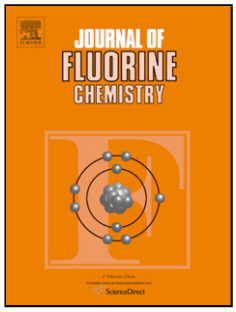

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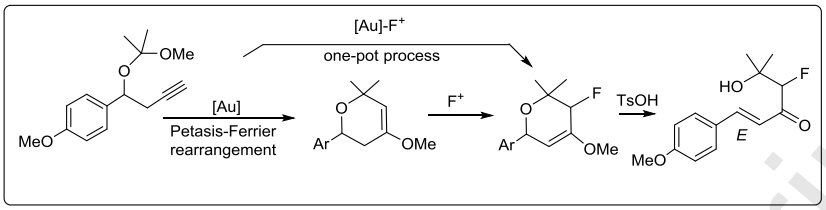
Graphical Abstract



Graphical Abstract (brief synopsis)

A one-pot gold(I)-catalysed regioselective method for the preparation of 3-fluoro-tetrahydropyran-4-one derivatives from homopropargyl acetal is described. The transformation is based on a Petasis-Ferrier rearrangement and a subsequent electrophilic fluorination. The 3-fluoro-pyran-4-one product acts as a protected precursor of alkylfluoro-α,β-(*E*)-unsaturated ketone.

Highlights:

- We report a one-pot gold(I)-catalysed regioselective method for the preparation of 3-fluoro-tetrahydropyran-4-one derivatives from homopropargyl acetal.
- The 3-fluoro-pyran-4-one product may act as a protected precursor of alkylfluoro-α,β-(*E*)-unsaturated ketone.
- The mechanism of the transformation is based on a Petasis-Ferrier rearrangement and a subsequent electrophilic fluorination.
- The corresponding hemiacetals were not suitable substrates in the one-pot cyclization-fluorination protocol.

SHORT COMMUNICATION

3-Fluorotetrahydropyran-4-one derivatives from homopropargyl acetal

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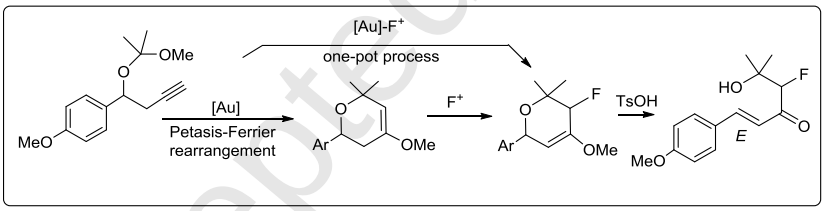
Abstract:

A gold(I)-catalysed regioselective method for the preparation of 3-fluoro-tetrahydropyran-4-one derivatives from homopropargyl acetal is reported. A one-pot procedure based on a gold(I)-catalysed Petasis-Ferrier rearrangement /cyclization and subsequent fluorination was developed. The 3-fluoro-pyran-4-one compound acts as a protected precursor of alkylfluoro-α,β-(*E*)-unsaturated ketone, which was readily obtained by ring-cleavage. Corresponding hemiacetals were not suitable substrates for the formation of the 3-halo-pyran derivatives. The present transformation would represent a useful method to readily afford highly substituted 3-fluoro-tetrahydropyran-4-ones.

Keywords: propargyl acetals / Gold / Petasis-Ferrier rearrangement /3-fluorinated tetrahydropyran-4-ones / fluoro-α,β-unsaturated ketone.

Graphical Abstract



Highlights:

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- The mechanism of the transformation is based on a Petasis-Ferrier rearrangement and a subsequent electrophilic fluorination.
- The corresponding hemiacetals were not suitable substrates in the one-pot cyclization-fluorination protocol.

1. Introduction

We have recently investigated a variety of cyclization pathways of propargyl substrates, in particular propargyl acetals, taking place by gold(I) catalysed reactions with vinylic compounds [1a-c]. Such propargyl derivatives are known to undergo gold(I)-catalysed migration-fragmentations to give gold carbenoid intermediates which can be trapped with different reagents, typically alkenes, to give different cycloaddition products. We have seen that the reaction pathway switches by changing from propargylic esters to acetals. In contrast to the regular olefin cyclopropanation [1a] normally taking place with propargyl esters, an atypical cyclopentenylation by a [2+3] cycloaddition reaction is the favoured reaction pathway for the respective acetals [1b]. Our recent studies have also shown that propargyl acetals undergo gold[I]-catalysed [2+5] cycloadditions with benzaldimines to afford benz[c]azepine products [1c]. An essential feature of the propargyl acetals was their significantly higher reactivity relative to corresponding propargyl esters.

Homopropargylic derivatives are also versatile substrates for gold(I)-catalysed reactions. Gold(I)-catalysed cyclization of homopropargyl substrates includes transformation of the respective alcohol [2a], ether [2b], amine [2c-e], amide [2f] carbonate [2g-h], azide [2i], sulfoxide [2j] as well as acetal [2k] homopropargyl derivatives. Such reactions often take place by simple 5-*exo*-*dig* or 6-*endo*-*dig* attack of the present heteroatom on the gold(I) activated alkyne moiety to give five- or six-membered heterocyclic products, as demonstrated by the gold-catalysed oxycyclizations of alkynols for the preparation of pyran derivatives [2l-m].

In contrast to the general 5-*exo*-*dig* or 6-*endo*-*dig* cyclizations of homopropargyl substrates, the gold(I)-catalysed Petasis-Ferrier rearrangement of homopropargyl (hemi)acetals takes place by inclusion of the acetal moiety in the final cyclic skeleton. This method has been developed for the cycloisomerization-rearrangement of homopropargyl hemiacetals (**I**) to give a range of tetrahydropyran-4-ones (**II**, Scheme 1a) [2k]. Gold-catalysed Petasis-Ferrier rearrangements have also been applied on propargyl substrates to afford benzo[b]oxepin-3(2H)-ones [3] and benzo[b]azepin-3-ones [4] from 2-(prop-2-ynyloxy)- and 2-(*N*-(prop-2-ynyl)-N-tosylamino-benzaldehydes, respectively.

The introduction of fluorine in potential drug candidates can give improvements of biological properties [5-7]. Such potential effects on biological activity have resulted in a dramatic increase in the interest for fluorinated drugs and precursors, such as α-fluoro ketones [8-14] which also have been prepared by gold catalysis [15], as shown by the gold(I)-catalysed alkoxyhalogenation [16] to give dihydro-α-fluoro-pyranones.

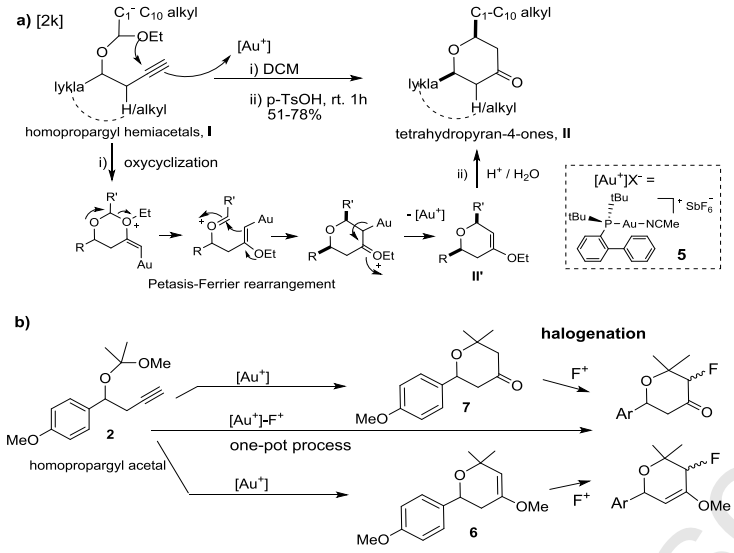
As tetrahydropyran-4-ones (Scheme 1) are valuable intermediates for the synthesis of a large variety of biologically active compounds [17], we wanted to apply our experience on the highly reactive propargyl acetals to study gold(I)-catalysed cyclization reaction of the extended homopropargyl acetal systems based on the Petasis-Ferrier rearrangement. In order to include the incorporation of fluorine in pyran derivatives, we were aiming at developing one-pot procedures, combining acetal formation, cyclization and halogenation. We herein report our investigations on such gold catalysed reactions to afford highly substituted fluorinated pyran-4-one derivatives (Scheme 1b).

2. Results and Discussion

2.1. Petasis-Ferrier rearrangement and substrates.

Our studies on propargyl Petasis-Ferrier rearrangements were mainly carried out on *aryl*homopropargyl *acetal* **2** (Scheme 1b), while previous studies [2k] were based on *alkyl*homopropargyl substrates with a *hemiacetal functionality* (**I**, 4-(ethoxyalkyl)oxy, Scheme 1a). In contrast to the hemiacetals (**I**), affording an additional stereogenic centre and diastereomeric tetrahydropyran-4-one products, the corresponding cyclization of acetals (e.g. **2**) would not afford diastereomeric products (e.g. **7**).

The proposed mechanism (Scheme 1a) [2k] involves oxycyclization of the hemiacetal and the gold(I)-activated alkyne moieties in substrate **I** to give a vinyl gold(I) intermediate. A subsequent Petasis-Ferrier rearrangement by a ring-opening-ring-closure process would proceed via an enolic gold(I) complex, favouring the *cis*-product. De-auration and a final hydrolysis of vinyl ether **II'** would regenerate the gold(I) catalyst and afford the tetrahydropyran-4-one product **II**.



Scheme 1. Gold(I)-catalysed cyclization reactions of homopropargyl (hemi)acetals

In our present study (Scheme 2), the homopropargyl alcohol precursor **1** was prepared in high yield (94%) by a Barbier type propargylation of the appropriate benzaldehyde by a reactive zinc-cupper couple [18]. The homopropargyl methyl acetal **2** (66%) and the ethyl hemiacetal **3** (54%) were generated according to literature [19], while the preparation of the bromo-analogue **4** (45%) was based on a modified literature protocol, including NBS [20]. Similar formation of the fluoro-analogue [21], replacing NBS with Selectfluor, was unsuccessful.

2.2 Two-step process

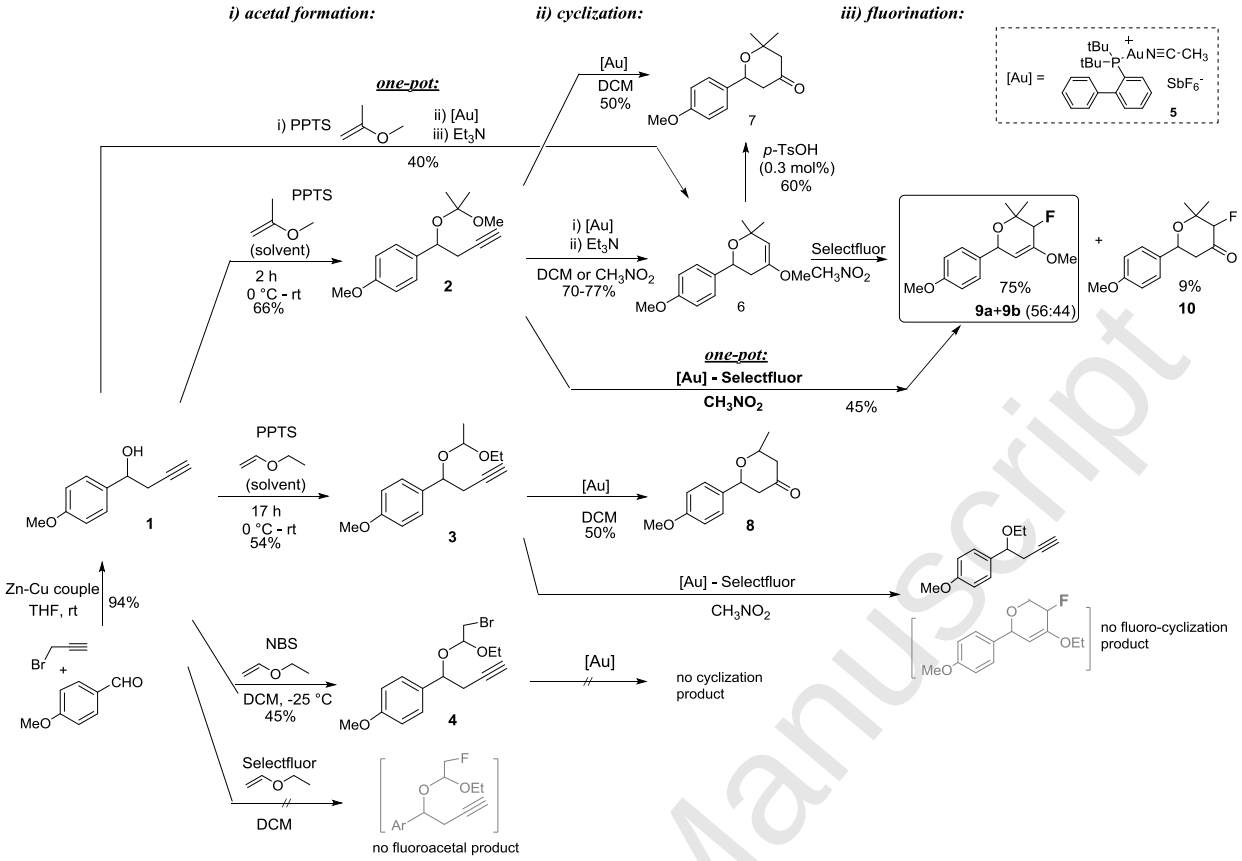
Gold (I)-catalysed cyclization of homopropargyl acetal **2** afforded the tetrahydropyran-4-one products **7** (50%) by Petasis-Ferrier rearrangement. Similar highly substituted tetrahydropyranones have been prepared by intramolecular hetero-Michael addition of β-hydroxyenones [22]. The reaction was carried out in DCM at room temperature and was completed in 15 min in the presence of 5 mol% of (acetonitrile)-[(2-biphenyl)di-tert-butylphosphine]gold(I) hexafluoroantimonate (**5**). In previous analogues methods [2k] of propargyl hemiacetals (**I**, Scheme 1a), an additional one hour treatment with *p*-TsOH have been required to afford hydrolysis of the vinyl ether precursor **II'** to give the final tetrahydropyran-4-one products (**II**).

In order to selectively afford the vinyl methyl ether product **6** (77%), similar to the suggested precursor **II'** in Scheme 1a, the work-up procedure was altered by including a basic quench with NEt_3. The vinyl pyran derivative **6** also readily provided ketone **7** (60%) by treatment with p-TsOH (30 mol%). Gold-catalysed cyclization of hemiacetal **3** to produce ketone **8** (50%) proved to be less reproducible and provided a more complex reaction mixture. The potential effect of triethylamine in the work-up was not as distinct as for the first reaction.

A one-pot procedure from homopropargyl alcohol, including acetal formation and the subsequent cyclization, successfully afforded product **6** in approximately the same yield (40%) as by preparation in two steps (50%). The bromo-analogues hemiacetal **4** was unreactive and failed to undergo cyclization, probably due to the deactivating effect of the bromo-ethoxy group in the initial oxycyclization step (Scheme1).

To adjust reaction conditions for further fluorination, which would require more polar solvents to dissolve the electrophilic halogenation agent, test reactions were carried out, replacing DCM by alternative solvents, such as acetonitrile and nitromethane. Nitromethane appeared to be a suitable alternative solvent, affording 70% of product **6** from acetal **2**. Reactions in acetonitrile gave complex product mixtures.

Direct fluorination of vinyl methyl ether **6** was performed with Selectfluor in nitromethane at room temperature. The fluorination took place in a 3-regioselective manner and the 3-fluoro diastereomeric products **9a/9b** (75% total yield) were obtained from vinyl ether **6** in a 56:44 ratio, applying one equivalent of Selectfluor. Minor amount (9%) of the 3-fluoro-keto product **10** was isolated, as well.



Scheme 2. Gold(I) promoted cyclization and fluorination of homopropargyl acetals

2.3. One-pot method

The compatibility of different gold catalysts with electrophilic halogenation reagents has previously been demonstrated [15, 16, 23]. Based on our introductory results, we were aiming at developing a one-pot procedure for the preparation of fluorinated pyran derivatives. Introductory, we also carried out a study on the development of analogous one-pot protocols for the corresponding Br- and I-pyran-4-ones [25].

Applying the combined [Au]-Selectfluor (1 equiv.) system, the 3-fluorinated pyran derivatives **9a/9b** (45%) were obtained from acetal **2** in slightly lower yield than by the corresponding two-step protocol (58%). Attempts to synthesise di-/poly-fluorinated pyran derivatives were not promising, as such reaction with [Au]-Selectfluor (1-2 equiv.) seemed to afford complex mixtures of mono-/difluorinated regio- and diastereomers. Also attempts to include the acetal formation step in a potential three-step one-pot process from alcohol **1** to the fluorinated products **9a/9b** were unsuccessful, as complex product mixtures were obtained.

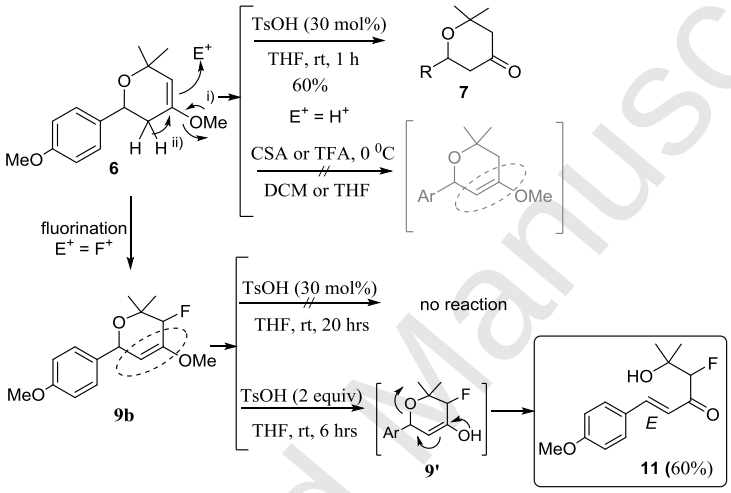
Through introductory studies, we successfully prepared brominated and iodinated pyran-4-one products, applying the corresponding [Au]-NBS and [Au]-NIS systems [25]. Also, the combined [Au]-NIS principle has previously been used for gold(I)-catalysed iodoalkoxylation of allenes, but failed to afford corresponding fluoro-incorporation with [Au]-Selectfluor [24]. This is in contrast to our successful fluoro-incorporation with the combined [Au]-Selectfluor reagent systems applied on the homopropargyl substrates. All the cyclizations, halogenations and the one-pot reaction were carried out within 15 min at room temperature, showing the high reactivity of both the homopropargyl acetal **2** and the pyran vinyl ether derivative **6** to undergo cyclization and fluorination, respectively. It seemed to be essential for successful one-pot reactions that the substrate and the gold(I) catalyst were mixed prior to the addition of the Selectfluor halogenation reagent.

Attempts to provide the corresponding fluoro-cyclization-product, analogous to compound **9**, in one-pot from hemiacetal **3** via pyranone intermediate **8**, applying the [Au]-Selectfluor system, were unsuccessful, and the internally ethoxy-substituted 1-ethoxybut-3-ynyl product was formed as the major product [25]. As the gold-catalysed cyclization of hemiacetal **3** also proved to be less reproducible (above), the homopropargyl hemiacetal turned out not to be a suitable substrate for the present one-pot preparation of fluorinated pyran derivatives. We have previously observed that the propargyl ethyl hemiacetal moiety may give deviating reactivity to afford different products [1c].

2.4. Acidic hydrolysis; product modification

The 3-fluorination reactions proceeded regioselectively through double-bond isomerization, as shown by the transformation of the 3,4-vinyl ether **6** into the 3-fluoro-4,5-vinyl ethers (**9**, Scheme 2). As the vinyl pyran derivative **6** was readily hydrolysed to provide ketone **7** by treatment with 30 mol% *p*-TsOH, compound **6** was treated with CSA or TFA at 0 ^{0}C (Scheme 3) in order to test whether a double-bond isomerization of the non-halogenated precursors would take place by acid catalysis. No isomerization into the 4,5-vinyl ether was observed, but some amounts of ketone **7** were detected. Thus, the 3,4- to 4,5-double-bond isomerization is only favoured through the halogenation process.

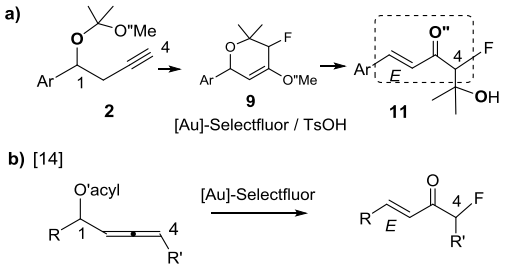
The fluorinated pyran product **9b** was also treated with *p*-TsOH with the purpose of performing hydrolysis. The 3-fluoro compound was more stable towards *p*-TsOH (30 mol%) hydrolysis than the non-fluorinated precursor **6**, and no conversion of the substrate was observed in 20 hrs (Scheme 3). On the other hand, by applying two equivalents of *p*-TsOH, the hydrolysis of fluoro-compound **9b** was successful. However, the instability of the hydrolysis product **9'** was demonstrated by the fact that a subsequent ring cleavage instantly took place and the α-fluoro conjugated keto product **11** (60%) was formed as the major product with exclusive *E*-selectivity. Treatment of 3-fluoropyran **9b** with TFA or CSA also failed to give selective hydrolysis and the formation of the open-chained product **11** was observed, as well.



Scheme 3. Acid catalysed transformations of pyran derivatives

2.5. Fluoroalkyl (E)-α,β-unsaturated ketones

are important structures, present in many bioactive agents [14]. To the best of our knowledge, the presently described method for preparation of the 4-fluoro-4-alkyl-(*E*)-alkene-3-one moiety from homopropargyl acetal, represented in product **11** (Scheme 4a), has not previously been reported. Basically, this new transformation includes both alkylation and fluorination of the terminal 4-propargyl position. The 3-fluoro-pyran compound **9** represents a protected version of the fluoro-α,β-unsaturated ketone **11**. Fluoroalkyl (*E*)-α,β-unsaturated ketones have previously been prepared from allenyl carbinol esters by gold catalytic acyloxy shift and subsequent reaction with Selectfluor (Scheme 4b) [14].



Scheme 4. Gold-catalysed transformations into fluoroalkyl (*E*)-α,β-unsaturated ketones

3. Conclusion

We have demonstrated the preparation of 3-fluoro-pyran-4-one derivative **9** from homopropargyl acetal **2** based on a gold(I)-catalysed Petasis-Ferrier rearrangement / cyclization and subsequent regioselective 3-fluoro incorporation. Both a one-pot protocol and a two-step procedure via the tetrahydropyran-4-one product **6** successfully afforded the fluoro-product **9**. Tetrahydropyran-4-one **6** could also be prepared in one-pot from homopropargyl alcohol **1** via acetal **2**. The corresponding homopropargyl hemiacetal **3** turned out not to be a suitable substrate for the formation of the 3-fluoro-pyran derivatives.

The present method may be useful to afford highly substituted 3-fluoro-tetrahydropyran-4-ones. 3-Fluoro-pyran-4-one derivative **9** acts as a protected derivative of alkylfluoro-α,β-unsaturated ketone **11**, which was readily obtained by acid catalysed ring-cleavage. Such fluorinated products may be interesting as potential bioactive compounds or drug precursors.

4. Experimental

4.1. General

All reactions were performed under argon atmosphere. Commercial grade reagents were used as received. Dry solvents were collected from a MB SPS-800 solvent purification system. All reactions were monitored by GLC and thin-layer chromatography (TLC) using E. Merck silica gel 60 F254 (0.25 mm thickness). Flash chromatography was carried out using Merck silica gel 60 (0.040-0.063 mm). High Throughput Flash Purification (HPFP) (SUPELCO®) was performed on prepacked cartridges (VersaPak™). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance DPX 300 or 400 MHz spectrometer, respectively. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS) as internal standard. Coupling constants (*J*) are reported in hertz (Hz). The attributions of the chemical shifts were determined by means of COSY, HMQC and HMBC experiments. Melting points (m.p.) were determined using a Stuart apparatus. High resolution mass spectra (HRMS) were determined with an Agilent 6520 QTOF MS instrument equipped with a MAT 95XL (TermoQuest Finnigan) MS instrument. IR spectra were obtained with a Nicolet 20SXC FT-IR spectrometer by using a Smart Endurance reflexion cell. (Acetonitrile)[(2-biphenyl)di-*tert*-butyl-phosphine)gold(I) hexafluoroantimonate (**5**) was purchased from Aldrich. 1-(4-Methoxyphenyl)but-3-yn-1-ol (**1**) [24] was prepared according to an adopted procedure described by Ma et al.[18].

4.2. 1-Methoxy-4-(1-(2-methoxypropan-2-yloxy)but-3-ynyl)benzene (2)

The title compound was prepared by a modified procedure described by Zhang and Zhang [19]. A solution of the homopropargylic alcohol **1** (590 mg, 3.35 mmol) in 2-methoxy-propene (3.5 ml) was cooled to 0 ºC. PPTS (20 mg, 3 mol%) was added, and the reaction continued for 20 min. The ice bath was removed and the reaction continued for 2 hours. The reaction mixture was diluted with DCM (40 ml) and washed with water (2 x 20 ml) and brine (20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified through silica gel flash column (VersaFlash) chromatography (1% EtOAc in *n*-pentane). Compound **2** was obtained in 66% (549 mg) yield as a colourless oil; R_f = 0.40 (5% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 2H, H_{Ar}), 6.86 (d, J = 8.9 Hz, 2H, H_{Ar}), 4.80 (t, J = 6.7 Hz, 1H, OCH), 3.80 (s, 3H, CH_3OAr), 3.12 (s, 3H,CH_3O), 2.65 (ddd, J = 16.7, 6.2, 2.7 Hz, 1H, CH_2), 2.51 (ddd, J = 16.6, 7.2, 2.7 Hz, 1H, CH_2), 1.93 (t, J = 2.6 Hz, 1H, H_{alkyne}), 1.41 (s, 3H, CH_3C), 1.15 (s, 3H, CH_3C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8 (C_{Ar}), 135.7 (C_{Ar}), 127.6 (C_{Ar}), 113.5 (C_{Ar}), 101.2 (OCO), 81.4 (CH_2C_{alkyne}), 71.2 (HCC_{Ar}), 70.1 (HC_{alkyne}), 55.2 (CH_3OC_{Ar}), 49.4 (CH_3O), 29.2 (CH_2), 26.0 (CH_3C), 25.1 (CH_3C). IR (neat, cm^{-1}) 3289 (w), 2991 (w), 1612 (w), 1512 (s), 1244 (s), 1146 (m), 1029 (s). HRMS (ESI) calcd for $C_{12}H_{17}O_3$ $(M\text{-}C_3H_3)^+$ 209.1172, obsd 209.1175.

4.3. 1-(1-(1-Ethoxyethoxy)but-3-ynyl)-4-methoxybenzene (3)

The title compound was prepared by a modified procedure described by Zhang and Zhang.[4] A solution of the homopropargylic alcohol **1** (423 mg, 2.40 mmol) in ethyl-vinyl ether (3 ml) at 0 ºC was added PPTS (24 mg, 4 mol%), and the reaction was stirred for 17 hrs, as the temperature gradually increased towards rt. The reaction mixture was diluted with DCM (30 ml) and washed with water (2 x 20 ml) and brine (20 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash (VersaFlash) chromatography (3% EtOAc in *n*-pentane) to give **3** (322 mg, 54%; diastereomeric mixture) as a colourless oil; R_f = 0.39 (5% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.7 Hz, 2H, H_{Ar}), 7.27 (d, J = 8.9 Hz, 2H, H_{Ar}), 6.88 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.87 (d, J = 8.7 Hz, 2H, H_{Ar}), 4.80 (q, J = 5.5 Hz, 1H, OCHO), 4.74 (t, J = 6.8 Hz, 1H, $OCHC_{Ar}$), 4.63 (t, J = 6.7 Hz, 1H, $OCHC_{Ar}$), 4.56 (q, J = 5.4 Hz, 1H, OCHO), 3.81 (s, 3H, CH_3O), 3.66-3.52 (m, 2H, CH_2CH_3), 3.29-3.17 (m, 2H, CH_2CH_3), 2.77-2.62 (m, 2H, CH_2C_{alkyne}), 2.60-2.47 (m, 2H, CH_2C_{alkyne}), 1.95 (t, J = 2.6 Hz, 1H, HC_{alkyne}), 1.94 (t, J = 2.6 Hz, 1H, HC_{alkyne}), 1.29 (d, J = 5.3 Hz, 3H, CH_3CH), 1.24 (d, J = 5.5 Hz, 3H, CH_3CH), 1.19 (7, J = 7.0 Hz, 3H, CH_3CH_2), 1.04 (7, J = 7.1 Hz, 3H, CH_3CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C_{Ar}), 159.2 (C_{Ar}), 134.1 (C_{Ar}), 133.0 (C_{Ar}), 128.1 (C_{Ar}), 127.7 (C_{Ar}), 113.7 (C_{Ar}), 113.6 (C_{Ar}), 99.4 (OCO), 97.7 (OCO), 81.1 (CH_2C_{alkyne}), 75.6 (OCC_{Ar}), 75.5 ($OCC_{Ar\ 1}$), 70.0 (HC_{alkyne}), 69.9 (HC_{alkyne}), 61.2 (CH_3CH_2O), 59.4 (CH_3CH_2O), 55.2 (CH_3O), 28.2 (CH_2C_{alkyne}), 20.4 (CH_3CH), 20.2 (CH_3CH), 15.4 (CH_3CH_2), 15.0

(CH_3CH_2). IR (neat, cm^{-1}) 3292 (w), 2977 (w), 1612 (m), 1512 (s), 1245 (s), 1173 (m), 1028 (s). HRMS (ESI) calcd for $C_{12}H_{17}O_3$ (M-C_3H_3)$^+$ 209.1172, obsd 209.1171.

4.4. 1-(1-(2-Bromo-1-ethoxyethoxy)but-3-ynyl)-4-methoxybenzene (4)

The title compound was prepared by a modified procedure described by Panday et al.[5]. *N*-Bromosuccinimide (293 mg, 1.65 mmol) was dissolved in dichloromethane (3 ml), cooled to -25 ºC and added ethyl-vinyl ether (150 µl, 1.57 mmol). After one hour, a solution of homopropargylic alcohol **1** (415 mg, 2.34 mmol) in dichloromethane (0.5 ml) was added. The temperature was left to rise slowly towards room temperature for 18 h. After removal of solvent, the crude mixture was re-dissolved in diethyl ether (50 ml) and washed with water (30 ml) and brine (30 ml). The organic phase was dried over $MgSO_4$. The residue was purified through silica gel flash column chromatography (3% EtOAc in *n*-pentane). Compound **4** was obtained in 45% yield (347 mg, diastereomeric mixture) as colourless oil; R_f = 0.41 (5% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 9.0 Hz, 2H, H_{Ar}), 7.29 (d, J = 8.9 Hz, 2H, H_{Ar}), 6.89 (d, J = 8.9 Hz, 2H, H_{Ar}), 6.88 (d, J = 8.9 Hz, 2H, H_{Ar}), 4.78 (dd, J = 4.8, 4.2 Hz, 1H, OCHO), 4.74 (t, J = 7.0 Hz, 1H, $OCHC_{Ar}$), 4.66 (t, J = 6.7 Hz, 1H, $OCHC_{Ar}$), 4.54 (t, J = 5.5 Hz, 1H, OCHO), 3.82 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 3.74-3.46 (m, 2H, CH_2CH_3), 3.45-3.22 (m, 2H, CH_2Br), 2.80-2.68 (m, 2H, CH_2C_{alkyne}), 2.62-2.50 (m, 2H, CH_2C_{alkyne}), 1.97 (t, J = 2.7 Hz, 1H, HC_{alkyne}), 1.96 (t, J = 2.6 Hz, 1H, HC_{alkyne}), 1.23 (t, J = 7.0 Hz, 3H, CH_3CH), 1.05 (t, J = 7.1 Hz, 3H, CH_3CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 (C_{Ar}), 159.5 (C_{Ar}), 133.1 (C_{Ar}), 131.8 (C_{Ar}), 128.3 (C_{Ar}), 127.9 (C_{Ar}), 113.9 (C_{Ar}), 113.8 (C_{Ar}), 101.3 (OCO), 98.9 (OCO), 80.8 (CH_2C_{alkyne}), 77.1 (OCC_{Ar}), 76.4 (OCC_{Ar}), 70.3 (HC_{alkyne}), 70.1 (HC_{alkyne}), 62.8 (CH_3CH_2O), 61.3 (CH_3CH_2O), 55.3 (CH_3O), 32.4 (CH_2Br), 31.8 (CH_2Br), 28.1 (CH_2C_{alkyne}), 28.0 (CH_2C_{alkyne}), 15.3 (CH_3CH_2), 14.8 (CH_3CH_2). IR (neat, cm^{-1}) 3296 (w), 2976 (w), 1611 (w), 1512 (s), 1247 (s), 1174 (m), 1109 (m), 1028 (s). HRMS (ESI) calcd for $C_{12}H_{16}O_3Br$ (M-C_3H_3)$^+$ 287.0277, obsd 287.0275.

4.5. General procedure for gold(I)-catalysed reactions (applied in Sections 4.6-8, 4.9b):

The gold catalyst **5** was dissolved in half of the total amount of dry solvent. Homopropargyl acetal was dissolved in the other half of the dry solvent, and added under vigorous stirring (c = 100 mM). After 15 min, the reaction mixture was added triethylamine (4-5 drops) prior to filtration, or was alternatively filtered directly. Purification of the crude product was performed by column chromatography.

4.6. 4-Methoxy-2-(4-methoxyphenyl)-6,6-dimethyl-3,6-dihydro-2H-pyran (6)

The gold catalyst (**5**) (8.3 mg, 5 mol%) was dissolved in dry dichloromethane (1.0 ml) and added a solution of acetal **2** (52 mg, 0.21 mmol) in dichloromethane (1.0 ml). After 15 min of vigorous stirring, the solution was added triethylamine (4 drops) and subsequently filtered through Celite. The concentrated crude material was purified by flash (VersaFlash) chromatography (3% EtOAc in *n*-pentane) to afford **6** (40 mg, 77%) as a colourless oil; R_f = 0.40 (3% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.89 (d, J = 8.7 Hz, 2H, H_{Ar}), 4.74 (dd, J = 10.8, 3.3 Hz, 1H, H-2), 4.61 (d, J = 1.9 Hz, 1H, H-5), 3.80 (s, 3H, CH_3OC_{Ar}), 3.55 (s, 3H,CH_3O), 2.38 (ddd, J = 16.1, 10.8, 2.0 Hz, 1H, H-3), 2.14 (dd, J = 16.1, 3.3 Hz, 1H, H-3), 1.36 (s, 6H, $(CH_3)_2C$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0 (C_{Ar}), 152.3 (C-4), 134.6 (C_{Ar}), 127.5 (C_{Ar}), 113.8 (C_{Ar}), 101.7 (C-5), 73.4 (C-6), 70.5 (C-2), 55.3 (CH_3OC_{Ar}), 54.0 (CH_3O), 35.3 (C-3), 31.3 (CH_3C), 27.3 (CH_3C). IR (neat, cm^{-1}) 2969 (w), 1672 (m), 1614 (m), 1513 (s), 1382 (m), 1246 (s), 1210 (s), 1077 (s), 1027 (s). HRMS (ESI) calcd for $C_{15}H_{20}O_3$ (M^+) 248.1407, obsd 248.1404.

4.7. 6-(4-Methoxyphenyl)-2,2-dimethyldihydro-2H-pyran-4(3H)-one (7)

Gold catalyst **5** (8.9 mg, 5 mol%) was dissolved in dry dichloromethane (1.3 ml) and added a solution of acetal **2** (57 mg, 0.23 mmol) in dichloromethane (1 ml). After 15 min of vigorous stirring, the solution was filtered through Celite. The concentrated crude material was purified by flash (VersaFlash) chromatography (5% EtOAc in *n*-pentane) to afford **7** (27 mg, 50%) as a colourless solid; m.p 58-60 ºC; R_f = 0.09 (5% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.90 (d, J = 8.9 Hz, 2H, H_{Ar}), 4.85 (t, J = 7.2 Hz, 1H, H-6), 3.80 (s, 3H, CH_3OC_{Ar}), 2.54 (d, J = 13.6 Hz, 1H, H-3), 2.52 (d, J = 7.5 Hz, 2H, H-5), 2.36 (d, J = 13.4 Hz, 1H, H-3), 1.45 (s, 3H, CH_3C), 1.30 (s, 3H, CH_3C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7 (C-4), 159.4 (C_{Ar}), 133.5 (C_{Ar}), 127.2 (C_{Ar}), 114.0 (C_{Ar}), 75.6 (C-2), 72.7 (C-6), 55.3 (CH_3O), 53.2 (C-3), 49.5 (C-5), 31.1 (CH_3C), 24.0 (CH_3C). IR (neat, cm^{-1}) 2971 (w), 1713 (s), 1613 (w), 1513 (s), 1240 (s), 1169 (m), 1033 (s). HRMS (ESI) calcd for $C_{14}H_{19}O_3$ ($M+H)^+$ 235.1329, obsd 235.1328.

4.8. 2-(4-Methoxyphenyl)-6-methyldihydro-2H-pyran-4(3H)-one (8)

Gold catalyst **5** (10 mg, 5 mol%) was dissolved in dry dichloromethane (1.4 ml) and added a solution of acetal **3** (60 mg, 0.24 mmol) in dichloromethane (1 ml). After 15 min of vigorous stirring, the solution was filtered through Celite. The concentrated crude material was purified by flash (VersaFlash) chromatography (5% EtOAc in *n*-pentane) to give **8** (27 mg, 50%) as a colourless oil; R_f = 0.24 (10% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.91 (d, J = 8.7 Hz, 2H, H_{Ar}), 4.60 (t, J = 7.2 Hz, 1H, H-2), 3.97-3.84 (m, 1H, H-6), 3.81 (s, 3H, CH_3OC_{Ar}), 2.57 (d, J = 7.5 Hz, 2H, H-5), 2.46 (dd, J = 14.3, 2.8 Hz, 1H, H-3), 2.36 (dd, J = 14.4, 11.0 Hz, 1H, H-3), 1.40 (d, J = 6.2 Hz, 3H, CH_3C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1 (C-4), 159.7 (C_{Ar}), 133.0 (C_{Ar}), 127.1 (C_{Ar}), 114.1 (C_{Ar}), 78.5 (C-2), 73.6 (C-6), 55.3 (CH_3O), 49.4 (C-3), 49.3 (C-5), 22.2 (CH_3C). IR (neat, cm^{-1}) 2970 (w), 1719 (s), 1612 (m), 1513 (s), 1246 (s), 1175 (s), 1032 (s). HRMS (ESI) calcd for $C_{13}H_{16}O_3$ (M^+) 220.1094, obsd 220.1096.

4.9. 3-Fluoro-4-methoxy-6-(4-methoxyphenyl)-2,2-dimethyl-3,6-dihydro-2H-pyran (9a/9b)

Method a: Synthesis from dihydropyran **6** above:
Selectfluor (29 mg, 1 equiv) in nitromethane (0.5 ml), at room temperature, was added a solution of dihydropyran **6** (20 mg, 0.081 mmol) in nitromethane (0.5 ml). TLC indicated full conversion after 7 min, but the reaction was continued for a total of 15 min. The reaction was added a saturated sodium bicarbonate solution (16 ml) and dichloromethane (16 ml). The separated organic phase was dried over $MgSO_4$. The concentrated crude material was purified by silica (VersaFlash) chromatography (3% EtOAc in *n*-pentane) to afford a total yield of 75% (16 mg) of **9a**/**9b** (ratio 56:44). Pure samples of **9a** and **9b** were isolated from the mixture for further characterization. Minor amounts (< 10%) of the keto-product **10** were also isolated.

Method b: One pot synthesis from acetal **2**
Gold catalyst **5** (8.0 mg, 5 mol%) was dissolved in dry nitromethane (1.0 ml) and added a solution of acetal **2** (50 mg, 0.20 mmol) in nitromethane (1.0 ml). After 3 min stirring, Selectfluor (71 mg, 1 equiv.) was added in one portion. The reaction continued for a total of 15 min, and filtered through Celite with the aid of dichloromethane (15 ml). A total yield of 45% (24 mg) of **9a**/**9b** (ratio 53:47) was obtained. Pure samples of **9a** and **9b** were isolated from the mixture for further characterization.
9a: R_f = 0.41 (5% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.88 (d, J = 8.7 Hz, 2H, H_{Ar}), 5.19 (dt, J = 5.8, 2.0 Hz, 1H, H-6), 4.84 (ddd, J = 52.3 Hz ($^2J_{(H-F)}$), 2.3, 0.7 Hz, 1H, H-3), 4.79 (s, 1H, H-5), 3.79 (s, 3H, CH_3OC_{Ar}), 3.61 (s, 3H, CH_3O), 1.40 (d, $^4J_{(H-F)}$ = 3.8 Hz, 3H, CH_3C), 1.38 (s, 3H, CH_3C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C_{Ar}), 149.8 (d, $^2J_{(C-F)}$ = 16.1 Hz, C-4), 134.1 (C_{Ar}), 128.7 (C_{Ar}), 113.9 (C_{Ar}), 99.8 (d, $^3J_{(C-F)}$ = 3.0 Hz, C-5), 88.9 (d, $^1J_{(C-F)}$ = 181.1 Hz, C-3), 74.0 (d, $^2J_{(C-F)}$ = 19.1 Hz, C-2), 71.6 (C-6), 55.3 (CH_3OC_{Ar}), 54.9 (CH_3O), 27.5 (d, $^3J_{(C-F)}$ = 1.1 Hz, CH_3C), 18.5 (d, $^3J_{(C-F)}$ = 4.0 Hz, CH_3C). IR (neat, cm^{-1}) 2936 (w), 1669 (w), 1610 (m), 1512 (s), 1248 (s), 1170 (s), 1032 (s). HRMS (ESI) calcd for $C_{15}H_{19}O_3F$ (M^+) 266.1313, obsd 266.1313.
9b: R_f = 0.32 (5% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.88 (d, J = 8.9 Hz, 2H, H_{Ar}), 5.14 (d, J = 11.3 Hz, 1H, H-6), 4.84 (m, 1H, H-5), 4.36 (d, $^2J_{(H-F)}$ = 50.9 Hz, 1H, H-3), 3.80 (s, 3H, CH_3OC_{Ar}), 3.58 (s, 3H, CH_3O), 1.40 (d, $^4J_{(H-F)}$ = 3.0 Hz, 3H, CH_3C), 1.33 (d, $^4J_{(H-F)}$ = 1.0 Hz, 3H, CH_3C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (C_{Ar}), 149.3 (d, $^2J_{(C-F)}$ = 16.1 Hz, C-4), 133.9 (C_{Ar}), 128.8 (C_{Ar}), 114.0 (C_{Ar}), 102.1 (d, $^3J_{(C-F)}$ = 7.0 Hz, C-5), 88.7 (d, $^1J_{(C-F)}$ = 179.0 Hz, C-3), 74.5 (d, $^2J_{(C-F)}$ = 19.0 Hz, C-2), 72.1 (d, $^4J_{(C-F)}$ = 3.0 Hz, C-6), 55.3 (CH_3OC_{Ar}), 54.6 (CH_3O), 24.7 (d, $^3J_{(C-F)}$ = 8.0 Hz, CH_3C), 21.4 (d, $^3J_{(C-F)}$ = 4.0 Hz, CH_3C). IR (neat, cm^{-1}) 2935 (w), 1671 (m), 1612 (w), 1513 (s), 1384 (m), 1248 (s), 1222 (s), 1171 (s), 1153 (s), 1034 (s). HRMS (ESI) calcd for $C_{15}H_{19}O_3F$ (M^+) 266.1313, obsd 266.1313.

4.10. 3-Fluoro-6-(4-methoxyphenyl)-2,2-dimethyldihydro-2H-pyran-4(3H)-one (10)
The title compound was isolated in less than 10% from the synthesis of **9a**/**9b**, from **6**, as described above in Section 4.9a; R_f = 0.27 (10% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 2H, H_{Ar}), 6.91 (d, J = 8.7 Hz, 2H, H_{Ar}), 4.87 (dd, J = 8.2, 5.9 Hz, 1H, H-6), 4.83 (d, $^2J_{(H-F)}$ = 49.1 Hz, 1H, H-3), 3.81 (s, 3H, CH_3OC_{Ar}), 2.75-2.69 (m, 2H, H-5), 1.54 (s, 3H, CH_3C), 1.31 (d, J = 2.6 Hz, 3H, CH_3C). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5 (d, $^2J_{(C-F)}$ = 14.0 Hz, C-4), 159.6 (C_{Ar}), 132.1 (C_{Ar}), 127.2 (C_{Ar}), 114.1 (C_{Ar}), 96.2 (d, $^1J_{(C-F)}$ = 200.8 Hz, C-3), 78.0 (d, $^2J_{(C-F)}$ = 19.7 Hz, C-2), 72.7 (C-6), 55.4 (CH_3O), 49.4 (C-5), 27.7 (CH_3C), 18.4 (CH_3C). IR (neat, cm^{-1}) 2979 (w), 1737 (s), 1612 (w), 1514 (s), 1246 (s), 1172 (s), 1080 (s). HRMS (ESI) calcd for $C_{14}H_{17}O_3F$ (M+) 252.1156, obsd 252.1157.

4.11. (*E*)-4-Fluoro-5-hydroxy-1-(4-methoxyphenyl)-5-methylhex-1-en-3-one (11)
Fluorodihydropyran **9b** (10 mg, 0.038 mmol) was dissolved in THF (2 ml) and added *p*-toluensulfonic acid monohydrate (14 mg, 2 equiv.). High conversion was observed (TLC) after 6 hrs of efficient stirring. Et_3N (3-4 drops) was added prior to filtration of the reaction mixture through Celite. The concentrated crude material was purified by flash (VersaFlash) chromatography (10% EtOAc in *n*-pentane) to afford **11**(5.7 mg, 60%); R_f = 0.09 (10% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 15.6 Hz, 1H, H-1), 7.59 (d, J = 8.7 Hz, 2H, H_{Ar}), 7.12 (dd, J = 16.0, $^4J_{(H-F)}$ = 4.2 Hz, 1H, H-2), 6.93 (d, J = 8.9 Hz, 2H, H_{Ar}), 4.67 (d, $^2J_{(H-F)}$ = 48.6 Hz, 1H, H-4), 3.86 (s, 3H, CH_3O), 3.11 (br s, 1H, OH), 1.34 (d, $^4J_{(H-F)}$ = 1.7 Hz, 3H, H-6), 1.28 (d, $^4J_{(H-F)}$ = 1.7 Hz, 3H, CH_3-H-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 (d, $^2J_{(C-F)}$ = 23.8 Hz, C-3), 162.3 (C_{Ar}), 145.5 (d, $^4J_{(C-F)}$ = 3.5 Hz, C-1), 130.9 (C_{Ar}), 127.0 (C_{Ar}), 117.7 (d, $^3J_{(C-F)}$ = 3.5 Hz, C-2), 114.5 (C_{Ar}), 98.4 (d, $^1J_{(C-F)}$ = 192.5 Hz, C-4), 72.1 (d, $^2J_{(C-F)}$ = 20.5 Hz, C-5), 55.5 (CH_3O), 25.9 (d, $^3J_{(C-F)}$ = 2.8 Hz, CH_3C), 24.6 (d, $^3J_{(C-F)}$ = 1.5 Hz, CH_3C). IR (neat, cm^{-1}) 3466 (br), 2977 (w), 1680 (w), 1587 (s), 1569 (s), 1511 (s), 1423 (m), 1255 (s), 1171 (s), 1029 (s), 734 (s). HRMS (ESI) calcd for $C_{14}H_{17}O_3F$ (M^+) 252.1156, obsd 252.1159.

4.12. General procedure for acid catalysed hydration of dihydropyrans 6 and 9b:
Experiments were performed with $TsOH.H_2O$, according to the protocol described by Bae and co-workers [2k]. Weaker acids, such as CSA and TFA were tested, as well. The amount of acid and the reaction times were also varied in modified protocols.

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