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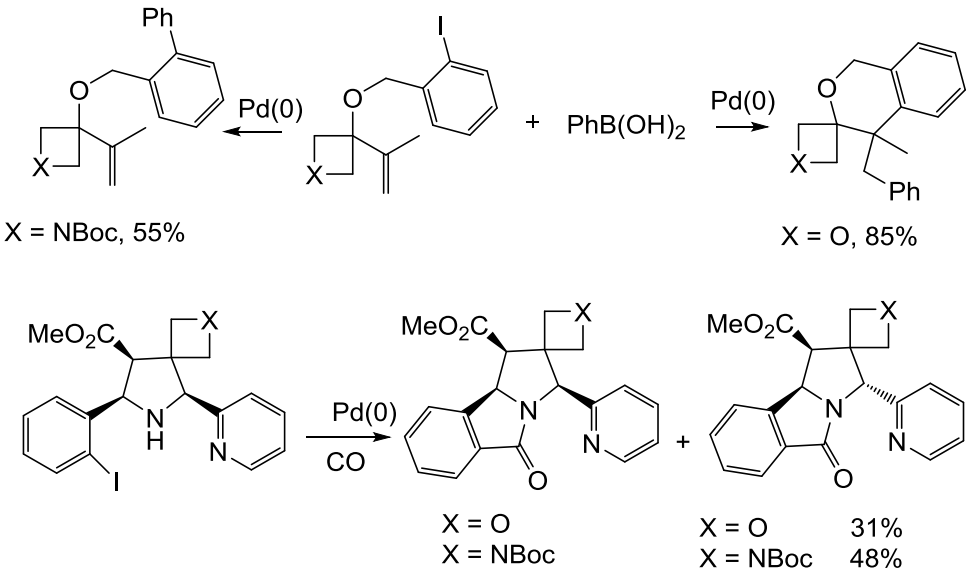

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ABSTRACT

Oxetane-benzopyran spirocycles were synthesised via a palladium catalysed cyclisation-cross coupling cascade reaction whilst oxetane/azetidine-pyrrolidino isoindolone spirocycles were synthesised via a silver catalysed 1,3-dipolar cycloaddition followed by a palladium catalysed carbonylation-amination process.

Oxetane rings in drug molecules have been found to have an influence on a multitude of different properties, including lipophilicity, aqueous solubility, metabolic stability, and conformational preference; they also greatly improve key pharmacokinetic properties when grafted onto molecular scaffolds.[1] Oxetanes also demonstrate diverse potential as bioisosteres for less desirable functional groups in drug design, such as gem-dimethyl and carbonyl groups. The potential for oxetanes to be used as gem-dimethyl bioisosteres was introduced by Carreira and co-workers; [2] it is common practice in drug discovery to introduce gem-dimethyl groups into metabolically labile methylene units. However, this also adds to the molecules lipophilicity, and can adversely affect its pharmacokinetic properties. Use of an oxetane instead of a gem-dimethyl group, bridging the two methyl groups with an electronegative oxygen, has been shown to add the desired bulk without altering the overall lipophilicity.[2] Furthermore, the van der Waals volume of oxetane is almost identical to that of the gem-dimethyl group, and their partial molar volumes in water are essentially identical. [3]

Benzopyran derivatives have been shown to have notable bioactivity, including anti-inflammatory and anti-hypertensive qualities. [4] Benzopyrans can be found in a multitude of divergent areas within chemistry; such as the metabolite eriodictyol, which has anti-inflammatory and antioxidant properties,[5] and the phytoalexin xanthyletin, which is found in citrus plants[6] (Fig. 1). Oxetane/pyrrolidine spirocycles are important structural motifs, possessing a wide range of medicinal properties including anti-viral[7] and anti-bacterial[8] (Fig. 1)

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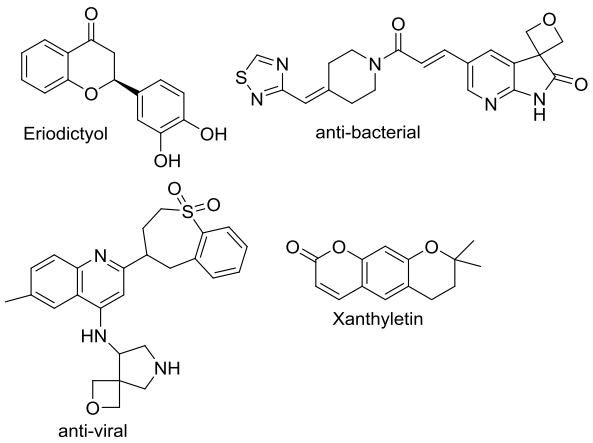
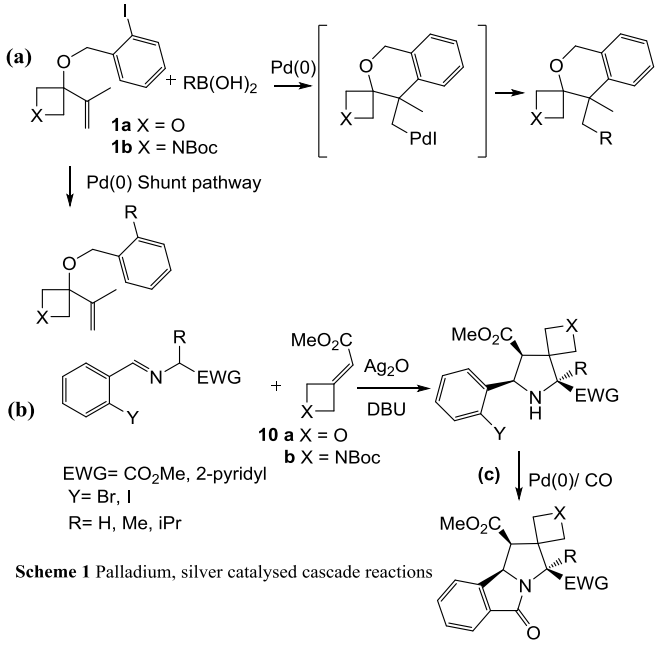


Figure 1. Examples of drug molecules containing the benzopyran motif and oxetane/pyrrolidine spirocycle

In this communication we report (i) A palladium catalysed cyclisation-cross coupling cascade reaction to the synthesis of oxetane-benzopyran spirocycles (Scheme 1a) and (ii) A silver catalysed 1,3-dipolar cycloaddition followed by a palladium catalysed carbonylation amination process to afford oxetane/azetidine-pyrolidino isoindolone spirocycle (Scheme 1b, c). Palladium catalysed cyclisation-cross coupling cascade reactions were used to synthesise benzopyran spirocycles with a tethered oxetane moiety. [9] Initially we explored the palladium catalysed cyclisation-cross coupling process using **1a** (1 mmol), phenyl boronic acid (2 mmol), $Pd(OAc)_2$ (10 mol%), dppf (10 mol%) and Cs_2CO_3 (2 mmol) in dioxane/water (15:1, 3 mL) stirred at 90 °C for 16 h which gave the cyclisation-cross coupling product **2** together

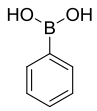
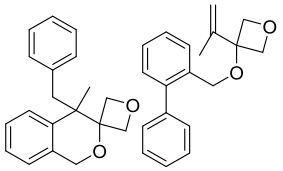
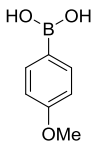
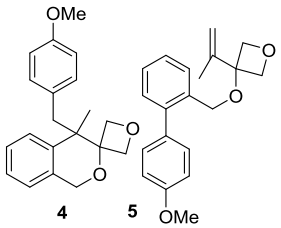
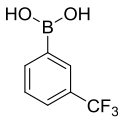
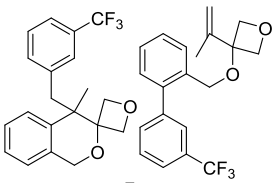
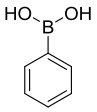
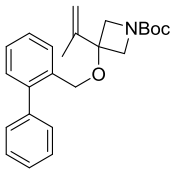
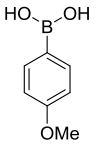
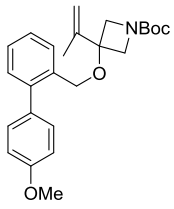
with the direct capture product **3** in 85% yield (Table 1, entry 1) favouring the cyclisation-cross coupling product **2**. Cyclisation-cross coupling reactions using **1a** and p-methoxyphenyl boronic acid gave the cyclisation cross coupling product **4** together with the direct capture product **5** in 50% yield (Table 1, entry 2) whilst m-triflouromethylphenylboronic acid gave the cyclisation-cross coupling product **6** and the direct capture product **7** in 24% yield (Table 1, entry 3). Lower yields of the products **6** and **7** (Table 1, entry 3) may be partly due to the boronic acid containing electron withdrawing group undergoes protodeborylation at a faster rate.

However, when a Boc-protected azetidine was tethered to alkene **1b** only the direct capture products **8** and **9** were observed (Table 1, entries 4, 5) in moderate yield suggesting that the transmetallation step occurs faster than the carbopalladation step (Scheme 1a). This is proposed to be due to the difference in puckering angle between the azetidine (≈33°) and oxetane (11°) rings.[10]



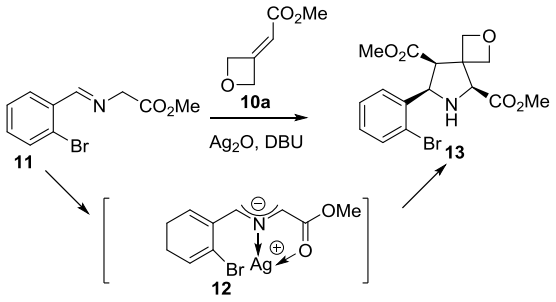
Scheme 1 Palladium, silver catalysed cascade reactions

Table 1. Palladium catalysed cyclisation-cross coupling cascade[a]

Entry	Zipper	Boronic acid	Product	Yield (%)[b]
1	**1a**		 **2** : **3** 13 : 1	85
2	**1a**		 **4** : **5** 3 : 1	50
3	**1a**		 **6** : **7** 3 : 1	24
4	**1b**		 **8**	55[c]
5	**1b**		 **9**	30[c]

a. **1** (1 mmol), boronic acid (2 mmol), $Pd(OAC)_2$ (10 mol%), dppf (10 mol%) and Cs_2CO_3 (2 mmol) in dioxane/water (15:1, 3 mL) stirred at 90 °C for 16 h; b. Isolated yield. c. Use of $Pd(PPh_3)_4$ also gave the direct capture product.

Next, we explored the silver catalysed 1, 3-dipolar cycloaddition followed by a palladium catalysed carbonylation amination process to afford oxetane/azetidine-pyrolidino isoindolone spirocycles (Scheme 1b). Initially we carried out the silver catalysed 1,3-dipolar cycloaddition reaction using methyl-(E)-N-[(2-bromophenyl)methylene]glycinate **11** (0.5 mmol), methyl 2-(oxetan-3-ylidene)acetate **10a** (0.5 mmol), Ag_2O (10 mol%) and DBU (0.5 mmol) in toluene (10 mL) at room temperature for 16 h, which gave the cycloadduct **13** in 53% yield (Table 2, entry 1). The cycloaddition was regio- and stereoselective and occurred via the endo transition state of the syn-dipole **12** (Scheme 2). [11] Single diastereomer was observed using tert-butyl-3-(2-methoxy-2-oxoethylidene) azetidine-1-carboxylate **10b** as a dipolarophile (Table 2, entry 2).

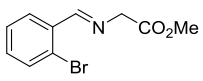
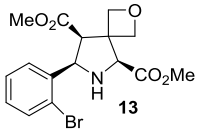
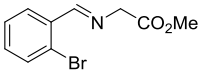
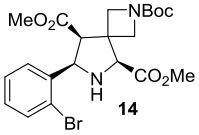
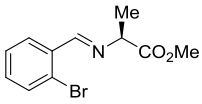
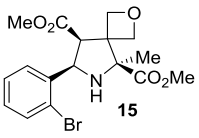
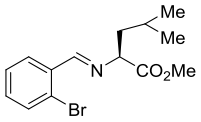
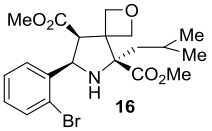
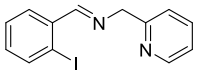
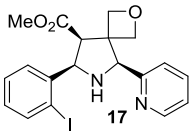
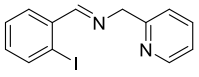
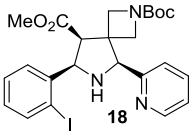


Scheme 2. Formation of the metallo dipole

Imines derived from alanine methyl ester/ leucine methyl ester also underwent the cycloaddition reaction with the dipolarophile **10a** to

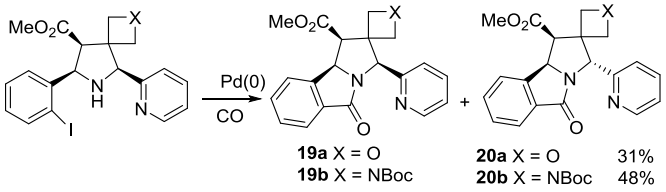
give cycloadducts **15** and **16** in moderate yields (Table 2, entries 3-4). We also varied the activating group in the imine. Thus, 2-pyridyl activating group on the imine resulted in good yields of cycloadducts **17** and **18** in moderate yields (Table 2, entries 5-6).

Table 2. Silver catalysed 1, 3-dipolar cycloaddition reaction[a]

Entry	Imine	Cycloadduct	Yield (%)[b]
1		 **13**	53
2		 **14**	46
3		 **15**	52
4		 **16**	25
5		 **17**	31
6		 **18**	46

a. Imine (0.5 mmol), dipolarophile (0.5 mmol), DBU (0.5 mmol) and Ag_2O (10 mmol%), toluene, room temperature 16-20 h. b. Isolated yield.

Finally we explored the palladium catalysed carbonylation (1 atm) - amination reaction (Scheme 1c). [12] Thus, **17** (1 mmol), Cs_2CO_3 (2 mmol), palladium acetate (10 mol%) and tris 2-furyl phosphine (20 mol%), under a carbon monoxide balloon in toluene at 100 °C for 24 h afforded the expected carbonylated product **19a** and the epimerised carbonylated product **20a** in a 1:1 ratio (Scheme 3). The structure of **20a** was confirmed by single crystal X-ray diffraction (Fig. 3). [13]



Scheme 3. Palladium catalysed carbonylation/amination reaction

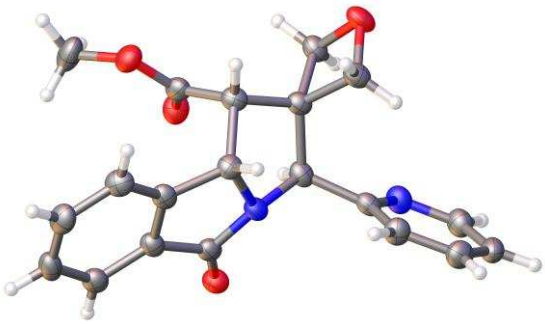


Figure 2. Molecular structure of compound **20a**

Epimerisation could occur before or after the carbonylation process. The reaction of cycloadduct **18** and carbon monoxide (1 atm) also afforded the expected carbonylated product **19b** and the epimerised carbonylated product **20b i**n an equlibrium 1:1 ratio and in 48% yield. However, the cycloducts **13-16** containg 2-bromophenyl group were reacted with carbon monoxide (1 atm) under essentially same catalytic conditions failed to give any carbonylated products may due to the sluggish oxidative addition process.

Conclusions

In summary, we have successfully carried out palladium catalysed cyclisation cross coupling cascades to synthesise benzopyran/oxetane spirocycles together with biaryl containing oxetane/azetidine in moderate to good yields. oxetane/azetidine in moderate to good yields. Oxetane/azetidine-pyrrolidino isoindolone spirocycles were synthesised via a silver catalysed 1, 3-dipolar cycloaddition followed by a palladium catalysed carbonylation-amination process in good yields.

Notes and references

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13 Deposition number for compound **20a** CCDC 1849751
Contains the supplementary crystallographic data for this structure. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.