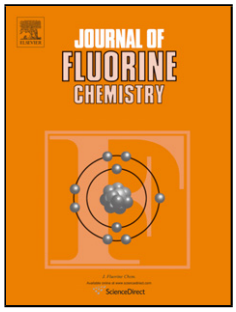

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PII: S0022-1139(18)30356-7
DOI: https://doi.org/10.1016/j.jfluchem.2018.09.009
Reference: FLUOR 9223

To appear in: *FLUOR*

Received date: 5-9-2018
Revised date: 25-9-2018
Accepted date: 26-9-2018

Please cite this article as: Hamel J-Denys, Paquin J-François, Au-Catalyzed Intramolecular Hydroalkoxylation of *gem*-Difluorinated Alkynols, *Journal of Fluorine Chemistry* (2018), https://doi.org/10.1016/j.jfluchem.2018.09.009

Au-Catalyzed Intramolecular Hydroalkoxylation of *gem*-Difluorinated Alkynols

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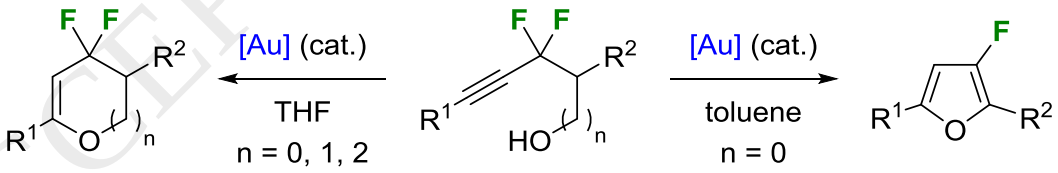
GRAPHICAL ABSTRACT



Different solvent, different product!

HIGHLIGHTS

- The intramolecular hydroalkoxylation of *gem*-difluorinated alkynols was found possible under Au catalysis.
- The nature of the solvent was found to be especially critical in the cyclization of *gem*-difluorohomopropargylic alcohols.
- In THF, *gem*-difluorohomopropargylic alcohols generated the corresponding 2,3-dihydrofurans.
- In toluene, the 2,3-dihydrofurans produced underwent subsequent aromatization to the furan.

ABSTRACT:

The intramolecular hydroalkoxylation of *gem*-difluorinated alkynols was found possible under Au catalysis, allowing for the preparation of a series of fluorinated heterocycles. The nature of the solvent was found to be especially critical in the cyclization of *gem*-difluorohomopropargylic alcohols as it dictated whether the resulting 2,3-dihydrofuran underwent subsequent aromatization to the corresponding furan or not.

abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, m = multiplet, bs = broad signal. High-resolution mass spectra were obtained on a LC/MS–TOF Agilent 6210 using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI). Infrared spectra were recorded using an ABB MB3000 FT-IR spectrometer. Melting points were recorded on a Stanford Research System OptiMelt capillary melting point apparatus and are uncorrected.

Keywords: gold catalysis; hydroalkoxylation; cyclization; propargylic *gem*-difluoride; alkynol; furan; dihydrofuran

1. Introduction

Recent years have seen a surge in Au-catalyzed nucleophilic addition reactions to alkynes owing to the strong propensity of gold catalysts to selectively activate alkynes over other functional groups [1]. Regarding *O*-based nucleophiles, one finds that such nucleophilic addition reactions typically give rise to the Markovnikov product [2,3]. A consequence of this is that transformations of terminal alkynes usually display excellent regioselectivity, whereas the use of internal alkynes generally results in poor regioselectivity. However, the electronic nature of the substituents bound to either side of the alkyne is known to affect the regioselectivity [4].

We have recently shown that the introduction of fluorine atoms can affect the course of such a nucleophilic attack on internal alkynes. Indeed, through a Au-catalyzed hydromethoxylation/hydrolysis sequence, we observed a perfect selectivity for the formation of 3,3-difluoroketones from propargylic *gem*-difluorides (**Scheme 1A**) [5]. Applying this method to a substrate featuring a terminal alkyne even led to a complete reversal of selectivity to the anti-Markovnikov product, a 3,3-difluoroaldehyde. The strong electron-withdrawing character of the fluorine atoms [6] would be at the source of those unusual regioselectivities, a proposal backed up by DFT calculations that show significant depletion of electron density at the carbon of the alkyne distal to the difluoromethylene unit [5]. Now, we wished to explore the possibility to perform such a Au-catalyzed addition

of a *O*-nucleophile to propargylic *gem*-difluorides in an intramolecular fashion. More precisely, we envisioned that exposure of *gem*-difluorinated alkynols to a Au catalyst might result in ring closure and the formation of fluorinated heterocyclic compounds. Such a cyclization has already been shown possible either in presence of a base [7] or a silver catalyst [8] for certain *gem*-difluorohomopropargylic alcohols (**Scheme 1B**) and our efforts towards the development of a Au-catalyzed variant are summarized herein (**Scheme 1C**).

2. Results and discussion

First, we sought to develop a general synthetic route to the required *gem*-difluorinated alkynols **1** that would allow for easy variation of the substituents. Moreover, inspired by our previous work [5], we wished to introduce the fluorine atoms via the deoxofluorination of ynones. We figured that either diols or α-hydroxyesters could be used as starting material for this endeavor (**Scheme 2**). Indeed, those could initially be converted into mono-THP-protected diols in one or two steps, respectively. Their subsequent oxidation to the corresponding aldehyde followed by nucleophilic addition of an acetylide led to ynols that could next be converted to the desired ynones upon another oxidation step. Gratifyingly, we found that the THP protecting group was compatible with the subsequent deoxofluorination step in neat DeoxoFluor [9]. In most cases, the HF-elimination side product was formed in small amounts and could be separated by means of silica gel chromatography. Finally, deprotection of the THP ether could be carried out in acidic methanol to provide the expected *gem*-difluorinated alkynols. Luckily, while pairs of diastereoisomers are formed at many points, this actually never complicated purifications to a significant extent. Overall, we succeeded in the preparation of 9 *gem*-difluorinated alkynols.

Now having a series of *gem*-difluorinated alkynols in hand, we elected *gem*-difluorohomopropargylic alcohol **1a** as the model substrate for the optimization study, and product distribution was assessed by ^{19}F NMR (**Table 1**). We once again took inspiration of our prior work on the formal hydration of propargylic *gem*-difluorides to set a starting point [5]. This had us choose $Ph_3PAuOTf$, generated *in situ* from Ph_3PAuCl and AgOTf, as the catalyst. However, as we did not wish to use methanol as solvent as to avoid a competing hydromethoxylation reaction, we opted for THF instead (**entry 1**). Three different fluorinated products arose from this transformation, all resulting from nucleophilic attack onto the alkyne at the carbon away from the fluorinated end: the expected intramolecular hydroalkoxylation product **2a**, the hydration product **3a** and the cyclization/aromatization product **4a**. Of those, 2,3-dihydrofuran **2a** came out as the major product at 74% as observed by ^{19}F NMR. Using Et_2O as the solvent afforded a pretty similar product distribution (**entry 2**). We surmised that trace H_2O in the solvent was the cause behind the generation of **3a**. As such, we found that the addition of molecular sieve to the reaction medium suppresses its formation with the added benefit of almost no conversion to **4a**, thus resulting in a quasi-quantitative yield of **2a** (**entry 3**). Conversely, going away from ethereal solvents, we found that furan **4a** was formed pretty much as the sole fluorinated product, with no trace of **2a** detectable after 18 hours (**entries 4-6**). In toluene, this resulted in a 80% yield of **4a** (**entry 6**). We hypothesize that this striking difference in behavior between THF and toluene can be related to the Lewis basicity of the solvent. Indeed, in toluene (a very weak Lewis base), any Lewis acidic species (Au, Ag, etc) present could potentially interact with the fluorine atoms and promote an elimination reaction leading to the furan. In THF (a stronger Lewis base), the same Lewis acidic species

would be trapped by the solvent, thus slow down significantly this side reaction. Regarding the cyclization to **2a**, we next wished to validate the necessity for both Ph_3PAuCl and AgOTf, especially since a silver salt had already been used in the cyclization of some *gem*-difluorohomopropargylic alcohols [8]. On its own, Ph_3PAuCl was found to be non-reactive (**entry 7**), whereas AgOTf resulted in a clean, but slow conversion to **2a** (**entry 8**). Further refinement of the system had us find that a reaction time of 1 hour was sufficient to reach full conversion to **2a** (**entry 9**), which stays true even when decreasing the catalyst loading down to 1 mol% (**entry 10**). The transformation is also possible at a catalyst loading of 0.1 mol%, but conversion is incomplete after 1 hour (**entry 11**). We thus judged conditions in entry 10 to be optimal for the cyclization of *gem*-difluorohomopropargylic alcohols to 2,3-dihydrofuran derivatives. Besides, although this was not the primary goal initially, the success we had in the preparation of **4a** with the conditions of entry 6 prompted us to keep those conditions for the preparation of other furan derivatives. Overall, the nature of the solvent here causes a drastic difference in selectivity towards a product or another.

[a] Estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene as an internal standard.

[b] 4Å MS was added to the reaction mixture.

Having established optimal conditions for the intramolecular hydroalkoxylation of *gem*-difluorohomopropargylic alcohols, we wished to study the scope of the transformation (**Scheme 3A**). However, we rapidly found that 2,3-dihydrofurans **2** could not be isolated by means of silica gel chromatography as this triggered their decomposition, mainly to the corresponding furan **4**. This instability of similar *gem*-difluorinated 2,3-dihydrofurans [8,10] and 2,3-dihydrothiophenes [11] has already been reported. Occasionally, simple evaporation of the crude reaction mixture led to spontaneous polymerization to dark purple

material. Unable to isolate compounds **2** [12], we thus resorted to NMR yields for the whole series. High to excellent yields of **2** were obtained in all cases, disregarding of the nature of R^1 and R^2. The best results came from substrates for which no substituent was present α to the alcohol (R^2 = H), namely in the preparation of 2,3-dihydrofurans **2a** and **2d**.

At this point, we had shown that the Au-catalyzed intramolecular hydroalkoxylation of *gem*-difluorohomopropargylic alcohols was a rapid and clean process, and we wondered what the influence of a longer spacer between the difluoromethylene unit and the alcohol would be. Gratifyingly, we found that the cyclization of **1h**, a *gem*-difluorinated alkynol with a two-carbon linker, was just as efficient under the exact same reaction conditions, with formation of 3,4-dihydro-2*H*-pyran **2h** in a 95% NMR yield (**Scheme 3B**). However, we found the product to decompose to 2,3-dihydro-4*H*-pyran-4-one **5** upon attempts at purification over silica gel. For its part, the formation of a 7-membered ring via the cyclization of **1i** was found to be much slower under the standard reaction conditions as the 2,3,4,5-tetrahydrooxepine **2i** was only observed in a 4% NMR yield. However, increasing the catalyst loading to 5 mol% and extending the reaction time to 18 hours allowed for a 52% NMR yield of **2i** along with full conversion of **1i** (**Scheme 3C**).

Finally, we sought to extend the cyclization/aromatization protocol to each *gem*-difluorohomopropargylic alcohol that we had synthesized, and although a few furans **4** were found to be somewhat unstable over time, we were nonetheless able to handle them long enough to carry out their purification by means of silica gel chromatography (**Scheme 4**). Here, the overall trend in yield is opposite to that of the cyclization in THF in the sense that better yields were obtained for *gem*-difluorohomopropargylic alcohols having a

substituent α to the alcohol ($R^2 \neq H$). The exception to this, however, is the reaction of compound **1i** featuring a terminal alkyne ($R^1 = H$), which places as the worst substrate for this transformation. Multiple products appear to be formed, of which furan **2g** accounts for a mere 9%, despite full conversion of the starting material.

3. Conclusion

In conclusion, based on our prior knowledge on the reactivity of propargylic *gem*-difluorides with *O*-based nucleophiles in presence of Au catalysts, we conceived that a regioselective intramolecular hydroalkoxylation reaction might be possible, provided that *gem*-difluorinated alkynols were prepared. We found that this transformation was best carried out in THF and was efficient at the formation of 5- to 7-membered rings, but that the cyclization products were unstable to purification. We also noticed a dramatic change in product selectivity when the cyclization of *gem*-difluorohomopropargylic alcohols was carried out in toluene, where aromatization of the expected 2,3-dihydrofuran to the corresponding furan was found to occur readily.

4. Experimental

4.1 General information

All reactions were carried out under an argon atmosphere with dry solvents. Et_2O, THF, CH_3CN, CH_2Cl_2 and toluene were purified using a Vacuum Atmospheres Inc. solvent purification system. All other commercially available compounds were used as received. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Silicycle silica gel 60 Å F254 TLC plates, and visualized under UV or by staining with either potassium permanganate, *p*-anisaldehyde or phosphomolybdic acid. Flash column chromatography was carried out on Silicycle silica gel 60 Å, 230–400 mesh. ^1H, ^{13}C and

^{19}F NMR spectra were recorded in $CDCl_3$ at room temperature using Agilent DD2 500 and Varian Inova 400 spectrometers. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield of tetramethylsilane and are respectively referenced to tetramethylsilane (δ = 0.00 ppm) and residual solvent (δ = 77.16 ppm). For ^{19}F NMR, $CFCl_3$ is used as the external standard. Multiplicities are reported using the following *4.2 Preparation of gem-difluorinated alkynols*

*4.2.1 Preparation of 2,2-difluoro-4-phenylbut-3-yn-1-ol (**1a**).*

*2-((Tetrahydro-2H-pyran-2-yl)oxy)ethan-1-ol (**6**).* Ethylene glycol (2.52 mL, 45.0 mmol) was dissolved in CH_2Cl_2 (92 mL) and pyridinium *p*-toluenesulfonate (113 mg, 0.450 mmol) was added. A solution of 3,4-dihydro-2*H*-pyran (2.74 mL, 30 mmol) in CH_2Cl_2 (22 mL) was then added dropwise over 1 hour. The resulting mixture was stirred at room temperature for 18 hours, after which H_2O was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (2.41 g, 55%) was isolated as a pale yellow oil by flash chromatography using 5% MeOH/CH_2Cl_2. Spectroscopic data was in agreement with the literature [13].

*2-((Tetrahydro-2H-pyran-2-yl)oxy)acetaldehyde (**7**).* To a -78 °C solution of oxalyl chloride (1.69 mL, 19.7 mmol) in CH_2Cl_2 (150 mL) was added DMSO (2.80 mL, 39.4 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of alcohol **6** (2.40 g, 16.4 mmol) in CH_2Cl_2 (14 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (13.7 mL, 98.5 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in*

vacuo. The desired product (1.80 g, 76%) was isolated as a yellow oil by flash chromatography using 20% acetone/hexanes. Spectroscopic data was in agreement with the literature [14].

*4-Phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)but-3-yn-2-ol (**8**).* To a -78 °C solution of phenylacetylene (1.50 mL, 13.7 mmol) in THF (35 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 5.47 mL, 13.7 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **7** (1.79 g, 12.4 mmol) in THF (6 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (2.64 g, 86%) was isolated as a yellow oil by flash chromatography using 25% EtOAc/hexanes. IR (ATR, diamond) ν = 3381, 2941, 2868, 2201, 1491, 1261, 1070, 1024, 756, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44-7.43 (m, 2H), 7.33-7.27 (m, 3H), 4.78-4.64 (m, 2H), 4.00-3.93 (m, 2H), 3.84-3.78 (m, 1H), 3.72 (m, 0.5H), 3.58-3.56 (m, 1H), 3.35 (d, 0.5H, J = 5.7 Hz), 1.88-1.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 131.88, 131.87, 128.57, 128.56, 128.4, 122.64, 122.59, 100.4, 100.3, 87.2, 86.7, 85.5, 73.6, 72.8, 63.5, 63.0, 62.7, 62.6, 30.8, 30.7, 25.3, 25.2, 20.0, 19.7; HRMS-ESI calcd for $C_{15}H_{19}O_3$ $[M+H]^+$ 247.1329; found 247.1329.

*4-Phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)but-3-yn-2-one (**9**).* To a -78 °C solution of oxalyl chloride (1.09 mL, 12.7 mmol) in CH_2Cl_2 (95 mL) was added DMSO (1.81 mL, 25.5 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of propargylic alcohol **8** (2.62 g, 10.6 mmol) in CH_2Cl_2 (11 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (8.9 mL, 63.7 mmol) was

added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (1.93 g, 74%) was isolated as a yellow oil by flash chromatography using 15% EtOAc/hexanes. IR (ATR, diamond) ν = 2943, 2199, 1688, 1670, 1489, 1259, 1202, 1034, 756, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, 2H, *J* = 7.1 Hz), 7.48 (t, 1H, *J* = 7.5 Hz), 7.30 (t, 2H, *J* = 7.6 Hz), 4.79 (t, 1H, *J* = 3.4 Hz), 4.46 (m, 2H), 3.89 (m, 1H), 3.56 (m, 1H), 1.96-1.87 (m, 1H), 1.85-1.77 (m, 2H), 1.67-1.54 (m, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 185.1, 133.3, 131.1, 128.8, 119.8, 98.5, 93.7, 86.0, 72.6, 62.2, 30.3, 25.4, 19.0; HRMS-ESI calcd for $C_{15}H_{17}O_3$ $[M+H]^+$ 245.1172; found 245.1171.

*2-((2,2-Difluoro-4-phenylbut-3-yn-1-yl)oxy)tetrahydro-2H-pyran (**10**).* Ynone **9** (1.78 g, 7.30 mmol) was charged into a polypropylene vial. DeoxoFluor (3.36 mL, 18.2 mmol) was added and the mixture was stirred at 55 °C for 18 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (864 mg, 44%) was isolated as a pale yellow oil by flash chromatography using 5% Et_2O/hexanes. IR (ATR, diamond) ν = 2943, 2872, 2239, 1491, 1315, 1067, 1036, 964, 766, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, 2H, *J* = 7.2 Hz), 7.43 (t, 1H, *J* = 7.4 Hz), 7.37 (t, 2H, *J* = 7.4 Hz), 4.85 (t, 1H, *J* = 3.3 Hz), 4.07 (q, 1H, *J* = 12.4 Hz), 3.96-3.89 (m, 2H), 3.58 (dtd, 1H, *J* = 11.1, 4.1, 1.4 Hz), 1.94-1.85 (m, 1H), 1.80-1.74 (m, 2H), 1.69-1.53 (m, 2H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -91.6 (dt, 1F, *J* = 277, 12.5 Hz), -92.2 (dt,

1F, J = 277, 11.7 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 132.3 (t, $J_{C\text{-}F}$ = 2.2 Hz), 130.1, 128.6, 120.2 (t, $J_{C\text{-}F}$ = 2.8 Hz), 112.8 (t, $J_{C\text{-}F}$ = 235 Hz), 98.8, 87.9 (t, $J_{C\text{-}F}$ = 6.8 Hz), 80.4 (t, $J_{C\text{-}F}$ = 38.9 Hz), 69.0 (t, $J_{C\text{-}F}$ = 31.2 Hz), 61.9, 30.2, 25.4, 18.7; HRMS-ESI calcd for $C_{15}H_{16}F_2NaO_2$ $[M+Na]^+$ 289.1011; found 289.1015.

*2,2-Difluoro-4-phenylbut-3-yn-1-ol (**1a**).* PPTS (78 mg, 0.31 mmol) was added to a solution of propargylic fluoride **10** (826 mg, 3.10 mmol) in MeOH (31 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (547 mg, 97%) was isolated as a colorless oil by flash chromatography using 20% EtOAc/hexanes. IR (ATR, diamond) ν = 3329, 2939, 2237, 1491, 1313, 1175, 1055, 912, 754, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, 2H, J = 7.2 Hz), 7.43 (t, 1H, J = 7.4 Hz), 7.37 (t, 2H, J = 7.4 Hz), 3.99 (td, 2H, J = 12.1, 7.4 Hz), 2.09 (t, 1H, J = 7.4 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -94.8 (t, 2F, J = 12.3 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 132.4 (t, $J_{C\text{-}F}$ = 2.3 Hz), 130.3, 128.7, 119.9 (t, $J_{C\text{-}F}$ = 2.8 Hz), 113.2 (t, $J_{C\text{-}F}$ = 235 Hz), 88.7 (t, $J_{C\text{-}F}$ = 6.9 Hz), 79.6 (t, $J_{C\text{-}F}$ = 39.3 Hz), 66.3 (t, $J_{C\text{-}F}$ = 31.5 Hz); HRMS-ESI calcd for $C_{10}H_8FO$ $[M\text{-}F]^+$ 163.0054; found 169.0044.

*4.2.1 Preparation of 3,3-difluoro-5-phenylpent-4-yn-2-ol (**1b**).*

*Ethyl 2-((tetrahydro-2H-pyran-2-yl)oxy)propanoate (**11**).* Ethyl lactate (1.15 mL, 10.0 mmol) was dissolved in CH_2Cl_2 (13 mL), after which both 3,4-dihydro-2*H*-pyran (1.19 mL, 13.0 mmol) and pyridinium *p*-toluenesulfonate (10 mg, 0.040 mmol) were added. The resulting mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The organic layer was separated, dried over Na_2SO_4,

filtered, and concentrated *in vacuo*. The desired product (2.02 g, 100%) was isolated as a colorless oil by flash chromatography using 15% EtOAc/hexanes. Spectroscopic data was in agreement with the literature [15].

*2-((Tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (**12**).* A suspension of $LiAlH_4$ (835 mg, 22.0 mmol) in Et_2O (10 mL) was cooled down to 0 °C, and to it was added a solution of ester **11** (2.02 g, 10.0 mmol) in Et_2O (20 mL) over 1 hour. The resulting mixture was stirred for an additional 1.5 hours at 0 °C, after which saturated NH_4Cl (5 mL) was added dropwise at 0 °C. It was stirred until no more gas evolved, and then filtered to remove the solids, making sure to wash them thoroughly with Et_2O. The resulting solution was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (1.56 g, 97%) was isolated as a yellow oil by flash chromatography using 4% MeOH/CH_2Cl_2. Spectroscopic data was in agreement with the literature [15].

*2-((Tetrahydro-2H-pyran-2-yl)oxy)propanal (**13**).* To a -78 °C solution of oxalyl chloride (0.87 mL, 10.1 mmol) in CH_2Cl_2 (75 mL) was added DMSO (1.44 mL, 20.3 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of alcohol **12** (3.37 g, 21.1 mmol) in CH_2Cl_2 (9 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (7.1 mL, 50.7 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (1.11 g, 83%) was isolated as a pale yellow oil by flash chromatography using 20% acetone/hexanes. Spectroscopic data was in agreement with the literature [16].

1-Phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)pent-1-yn-3-ol ***(14)***. To a -78 °C solution of phenylacetylene (0.83 mL, 7.6 mmol) in THF (18 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 3.04 mL, 7.60 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **13** (1.09 g, 6.91 mmol) in THF (5 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The formation of the 4 possible pairs of diastereoisomers was confirmed by NMR analysis of the crude reaction mixture. The crude reaction mixture was used as is in the subsequent oxidation step with the transformation being considered quantitative.

1-Phenyl-4-((tetrahydro-2H-pyran-2-yl)oxy)pent-1-yn-3-one ***(15)***. To a -78 °C solution of oxalyl chloride (0.71 mL, 8.29 mmol) in CH_2Cl_2 (60 mL) was added DMSO (1.18 mL, 16.6 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of crude propargylic alcohol **14** (assumed to be quantitative, 6.91 mmol) in CH_2Cl_2 (9 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (5.8 mL, 41.5 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (1.67 g, 94%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 2943, 2870, 2195, 1672, 1121, 1020, 970, 876, 758, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.61-7.58 (m, 2H), 7.50-7.45 (m, 1H), 7.41-7.38 (m, 2H), 4.82

(t, 0.5H, *J* = 3.5 Hz), 4.78 (dd, 0.5H, *J* = 4.4, 3.0 Hz), 4.52 (q, 0.5H, *J* = 7.0 Hz), 4.34 (q, 0.5H, *J* = 6.8 Hz), 4.02 (ddd, 0.5H, *J* = 12.1, 9.3, 3.1 Hz), 3.90 (ddd, 0.5H, *J* = 11.1, 8.0, 3.3 Hz), 3.57-3.49 (m, 1H), 1.99-1.70 (m, 3H), 1.66-1.54 (m, 3H), 1.53 (d, 1.5H, *J* = 7.1 Hz), 1.45 (d, 1.5H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.8, 188.7, 133.30, 133.26, 131.1, 130.9, 128.83, 128.77, 120.3, 120.0, 98.3, 97.5, 94.2, 93.8, 86.8, 86.4, 78.1, 77.4, 62.8, 62.4, 30.7, 30.6, 25.50, 25.49, 19.4, 19.2, 18.3, 16.9; HRMS-ESI calcd for $C_{16}H_{19}O_3$ $[M+H]^+$ 259.1329; found 259.1322.

*2-((3,3-Difluoro-5-phenylpent-4-yn-2-yl)oxy)tetrahydro-2H-pyran (**16**).* Ynone **15** (1.51 g, 5.83 mmol) was charged into a polypropylene vial. DeoxoFluor (2.69 mL, 14.6 mmol) was added and the mixture was stirred at 55 °C for 24 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (608 mg) was isolated as a yellow oil by flash chromatography using 5% Et_2O/hexanes, but partial loss of the THP protecting group occurred after evaporation. The product was thus used as is in the subsequent THP removal step and the yield was determined over two steps.

*3,3-Difluoro-5-phenylpent-4-yn-2-ol (**1b**).* PPTS (55 mg, 0.22 mmol) was added to a solution of semi-pure propargylic fluoride **16** (608 mg) in MeOH (22 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (411 mg, 36%) was isolated as a yellow oil by flash chromatography using 20%

EtOAc/hexanes. IR (ATR, diamond) ν = 3387, 2991, 2241, 1375, 1275, 1109, 1047, 987, 754, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (d, 2H, *J* = 7.1 Hz), 7.43 (t, 1H, *J* = 7.4 Hz), 7.37 (t, 2H, *J* = 7.4 Hz), 4.12 (m, 1H), 2.20 (d, 1H, *J* = 5.4 Hz), 1.42 (d, 3H, *J* = 6.4 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -95.9 (dd, 1F, *J* = 275, 6.9 Hz), -97.0 (dd, 1F, *J* = 274, 9.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 132.4 (t, J_{C-F} = 2.5 Hz), 130.2, 128.6, 120.0 (t, J_{C-F} = 2.7 Hz), 115.3 (t, J_{C-F} = 236 Hz), 88.9 (t, J_{C-F} = 6.8 Hz), 79.3 (t, J_{C-F} = 39.6 Hz), 70.7 (dd, J_{C-F} = 30.5, 28.6 Hz), 16.5 (t, J_{C-F} = 2.5 Hz); HRMS-ESI calcd for $C_{11}H_{10}FO$ $[M-F]^+$ 177.0710; found 177.0711.

*4.2.3 Preparation of 2,2-difluoro-1,4-diphenylbut-3-yn-1-ol (**1c**).*

*Methyl 2-phenyl-2-((tetrahydro-2H-pyran-2-yl)oxy)acetate (**17**).* Methyl mandelate (3324 mg, 20.0 mmol) was dissolved in CH_2Cl_2 (27 mL), after which both 3,4-dihydro-2*H*-pyran (2.37 mL, 26.0 mmol) and pyridinium *p*-toluenesulfonate (20 mg, 0.080 mmol) were added. The resulting mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (3.00 g, 60%) was isolated as a colorless oil by flash chromatography using 15% EtOAc/hexanes. IR (ATR, diamond) ν = 2945, 2872, 1751, 1456, 1259, 1202, 1121, 1036, 966, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.45 (m, 2H), 7.39-7.31 (m, 3H), 5.33 (s, 0.5 H), 5.25 (s, 0.5 H), 4.89 (t, 0.5H, *J* = 3.0 Hz), 4.58 (t, 0.5H, *J* = 3.5 Hz), 3.95 (ddd, 0.5 H, *J* = 11.6, 7.8, 4.5 Hz), 3.73-3.67 (m, 3.5H), 3.54-3.46 (m, 1H), 1.98-1.70 (m, 3H), 1.65-1.47 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 172.0, 171.3, 136.8, 136.4, 128.8, 128.7, 128.6, 128.5, 127.7, 127.3, 97.2, 96.7, 75.7, 62.5, 62.0, 52.41, 52.36, 30.4, 30.3, 25.44, 25.42, 19.2, 18.8; HRMS-ESI calcd for $C_{14}H_{19}O_4$ $[M+H]^+$ 251.1278; found 251.1282.

*2-Phenyl-2-((tetrahydro-2H-pyran-2-yl)oxy)ethan-1-ol (**18**).* A suspension of $LiAlH_4$ (993 mg, 26.2 mmol) in Et_2O (12 mL) was cooled down to 0 °C, and to it was added a solution of ester **17** (2.98 g, 11.9 mmol) in Et_2O (24 mL) over 1 hour. The resulting mixture was stirred for an additional 1.5 hours at 0 °C, and then at room temperature overnight, after which saturated NH_4Cl (5 mL) was added dropwise at 0 °C. It was stirred until no more gas evolved, and then filtered to remove the solids, making sure to wash them thoroughly with Et_2O. The resulting solution was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (2634 mg, 100%) was isolated as a pale yellow oil by flash chromatography using 3% MeOH/CH_2Cl_2. Spectroscopic data was in agreement with the literature [17].

*2-Phenyl-2-((tetrahydro-2H-pyran-2-yl)oxy)acetaldehyde (**19**).* To a -78 °C solution of oxalyl chloride (1.21 mL, 14.1 mmol) in CH_2Cl_2 (100 mL) was added DMSO (2.01 mL, 28.3 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of alcohol **18** (2.62 g, 11.8 mmol) in CH_2Cl_2 (18 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (9.85 mL, 70.6 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (2.13 g, 76%) was isolated as a pale yellow oil by flash chromatography using 20% EtOAc/hexanes. IR (ATR, diamond) ν = 2943, 2870, 1732, 1452, 1202, 1121, 1020, 970, 816, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.65 (d, 0.6H, *J* = 2.1 Hz), 9.62 (d, 0.4H, *J* = 1.7 Hz), 7.45-7.33 (m, 5H), 5.20 (d, 0.4H, *J* = 1.7 Hz), 5.05 (d, 0.6H, 2.1 Hz), 4.93 (t, 0.4H, *J* = 3.2 Hz), 4.66 (dd, 0.6H, *J* = 4.6, 3.1 Hz), 3.95 (dt,

0.6H, *J* = 11.3, 5.2 Hz), 3.70 (ddd, 0.4H, *J* = 12.3, 9.4, 3.2 Hz), 3.54 (ddd, 0.6H, *J* = 10.8, 7.0, 3.6 Hz), 3.46 (dt, 0.4H, *J* = 10.3, 4.0 Hz), 1.99-1.72 (m, 3H), 1.65-1.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 199.3, 198.7, 134.2, 134.2, 129.1, 129.0, 128.9, 128.7, 127.6, 127.5, 97.7, 97.7, 83.5, 81.8, 63.1, 62.3, 30.5, 30.4, 25.4, 19.6, 18.9; HRMS-ESI calcd for $C_{13}H_{17}O_3$ $[M+H]^+$ 221.1172; found 221.1179.

1,4-Diphenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)but-3-yn-2-ol ***(20)****.* To a -78 °C solution of phenylacetylene (0.36 mL, 3.30 mmol) in THF (7 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 1.32 mL, 3.30 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **19** (661 mg, 3.00 mmol) in THF (3 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The formation of the 4 possible pairs of diastereoisomers was confirmed by NMR analysis of the crude reaction mixture. The crude reaction mixture was used as is in the subsequent oxidation step with the transformation being considered quantitative.

1,4-Diphenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)but-3-yn-2-one ***(21)****.* To a -78 °C solution of oxalyl chloride (0.31 mL, 3.6 mmol) in CH_2Cl_2 (25 mL) was added DMSO (0.51 mL, 7.2 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of crude propargylic alcohol **20** (assumed to be quantitative, 3.00 mmol) in CH_2Cl_2 (5 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (2.51 mL, 18.0 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added

and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (559 mg, 58%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 2941, 2868, 2203, 1672, 1119, 1022, 966, 908, 756, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.56 (d, 1H, *J* = 7.3 Hz), 7.53-7.49 (m, 3H), 7.45 (t, 1H, *J* = 7.4 Hz), 7.41-7.33 (m, 5H), 5.43 (s, 0.5H), 5.35 (s, 0.5H), 4.98 (t, 0.5H, *J* = 3.1 Hz), 4.68 (t, 0.5H, *J* = 3.3 Hz), 4.02 (m, 0.5H), 3.73 (m, 0.5H), 3.57 (m, 0.5H), 3.50 (m, 0.5H), 2.06-1.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 186.8, 184.8, 135.9, 135.6, 133.3, 133.2, 131.1, 131.0, 129.0, 128.9, 128.8, 128.75, 128.70, 128.2, 127.7, 120.1, 119.9, 97.6, 96.2, 95.3, 94.8, 86.7, 86.5, 83.3, 82.9, 62.17, 62.19, 30.5, 30.4, 25.5, 25.4, 19.0, 18.9; HRMS-ESI calcd for $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485; found 321.1477.

*2-((2,2-Difluoro-1,4-diphenylbut-3-yn-1-yl)oxy)tetrahydro-2H-pyran (**22**).* Ynone **21** (538 mg, 1.68 mmol) was charged into a polypropylene vial. DeoxoFluor (0.77 mL, 4.2 mmol) was added and the mixture was stirred at 55 °C for 24 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (171 mg) was isolated as a yellow oil by flash chromatography using 5% Et_2O/hexanes, but could not be separated from impurities. The product was thus used as is in the subsequent THP removal step and the yield was determined over two steps.

*2,2-Difluoro-1,4-diphenylbut-3-yn-1-ol (**1c**).* PPTS (42 mg, 0.17 mmol) was added to a solution of semi-pure propargylic fluoride **22** (171 mg) in MeOH (8 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room

temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (84 mg, 19%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 3352, 3036, 2241, 1491, 1338, 1153, 1086, 1047, 752, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.57-7.55 (m, 2H), 7.44-7.32 (m, 6H), 7.34 (t, 2H, *J* = 7.4 Hz), 5.05 (ddd, 1H, *J* = 9.6, 7.6, 4.0 Hz), 2.71 (d, 1H, *J* = 4.0 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -93.0 (dd, 1F, *J* = 273, 7.2 Hz), -94.1 (dd, 1F, *J* = 274, 9.8 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.4 (m), 132.3 (t, *J* = 2.4 Hz), 130.2, 129.3, 128.6, 128.4, 127.9, 120.0 (t, *J* = 2.7 Hz), 114.4 (t, *J* = 238 Hz), 89.8 (t, *J* = 6.9 Hz), 79.4 (t, *J* = 39.2 Hz), 76.7 (dd, *J* = 30.5, 28.6 Hz).; HRMS-ESI calcd for $C_{16}H_{11}F_2$ $[M+H]^+$-$[H_2O]$ 241.0823; found 241.0830.

*4.2.4 Preparation of 2,2-difluorododec-3-yn-1-ol (**1d**).*

*1-((Tetrahydro-2H-pyran-2-yl)oxy)dodec-3-yn-2-ol (**23**).* To a -78 °C solution of 1-decyne (0.60 mL, 3.3 mmol) in THF (7 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 1.32 mL, 3.30 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **7** (433 mg, 3.00 mmol) in THF (3 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (400 mg, 43%) was isolated as a colorless oil by flash chromatography using 20% EtOAc/hexanes. IR (ATR, diamond) ν = 3427, 2924, 2854, 1454, 1202, 1122, 1030, 906, 810, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.65 (dd, 0.5H, *J* = 4.7, 3.0 Hz), 4.59 (dd, 0.5H, *J* = 5.3, 2.8 Hz), 4.54-4.50 (m, 1H), 3.97-3.92 (m, 1H),

3.82 (d, 0.5H, *J* = 3.0 Hz), 3.81 (d, 0.5H, *J* = 2.9 Hz), 3.69-3.61 (m, 1H), 3.56-3.51 (m, 1.5H), 3.00 (d, 0.5H, *J* = 5.5 Hz), 2.22-2.18 (m, 2H), 1.87-1.74 (m, 2H), 1.66-1.47 (m, 7H), 1.37-1.27 (m, 10H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 100.2, 100.1, 86.45, 86.47, 77.8, 77.4, 74.0, 73.0, 63.4, 62.8, 62.2, 31.8, 30.7, 30.6, 29.2, 29.1, 28.8, 28.5, 25.2, 25.1, 22.7, 19.9, 19.6, 18.72, 18.73, 14.1; HRMS-ESI calcd for $C_{17}H_{31}O_3$ $[M+H]^+$ 283.2268; found 283.2271.

*1-((Tetrahydro-2H-pyran-2-yl)oxy)dodec-3-yn-2-one (**24**).* To a -78 °C solution of oxalyl chloride (0.14 mL, 1.7 mmol) in CH_2Cl_2 (12 mL) was added DMSO (0.24 mL, 3.34 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of propargylic alcohol **23** (393 mg, 1.39 mmol) in CH_2Cl_2 (2 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (1.16 mL, 8.35 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (328 mg, 81%) was isolated as a colorless oil by flash chromatography using 15% EtOAc/hexanes. IR (ATR, diamond) ν = 2926, 2854, 2208, 1691, 1674, 1263, 1132, 1038, 905, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.72 (t, 1H, *J* = 3.4 Hz), 4.33 (s, 1H), 3.85 (ddd, 1H, *J* = 11.7, 9.3, 3.1 Hz), 3.53 (dtd, 1H, *J* = 11.3, 4.3, 1.7 Hz), 2.38 (t, 2H, *J* = 7.1 Hz), 1.91-1.83 (m, 1H), 1.78-1.72 (m, 2H), 1.65-1.52 (m, 5H), 1.40 (p, 2H, *J* = 6.7 Hz), 1.33-1.27 (m, 8H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 185.1, 98.4, 97.6, 78.9, 72.6, 62.2, 31.9, 30.2, 29.2, 29.1, 29.0, 27.7, 25.4, 22.8, 19.2, 19.0, 14.2; HRMS-ESI calcd for $C_{17}H_{29}O_3$ [M+H]+ 281.2111; found 281.2101.

*2-((2,2-Difluorododec-3-yn-1-yl)oxy)tetrahydro-2H-pyran (**25**).* Ynone **24** **(**321 mg, 1.14 mmol) was charged into a polypropylene vial. DeoxoFluor (0.53 mL, 2.9 mmol) was added and the mixture was stirred at 55 °C for 24 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (192 mg, 55%) was isolated as a yellow oil by flash chromatography using 5% Et_2O/hexanes. IR (ATR, diamond) ν = 2928, 2856, 2253, 1456, 1300, 1128, 1076, 1038, 906, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.79 (t, 1H, *J* = 3.2 Hz), 3.93 (td, 1H, *J* = 12.8, 11.8 Hz), 3.86 (dddd, 1H, *J* = 11.1, 9.5, 2.7, 0.5 Hz), 3.78 (q, 1H, *J* = 12.0 Hz), 3.55 (dtd, 1H, *J* = 11.3, 4.1, 1.8 Hz), 2.28 (tt, 2H, *J* = 7.2, 5.2 Hz), 1.91-1.82 (m, 1H), 1.74-1.71 (m, 1H), 1.66-1.51 (m, 5H), 1.41-1.36 (m, 2H), 1.32-1.24 (m, 8H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -91.0 (m, 2F); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 112.4 (t, $J_{C\text{-}F}$ = 233.4 Hz), 98.7, 90.3 (t, $J_{C\text{-}F}$ = 6.7 Hz), 72.6 (t, $J_{C\text{-}F}$ = 38.4 Hz), 69.1 (t, $J_{C\text{-}F}$ = 31.2 Hz), 61.9, 31.9, 30.2, 29.3, 29.1, 28.9, 27.8 (t, $J_{C\text{-}F}$ = 1.9 Hz), 25.4, 22.8, 18.8, 18.6 (t, $J_{C\text{-}F}$ = 2.3 Hz), 14.2; HRMS-ESI calcd for $C_{17}H_{32}F_2NO_2$ $[M+NH_4]^+$ 320.2396; found 320.2390.

*2,2-Difluorododec-3-yn-1-ol (**1d**).* PPTS (15 mg, 0.059 mmol) was added to a solution of propargylic fluoride **25** (179 mg, 0.592 mmol) in MeOH (5.9 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (124 mg, 96%) was isolated as a pale yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 3360, 2928, 2856, 2253, 1468, 1298, 1219, 1063,

908, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.85 (tdt, 2H, *J* = 12.1, 7.4 Hz), 2.29 (tt, 2H, *J* = 7.2, 5.2 Hz), 1.99 (tdt, 1H, *J* = 7.4, 1.8, 0.9 Hz), 1.59-1.53 (m, 2H), 1.41-1.26 (m, 10H), 0.88 (t, 3H, *J* = 7.0 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -93.9 (m, 2F); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 112.7 (t, J_{C-F} = 233 Hz) 91.2 (t, J_{C-F} = 6.7 Hz), 71.9 (t, J_{C-F} = 38.9 Hz), 66.4 (t, J_{C-F} = 31.7 Hz), 31.9, 29.2, 29.1, 28.9, 27.8 (t, J_{C-F} = 1.9 Hz), 22.8, 18.6 (t, J_{C-F} = 2.4 Hz), 14.2; HRMS-ESI calcd for $C_{12}H_{24}F_2NO$ $[M+NH_4]^+$ 236.1820; found 236.1799.

*4.2.5 Preparation of 3,3-difluorotridec-4-yn-2-ol (**1e**).*

*2-((Tetrahydro-2H-pyran-2-yl)oxy)tridec-4-yn-3-ol (**26**).* To a -78 °C solution of 1-decyne (0.60 mL, 3.3 mmol) in THF (7 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 1.32 mL, 3.30 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **13** (475 mg, 3.00 mmol) in THF (3 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The formation of the 4 possible pairs of diastereoisomers was confirmed by NMR analysis of the crude reaction mixture. The crude reaction mixture was used as is in the subsequent oxidation step with the transformation being considered quantitative.

*2-((Tetrahydro-2H-pyran-2-yl)oxy)tridec-4-yn-3-one (**27**).* To a -78 °C solution of oxalyl chloride (0.31 mL, 3.6 mmol) in CH_2Cl_2 (25 mL) was added DMSO (0.51 mL, 7.2 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of crude propargylic alcohol **26** (assumed to be quantitative, 3.00 mmol) in CH_2Cl_2 (5 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (2.51 mL, 18.0 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach

room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (564 mg, 64%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes.IR (ATR, diamond) ν = 2926, 2854, 2206, 1676, 1456, 1202, 1124, 1020, 984, 874 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.78 (t, 0.5H, *J* = 3.5 Hz), 4.68 (t, 0.5H, *J* = 3.6 Hz), 4.40 (q, 0.5H, *J* = 7.1 Hz), 4.21 (q, 1H, *J* = 6.8 Hz), 3.95 (ddd, 0.5H, *J* = 11.9, 9.3, 3.2 Hz), 3.87 (ddd, 0.5H, *J* = 11.0, 7.9, 3.1 Hz), 3.53-3.46 (m, 1H), 2.40 (q, 2H, *J* = 6.8 Hz), 1.92-1.53 (m, 8H), 1.46-1.37 (m, 5H), 1.31-1.23 (m, 8H), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 189.6, 188.6, 98.03, 97.99, 97.6, 97.4, 79.3, 79.1, 78.1, 77.2, 62.6, 62.2, 31.80, 31.78, 30.5, 30.4, 29.11, 29.10, 29.01, 28.98, 28.9, 27.70, 27.65, 25.4, 22.6, 19.3, 19.2, 19.1, 19.0, 18.0, 16.8, 14.1; HRMS-ESI calcd for $C_{18}H_{31}O_3$ $[M+H]^+$ 295.2268; found 295.2262.

*2-((3,3-Difluorotridec-4-yn-2-yl)oxy)tetrahydro-2H-pyran (**28**).* Ynone **27** (557 mg, 1.89 mmol) was charged into a polypropylene vial. DeoxoFluor (0.87 mL, 4.7 mmol) was added and the mixture was stirred at 55 °C for 24 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (306 mg, 51%) was isolated as a yellow oil by flash chromatography using 5% Et_2O/hexanes. IR (ATR, diamond) ν = 2928, 2856, 2253, 1456, 1340, 1223, 1124, 978, 910, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.82 (t, 0.7H, *J* = 3.7 Hz), 4.82 (t, 0.3H, *J* = 3.1 Hz), 410-3.95 (m, 1.3H), 3.90 (ddd, 0.7H, *J* = 11.4, 8.0, 3.1 Hz), 3.55-3.50 (m, 1H), 2.30-2.26 (m, 2H), 1.88-1.52 (m, 8H), 1.39-1.27 (m, 13H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ

-92.6 (ddt, 0.3F, J = 272, 9.7, 4.8 Hz), -92.8 (dm, 0.7F, J = 273 Hz), -93.4 (dm, 0.3F, J = 272 Hz), -93.8 (ddt, 0.7F, J = 273, 9.8, 4.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 114.8 (t, $J_{C\text{-}F}$ = 236 Hz), 114.1 (t, $J_{C\text{-}F}$ = 235 Hz), 100.1, 94.5, 90.4 (t, $J_{C\text{-}F}$ = 6.6 Hz), 90.0 (t, $J_{C\text{-}F}$ = 6.7 Hz), 74.8 (dd, $J_{C\text{-}F}$ = 29.0, 27.3 Hz), 72.4 (dd, $J_{C\text{-}F}$ = 77.0, 31.0 Hz), 72.2 (dd, $J_{C\text{-}F}$ = 59.2, 29.7 Hz) 62.7, 61.4, 31.9, 30.6, 30.5, 29.3, 29.1, 29.1, 28.9, 27.9, 25.6, 25.5, 22.8, 19.4, 18.6 (m), 16.1 (t, $J_{C\text{-}F}$ = 2.6 Hz), 14.2, 13.3 (t, $J_{C\text{-}F}$ = 2.5 Hz); HRMS-ESI calcd for $C_{18}H_{34}F_2NO_2$ $[M+NH_4]^+$ 334.2552; found 334.2528.

*3,3-Difluorotridec-4-yn-2-ol (**1e**).* PPTS (23.6 mg, 0.094 mmol) was added to a solution of propargylic fluoride **28** (297 mg, 0.939 mmol) in MeOH (9.4 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (157 mg, 72%) was isolated as a pale yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 3389, 2928, 2856, 2253, 1456, 1352, 1223, 1051, 906, 735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.98 (dq, 1H, J = 10.1, 6.3 Hz), 2.30 (tt, 2H, J = 7.2, 5.1 Hz), 2.08 (bs, 1H), 1.57 (p, 2H, J = 7.2 Hz), 1.42-1.24 (m, 13H), 0.88 (t, 3H, J = 6.9 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -94.9 (dm, 1F, J = 271 Hz), -96.1 (ddt, 1F, J = 271, 10.0, 5.0 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 114.9 (t, $J_{C\text{-}F}$ = 235 Hz), 91.3 (t, $J_{C\text{-}F}$ = 6.6 Hz), 71.4 (t, $J_{C\text{-}F}$ = 39.3 Hz), 70.7 (dd, $J_{C\text{-}F}$ = 30.9, 28.6 Hz), 31.9, 29.2, 29.1, 28.9, 27.9 (t, $J_{C\text{-}F}$ = 2.0 Hz), 22.8, 18.6 (t, $J_{C\text{-}F}$ = 2.4 Hz), 16.4 (t, $J_{C\text{-}F}$ = 2.4 Hz), 14.2.; HRMS-ESI calcd for $C_{13}H_{26}F_2NO$ $[M+NH_4]^+$ 250.1977; found 250.1960.

*4.2.6 Preparation of 2,2-difluoro-1-phenyldodec-3-yn-1-ol (**1f**).*

1-Phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)dodec-3-yn-2-ol ***(29)***. To a -78 °C solution of 1-decyne (0.60 mL, 3.30 mmol) in THF (7 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 1.32 mL, 3.30 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **19** (661 mg, 3.00 mmol) in THF (3 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The formation of the 4 possible pairs of diastereoisomers was confirmed by NMR analysis of the crude reaction mixture. The crude reaction mixture was used as is in the subsequent oxidation step with the transformation being considered quantitative.

1-Phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)dodec-3-yn-2-one ***(30)***. To a -78 °C solution of oxalyl chloride (0.31 mL, 3.6 mmol) in CH_2Cl_2 (25 mL) was added DMSO (0.51 mL, 7.2 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of crude propargylic alcohol **29** (assumed to be quantitative, 3.00 mmol) in CH_2Cl_2 (5 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (2.51 mL, 18.0 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (584 mg, 55%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 2926, 2854, 2210, 1676, 1452, 1202, 1121, 1036, 908, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48 (d, 0.8H, J = 7.0 Hz), 7.42 (d, 1.2H, J

= 6.5 Hz), 7.38-7.33 (m, 3H), 5.31 (s, 0.4H), 5.23 (s, 0.6H), 4.89 (t, 0.4H, *J* = 3.2 Hz), 4.61 (t, 0.6H, *J* = 3.4 Hz), 3.98 (m, 0.6H), 3.70 (m, 0.4H), 3.56-3.46 (m, 1H), 2.35-2.31 (m, 2H), 1.99-1.48 (m, 8H), 1.35-1.26 (m, 10H), 0.89 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 186.8, 184.8, 135.9, 135.6, 128.84, 128.76, 128.65, 128.58, 128.2, 127.8, 99.3, 98.8, 97.4, 96.1, 83.3, 82.9, 79.5, 79.4, 62.2, 62.1, 32.0, 31.9, 30.4, 29.3, 29.2, 29.15, 29.13, 28.9, 27.71, 27.69, 25.5, 25.4, 22.8, 19.30, 19.27, 19.0, 18.9, 14.2; HRMS-ESI calcd for $C_{23}H_{33}O_3$ $[M+H]^+$ 357.2424; found 357.2402.

*2-((2,2-Difluoro-1-phenyldodec-3-yn-1-yl)oxy)tetrahydro-2H-pyran (**31**).* Ynone **30** (576 mg, 1.62 mmol) was charged into a polypropylene vial. DeoxoFluor (0.75 mL, 4.0 mmol) was added and the mixture was stirred at 55 °C for 24 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (154 mg) was isolated as a yellow oil by flash chromatography using 5% Et_2O/hexanes, but could not be separated from impurities. The product was thus used as is in the subsequent THP removal step and the yield was determined over two steps.

*2,2-Difluoro-1-phenyldodec-3-yn-1-ol (**1f**).* PPTS (41 mg, 0.16 mmol) was added to a solution of semi-pure propargylic fluoride **31** (154 mg) in MeOH (8 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (111 mg, 23%) was isolated as an orange oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 3416, 2926, 2856, 2253, 1456, 1335, 1198, 1051,

847, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50-7.48 (m, 2H), 7.40-7.35 (m, 3H), 4.92 (td, 1H, *J* = 8.8, 4.0 Hz), 2.61 (d, 1H, *J* = 4.1 Hz), 2.23 (tt, 2H, *J* = 7.1, 5.2 Hz), 1.48 (p, 2H, *J* = 7.2 Hz), 1.31-1.23 (m, 10H), 0.89 (t, 3H, *J* = 6.9 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -91.9 (dq, 1F, *J* = 270, 5.7 Hz), -92.8 (ddt, 1F, *J* = 271, 9.7, 5.1 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 135.5 (t, J_{C-F} = 2.1 Hz), 129.1, 128.2, 127.9, 113.9 (t, J_{C-F} = 237 Hz), 92.3 (t, J_{C-F} = 6.6 Hz), 76.6 (t, J_{C-F} = 29.7), 71.5 (t, J_{C-F} = 38.7 Hz), 31.9, 29.2, 29.1, 28.8, 27.7 (t, J_{C-F} = 1.9 Hz), 22.8, 18.6 (t, J_{C-F} = 2.3 Hz), 14.3; HRMS-ESI calcd for $C_{18}H_{28}F_2NO$ $[M+NH_4]^+$ found 312.2133; found 312.2110.

*4.2.7 Preparation of 2,2-difluoro-1-phenylbut-3-yn-1-ol (**1g**).*

*1-Phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)but-3-yn-2-ol (**32**).* To a 0 °C solution of aldehyde **19** (740 mg, 3.36 mmol) in Et_2O (6.7 mL) was slowly added ethynylmagnesium bromide (0.5 M in THF, 8.1 mL, 4.0 mmol), and the resulting mixture was stirred at 0 °C for 30 minutes, and then at room temperature for 2 hours. Saturated NH_4Cl was added and the mixture was extracted with Et_2O (3x), washed with brine (1x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The formation of the 4 possible pairs of diastereoisomers was confirmed by NMR analysis of the crude reaction mixture. The crude reaction mixture was used as is in the subsequent oxidation step with the transformation being considered quantitative.

*1-Phenyl-1-((tetrahydro-2H-pyran-2-yl)oxy)but-3-yn-2-one (**33**).* To a 30 °C solution of crude propargylic alcohol **32** (assumed to be quantitative, 3.36 mmol) in THF (5.4 mL) and DMSO (21.5 mL) was added 2-iodoxybenzoic acid (IBX, 2.82 g, 10.1 mmol). The resulting mixture was stirred at 30 °C for 18 hours, after which water was added and stirring was continued for 10 minutes. The suspension was filtered to remove the solids. It

was then extracted with Et_2O, washed with brine (1x), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The desired product (460 mg, 56%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 3358, 2943, 2872, 2098, 1684, 1452, 1119, 1022, 966, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.49-7.35 (m, 5H), 5.36 (s, 0.3H), 5.26 (s, 0.7H), 4.89 (t, 0.3H, *J* = 3.1 Hz), 4.63 (t, 0.7H, *J* = 3.5 Hz), 3.96 (ddd, 0.7H, *J* = 11.7, 8.5, 3.8 Hz), 3.69 (ddd, 0.3H, *J* = 11.1, 9.7, 3.2 Hz), 3.54 (m, 0.7H), 3.48 (m, 0.3H), 3.31 (s, 0.7H), 3.30 (s, 0.3H), 1.99-1.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 186.2, 184.2, 135.0, 134.7, 129.1, 128.93, 128.89, 128.8, 128.1, 127.8, 97.5, 96.6, 83.3, 82.7, 82.31, 82.30, 79.9, 79.8 62.5, 62.1, 30.34, 30.30, 25.42, 25.36, 19.1, 18.8; HRMS-ESI calcd for $C_{15}H_{17}O_3$ $[M+H]^+$ 245.1172; found 245.1156.

*2-((2,2-Difluoro-1-phenylbut-3-yn-1-yl)oxy)tetrahydro-2H-pyran (**34**).* Ynone **33** (446 mg, 1.82 mmol) was charged into a polypropylene vial. DeoxoFluor (0.84 mL, 4.6 mmol) was added and the mixture was stirred at 55 °C for 24 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (173 mg) was isolated as a yellow oil by flash chromatography using 10% Et_2O/hexanes, but could not be separated from impurities. The product was thus used as is in the subsequent THP removal step and the yield was determined over two steps.

*2,2-Difluoro-1-phenylbut-3-yn-1-ol (**1g**).* PPTS (47 mg, 0.183 mmol) was added to a solution of semi-pure propargylic fluoride **34** (173 mg) in MeOH (8 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with

CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (83 mg, 25%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 3414, 3296, 3038, 2135, 1456, 1167, 1047, 851, 696, 623 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.51-7.49 (m, 2H), 7.42-7.38 (m, 3H), 4.96 (td, 1H, *J* = 8.9, 4.1 Hz), 2.80 (t, 1H, *J* = 5.1 Hz), 2.66 (d, 1H, *J* = 4.1 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -94.5 (ddd, 1F, *J* = 278, 9.9, 4.7 Hz), -95.3 (ddd, 1F, *J* = 278, 8.0, 5.2 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 134.9 (t, J_{C-F} = 2.0 Hz), 129.4, 128.4, 127.9 (t, J_{C-F} = 1.1 Hz), 113.2 (t, J_{C-F} = 239 Hz), 78.2 (t, J_{C-F} = 6.7 Hz), 76.2 (t, J_{C-F} = 28.9 Hz), 74.3 (t, J_{C-F} = 39.3 Hz).; HRMS-ESI calcd for $C_{10}H_7F_2$ $[M+H]^+$-$[H_2O]$ 165.0510; found 165.0502.

*4.2.8 Preparation of 3,3-difluoro-5-phenylpent-4-yn-1-ol (**1h**).*

*3-((Tetrahydro-2H-pyran-2-yl)oxy)propan-1-ol (**35**).* Propane-1,3-diol (3.26 mL, 45.0 mmol) was dissolved in CH_2Cl_2 (92 mL) and pyridinium *p*-toluenesulfonate (113 mg, 0.450 mmol) was added. A solution of 3,4-dihydro-2*H*-pyran (2.74 mL, 30.0 mmol) in CH_2Cl_2 (22 mL) was then added dropwise over 1 hour. The resulting mixture was stirred at room temperature for 18 hours, after which H_2O was added. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (3.28 g, 70%) was isolated as a pale yellow oil by flash chromatography using 5% MeOH/CH_2Cl_2. Spectroscopic data was in agreement with the literature [18].

*3-((Tetrahydro-2H-pyran-2-yl)oxy)propanal (**36**).* To a -78 °C solution of oxalyl chloride (2.17 mL, 25.3 mmol) in CH_2Cl_2 (190 mL) was added DMSO (3.59 mL, 50.5 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of alcohol **35** (3.37 g, 21.1 mmol) in CH_2Cl_2 (20 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (17.6 mL, 126 mmol) was added, the solution was stirred

at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (2.84 g, 85%) was isolated as a yellow oil by flash chromatography using 15% acetone/hexanes. Spectroscopic data was in agreement with the literature [19].

*1-Phenyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-1-yn-3-ol (**37**).* To a -78 °C solution of phenylacetylene (2.15 mL, 19.6 mmol) in THF (50 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 7.85 mL, 19.6 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **36** (2.82 g, 17.8 mmol) in THF (9 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (4.12 g, 89%) was isolated as a yellow oil by flash chromatography using 20% EtOAc/hexanes. Spectroscopic data was in agreement with the literature [20].

*1-Phenyl-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-1-yn-3-one (**38**).* To a -78 °C solution of oxalyl chloride (1.61 mL, 18.8 mmol) in CH_2Cl_2 (140 mL) was added DMSO (2.66 mL, 37.5 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of propargylic alcohol **37** (4.07 g, 15.6 mmol) in CH_2Cl_2 (16 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (13.1 mL, 93.8 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for

30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (3.56 g, 88%) was isolated as a yellow oil by flash chromatography using 15% EtOAc/hexanes. IR (ATR, diamond) ν = 2941, 2199, 1666, 1489, 1283, 1121, 1028, 870, 758, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, 2H, *J* = 7.4 Hz), 7.46 (t, 1H, *J* = 7.5 Hz), 7.39 (t, 2H, *J* = 7.6 Hz), 4.67 (t, 1H, *J* = 3.4 Hz), 4.16 (td, 1H, *J* = 10.3, 6.1 Hz), 3.91-3.82 (m, 2H), 3.52 (dt, 1H, *J* = 10.5, 4.6 Hz), 2.96 (t, 2H, *J* = 6.1 Hz), 1.84-1.77 (m, 1H), 1.72-1.66 (m, 1H), 1.60-1.49 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 185.9, 133.2, 130.9, 128.8, 120.0, 99.1, 91.3, 87.9, 62.4, 62.2, 45.8, 30.6, 25.5, 19.4; HRMS-ESI calcd for $C_{16}H_{19}O_3$ $[M+H]^+$ 259.1329; found 259.1325.

*2-((3,3-Difluoro-5-phenylpent-4-yn-1-yl)oxy)tetrahydro-2H-pyran (**39**).* Ynone **38** (3.38 g, 13.1 mmol) was charged into a polypropylene vial. DeoxoFluor (6.03 mL, 32.7 mmol) was added and the mixture was stirred at 55 °C for 18 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (1.04 g, 28%) was isolated as a pale yellow oil by flash chromatography using 5% Et_2O/hexanes. IR (ATR, diamond) ν = 2943, 2874, 2239, 1491, 1317, 1124, 1024, 972, 756, 687 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.50 (d, 2H, *J* = 7.4 Hz), 7.41 (t, 1H, *J* = 7.3 Hz), 7.36 (t, 2H, *J* = 7.5 Hz), 4.65 (t, 1H, *J* = 3.6 Hz), 4.05 (dt, 1H, *J* = 10.4, 7.0 Hz), 3.89 (ddd, 1H, *J* = 11.3, 8.5, 2.9 Hz), 3.71 (dt, 1H, *J* = 10.2, 6.9 Hz), 3.52 (dt, 1H, *J* = 10.3, 4.5 Hz), 2.51 (ttd, 2H, *J* = 14.4, 7.0, 2.7 Hz), 1.86-1.78 (m, 1H), 1.74-1.68 (m, 1H), 1.62-1.48 (m, 4H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -80.9 (t, 1F, *J* = 14.2 Hz); ^{13}C NMR ($CDCl_3$, 126

MHz) δ 132.2 (t, $J_{C\text{-}F}$ = 2.3 Hz), 130.0, 128.6, 120.3 (t, $J_{C\text{-}F}$ = 2.8 Hz), 114.1 (t, $J_{C\text{-}F}$ = 233 Hz), 99.0, 87.1 (t, $J_{C\text{-}F}$ = 6.7 Hz), 81.5 (t, $J_{C\text{-}F}$ = 40.3 Hz), 62.2, 61.7 (t, $J_{C\text{-}F}$ = 4.7 Hz), 39.8 (t, $J_{C\text{-}F}$ = 26.5 Hz), 30.6, 25.5, 19.4.; HRMS-ESI calcd for $C_{16}H_{18}F_2NaO_2$ $[M+Na]^+$ 303.1167; found 303.1161.

*3,3-Difluoro-5-phenylpent-4-yn-1-ol (**1h**).* PPTS (89 mg, 0.356 mmol) was added to a solution of propargylic fluoride **39** (997 mg, 3.56 mmol) in MeOH (36 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (672 mg, 96%) was isolated as a colorless oil by flash chromatography using 20% EtOAc/hexanes. IR (ATR, diamond) ν = 3344, 2972, 2897, 2239, 1319, 1163, 1078, 970, 754, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, 2H, *J* = 7.1 Hz), 7.42 (t, 1H, *J* = 7.4 Hz), 7.36 (t, 2H, *J* = 7.4 Hz), 3.99 (q, 2H, *J* = 5.9 Hz), 2.47 (tt, 2H, *J* = 14.7, 6.2 Hz), 1.75 (t, 2H, *J* = 5.8 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -80.8 (t, 2F, *J* = 14.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 132.3 (t, $J_{C\text{-}F}$ = 2.4 Hz), 130.2, 128.7, 120.0 (t, $J_{C\text{-}F}$ = 2.8 Hz), 114.6 (t, $J_{C\text{-}F}$ = 233 Hz), 87.6 (t, $J_{C\text{-}F}$ = 6.8 Hz), 81.3 (t, $J_{C\text{-}F}$ = 40.1 Hz), 57.5 (t, $J_{C\text{-}F}$ = 4.4 Hz), 42.3 (t, $J_{C\text{-}F}$ = 25.4 Hz); HRMS-ESI calcd for $C_{11}H_{10}FO$ $[M-F]^+$ 177.0710; found 177.0726.

*4.2.9 Preparation of 4,4-difluoro-6-phenylhex-5-yn-1-ol (**1i**).*

*4-((Tetrahydro-2H-pyran-2-yl)oxy)butan-1-ol (**40**).* Butane-1,4-diol (589 mg, 6.54 mmol) was dissolved in CH_2Cl_2 (12 mL) and pyridinium *p*-toluenesulfonate (25 mg, 0.098 mmol) was added. A solution of 3,4-dihydro-2*H*-pyran (0.60 mL, 6.54 mmol) in CH_2Cl_2 (4 mL) was then added dropwise over 1 hour. The resulting mixture was stirred at room temperature for 18 hours, after which H_2O was added. The organic layer was separated,

washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (545 mg, 48%) was isolated as a pale yellow oil by flash chromatography using 5% MeOH/CH_2Cl_2. Spectroscopic data was in agreement with the literature [21].

*4-((Tetrahydro-2H-pyran-2-yl)oxy)butanal (**41**).* To a -78 °C solution of oxalyl chloride (0.32 mL, 3.75 mmol) in CH_2Cl_2 (25 mL) was added DMSO (0.53 mL, 7.5 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of alcohol **40** (545 mg, 3.13 mmol) in CH_2Cl_2 (6 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (2.62 mL, 18.8 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (473 mg, 88%) was isolated as a colorless oil by flash chromatography using 15% acetone/hexanes. Spectroscopic data was in agreement with the literature [22].

*1-Phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)hex-1-yn-3-ol (**42**).* To a -78 °C solution of phenylacetylene (0.33 mL, 3.0 mmol) in THF (7 mL) was added *n*-BuLi (2.5 mol/L in hexanes, 1.21 mL, 3.0 mmol) and the mixture was stirred at -78 °C for 30 minutes, and then at room temperature for 30 minutes. The solution was brought back to -78 °C and a solution of aldehyde **41** (473 mg, 2.75 mmol) in THF (2 mL) was added. The mixture was stirred at room temperature for 1 hour, after which saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (477 mg, 63%) was isolated as a brown oil by flash chromatography using 20% EtOAc/hexanes. IR (ATR, diamond) ν = 3396, 2941, 2870, 1489, 1202, 1136, 1072, 1020, 905, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.44-

7.42 (m, 2H), 7.31-7.29 (m, 3H), 4.68-4.63 (m, 2H), 3.90-3.81 (m, 2H), 3.54-3.46 (m, 2H), 2.92-2.88 (m, 1H), 1.99-1.90 (m, 3H), 1.87-1.81 (m, 2H), 1.76-1.70 (m, 1H), 1.65-1.51 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 131.68 (2), 131.7, 128.31, 128.26, 128.25, 122.75, 122.74, 98.8, 98.7, 90.1, 84.8, 84.7, 67.3, 67.2, 62.67, 62.66, 62.26, 62.27, 35.34, 35.32, 30.6, 30.5, 25.6, 25.5, 25.4, 19.4; HRMS-ESI calcd for $C_{17}H_{23}O_3$ $[M+H]^+$ 275.1642; found 275.1640.

*1-Phenyl-6-((tetrahydro-2H-pyran-2-yl)oxy)hex-1-yn-3-one (**43**).* To a -78 °C solution of oxalyl chloride (0.18 mL, 2.1 mmol) in CH_2Cl_2 (14 mL) was added DMSO (0.29 mL, 4.1 mmol) and stirring was continued at -78 °C for 15 minutes. A solution of propargylic alcohol **42** (468 mg, 1.71 mmol) in CH_2Cl_2 (3 mL) was slowly added and the resulting solution was stirred at -78 °C for 15 minutes. Et_3N (1.43 mL, 10.2 mmol) was added, the solution was stirred at -78 °C for 20 minutes, and then allowed to reach room temperature over 40 minutes. Saturated $NaHCO_3$ was added and stirring was continued for 30 minutes. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (378 mg, 81%) was isolated as a yellow oil by flash chromatography using 10% EtOAc/hexanes. IR (ATR, diamond) ν = 2939, 2870, 2201, 1668, 1489, 1261, 1119, 1032, 758, 689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, 2H, *J* = 7.2 Hz), 7.46 (t, 1H, *J* = 7.5 Hz), 7.39 (t, 2H, *J* = 7.5 Hz), 4.59 (dd, 1H, *J* = 4.5, 2.9 Hz), 3.86 (ddd, 1H, *J* = 11.5, 8.2, 3.4 Hz), 3.81 (dt, 1H, *J* = 9.7, 6.4 Hz), 3.53-3.44 (m, 2H), 2.80 (td, 2H, *J* = 7.2, 3.2 Hz), 2.05 (p, 2H, *J* = 6.8 Hz), 1.87-1.79 (m, 1H), 1.74-1.68 (m, 1H), 1.61-1.50 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 187.8, 133.2, 130.8, 128.7, 120.1, 99.0, 90.8, 87.9, 66.4, 62.4, 42.6, 30.8, 25.6, 24.5, 19.7; HRMS-ESI calcd for $C_{17}H_{21}O_3$ $[M+H]^+$ 273.1485; found 273.1472.

*2-((4,4-Difluoro-6-phenylhex-5-yn-1-yl)oxy)tetrahydro-2H-pyran (**44**).* Ynone **43** (370 mg, 1.36 mmol) was charged into a polypropylene vial. DeoxoFluor (0.63 mL, 3.4 mmol) was added and the mixture was stirred at 55 °C for 24 hours. It was brought back to 0 °C, diluted with EtOAc and poured into a stirring mixture of EtOAc and saturated $NaHCO_3$. The mixture was stirred for 30 minutes, after which the organic layer was separated, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired compound (164 mg, 41%, contaminated with ca. 7% of elimination side product) was isolated as a yellow oil by flash chromatography using 10% Et_2O/hexanes. IR (ATR, diamond) ν = 2941, 2872, 2241, 1491, 1323, 1121, 1032, 978, 756, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, 2H, *J* = 7.0 Hz), 7.41 (t, 1H, *J* = 7.4 Hz), 7.36 (t, 2H, *J* = 7.3 Hz), 4.60 (tt, 1H, *J* = 4.4, 2.9 Hz), 3.88-3.81 (m, 2H), 3.53-3.47 (m, 2H), 2.31-2.21 (m, 2H), 1.97-1.91 (m, 2H), 1.86-1.80 (m, 1H), 1.75-1.69 (m, 2H), 1.60-1.51 (m, 5H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -82.3 (t, 2F, *J* = 14.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 132.1 (t, $J_{C\text{-}F}$ = 2.1 Hz), 129.8, 128.5, 120.2 (t, $J_{C\text{-}F}$ = 2.7 Hz), 115.4 (t, $J_{C\text{-}F}$ = 232 Hz), 98.8, 86.7 (t, $J_{C\text{-}F}$ = 6.8 Hz), 81.6 (t, $J_{C\text{-}F}$ = 40.8 Hz), 66.2, 62.3, 36.5 (t, $J_{C\text{-}F}$ = 26.8 Hz), 30.7, 25.4, 23.5 (t, $J_{C\text{-}F}$ = 3.5 Hz), 19.6; HRMS-ESI calcd for $C_{17}H_{21}F_2O_2$ $[M+H]^+$ 295.1504; found 295.1487.

*4,4-Difluoro-6-phenylhex-5-yn-1-ol (**1i**).* PPTS (12.8 mg, 0.051 mmol) was added to a solution of propargylic fluoride **44** (150 mg, 0.510 mmol) in MeOH (5.1 mL). The resulting mixture was stirred at 50 °C for 18 hours, at which point it was brought back to room temperature and saturated $NaHCO_3$ was added. The resulting mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (69 mg, 64%, contaminated with ca. 7% of elimination side product) was isolated as a pale yellow oil by flash chromatography using 20% EtOAc/hexanes. IR (ATR,

diamond) ν = 3342, 2939, 2883, 2241, 1491, 1323, 1167, 989, 908, 731 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, 2H, *J* = 7.1 Hz), 7.41 (t, 1H, *J* = 7.4 Hz), 7.36 (t, 2H, *J* = 7.4 Hz), 3.76 (t, 2H, *J* = 6.4 Hz), 2.31-2.22 (m, 2H), 1.94-1.88 (m, 2H), 1.41 (bs, 1H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -82.2 (t, 2F, *J* = 14.8 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 132.2 (t, J_{C-F} = 2.3 Hz), 130.0, 128.6, 120.3 (t, J_{C-F} = 2.8 Hz), 115.4 (t, J_{C-F} = 232 Hz), 87.0 (t, J_{C-F} = 6.8 Hz), 81.6 (t, J_{C-F} = 40.7 Hz), 61.9, 36.1 (t, J_{C-F} = 26.9 Hz), 26.3 (t, J_{C-F} = 3.2 Hz); HRMS-ESI calcd for $C_{12}H_{16}F_2NO$ $[M+NH_4]^+$ 228.1194; found 228.1177.

4.3 Cyclization of gem-difluorinated alkynols

*4.3.1 3,3-Difluoro-5-phenyl-2,3-dihydrofuran (**2a**).* Chloro(triphenylphosphine) gold(I) (0.8 mg, 0.0016 mmol, 1 mol%), silver trifluoromethanesulfonate (0.4 mg, 0.0016 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1a** (30 mg, 0.165 mmol) in THF (1.65 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 100% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (25.3 mg, 0.1631 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -82.2 (t, 2F, *J* = 16.9 Hz, 0.1652 mmol, 100%).

*4.3.2 3,3-Difluoro-2-methyl-5-phenyl-2,3-dihydrofuran (**2b**).* Chloro(triphenylphosphine) gold(I) (0.8 mg, 0.0015 mmol, 1 mol%), silver trifluoromethanesulfonate (0.4 mg, 0.0015 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1b** (30

mg, 0.153 mmol) in THF (1.53 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 92% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (29.0 mg, 0.1869 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -83.5 (dd, 1F, *J* = 250, 19.9 Hz, 0.1414 mmol, 93%), -94.0 (dd, 1F, *J* = 250, 13.0 Hz, 0.1400 mmol, 92%).

*4.3.3 3,3-Difluoro-2,5-diphenyl-2,3-dihydrofuran (**2c**).* Chloro(triphenylphosphine) gold(I) (0.6 mg, 0.0012 mmol, 1 mol%), silver trifluoromethanesulfonate (0.3 mg, 0.0012 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1c** (30 mg, 0.116 mmol) in THF (1.16 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 78% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (19,.5 mg, 0.1257 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -81.7 (dd, 1F, *J* = 248, 19.2 Hz, 0.0904 mmol, 78%), -85.5 (dd, 1F, *J* = 248, 12.7 Hz, 0.0904 mmol, 78%).

*4.3.4 3,3-Difluoro-5-octyl-2,3-dihydrofuran (**2d**).* Chloro(triphenylphosphine) gold(I) (0.5 mg, 0.0011 mmol, 1 mol%), silver trifluoromethanesulfonate (0.3 mg, 0.0011 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1d** (30 mg, 0.102 mmol) in THF (1.02 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 97% was estimated by ^{19}F NMR

analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (20.0 mg, 0.1289 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -82.2 (m, 2F, 0.1334 mmol, 97%).

*4.3.5 3,3-Difluoro-2-methyl-5-octyl-2,3-dihydrofuran (**2e**).* Chloro(triphenylphosphine) gold(I) (0.6 mg, 0.0013 mmol, 1 mol%), silver trifluoromethanesulfonate (0.3 mg, 0.0013 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1e** (30 mg, 0.129 mmol) in THF (1.29 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 85% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (21.8 mg, 0.1405 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -83.3 (dd, 1F, J = 247, 20.3 Hz, 0.1198 mmol, 85%), -94.4 (dd, 1F, J = 247, 12.8 Hz, 0.1199 mmol, 85%).

*4.3.6 3,3-Difluoro-5-octyl-2-phenyl-2,3-dihydrofuran (**2f**).* Chloro(triphenylphosphine) gold(I) (0.5 mg, 0.0011 mmol, 1 mol%), silver trifluoromethanesulfonate (0.3 mg, 0.0011 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1f** (30 mg, 0.102 mmol) in THF (1.02 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 75% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (22.3 mg, 0.1438 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -81.9 (dd, 1F, J = 245, 20.0 Hz, 0.0739 mmol, 73%), -85.6 (dd, 1F, J = 245, 13.2 Hz, 0.0789 mmol, 77%).

*4.3.7 3,3-Difluoro-2-phenyl-2,3-dihydrofuran (**2g**).* Chloro(triphenylphosphine) gold(I) (0.8 mg, 0.0016 mmol, 1 mol%), silver trifluoromethanesulfonate (0.4 mg, 0.0016 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1g** (30 mg, 0.165 mmol) in THF (1.65 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 80% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (22.4 mg, 0.1444 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -94.0 (ddd, 1F, J = 277, 10.1, 5.1 Hz, 0.1361 mmol, 83%), -95.0 (dt, 1F, J = 277, 6.7 Hz, 0.1280 mmol, 78%).

*4.3.8 4,4-Difluoro-6-phenyl-3,4-dihydro-2H-pyran (**2h**).* Chloro(triphenylphosphine) gold(I) (0.8 mg, 0.0015 mmol, 1 mol%), silver trifluoromethanesulfonate (0.4 mg, 0.0015 mmol, 1 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1h** (30 mg, 0.153 mmol) in THF (1.53 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 1 hour. A sample was taken and a yield of 95% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (22.5 mg, 0.1450 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -86.9 (t, 2F, J = 12.4 Hz, 0.1446 mmol, 95%).

*4.3.9 5,5-Difluoro-7-phenyl-2,3,4,5-tetrahydrooxepine (**2i**).* Chloro(triphenylphosphine) gold(I) (0.6 mg, 0.0042 mmol, 5 mol%), silver trifluoromethanesulfonate (1.1 mg, 0.0042 mmol, 5 mol%) and 4 Å molecular sieve (10 mg) were charged into a glass vial. A magnetic

stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1i** (18 mg, 0.0842 mmol) in THF (0.84 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 18 hours. A sample was taken and a yield of 52% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (21.4 mg, 0.1379 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -92.1 (m, 2F, 0.0875 mmol, 52%).

4.4 Cyclization/aromatization of gem-difluorohomopropargylic alcohols

*4.4.1 4-Fluoro-2-phenylfuran (**4a**).* Chloro(triphenylphosphine) gold(I) (4.1 mg, 0.0082 mmol, 5 mol%) and silver trifluoromethanesulfonate (2.1 mg, 0.0082 mmol, 5 mol%) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1a** (30 mg, 0.165 mmol) in THF (1.65 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (16.9 mg, 63%) was isolated as a colorless oil by flash chromatography using hexanes. IR (ATR, diamond) ν = 3165, 3126, 3063, 1618, 1541, 1400, 1225, 993, 903, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, 2H, J = 7.4 Hz), 7.41-7.37 (m, 3H), 7.29 (t, 1H, J = 7.4 Hz), 6.57 (s, 1H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -168.6 (d, 1F, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.7 (d, $J_{C\text{-}F}$ = 249 Hz), 152.5 (d, $J_{C\text{-}F}$ = 7.7 Hz), 130.5 (d, $J_{C\text{-}F}$ = 2.3 Hz), 128.9, 128.2, 125.6 (d, $J_{C\text{-}F}$ = 29.5 Hz), 123.9, 97.6 (d, $J_{C\text{-}F}$ = 20.0 Hz); In all conditions tested (HRMS-ESI, HRMS-APPI, GC/MS-EI and GC/MS-CI), no fragment originating from **4a** could be identified.

*4.4.2 3-Fluoro-2-methyl-5-phenylfuran (**4b**).* Chloro(triphenylphosphine) gold(I) (3.8 mg, 0.0076 mmol, 5 mol%) and silver trifluoromethanesulfonate (2.1 mg, 0.0076 mmol, 5 mol%) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1b** (30 mg, 0.153 mmol) in THF (1.53 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (17.3 mg, 72%) was isolated as a pale yellow oil by flash chromatography using hexanes. IR (ATR, diamond) ν = 3132, 3063, 2922, 1657, 1489, 1429, 1313, 1182, 1136, 924 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, 2H, J = 6.9 Hz), 7.36 (t, 2H, J = 7.8 Hz), 7.24 (t, 1H, J = 7.4 Hz), 6.50 (d, 1H, J = 1.6 Hz), 2.32 (d, 3H, J = 2.1 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -172.3 (s, 1F); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.0 (d, J_{C-F} = 244 Hz), 149.3 (d, J_{C-F} = 8.6 Hz), 134.3 (d, J_{C-F} = 27.1 Hz), 130.8 (d, J_{C-F} = 1.8 Hz), 128.8, 127.6, 123.4, 98.0 (d, J_{C-F} = 20.5 Hz), 10.3 (d, J_{C-F} = 3.4 Hz); In all conditions tested (HRMS-ESI, HRMS-APPI, GC/MS-EI and GC/MS-CI), no fragment originating from **4b** could be identified.

*4.4.3 3-Fluoro-2,5-diphenylfuran (**4c**).* Chloro(triphenylphosphine) gold(I) (2.4 mg, 0.0048 mmol, 5 mol%) and silver trifluoromethanesulfonate (1.2 mg, 0.0048 mmol, 5 mol%) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1c** (30 mg, 0.0968 mmol) in THF (0.97 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3x), dried over

Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (20.8 mg, 90%) was isolated as a white solid by flash chromatography using hexanes. mp 65-67 °C; IR (ATR, diamond) ν = 3214, 3057, 2920, 1630, 1425, 1151, 1072, 924, 764, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77 (d, 2H, *J* = 7.4 Hz), 7.70 (d, 2H, *J* = 7.3 Hz), 7.45-7.40 (m, 4H), 7.32-7.25 (m, 2H), 6.67 (d, 1H, *J* = 1.2 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -161.4 (s, 1F); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.6 (d, J_{C-F} = 254 Hz), 150.2 (d, J_{C-F} = 9.0 Hz), 136.0 (d, J_{C-F} = 20.3 Hz), 130.3 (d, J_{C-F} = 2.1 Hz), 129.1 (d, J_{C-F} = 5.0 Hz), 128.9, 128.9, 128.2, 127.2 (d, J_{C-F} = 1.5 Hz), 123.8, 123.6 (d, J_{C-F} = 5.5 Hz), 99.4 (d, J_{C-F} = 20.0 Hz); HRMS-ESI calcd for $C_{16}H_{12}FO$ $[M+H]^+$ 239.0867; found 239.0889.

*4.4.4 4-Fluoro-2-octylfuran (**4d**).* Chloro(triphenylphosphine) gold(I) (3.4 mg, 0.0069 mmol, 5 mol%) and silver trifluoromethanesulfonate (1.8 mg, 0.0069 mmol, 5 mol%) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1d** (30 mg, 0.137 mmol) in THF (1.37 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (9.8 mg, 36%) was isolated as a colorless oil by flash chromatography using hexanes. IR (ATR, diamond) ν = 2926, 2856, 1624, 1404, 1284, 1138, 993, 920, 781, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21 (dd, 1H, *J* = 5.0, 1.0 Hz), 5.94 (m, 1H), 2.52 (m, 2H), 1.59 (p, 2H, *J* = 7.7 Hz), 1.33-1.25 (m, 10H), 0.88 (t, 3H, *J* = 7.2 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -170.5 (d, 1F, *J* = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.8 (d, J_{C-F} = 7.6 Hz), 153.8 (d, J_{C-F} = 248 Hz), 124.0 (d, J_{C-F} = 29.8 Hz), 98.2 (d, J_{C-F} = 20.0 Hz), 32.0, 29.4, 29.3, 29.2, 28.7, 27.8, 22.8, 14.3; In

all conditions tested (HRMS-ESI, HRMS-APPI, GC/MS-EI and GC/MS-CI), no fragment originating from **4d** could be identified.

*4.4.5 3-Fluoro-2-methyl-5-octylfuran (**4e**).* Chloro(triphenylphosphine) gold(I) (3.2 mg, 0.0065 mmol, 5 mol%) and silver trifluoromethanesulfonate (1.7 mg, 0.0065 mmol, 5 mol%) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1e** (30 mg, 0.129 mmol) in THF (1.29 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (21.5 mg, 78%) was isolated as a colorless oil by flash chromatography using hexanes. IR (ATR, diamond) ν = 2926, 2856, 1668, 1433, 1377, 1236, 1132, 991, 932, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.85 (s, 1H), 2.48 (t, 2H, J = 7.6 Hz), 2.19 (d, 3H, J = 2.0 Hz), 1.57 (p, 2H, J = 7.0 Hz), 1.34-1.25 (m, 10H), 0.88 (t, 3H, J = 6.9 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -174.4 (s, 1F); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.4 (d, $J_{C\text{-}F}$ = 8.4 Hz), 148.9 (d, $J_{C\text{-}F}$ = 243 Hz), 132.1 (d, $J_{C\text{-}F}$ = 26.7 Hz), 98.3 (d, $J_{C\text{-}F}$ = 20.0 Hz), 32.0, 29.4, 29.4, 29.2, 28.6 (d, $J_{C\text{-}F}$ = 1.2 Hz), 28.0, 22.8, 14.3, 10.0 (d, $J_{C\text{-}F}$ = 2.9 Hz); HRMS-ESI calcd for $C_{13}H_{22}FO$ $[M+H]^+$ 213.1649; found 213.1631.

*4.4.6 3-Fluoro-5-octyl-2-phenylfuran (**4f**).* Chloro(triphenylphosphine) gold(I) (2.5 mg, 0.0051 mmol, 5 mol%) and silver trifluoromethanesulfonate (1.3 mg, 0.0051 mmol, 5 mol%) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1f** (30 mg, 0.102 mmol) in THF (1.02 mL) was added. The vial was wrapped with aluminum foil,

and the reaction mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (15.3 mg, 55%) was isolated as a colorless oil by flash chromatography using hexanes. IR (ATR, diamond) ν = 2926, 2854, 1637, 1423, 1144, 1009, 908, 773, 758, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.64 (d, 1H, *J* = 7.7 Hz), 7.38 (t, 1H, *J* = 7.8 Hz), 7.20 (t, 1H, *J* = 7.4 Hz), 6.04 (s, 1H), 2.61 (t, 2H, *J* = 7.6 Hz), 1.65 (p. 2H, *J* = 7.5 Hz), 1.38-1.26 (m, 10H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ -163.0 (s, 1F); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.1 (d, J_{C-F} = 8.6 Hz), 149.8 (d, J_{C-F} = 253 Hz), 134.5 (d, J_{C-F} = 20.5 Hz), 129.6 (d, J_{C-F} = 5.1 Hz), 128.7, 126.5 (d, J_{C-F} = 1.8 Hz), 123.1 (d, J_{C-F} = 5.3 Hz), 100.0 (d, J_{C-F} = 19.7 Hz), 32.0, 29.4, 29.3, 29.2, 28.8 (d, J_{C-F} = 1.2 Hz), 27.9, 22.8, 14.3; HRMS-ESI calcd for $C_{18}H_{24}FO$ $[M+H]^+$ 275.1806; found 275.1828.

*4.4.7 3-Fluoro-2-phenylfuran (**4g**).* Chloro(triphenylphosphine) gold(I) (4.1 mg, 0.0082 mmol, 5 mol%) and silver trifluoromethanesulfonate (2.1 mg, 0.0082 mmol, 5 mol%) were charged into a glass vial. A magnetic stir bar was added, and then the vial was sealed and flushed with argon, after which a solution of propargylic *gem*-difluoride **1g** (30 mg, 0.165 mmol) in THF (1.65 mL) was added. The vial was wrapped with aluminum foil, and the reaction mixture was stirred at room temperature for 18 hours, after which saturated $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 (3x), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. A yield of 9% was estimated by ^{19}F NMR analysis of the crude reaction mixture using 2-fluoro-4-nitrotoluene (17.9 mg, 0.1154 mmol) as an internal standard. ^{19}F NMR ($CDCl_3$, 470 MHz) δ -165.0 (m, 1F, 0.0142 mmol, 9%) [23].

Acknowledgments

We acknowledge the financial support of the Natural Sciences and Engineering Research Council of Canada (NSERC) and Université Laval. J. D. H. thanks NSERC for a Vanier Canada Graduate Scholarship.

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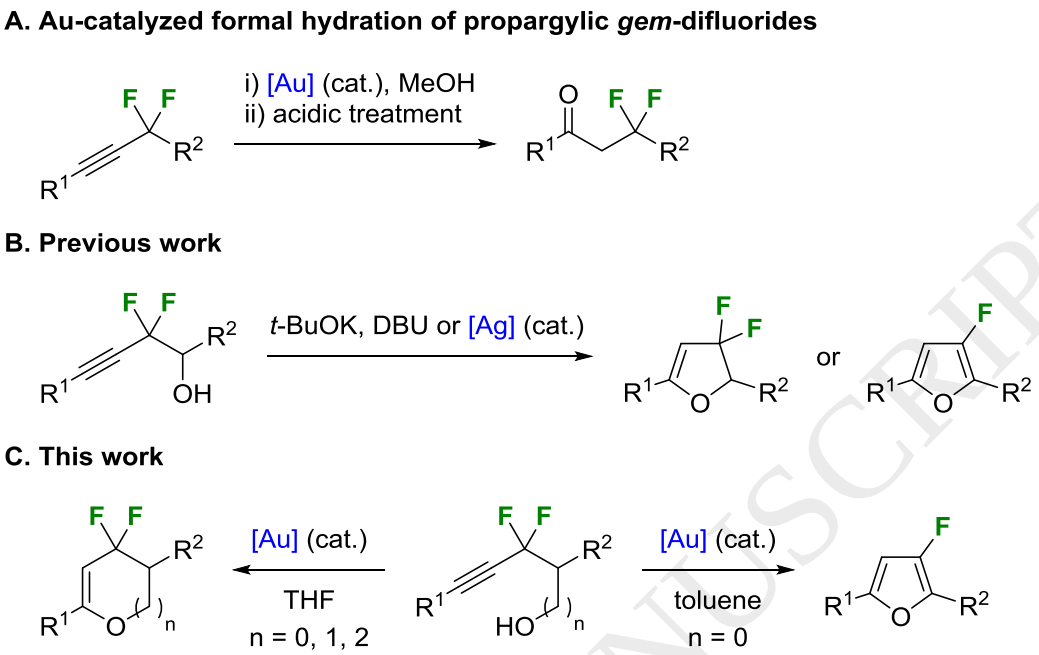
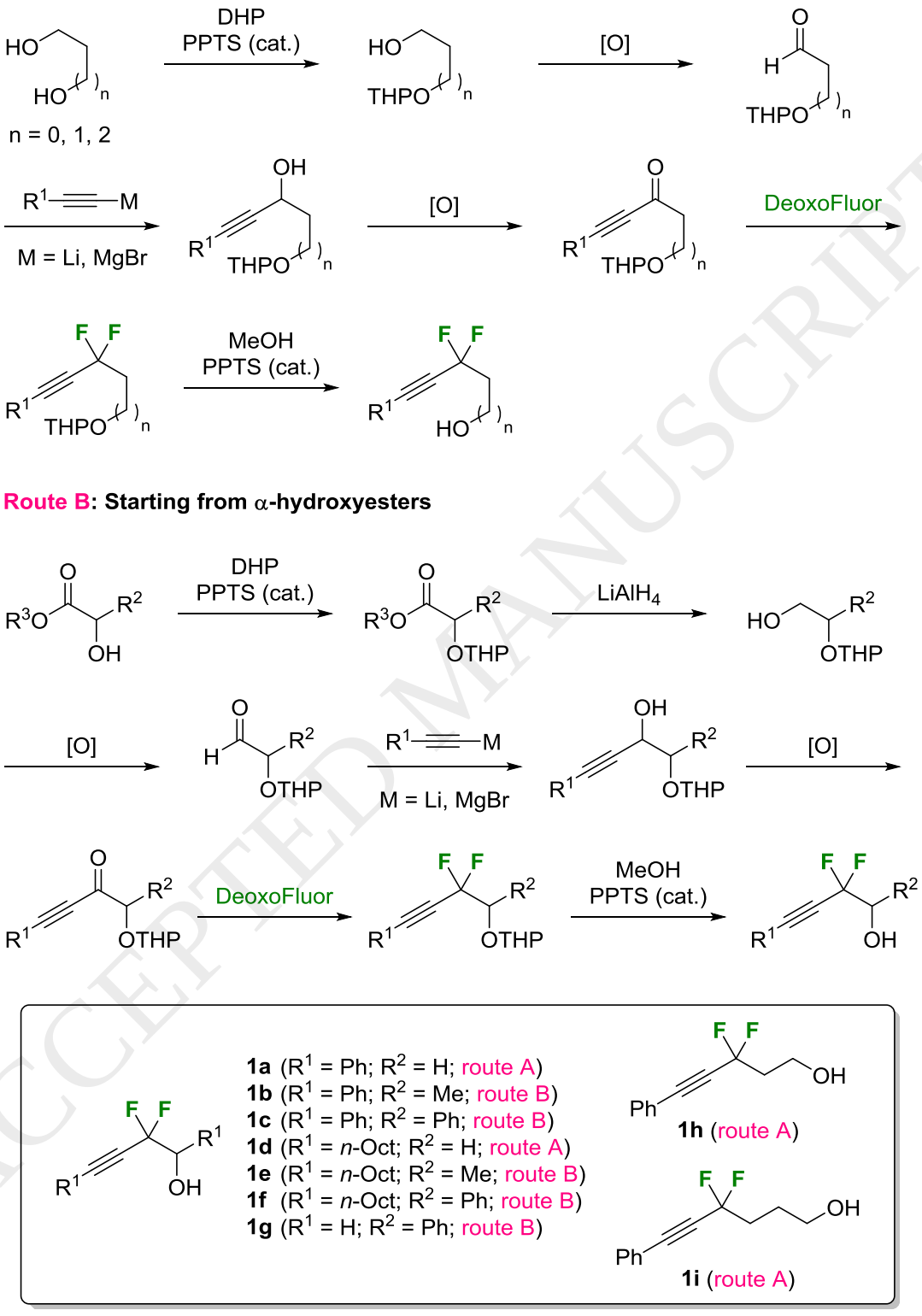
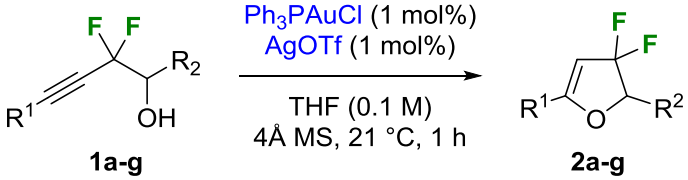


Scheme 1. Transformations involving the inter- or intramolecular hydroalkoxylation of propargylic *gem*-difluorides.

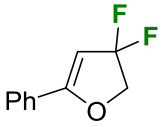


Scheme 2. Synthetic routes for the preparation of *gem*-difluorinated alkynols.

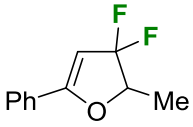
A. Formation of a 5-membered ring (2,3-dihydrofuran)



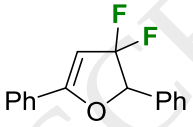
1a-g **2a-g**



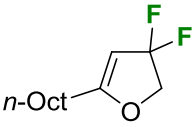
2a (>97%)



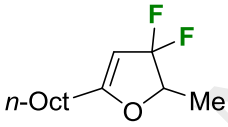
2b (92%)



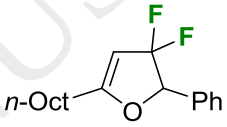
2c (78%)



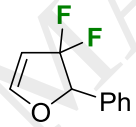
2d (97%)



2e (85%)

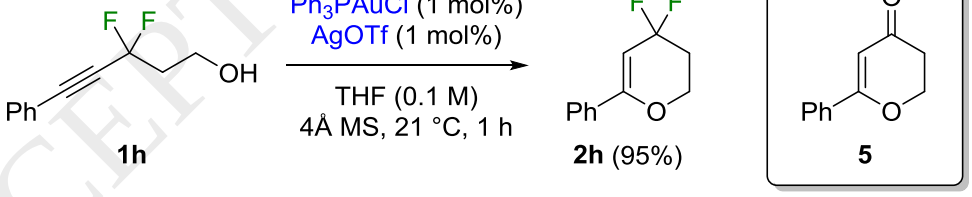


2f (75%)



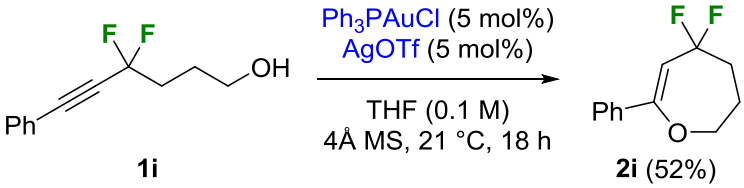
2g (78%)

B. Formation of a 6-membered ring (3,4-dihydro-2*H*-pyran)



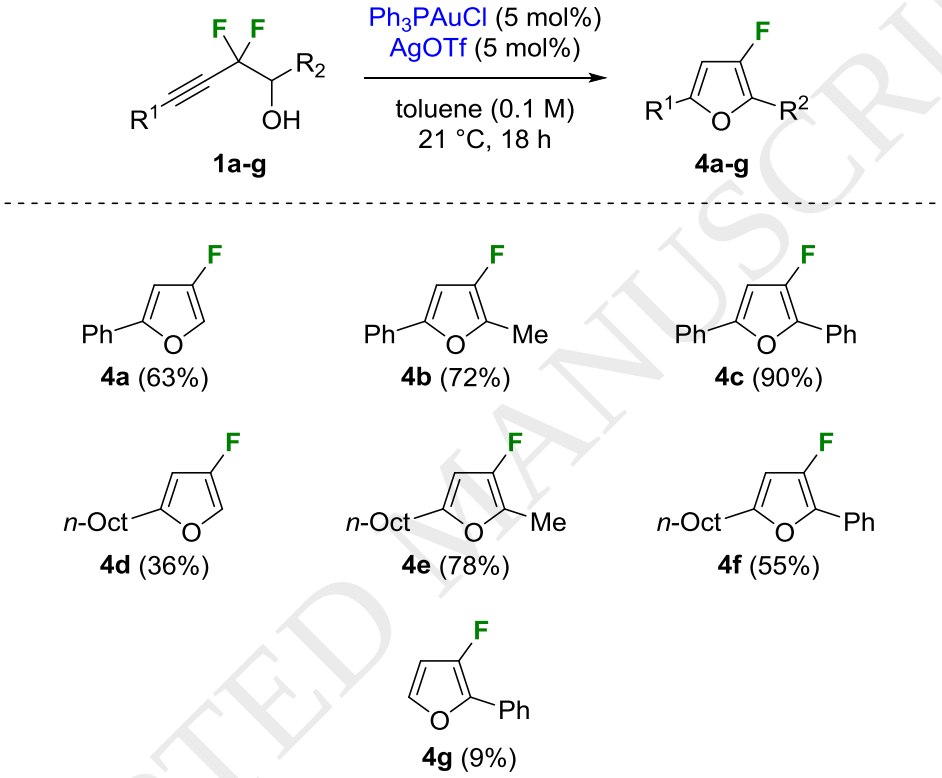
1h **2h** (95%) **5**

C. Formation of a 7-membered ring (2,3,4,5-tetrahydrooxepine)



1i **2i** (52%)

Scheme 3. Scope of the Au-catalyzed intramolecular hydroalkoxylation of *gem*-difluorinated alkynols. The yields are estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene as an internal standard.



Scheme 4. Scope of the Au-catalyzed intramolecular hydroalkoxylation/aromatization of *gem*-difluorohomopropargylic alcohols to access furan derivatives. The isolated yields are given in parentheses except for **4g**, where the yield is estimated by ^{19}F NMR using 2-fluoro-4-nitrotoluene as an internal standard.

Table 1. Optimization of the intramolecular hydroalkoxylation of *gem*-difluorohomopropargylic alcohols.

<InlineImage5>

Entry	[Au] (mol%)	[Ag] (mol%)	Solvent	Time (h)	Conv.[a] (%)	**2a**[a] (%)	**3a**[a] (%)	**4a**[a] (%)
1	5	5	THF	18	100	74	16	6
2	5	5	Et_2O	18	100	74	13	10
3	5	5	THF[b]	18	100	>97	<1	<1
4	5	5	CH_3CN	18	100	-	2	49
5	5	5	CH_2Cl_2	18	100	-	-	19
6	5	5	toluene	18	100	-	-	80
7	5	0	THF	18	0	-	-	-
8	0	5	THF	18	29	28	-	-
9	5	5	THF	1	100	>97	-	-
10	1	1	THF	1	100	>97	-	-
11	0.1	0.1	THF	1	59	60	-	-