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Synthesis of oxetane and azetidine ethers as ester isosteres by Brønsted acid catalysed alkylation of alcohols with 3-aryl-oxetanols and 3-aryl-azetidins[†]

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Oxetanes and azetidines continue to draw significant interest in medicinal chemistry, as small, polar and non-planar motifs. Oxetanes also represent interesting surrogates for carbonyl-containing functional groups. Here we report a synthesis of 3,3-disubstituted oxetane- and azetidine-ethers, with comparisons made to the ester functional group. The tertiary benzylic alcohols of the 4-membered rings are selectively activated using Brønsted acid catalysis and reacted with simple alcohols to form the ethers and maintain the oxetane ring intact. This approach avoids the use of strong bases and halide alkylating agents and allows alcohol libraries to be leveraged. Oxetane ethers demonstrate excellent chemical stability across a range of conditions and an improved stability *vis-à-vis* analogous esters under basic and reducing conditions.

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Introduction

Medicinal chemistry programs can benefit from the introduction of small motifs that access new chemical- and intellectual property space, and offer advantageous physico-chemical properties. Small 4-membered heterocyclic rings, oxetanes and azetidines, present attractive motifs in this regard due to their high polarity, low molecular weight and non-planar features.^{1,2} In 2006, Carreira compared 3,3-disubstituted oxetanes to *gem*-dimethyl groups, to provide improved metabolic stability and polarity.³ Later, the comparison with alkyl-ketones was made, whereby the oxetane ring presented similar polarity, H-bonding capacity and lone pair orientation to the carbonyl group.⁴ Since then, oxetanes have been studied as possible replacement motifs for several carbonyl-containing functional groups such as amides, aryl-ketones, thioesters and carboxylic acids (Fig. 1a),^{5–8} and are increasingly employed in medicinal chemistry. Their development has been accompanied with considerable advances in the synthesis of oxetane motifs.^{1,3–9}

While the comparison of oxetane ethers with esters has been postulated,⁴ this remains to be exemplified. Indeed, to date there are few studies that prepare¹⁰ the oxetane ether motif and/or investigate their stability.¹¹ Very recently, 3,3-di-

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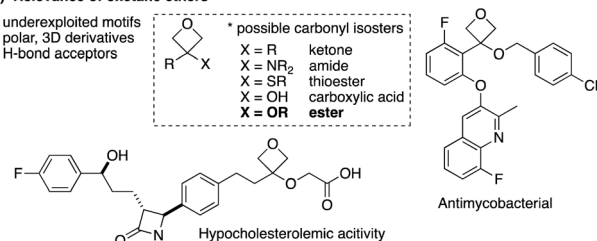
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[†]Electronic supplementary information (ESI) available: X-ray crystallographic data; additional optimization; compound stability to stationary phases; experimental procedures; characterization data and copies NMR spectra. CCDC 2250896 and 2250897. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3ob00731f>

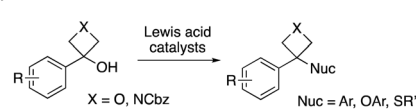
a) Relevance of oxetane ethers

* underexploited motifs
* polar, 3D derivatives
* H-bond acceptors

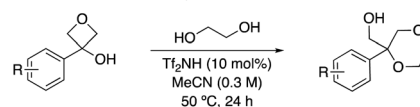
possible carbonyl isosteres:
X = R ketone
X = NR₂ amide
X = SR thioester
X = OH carboxylic acid
X = OR ester



b) Previous work



c) 1,4-Dioxanes from oxetanols and 1,2-diols



d) This work: oxetane and azetidine ethers from alcohols

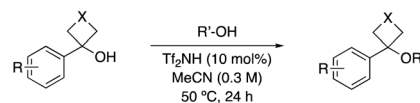


Fig. 1 Oxetane and azetidine ethers.



substituted oxetane benzyl ethers were reported to display antimycobacterial activity,¹² and have also appeared in the patent literature in compounds for the reduction of cholesterol levels (Fig. 1a).¹³

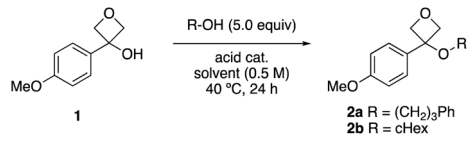
Azetidine ether motifs have been prepared by S_N2 reaction of azetidins with alkyl halides, or by Mitsunobu reactions.¹⁴ 3,3-Disubstituted azetidines showed biological activity relevant to cancer and SLE (systemic lupus erythematosus).^{14f,g} 3,3-Disubstituted oxetane ethers have also been exploited as intermediates in the synthesis of heterocycles through intramolecular oxetane opening.^{15,16} In these cases, the ethers are typically prepared from oxetanols with strong bases and halide alkylating agents. We have recently developed catalytic approaches to use benzylic oxetanols and azetidins as alkylating agents for the preparation of 3-aryl-3-functionalised-oxetanes and azetidines *via* carbocation intermediates (Fig. 1b).^{17–19,20} Lewis acid catalysts (Li⁺, Ca²⁺ and Fe³⁺ salts) were successful for selective alcohol activation for Friedel–Crafts alkylation reactions and reactions with thiols. Interestingly, in the Friedel–Crafts reaction with phenols, aryl oxetane ethers were identified as reversible off-cycle intermediates.^{17c} We envisaged that the use of aliphatic alcohols as nucleophiles in a related process would provide an advantageous approach to the preparation of oxetane ethers, avoiding the use of alkyl halides. Recently, we reported the annulation of aryl-oxetanols with 1,2-diols to form 1,4-dioxanes (Fig. 1c).^{16,20} In this instance we proposed an intermediate oxetane ether and intramolecular oxetane opening, but this ether intermediate was neither isolated nor observed spectroscopically.

Here, we report the first preparation of oxetane and azetidines *via* 4-membered ring carbocation intermediates, using a Brønsted acid catalyst (Fig. 1d). These small-ring ethers present an underexplored motif for medicinal chemistry, and the chemical stabilities of selected oxetane ether/ester pairs were tested under various conditions.

Results and discussion

Our study began with electron rich 3-(4-methoxyphenyl)-oxetan-3-ol **1** known to be suitable to stabilise the strained ring carbocation,¹⁷ and used 3-phenyl propanol as the nucleophile. Attempts to use Lewis acid catalysts that had been previously successful for thiol and phenol nucleophiles were unsuccessful in the presence of the alcohols. On the other hand, using catalytic triflic acid (5 mol%) in chlorinated solvents (0.5 M **1**) gave promising conversion with an excess of the alcohol reagent (Table 1, entries 1–3).²¹ Varying the solvent indicated that MeCN was optimal (entries 4–7). Varying the acid indicated an improvement using triflimidic acid over triflic or tosic acids (entries 7–9), related to the increasing acidity of the catalysts. For comparison, FeCl₃ in toluene^{18a} gave 8% of the product with a high amount of recovered oxetan-3-ol (entry 10). Using 10 mol% acid loading gave the best yields, at a reaction temperature of 50 °C (entries 9, 11–13).

Table 1 Optimisation of the synthesis of oxetane ethers



Entry	–R	Acid	Acid loading (mol %)	Solvent	Yield 2a or 2b ^a (%)	RSM 1 ^{a,b} (%)
1	–(CH ₂) ₃ Ph	TfOH	5	CHCl ₃	22	33
2	–(CH ₂) ₃ Ph	TfOH	5	CH ₂ Cl ₂	22	28
3	–(CH ₂) ₃ Ph	TfOH	5	DCE	40	18
4	–(CH ₂) ₃ Ph	TfOH	5	Toluene	18	24
5	–(CH ₂) ₃ Ph	TfOH	10	DCE	45	0
6	–(CH ₂) ₃ Ph	TfOH	10	DMSO	0	56
7	–(CH ₂) ₃ Ph	TsOH	10	MeCN	19	56
8	–(CH ₂) ₃ Ph	TfOH	10	MeCN	64	4
9	–(CH ₂) ₃ Ph	Tf ₂ NH	10	MeCN	70	4
10	–(CH ₂) ₃ Ph	FeCl ₃	7.5	Toluene	6	87
11	–(CH ₂) ₃ Ph	Tf ₂ NH	5	MeCN	56	23
12	–(CH ₂) ₃ Ph	Tf ₂ NH	20	MeCN	54	5
13 ^c	–(CH ₂) ₃ Ph	Tf ₂ NH	10	MeCN	65	18
14 ^{d,e}	–(CH ₂) ₃ Ph	Tf ₂ NH	10	MeCN	70	8
15 ^d	–cHex	Tf ₂ NH	10	MeCN	42	21
16 ^{d,e}	–cHex	Tf ₂ NH	10	MeCN	52	33
17 ^{d,e,f}	–cHex	Tf ₂ NH	10	MeCN	17	68
18 ^{d,e,g}	–cHex	Tf ₂ NH	10	MeCN	50	nd

Reactions performed on a 0.25 mmol scale. ^a Calculated by ¹H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. ^b Recovered oxetan-3-ol. ^c Reaction performed at 30 °C. ^d Reaction performed at 50 °C. ^e Reaction performed at concentration of 0.3 M. ^f Using 1.0 equiv. cyclohexanol. ^g Using cyclohexanol as limiting reagent, with 5.0 equiv. oxetan-3-ol.

Unfortunately, applying these conditions directly to the secondary alcohol cyclohexanol gave relatively low yields (42%, entry 15). Reducing the concentration to 0.3 M gave an improved yield of 52% (entry 16). These conditions with the primary alcohol gave similar results (entry 14) and were selected for further study. For comparison using 1 equiv. of the alcohol gave a low yield of 17% and significant recovered oxetan-3-ol (entry 17). Alternatively, a useful yield could be obtained using excess oxetan-3-ol, with the alcohol as the limiting reagent, useful for the oxetane-functionalisation of valuable alcohol substrates (entry 18).

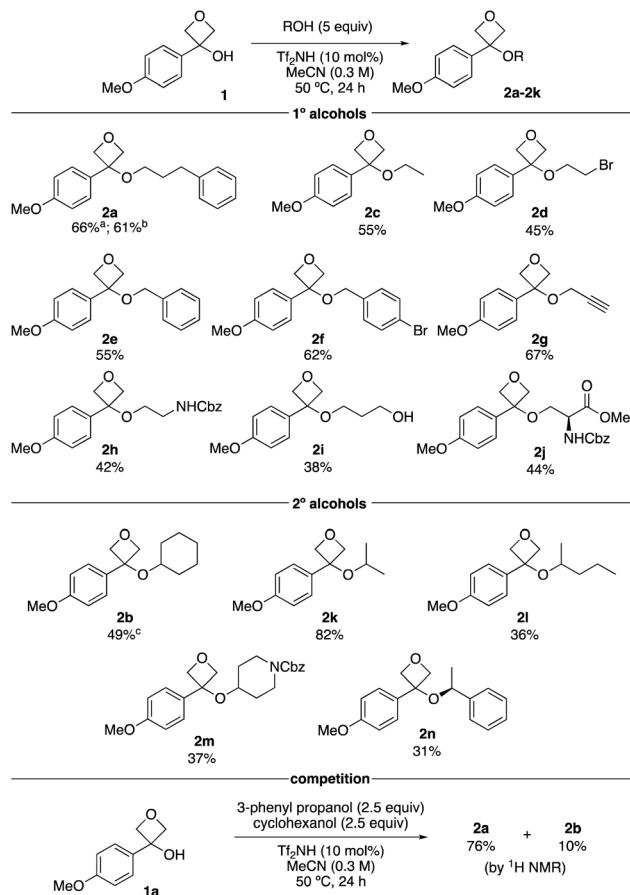
With optimised reaction conditions, the substrate scope of alcohols was investigated using primary and secondary alcohols (Scheme 2). The standard alcohol, 3-phenylpropanol, provided the oxetane ether **2a** in 66% on a 2.0 mmol scale, and 61% on a 6 mmol scale (1.04 g, **2a**). Ethanol gave ethyl ether **2c** in 55%. Notably, bromoethanol was also successful, yielding oxetane ether **2d** (45%), which would not be readily obtained under S_N2 conditions with oxetan-3-ol and alkyl halides. Benzylic alcohols worked well providing bis-benzylic oxetane ethers **2e** and **2f** in 55% and 62% respectively. Propargylic alcohol could be employed (**2g**), introducing a potential click handle. Whereas ethylene glycol under these reaction conditions gives a dioxane product,¹⁶ Ncbz-amino ethanol gave oxetane ether **2h** in 42% yield. 1,3-Dihydroxy propane provided



oxetane ether **2i** as the major product in 38% yield without ring-opening of oxetane. Using serine gave the modified amino acid product **2j** in 44% yield.

Cyclohexanol gave a moderate yield of the desired product **2b**. This product displayed some instability on silica caused by the acidity of the stationary phase. Assessment of stationary phases for purification²² indicated basic alumina (activity IV) would be most suitable, which raised the isolated yield from 33% to 49%. Isopropanol afforded oxetane ether **2k** in 82%, indicating lower steric demands than cyclohexanol. 2-Pentanol gave the ether **2l** in 36% yield. A heterocyclic secondary alcohol, Cbz-piperidinol, provided ether **2m** in 37%. However, Boc-piperidinol did not afford the desired ether. Using (*S*)-1-phenylethanol gave the ether product **2n** in 31% yield and maintained high levels of enantioenrichment (92 : 8 er). The tertiary alcohol *tert*-butanol was unsuccessful.

A competition reaction between primary and secondary alcohols was then performed, whereby ether **2a** from 3-phenyl propanol dominated with 76% yield (Scheme 1). The secondary cyclohexanol gave oxetane ether **2b** in only 10% yield, further indicating the selectivity based on steric grounds.



Scheme 1 Reaction scope varying the alcohol using oxetanol **1**. Reactions performed on a 0.25 mmol scale. ^aReaction performed on a 2.0 mmol scale. ^bReaction performed on a 6.0 mmol scale. ^cProduct isolated using chromatography on basic alumina (activity IV).

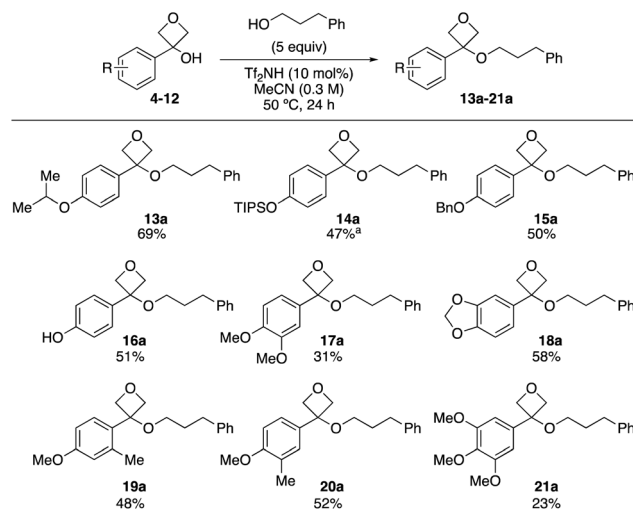
Interestingly, attempts to use methoxyethanol and ethoxy ethanol did not form the oxetane ether. Instead, dioxane **3** was formed in 71% and 43%, respectively, as a result of cyclisation comparable to our previous report using ethylene glycol (Table 2, entries 1–3).¹⁶ Using isopropoxyethanol with the bulkier *i*Pr group gave both oxetane ether **2o** (22%) and dioxane **3** (33%) products (entry 4), and with phenoxy ethanol, dioxane **3** was not observed (entry 5). Mechanistically, formation of dioxane **3** may proceed *via* etherification then oxetane ring opening to produce an oxonium ion followed by loss of the alkyl group either by an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism. Resubjecting **2o** to the reaction conditions gave dioxane **3** as the only product (25% yield by ^1H NMR), confirming the viability of this route.

Variation of the oxetanol substrate was investigated using 3-phenyl propanol as a nucleophile (Scheme 2). 4-Isopropoxy derivative (**13a**) was formed in a similar yield to the methoxy-example. Protected phenolic derivatives bearing OTIPS and

Table 2 Competing cyclisation with alkoxyethanols

Entry	R	Isolated yield (%)	
		Oxetane ether	Dioxane 3
1 ^a	H	0	90
2	Me	0	71
3	Et	0	43
4	<i>i</i> Pr	22 (2o)	33
5	Ph	53 (2p)	0

Reactions performed on a 0.25 mmol scale. ^aResult from ref. 16.



Scheme 2 Reaction scope varying oxetan-3-ol substrate. Reactions performed on a 0.25 mmol scale. ^aProduct isolated using chromatography on basic alumina (activity IV).



OBn groups at the 4-position were also successful (**14a** and **15a**). TIPS protected product **14a** displayed instability on acidic silica and was obtained in 47% using basic alumina (activity IV) for chromatography. The free phenol could also be applied and **16a** was obtained in 51% yield. Di-substituted phenyl oxetanols also underwent etherification, providing the ethers in moderate yield (**17a–20a**). The lower yield observed with dimethoxy phenyl (**17a**) was ascribed to rapid formation of the carbocation, followed by degradation, since the dimethoxy substitution pattern is expected to best stabilize the transition state to form the oxetane carbocation.^{7a} 3,4,5-Trimethoxy-substituted derivative gave the product (**21a**) in 23% yield, presumably due to the deactivating electronic effect from the 3- and 5-positions which prevent effective planarization and conjugation from the 4-methoxy group.^{7a} The lower yield observed with both the carbocation-stabilising dimethoxy- (**17a**) and the carbocation-destabilising trimethoxy substitution pattern (**21a**) highlight the requirement of the etherification reaction for a defined stability window of the oxetane carbocation to prevent its degradation due to too rapid formation (dimethoxy) or insufficient stability (trimethoxy). Less electron rich aromatic groups were unreactive: the desired oxetane ether was not obtained in the reaction with 3-phenyl oxetan-3-ol, nor *ortho/meta*-methoxy phenyl derivatives.

The conformation of oxetane ethers **2a** and **2b**, determined by X-ray crystallography, differs to that of related esters (Fig. 2). The absence of the π -carbonyl- p_O conjugated system in the oxetane structure confers oxetane ethers with increased 3-dimensionality. The aryl ring is twisted at *ca.* 80° out of the O3–C1–C_{Ar} plane (C_{Ar} = C15 in **2a** and C12 in **2b**). In benzoates on the other hand, the aryl ring is only *ca.* 3° out of plane to maximize π -conjugation resulting in a flat conformation. As observed in our previous analysis on 3-aryl-3-alkyl-oxetanes,²³ the increased steric requirement of the oxetane ring provokes a switch in conformational preference of the ethereal substituent which lies on the aryl side in oxetane ethers in a *quasi*-staggered conformation, but on the carbonyl side in benzoate structures.

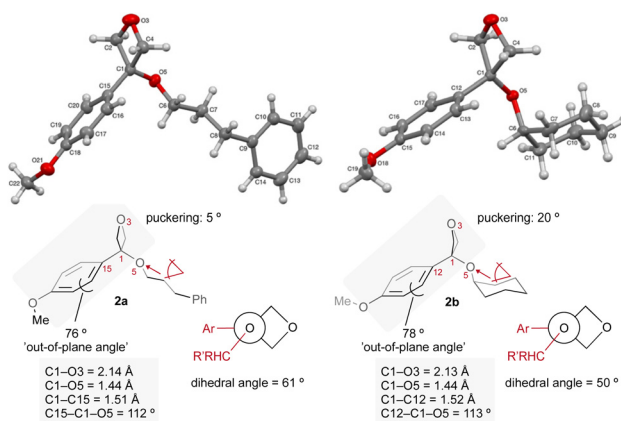
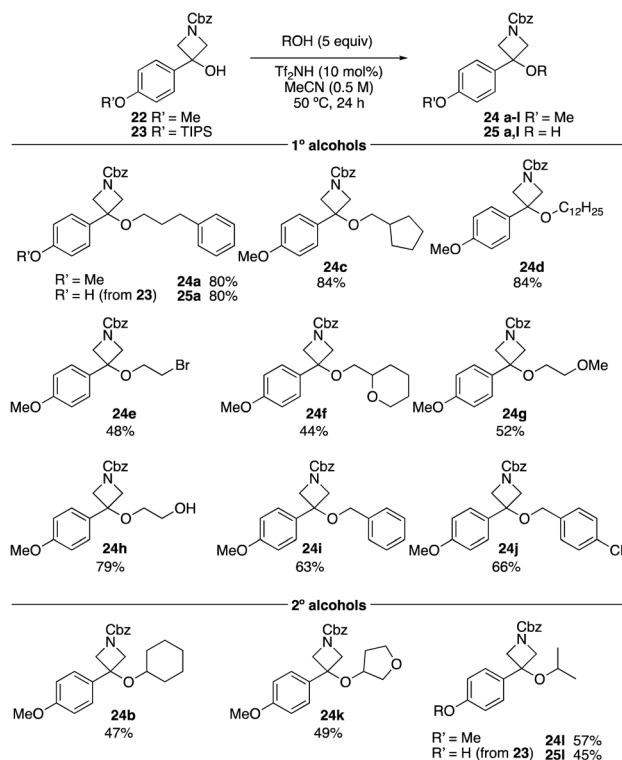


Fig. 2 X-ray structures (50% probability ellipsoids) of oxetane ethers **2a** and **2b**.

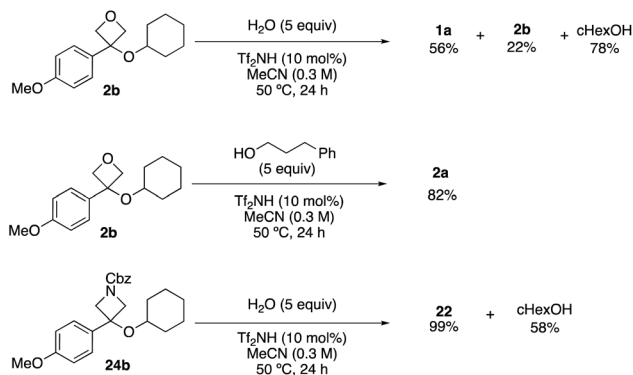
Similar optimisation was conducted on N-Cbz 3-PMP-azetidin-3-ol **22**. Using very similar conditions, at 0.5 M concentration, slightly improved yields were obtained for the azetidine ether derivatives (Scheme 3). The reaction with primary alcohols yielded the desired products in moderate to high yields (**24a**, **24c–24j**). Interestingly, methoxy ethanol and ethylene glycol gave azetidine ethers **24g** and **24h** in 52% and 79% yield without ring-opening. The secondary alcohols, cyclohexanol, 3-hydroxytetrahydrofuran and isopropanol, gave the azetidine ether products in 47%, 49%, and 57%, respectively. With OTIPS-azetidinol **23**, alkylation and TIPS deprotection were observed, which was not seen in the oxetane derivatives, though the yield was similar to that obtained with the methoxyphenyl derivative **22**.

Throughout the study, the requirement for excess nucleophile suggested the reaction may be reversible. This was confirmed by resubmitting oxetane and azetidine ethers to the reaction conditions in the presence of water, which led to formation of the corresponding alcohols (Scheme 4). The oxetane ether was recovered in 22% with oxetanol and cyclohexanol formed in 58% and 78%, in similar proportions to the forward reaction. Oxetane ether **2b** was resubmitted to the reaction conditions in the presence of 3-phenylpropanol which yielded the trans-etherification product (**2a**) in 82%. Azetidine ether **24b** gave back azetidin-3-ol **22** in 99% yield, consistent with a more rapid carbocation formation and preferential trapping by the smaller nucleophile (H₂O) potentially due to increased



Scheme 3 Reaction scope varying the alcohol using azetidinols **22** and **23**. Reactions performed on a 0.5 mmol scale.

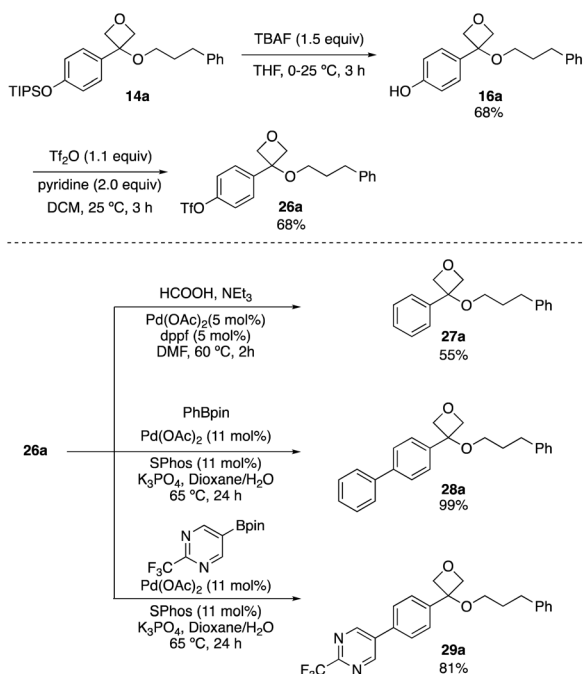




Scheme 4 Control experiments indicating reaction reversibility.

steric hindrance around the azetidinium carbocation caused by the Cbz group.^{18b,24}

As the reaction was limited to electron-rich aryl groups, we next examined the potential to diversify the arene through cross-coupling reactions. TIPSO-phenyl oxetane ether **14a** was readily deprotected with TBAF to form phenol **16a**, and triflate **26a** was formed on reaction with triflic anhydride. This proved to be a versatile intermediate for palladium-catalysed cross coupling processes. Reduction to the unsubstituted phenyl ring (**27a**) was achieved using formic acid, triethylamine with palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (dppf) ligand at 60 °C (Scheme 5).²⁵ Applying triflate **26a** to Suzuki–Miyaura reactions with pinacol boronates gave biaryls **28a** and **29a** in 99% and 81% yield respectively, including the incorporation of the (trifluoromethyl)pyrimidine motif (Scheme 5). These reactions occurred without degradation of



Scheme 5 Cross-couplings of oxetane ether triflate **26a**.

the oxetane ether motif and demonstrated the potential for incorporation into more complex molecules.

The oxetane and azetidinium ethers present potentially interesting motifs for application in drug discovery programmes, to provide an unusual 3D motif. Also of interest is the comparison with the corresponding esters. Esters typically hydrolyse rapidly under physiological conditions, catalysed by esterase enzymes, and so are extensively employed as pro-drugs which can improve solubility.²⁶

The stability of oxetane ethers in comparison with analogous esters was investigated by subjecting oxetane ether **2a** and ester 'pair' **30** to different reaction conditions to assess compound recovery (Table 3). Initially, heating at 80 °C in DMSO and toluene for 24 h gave excellent recovery for both compounds (entries 1 and 2). Generally, esters are easily hydrolysed under acidic or basic aqueous conditions. The oxetane ether/ester pairs were treated with 1 M HCl at 37 °C (entry 3), related to average body temperature, though neither substrate was lost through hydrolysis. On the other hand, 1 M NaOH at rt gave significant loss of the ester (36% recovery), but full recovery of the oxetane (entry 4). Nucleophilic reagents NaI/acetone gave good recovery for both. The oxetane ether was also stable to LiBH₄ whereas the ester underwent reduction, giving only 13% recovery (entry 6). The oxetane ether was treated with MeO-cysteine to mimic glutathione and was unreactive. Taken together, these results demonstrate high stability for the oxetane ether **2a** under acidic, basic and nucleophilic conditions. Secondary alcohol oxetane ether **2b** showed some instability in acid conditions in 1 M aqueous HCl solution (94% recovery 1 h at rt; 77% recovery 1 h, 37 °C, 31% recovery 24 h, 37 °C), presumed to proceed through the re-formation of the oxetane carbocation. This further indicated a steric influence on compound stability.

Table 3 Comparisons of chemical stability of oxetane ether **2a** and ester **30**

Entry	Conditions	Recovery (%) ^c	
		Oxetane ether 2a	Ester 30
1 ^a	Toluene 80 °C for 24 h	99	100
2 ^a	DMSO 80 °C for 24 h	99	100
3 ^a	1 M aq. HCl, 37 °C, 24 h	96	96
4 ^a	1 M aq. NaOH, rt, 24 h	99	36
5 ^b	10 equiv. NaI in acetone, 50 °C, 1 h	96	97
6 ^b	5 equiv. LiBH ₄ in THF, 65 °C, 1 h	99	13
7 ^b	1 equiv. MeO-cysteine, DMF/H ₂ O, rt, 12 h	99	99

^a Reactions performed on a 0.05 mmol scale. ^b Reactions performed on a 0.1 mmol scale. ^c Amount of recovered compound was calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.



Conclusions

A protocol for the preparation of oxetane and azetidine ethers using oxetanols and azetidinols as electrophiles with alcohol nucleophiles has been developed. This avoids the requirement for alkyl halide reagents, and produces water as the only by-product. The condensation reaction requires a Brønsted acid catalyst and proceeds through an oxetane carbocation intermediate. The reaction was shown to be reversible under the reaction conditions. Oxetane ether products were diversified on a reactive phenol handle to access more complex aromatic structures. Oxetane ethers showed a significantly higher stability to basic and reducing conditions in comparison to the corresponding ester, as well as stability to high temperatures, acidic aqueous conditions, and thiols.

Conflicts of interest

There are no conflicts to declare.

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