Au-catalyzed hydroalkoxylation of internal alkynes. DFT calculations suggest that this unusual regioselectivity originates from the significant electronic bias imposed by the difluoromethylene unit. Importantly, the recent development of novel and practical methods to access propargylic *gem*-difluorides[36] other than the deoxofluorination of ynones should facilitate the use and extension of the work presented herein.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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