Synthesis of oxygen heterocycles by regioselective Heck reaction

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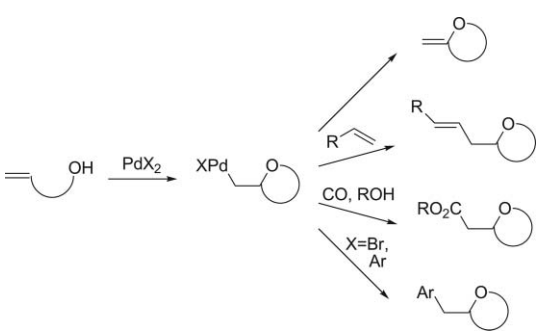
Received 28th July 2010, Accepted 3rd September 2010
DOI: 10.1039/c0ob00508h

The regioselective Heck arylation of unsaturated alcohols is utilized as the key step in a convenient one-pot procedure for the production of 2,2-disubstituted tetrahydrofurans and tetrahydropyrans. The arylation reaction is effected with a palladium-diphosphine catalyst alongside a hydrogen bond donor; this is followed by the introduction of a Brønsted acid to the reaction mixture, affording the oxygen heterocycles in moderate yields.

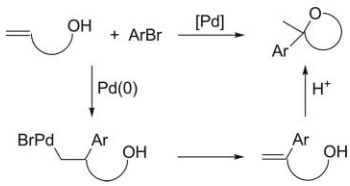
Introduction

Saturated oxygen heterocycles, particularly tetrahydrofurans (THFs) and tetrahydropyrans (THPs), are present in a multitude of biologically active molecules and natural products.[1] They are commonly prepared by electrophile-promoted ring closure of unsaturated alcohols.[2] They can also be readily accessed by palladium-catalysed reactions of unsaturated alcohols *via* a Wacker type process.[3] In these reactions, a Pd(II) catalyst interacts with the C=C double bond of the substrate, triggering nucleophilic attack of the hydroxyl group and leading to ring closure. The resulting Pd-alkyl intermediate undergoes a variety of reactions, furnishing various substituted oxygen heterocycles (Scheme 1).[3] For instance, Semmelhack developed an alkoxypalladation-carbonylation sequence that allows carboxylated THFs and THPs with a new stereocentre in the 2-position to be synthesised.[4b,c] The Pd-alkyl species can also be intercepted by an olefin, such as acrylates and styrene.[4a] Recently, Wolfe disclosed a process in which the Pd-alkyl undergoes reductive elimination with a preinstalled aryl group on the palladium, yielding saturated heterocycles containing benzylic substituents at the 2-position.[5] To the best of our knowledge, however, there appear to be no catalytic methods for the production of 2-aryl THFs and THPs, where the stereocentre is quaternary.



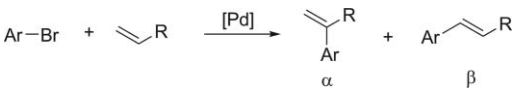
Scheme 1 Schematic illustration of examples of palladium-catalysed synthesis of substituted THFs and THPs.

During our studies on the Heck reaction of electron-rich olefins,[6] we envisaged a one-pot procedure whereby 2-aryl-2-methyl-disubstituted THFs and THPs could be accessed from aryl bromides and unsaturated alcohols. Our intended reaction was a regioselective internal Heck arylation of an unsaturated alcohol followed by an acid-catalysed intramolecular hydroalkoxylation (Scheme 2).[7]



Scheme 2 Carboetherification reaction proposed in this study.

A potential problem to this approach is the regioselectivity of the initial arylation. As our and other groups' work has shown, Heck reactions of electron-rich or electron-neutral olefins, such as unsaturated alcohols, often afford mixtures of α and β regioisomers, which limits their synthetic utility (Scheme 3).[6,8] This is in stark contrast to reactions of electron-deficient olefins, where almost exclusive β substitution usually occurs.[9]



Scheme 3 Heck reaction of electron-rich olefins affording regioisomers.

Results and discussion

In order to obtain the desired products (Scheme 2), we required the initial Heck reaction to be α-selective. There exist in the literature several methods for obtaining α-selectivity in reactions with electron-rich olefins by palladium catalysis. These include the use of bidentate ligands,[8,10] halide scavengers,[11] labile counterions,[12] ionic liquid solvents,[6d,e,9a,13] H-bond donors[6c] and protic solvents.[6b,14] However, in the vast majority of examples concerning the Heck reactions of unsaturated alcohols, arylation occurs in the β position.[15] There are only a few reports that deal with regioselective α arylation of unsaturated alcohols,[13a,b,16] only two of which use aryl bromides.[13a,b] Hence, our first task was to find suitable conditions for the Heck reaction. Previous work in

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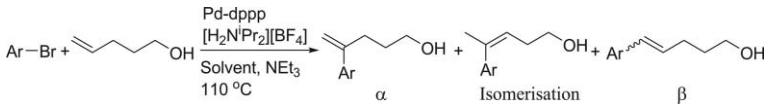
Table 1 Optimization of Heck reaction of unsaturated alcohol[a]



Entry	Solvent	Additive	α : β	Isomerisation (% of α)	Yield[b] (%)
1	DMSO	1.5	88 : 12	5	75
2	DMSO	None	55 : 45	7	60
3	DMF	1.5	79 : 21	12	72
4	Toluene	1.5	82 : 18	17	50
5	MeCN	1.5	74 : 26	19	83
6	Dioxane	None	—	—	—
7	Dioxane	1.5	90 : 10	10	75
8	Dioxane	3	90 : 10	12	73

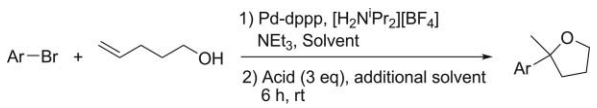
[a] Reaction conditions: 4-bromoacetophenone (1 mmol), 4-pentene-1-ol (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), NEt_3 (3 mmol), 1 mL solvent, 110 °C, 24 h. [b] Isolated yield of the α, β and isomerisation products.

this group had shown that the Heck arylation of unsaturated alcohols could be performed in a 1 : 1 mixture of DMSO and an imidazolium ionic liquid by Pd-dppp catalysis [dppp = 1,3-bis(diphenylphosphino)propane)].[13a] However, the cyclisation we intended failed in DMSO (*vide infra*); hence it was necessary to develop a new protocol for the arylation.

We wondered whether it might be possible to utilize hydrogen-bond donating salts to promote the α arylation, which had been successful for other electron-rich olefins in common solvents.[6c] A screening was undertaken for the arylation of 4-pentene-1-ol with 4-bromoacetophenone, with the catalyst *in situ* derived from $Pd(OAc)_2$ and dppp. The results are shown in Table 1. Entry 1 shows that this was indeed possible and the addition of $[H_2N^iPr_2][BF_4]$ (1.5 eq.) to DMSO allowed us to obtain the substituted alcohols in 75% overall yield with an α:β ratio of 88 : 12. In the absence of the ammonium salt the selectivity and yield were both diminished (entry 2). DMF also gave satisfactory results, but only when used in conjunction with the H-bond donor (entry 3). Toluene, although affording acceptable regioselectivity, gave only a moderate yield of the desired product (entry 4). Acetonitrile proved to be an excellent solvent for our reaction, giving a promising 83% yield and 74 : 26 α : β ratio (entry 5). A dramatic effect of the H-bond donor is seen in the reaction in dioxane. No reaction was observed in the absence of the ammonium salt; however, a high α : β ratio of 90 : 10 was obtained alongside a good yield when 1.5 eq $[H_2N^iPr_2][BF_4]$ was added (entries 6 & 7). A further increase to 3 equivalents of the additive had negligible effect on the regioselectivity or isolated yield (entry 8). It should be noted that double bond migration in the α arylation product occurred in all the reactions, giving tri-substituted alkenes shown in Table 1. This was not a concern, however, as the product of cyclisation (Scheme 2) would be the same as that arising from the terminal olefin initially produced in the Heck reaction.

With a promising variety of conditions in hand, we turned our attention to developing a one-pot procedure. After completion of the Heck reaction, the flask was cooled to room temperature, and an additional solvent and a protic acid were introduced. The additional solvent was intended to lower the concentration of the olefin product and the acid to minimise possible side reactions; excess acid was required to neutralise the excess NEt_3 left after the Heck reaction.

Table 2 Optimisation of the one-pot Heck-cyclisation procedure[a]

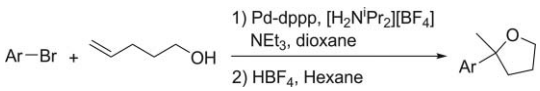


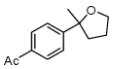
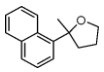
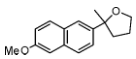
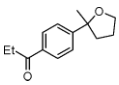
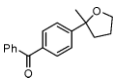
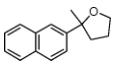
Entry	Solvent	Additional solvent	Acid	Yield[b] (%)
1	Dioxane	None	HBF_4	28
2	Dioxane	Dioxane	HBF_4	40
3	Dioxane	DCM	HBF_4	50
4	Dioxane	Toluene	HBF_4	52
5	Dioxane	Toluene	H_2SO_4	33
6	Dioxane	Toluene	HNO_3	28
7	Dioxane	Hexane	HBF_4	62
8	DMSO	DMSO	HBF_4	0
9	DMSO	DMSO	TfOH	0
10	MeCN	MeCN	HBF_4	22
11	MeCN	MeCN	TfOH	15

[a] Reaction conditions: 4-bromoacetophenone (1 mmol), 4-pentene-1-ol (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), $[H_2N^iPr_2][BF_4]$ (1.5 mmol), NEt_3 (3 mmol), 1 mL solvent, 110 °C, 24 h; then 4 mL additional solvent followed by 3 eq. acid, rt, 12 h. [b] Isolated yield.

The results are shown in Table 2. Entry 1 shows that when HBF_4 was added to the original dioxane solution of the Heck product without any pretreatment, cyclisation did occur, affording a 2-arylated 2-methyl THF in 28% yield. The effect of additional solvent is seen in entry 2: the yield increased to 40% when more dioxane was added before introducing the acid. We then moved on to test solvents other than dioxane for the cyclisation. DCM was first attempted, as it had been used in previous reports on cyclisations of this type.[7a] Using HBF_4 with this solvent system led to a 50% yield over the two steps (entry 3). On switching to toluene we obtained similar results, achieving 52% overall yield (entry 4). Changing the acid to the weaker H_2SO_4 or HNO_3 reduced the yield (entries 5 and 6). In DMSO, however, although consumption of the intermediate alcohol was complete, no desired product was obtained, regardless of the acid chosen (entries 8 & 9). MeCN had proved to be an excellent solvent for the initial arylation; but upon addition of TfOH or HBF_4 only low yields of the substituted THF were obtained (entries 10 & 11). In the end, we were delighted to find that HBF_4 combined with dioxane/hexane

Table 3 One-pot synthesis of THFs *via* regioselective Heck reaction[a]



Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1		62	6		51
2		55	7		50
3		54	8		62
4		55	9		58
5		54	10		65

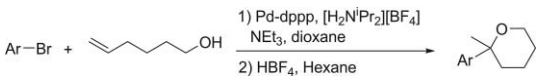
[a] Reaction conditions: ArBr (1 mmol), 4-pentene-1-ol (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), $[H_2N^iPr_2][BF_4]$ (1.5 mmol), NEt_3 (3 mmol), 1 mL dioxane, 110 °C, 24 h; then hexane (4 mL), HBF_4 (2.3–3 eq), rt, 3–8 h. [b] Isolated yield.

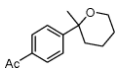
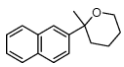
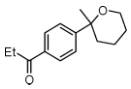
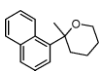
allowed us to obtain the desired 2,2-disubstituted THF in a 62% overall isolated yield (entry 7). This result compares favourably to a two-step procedure, where the intermediate alcohol was isolated and cyclised in a separate step, affording the THF in 58% overall yield.

Having established suitable conditions for the one-pot Heck-cyclisation reaction, we then focussed our efforts on expanding the scope of the reaction with respect to the aryl bromide. The results are shown in Table 3. A range of aryl bromides were converted smoothly into the corresponding alcohol and subsequently the 2,2-disubtituted THFs in moderate to good yields. Electron deficient (entries 1–4), electron-rich (entries 7–10) and sterically more demanding (entries 6 and 9) substrates can all be tolerated by this convenient one-pot procedure. The level of excess acid could be dropped from 1 eq (entries 1–4) to 0.6 eq for the napthyl derivatives (entries 5–7), and to as low as 0.3 eq for electron-rich bromides (entries 8–10).[17]

In order to further expand the scope of the reaction we investigated the possibility of changing the starting unsaturated alcohol with a view to producing different ring sizes. Hence, 5-hexene-1-ol was reacted under conditions similar to those in Table 3 with a range of aryl bromides, yielding a variety of 2,2-substituted THPs in moderate yields; the results are shown in Table 4. As with the formation of THFs in Table 3, electron-deficient (entries 1–3), electron-rich (entries 6–8) and sterically demanding aryl bromides (entries 4 and 6) were all viable. The yield of THPs is generally lower, however. This can be attributed to an inherently lower regioselectivity in the Heck reaction of 5-hexene-1-ol when compared to that of 4-pentene-1-ol (75 : 25 *vs.* 90 : 10).

Table 4 One-pot synthesis of THPs *via* regioselective Heck reaction[a]



Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1		41	5		45
2		43	6		42
3		40	7		48
4		40	8		53

[a] Reaction conditions: ArBr (1 mmol), 5-hexene-1-ol (1.2 mmol), $Pd(OAc)_2$ (0.03 mmol), dppp (0.06 mmol), $[H_2N^iPr_2][BF_4]$ (1.5 mmol), NEt_3 (3 mmol), 1 mL solvent, 110 °C, 24 h; then hexane (4 mL), HBF_4 (2.3–3 eq), rt, 3–8 h. [b] Isolated yield.

Conclusion

In conclusion, we have developed a one-pot, catalytic procedure for the synthesis of 2,2-substituted THFs and THPs from readily available aryl bromides and unsaturated alcohols. The products possess an aryl-substituted quaternary stereogenic centre, a feature not easily installed by other methods. The key step is a regioselective internal Heck arylation that is mediated by a hydrogen-bonding ammonium salt. As in the case of other electron-rich olefins, the ammonium salt probably plays a role in promoting the ionic pathway of the Heck reaction,[6b,c] which favours α arylation.[8,18]

Experimental Section

General

All reactions were carried out under a nitrogen atmosphere. Chromatographic purifications were performed on silica gel (mesh 230–400) by the flash technique. Diisopropylammonium tetrafluoroborate ($[H_2N^iPr_2][BF_4]$) was prepared according to a known procedure.[19] $Pd(OAc)_2$, dppp, 4-pentene-1-ol, 5-hexene-1-ol, aryl bromides and triethylamine were purchased from commercial sources and used as received. ^1H and ^{13}C NMR spectra were recorded at 400 (^1H), 100 (^{13}C) MHz in ppm with reference to TMS as an internal standard in $CDCl_3$. Mass spectra were obtained by chemical ionization (CI). All compounds were characterised by ^1H and ^{13}C NMR, MS, HRMS and micro-analysis.

Typical experimental procedure

An oven-dried, two-necked round-bottom flask containing a stir bar was charged with $Pd(OAc)_2$ (0.03 mmol, 6.7 mg), dppp (0.06 mmol, 24.6 mg), $[H_2N^iPr_2][BF_4]$ (1.5 mmol, 283 mg), 4-bromoacetophenone (1 mmol, 199 mg) and 4-pentene-1-ol

(1.2 mmol, 103 mg, 0.12 mL) (or 5-hexene-1-ol) and 1 mL dioxane. The flask was degassed and backfilled with nitrogen for three times. NEt_3 (3 mmol, 303 mg, 0.4 mL) was then injected. The flask was heated at 110 °C and the biphasic mixture stirred vigorously for 24 h, after which the mixture was cooled to room temperature and hexane (4 mL) and HBF_4. (54% wt. in Et_2O) (3 mmol) were injected sequentially. The biphasic mixture was stirred vigorously until TLC analysis showed consumption of the substituted alcohol was complete (3–8 h). NEt_3 (2 mmol, 0.3 mL, 202 mg) and water (15 mL) was added and the mixture extracted with Et_2O (3 × 15 mL). The combined extracts were concentrated *in vacuo* and the crude residue purified by flash chromatography on silica gel (hexane–EtOAc).

1-(4-(2-Methyltetrahydrofuran-2-yl)phenyl)ethanone (Table 3, entry 1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 2 H), 7.49 (d, J = 8.4 Hz, 2 H), 4.15–3.99 (m, 1 H), 3.98–3.88 (m, 1 H), 2.60 (s, 3 H), 2.29–2.13 (m, 1 H), 2.13–1.94 (m, 2 H), 1.89–1.75 (m, 1 H), 1.53 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 152.5, 129.4, 126.1, 113.4, 82.5, 69.1, 39.5, 30.0, 28.2, 26.7; CI-HRMS Calcd for $C_{13}H_{17}O_2$ (M + H)$^+$: 205.1223. Found: 205.1223; Anal Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.40; H, 7.89.

1-(3-(2-Methyltetrahydrofuran-2-yl)phenyl)ethanone (Table 3, entry 2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (t, J = 1.6 Hz, 1 H), 7.82 (dt, J = 7.6, 1.2 Hz, 1 H), 7.65–7.61 (m, 1 H), 7.42 (t, J = 9.2 Hz, 1 H), 4.08–4.00 (m, 1 H), 3.96–3.89 (m, 1 H), 2.62 (s, 3 H), 2.27–2.16 (m, 1 H), 2.11–1.95 (m, 2 H), 1.89–1.75 (m, 1 H), 1.54 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 149.3, 137.2, 130.0, 128.8, 127.0, 124.9, 84.5, 68.1, 39.9, 30.0, 27.2, 26.2; CI-HRMS Calcd for $C_{13}H_{20}O_2N$ (M + NH_4)$^+$: 222.1489. Found: 222.1491; Anal Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.51; H, 7.93.

1-(4-(2-Methyltetrahydrofuran-2-yl)phenyl)propan-1-one (Table 3, entry 3)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 8.4 Hz, 2 H), 7.72 (d, J = 8.4 Hz, 2 H), 4.11–4.00 (m, 1 H), 3.97–3.88 (m, 1 H), 2.99 (q, J = 7.2 Hz, 2 H), 2.25–2.14 (m, 1 H), 2.12–1.94 (m, 2 H), 1.86–1.75 (m, 1 H), 1.54 (s, 3 H), 1.22 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 153.8, 144.6, 135.6, 128.4, 124.8, 84.7, 68.1, 36.4, 29.8, 26.2, 8.6; CI-HRMS Calcd for $C_{14}H_{19}O_2$ (M + H)$^+$: 219.1385. Found: 219.1387; Anal Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.06; H, 8.33.

(4-(2-Methyltetrahydrofuran-2-yl)phenyl)(phenyl)methanone (Table 3, entry 4)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85–7.75 (m, 4 H), 7.62–7.55 (m, 1 H), 7.54–7.45 (m, 4 H), 4.10–4.00 (m, 1 H), 3.99–3.90 (m, 1 H), 2.28–2.18 (m, 1 H), 2.14–1.95 (m, 2 H), 1.89–1.75 (m, 1 H) 1.56 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 153.5, 138.2, 136.1, 132.7, 130.8, 130.6, 128.7, 125.4, 84.7, 68.2, 39.9, 29.6, 26.1; CI-HRMS Calcd for $C_{18}H_{18}O_2Na$ (M + Na)$^+$: 289.1204. Found: 289.1197; Anal Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.39; H, 6.85.

2-Methyl-2-(naphthalen-2-yl)tetrahydrofuran (Table 3, entry 5)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96–7.78 (m, 4 H), 7.56–7.40 (m, 3 H), 4.12–4.03 (m, 1 H), 4.03–3.95 (m, 1 H), 2.35–2.27 (m, 1 H), 2.15–1.95 (m, 2 H), 1.90–1.75 (m, 1 H), 1.60 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 133.6, 132.6, 128.5, 128.3, 127.9, 126.4, 125.9, 124.2, 123.2, 84.8, 68.1, 39.8, 30.0, 26.2; CI-HRMS Calcd for $C_{15}H_{17}O$ (M + H)$^+$: 213.1274. Found: 213.1270; Anal Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.95; H, 7.62

2-Methyl-2-(naphthalen-1-yl)tetrahydrofuran (Table 3, entry 6)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31– 8.13 (m, 1 H), 7.99–7.67 (m, 3 H), 7.64–7.34 (m, 3 H), 4.17 (td, J = 8.0, 4.8 Hz, 1 H), 3.97–3.78 (m, 1 H), 2.64–2.56 (m, 1 H), 2.53–2.29 (m, 1 H), 2.22–1.96 (m, 1 H), 1.94–1.80 (m, 1 H), 1.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 135.2, 130.4, 129.7, 128.8, 128.3, 126.4, 125.8, 125.6, 122.9, 85.0, 67.1, 39.8, 30.1, 26.9; CI-HRMS Calcd for $C_{15}H_{17}O$ (M + H)$^+$: 213.1274. Found: 213.1270; Anal Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.10; H, 7.65.

2-(6-Methoxynaphthalen-2-yl)-2-methyltetrahydrofuran (Table 3, entry 7)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1 H), 7.71 (t, J = 9.2 Hz, 2 H), 7.45 (dd, J = 8.4, 1.6 Hz, 1 H), 7.17–7.10 (m, 2 H), 4.11–4.02 (m, 1 H), 4.02–3.94 (m, 1 H), 3.91 (s, 3 H), 2.36–2.25 (m, 1 H), 2.15–1.95 (m, 2 H), 1.90–1.76 (m, 1 H), 1.59 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 143.6, 133.7, 129.9, 129.1, 127.1, 124.7, 123.1, 119.1, 105.9, 84.8, 68.0, 55.7, 39.8, 30.1, 26.2; ES-HRMS Calcd for $C_{16}H_{18}O_2Na$ (M + Na)$^+$: 265.1204. Found: 265.1194; Anal Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.60. Found: C, 79.25; H, 7.58.

2-Methyl-2-(*m*-tolyl)tetrahydrofuran (Table 3, entry 8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.15 (m, 3 H), 7.06–7.00 (m, 1 H), 4.08–3.97 (m, 1 H), 3.95–3.86 (m, 1 H), 2.35 (s, 3 H), 2.27–2.14 (m, 1 H), 2.10–1.90 (m, 2 H), 1.85–1.74 (m, 1 H), 1.51 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.6, 138.1, 128.4, 127.5, 125.8, 122.2, 84.7, 67.9, 39.9, 30.2, 26.2, 22.0; CI-HRMS Calcd for $C_{12}H_{20}ON$ (M + NH_4)$^+$: 194.1539. Found: 194.1537; Anal Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.80; H, 9.16.

2-Methyl-2-(*o*-tolyl)tetrahydrofuran (Table 3, entry 9)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.65 (m, 1 H), 7.25–7.09 (m, 3 H), 4.11–3.97 (m, 1 H), 3.90–3.74 (m, 1H), 3.44 (s, 3 H), 2.42–2.11 (m, 2 H), 2.12–1.92 (m, 1 H), 1.91–1.79 (m, 1 H), 1.54 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 134.3, 132.4, 130.5, 126.1, 125.5, 84.9, 67.2, 39.0, 28.6, 26.8, 22.0; CI-HRMS Calcd for $C_{12}H_{20}ON$ (M + NH_4)$^+$: 194.1539. Found: 194.1541; Anal Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.83; H, 9.16.

2-(3-Methoxyphenyl)-2-methyltetrahydrofuran (Table 3, entry 10)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, J = 8.0 Hz, 1 H), 6.99 (t, J = 2.0 Hz, 1 H), 6.98–6.75 (m, 1 H), 6.75 (dd, J = 8.0, 2.4 Hz, 1 H), 4.07–3.96 (m, 1 H), 3.95–3.87 (m, 1 H), 3.81 (s, 3 H), 2.26–2.15 (m, 1 H), 2.08–1.90 (m, 2 H), 1.87–1.75 (m, 1 H), 1.52 (s, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 150.5, 129.6, 117.6,

111.9, 111.0, 84.7, 68.0, 55.6, 39.9, 30.1, 26.2; CI-HRMS Calcd for $C_{12}H_{17}O_2$ $(M + H)^+$: 193.1223. Found: 193.1225; Anal Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.81; H, 8.35.

1-(4-(2-Methyltetrahydro-2*H*-pyran-2-yl)phenyl)ethanone (Table 4, entry 1)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 8.4 Hz, 2 H), 7.51 (d, J = 8.4 Hz, 2 H), 3.83–3.73 (m, 1 H), 3.56–3.42 (m, 1 H), 2.61 (s, 3 H), 2.37–2.25 (m, 1 H), 1.86–1.55 (m, 3 H), 1.53–1.40 (m, 2 H), 1.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 151.7, 135.9, 129.1, 126.6, 76.4, 63.4, 35.1, 27.0, 26.2, 20.5; CI-HRMS Calcd for $C_{14}H_{19}O_2$ $(M + H)^+$: 219.1383. Found: 219.1380; Anal Calcd for $C_{14}H_{18}O_2$: C, 77.55; H, 8.68. Found: C, 77.47; H, 8.64.

1-(3-(2-Methyltetrahydro-2*H*-pyran-2-yl)phenyl)ethanone (Table 4, entry 2)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1 H), 7.84 (d, J = 7.8 Hz, 1 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.48 (t, J = 8.2 Hz, 1 H), 3.85–3.75 (m, 1 H), 3.54–3.42 (m, 1 H), 2.63 (s, 3 H), 2.40–2.27 (m, 1 H), 1.86–1.76 (m, 1 H), 1.74–1.58 (m, 2 H), 1.54–1.42 (m, 2 H), 1.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 146.8, 137.8, 131.3, 129.2, 127.1, 126.1, 76.2, 63.3, 35.0, 32.5, 26.3, 20.4; CI-HRMS Calcd for $C_{14}H_{19}O_2$ $(M + H)^+$: 219.1383. Found: 219.1383; Anal Calcd for $C_{14}H_{18}O_2$: C, 77.55; H, 8.68. Found: C, 77.72; H, 8.71.

1-(4-(2-Methyltetrahydro-2*H*-pyran-2-yl)phenyl)propan-1-one (Table 4, entry 3)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, J = 8.8 Hz, 2 H), 7.43 (d, J = 8.8 Hz, 2 H), 3.74–3.65 (m, 2 H), 3.45–3.34 (m, 1 H), 2.98 (q, J = 7.4 Hz, 2 H), 1.77–1.50 (m, 3 H), 1.46–1.31 (m, 2 H), 1.30 (s, 3 H), 1.15 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.9, 171.5, 151.4, 135.7, 128.7, 126.5, 76.4, 63.3, 35.0, 32.4, 32.2, 26.2, 8.7; CI-HRMS Calcd for $C_{15}H_{21}O_2$ $(M + H)^+$: 233.1541. Found: 233.1537; Anal Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.45; H, 8.64.

2-Methyl-2-(naphthalen-1-yl)tetrahydro-2*H*-pyran (Table 4, entry 4)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11–9.01 (m, 1 H), 7.90–7.80 (m, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.57–7.37 (m, 4 H), 3.75–3.66 (m, 1 H), 3.19 (td, J = 9.2, 2.4 Hz, 1 H), 2.70–2.55 (m, 1 H), 1.95–1.80 (m, 2 H), 1.78–1.67 (m, 2 H), 1.67 (s, 3 H), 1.45–1.35 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 135.4, 132.5, 129.4, 128.8, 127.5, 126.2, 125.9, 125.7, 125.2, 79.0, 63.5, 36.7, 31.7, 26.0, 20.3; CI-HRMS Calcd for $C_{16}H_{22}ON$ $(M + NH_4)^+$: 244.1695. Found: 244.1695; Anal Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 85.12; H, 8.08.

2-Methyl-2-(naphthalen-2-yl)tetrahydro-2*H*-pyran (Table 4, entry 5)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.80 (m, 4 H), 7.60 (dd, J = 8.8, 1.6 Hz, 1 H), 7.53–7.42 (m, 2 H), 3.84–3.74 (m, 1 H), 3.51 (td, J = 11.2, 2.8 Hz, 1 H), 2.53–2.41 (m, 1 H), 1.92–1.79 (m, 1 H), 1.78–1.54 (m, 3 H), 1.46 (s, 3 H), 1.45–1.37 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 133.9, 132.7, 128.7, 128.4, 127.9, 126.3, 126.1, 125.1, 125.0, 76.5, 63.4, 35.0, 33.1, 26.4, 20.6; CI-HRMS Calcd for $C_{16}H_{22}NO(M + NH_4)^+$: 244.1695. Found: 244.1699; Anal Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.99; H, 8.03.

2-Methyl-2-(*o*-tolyl)tetrahydro-2*H*-pyran (Table 4, entry 6)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.22 (m, 1 H), 7.21–7.10 (m, 3 H), 3.80–3.67 (m, 1 H), 3.35–3.22 (m, 1 H), 2.51 (s, 3 H), 2.50–2.42 (m, 1 H), 1.80–1.62 (m, 4 H), 1.44 (s, 3 H), 1.43–1.36 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 137.8, 133.5, 128.1, 127.2, 126.1, 78.3, 63.1, 36.3, 30.6, 26.3, 22.4, 20.5; CI-HRMS Calcd for $C_{13}H_{22}NO$ $(M + NH_4)^+$: 208.1696. Found: 208.1699; Anal Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.28; H, 9.57.

2-Methyl-2-(*m*-tolyl)tetrahydro-2*H*-pyran (Table 4, entry 7)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.17 (m, 3 H), 7.10–7.03 (m, 1 H), 3.80–3.69 (m, 1 H), 3.49 (td, J = 10.8, 2.8 Hz, 1 H), 2.36 (s, 3 H), 2.34–2.25 (m, 1 H), 1.85–1.56 (m, 3 H), 1.55–1.40 (m, 2 H), 1.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.3, 147.6, 129.8, 118.7, 112.5, 111.9, 76.4, 63.3, 55.6, 35.0, 33.1, 26.3, 20.5; CI-HRMS Calcd for $C_{13}H_{22}NO$ $(M + NH_4)^+$: 208.1696. Found: 208.1692; Anal Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.15; H, 9.54.

2-(3-Methoxyphenyl)-2-methyltetrahydro-2*H*-pyran (Table 4, entry 8)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (t, J = 8.8 Hz, 1 H), 7.08–6.96 (m, 2 H), 7.78 (dd, J = 8.0, 2.8 Hz, 1 H), 3.81 (s, 3 H), 3.77–3.69 (m, 1 H), 3.50 (td, J = 11.2, 2.8 Hz, 1 H), 2.27 (dt, J = 13.6, 4.6 Hz, 1 H), 1.80–1.46 (m, 3 H), 1.45–1.39 (m, 2 H), 1.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 138.4, 128.8, 127.6, 127.1, 123.4, 76.4, 63.2, 35.1, 33.1, 26.4, 22.1, 20.6; CI-HRMS Calcd for $C_{13}H_{19}O_2$ $(M + H)^+$: 207.1380 Found: 207.1377; Anal Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.80; H, 8.83.

Acknowledgements

We are grateful to NPIL pharma UK and the EPSRC for financial support.

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