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The stereocontrolled synthesis of complex spirotricyclic systems containing an embedded *syn*-1,2-diaminocyclohexane unit is reported, based upon a dearomatising oxidation of phenols bearing pendant ureas capable of acting as double nucleophiles. This complexity-generating transformation yields products with rich functionality suitable for application in the synthesis of potentially bioactive compounds.

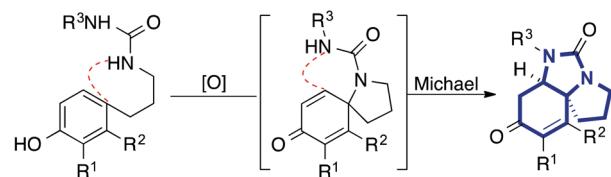
Dearomatisation reactions can be powerful tools to rapidly increase molecular complexity and access highly three-dimensional, sp^3 -rich molecular scaffolds from simple sp^2 -rich monocyclic precursors.^{1,2} In order to create diverse sp^3 -rich scaffolds for the synthesis of lead-like molecules³ and fragments,⁴ we were interested in developing a method that would allow the concise synthesis of highly functionalised 1,2-diaminocyclohexanes, motifs that are embedded in a wide range of natural and non-natural bioactive skeleta.

The formation of nitrogen-containing spirocycles by dearomatisation reactions⁵ may be triggered by reaction of phenol with external oxidants⁶ or electrophilic reagents⁷ followed by attack by a pendant nitrogen nucleophile, or alternatively by direct intramolecular attack of the arene on an electrophilic nitrogen species.⁸ We envisioned that by performing an oxidative cyclisation using a urea as the nucleophile, we might be able to effect a subsequent aza-Michael addition on the resulting spirocyclic dienone derivative, leading to formation of a spirotricyclic derivative containing an embedded 1,2-diamine in a single operation (Fig. 1a). While the intramolecular

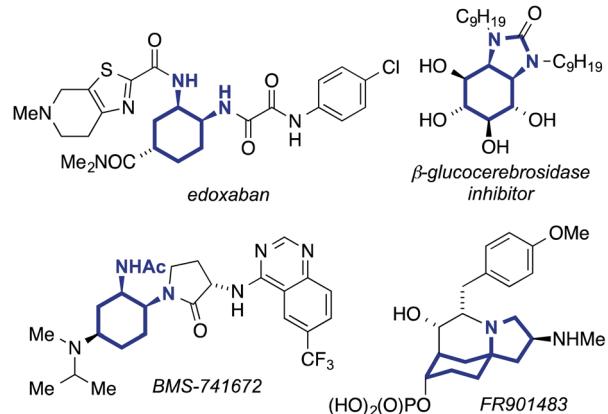
aza-Michael reaction of amides, carbamates and sulfonamides to cyclohexadienones has been widely exploited in biomimetic and other syntheses,^{9,10} there is to our knowledge only one example of a urea acting as a nucleophile, and this involved sequential dearomatisation and urea formation/asymmetric cyclisation reactions.¹¹

The intended products contain substructures that are embedded in a number of biologically-relevant skeleta. Vicinal 1,2-diamines are common motifs in many drugs and functional molecules,¹² and the 1,2-diaminocyclohexane structure is found in small molecule bioactives such as the anti-coagulant

(a) proposed oxidative dearomatising diamination of phenols



(b) biologically-active diamino- and spiropyrrolidinyl cyclohexanes



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† Electronic supplementary information (ESI) available: Full preparative experimental procedures and compound characterisation data for all numbered compounds presented in the paper; copies of ^1H and ^{13}C NMR spectra of all compounds; and X-ray crystallographic data for relevant compounds. CCDC 2174965, 2174962, 2174967, 2175094 and 2174963. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2cc06137f>

Fig. 1 Proposed oxidative diamination and related biologically-active structures.



edoxaban¹³ and the CCR2 antagonist BMS-741672¹⁴ (Fig. 1b), while derived ureas¹⁵ show activity as, for example, inhibitors of β -glucocerebrosidase.¹⁶ Additionally, the tricycles contain an embedded 1-azaspiro[4.5]decane, a structure found in myriad bioactive products^{17,18} such as the immunosuppressive agent FR-901483.¹⁹ We therefore envisaged that the spirotricyclic products might be useful starting points for the synthesis of potentially bioactive compounds, and report herein their successful synthesis through the single-step oxidative dearomatisation.

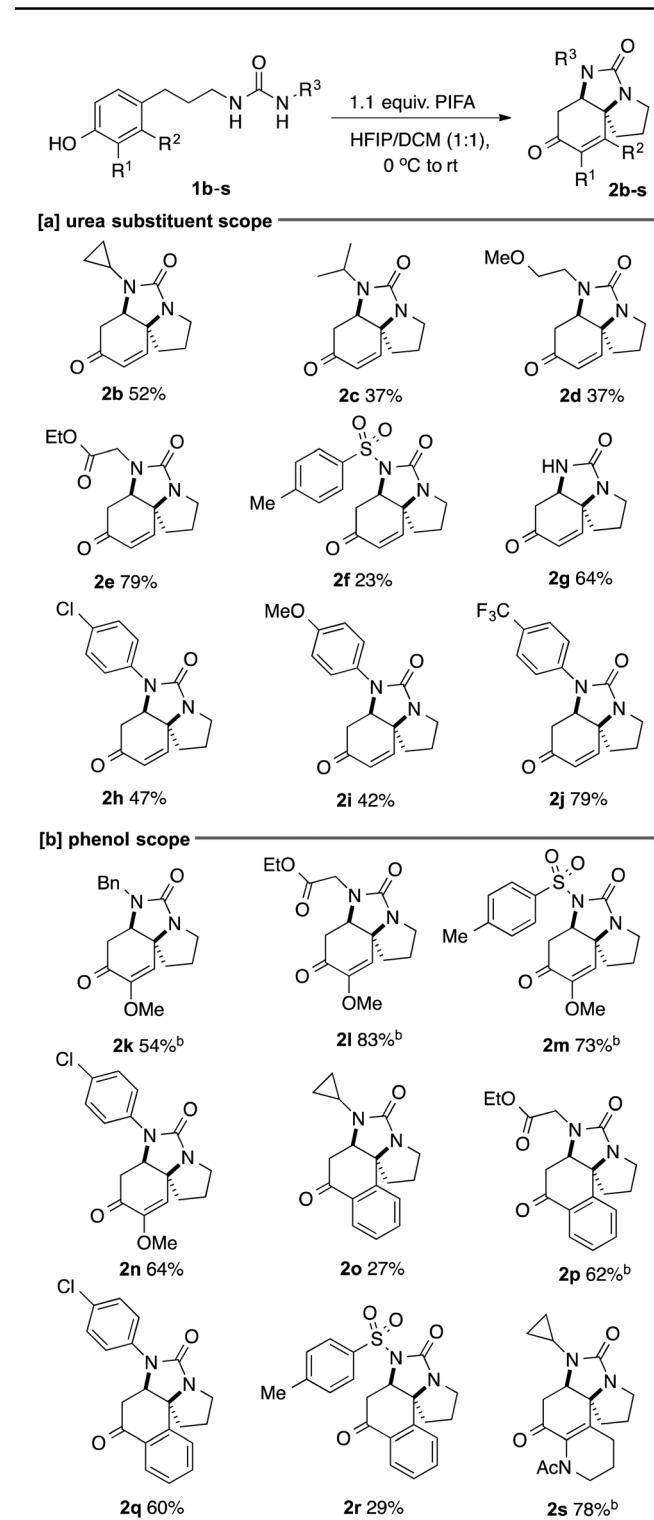
Investigations started by subjecting the (4-hydroxyphenylpropyl)urea **1a** to proposed dearomatisation conditions, using phenyliodine(III) bis(acetate)/bis(trifluoroacetate) (PIDA/PIFA respectively) as oxidants (Table 1) in hexafluoroisopropanol (HFIP).^{6b,e} While no reaction occurred with PIDA under the conditions shown, we were pleased to see that using PIFA direct conversion to the desired tricyclic structure **2a** was observed by NMR analysis (entry 2). The reaction was also successful in other fluorinated solvents (entries 3 and 4) and while lower conversions were observed in cheaper non-fluorinated solvents (entries 5 and 6), the use of a mixed HFIP/dichloromethane solvent system at higher (0.2 M) concentration gave acceptable yields. The reaction was carried out on a 7 mmol preparative scale to yield **2a** in 68% isolated yield (>1 g).

The substrate scope of the reaction was then probed, and the results are shown Table 2. We first examined the effect of different urea substituents using ureas **1b–j**, typically prepared from the reaction between 3-(4-hydroxyphenyl)propylamine and the relevant isocyanate (ESI[†]). Under the optimised reaction conditions, a range of *N*-alkyl ureas gave the tricyclic derivatives **2b–e** in moderate to good yield (panel a). The presence of an electron-withdrawing *N*-sulfonyl group resulted in a slightly lower yield (**2f**, 23%), but pleasingly the primary urea **1g** cyclised to give the free N-H tricyclic urea **2g** in 64% yield. Finally, a range of *N*-aryl urea substituents were also tolerated in the reaction, yielding tricycles **2h–j**. The compounds were formed exclusively as the *cis*-fused ureas in all cases, as expected: the structure of **2f** was confirmed by X-ray crystallography (ESI[†]).

Table 1 Reaction optimisation

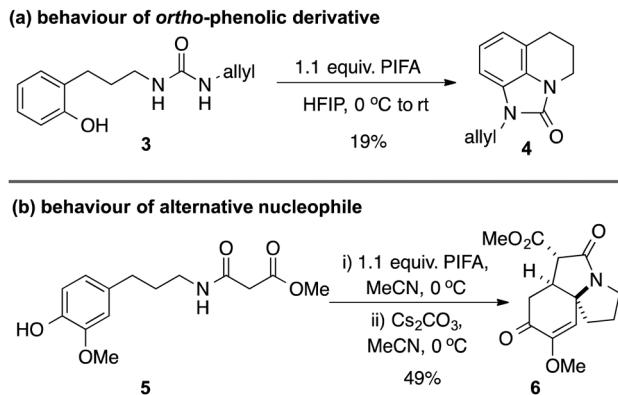
Entry ^a	I(III) source	Solvent	Yield ^b (%)	Reaction conditions: 1a + 1.1 eq. PIFA(O ₂ CR) ₂ , 0 °C to rt	
				solvent	0 °C to rt
1	PhI(OAc) ₂	HFIP	0		
2	PhI(O ₂ CCF ₃) ₂	HFIP	49		
3	PhI(O ₂ CCF ₃) ₂	TFE	48		
4	PhI(O ₂ CCF ₃) ₂	TFA	56		
5	PhI(O ₂ CCF ₃) ₂	MeCN	25		
6	PhI(O ₂ CCF ₃) ₂	DCM	12		
7	PhI(O ₂ CCF ₃) ₂	HFIP/DCM ^c	60 (68) ^d		

^a Method: substrate (1.0 eq.), PIDA/PIFA (1.1 eq.), 0.1 M in solvent, 0 °C (2 h) then rt. ^b NMR conversion. ^c Reaction carried out at 0.2 M concentration. ^d Isolated yield, 7 mmol scale.

Table 2 Substrate scope of the dearomatising diamination^{ab}

^a Conditions: phenol (1.0 eq.), PIFA (1.1 eq.), HFIP-DCM (1:1), 0.2 M, 0 °C (2 h), then rt to completion (3–24 h). ^b Reactions carried out in HFIP at 0.1 M.

Variation in the phenolic component was next investigated (panel b). The use of 3-methoxy-4-hydroxyphenyl groups also gave good yields of the tricyclic products **2k–2n**; notably these



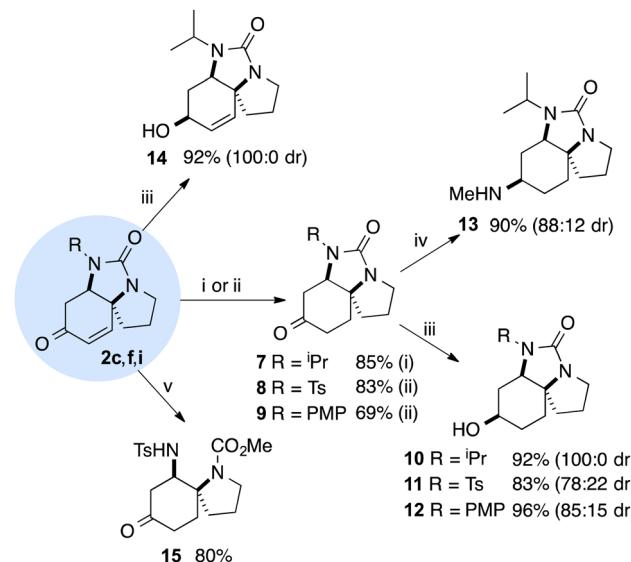
Scheme 1 Alternative cyclisation substrates.

were formed as single regioisomers, with Michael addition occurring at the more electrophilic alkene in the presumed intermediate cyclohexadienone. Hydroxynaphthalenes could also be cyclised effectively, leading to polycyclic tetralone derivatives **20–r**. Finally, cyclisation of an 8-hydroxytetrahydroquinoline-containing substrate gave the tetracycle enamine **2s** in good yield.

We also investigated the behaviour of some alternative substrates (Scheme 1). Activation of *ortho*-substituted phenol **3** with PIFA under the standard conditions did not produce a regioisomeric spirocycle to products **2**, but rather gave fused tricyclic urea **4** in 19% yield. The precise order of events leading to **4** is unknown, but such motifs have previously been prepared by intramolecular oxidative cyclisation of tetrahydroquinolinyl ureas using hypervalent iodine reagents.²⁰

The potential to employ nucleophiles other than ureas in the Michael addition step was also probed. Attempted cyclisation of the thiourea variant of **2a** or of Boc-glycyl amides (in place of the urea, designed to give a six-membered ring in the Michael addition) both gave complex mixtures, but success was achieved using β -amidoester **5**.²¹ Oxidation to the spirocyclohexenone occurred smoothly but the expected conjugate addition did not occur under the mildly acidic reaction conditions; instead, cyclisation could be effected as a separate step under basic conditions using cesium carbonate. The product was again formed as a single regioisomer *via* attack at the less-substituted alkene, and as a single diastereomer whose stereochemistry was determined by X-ray crystallography (ESI[†]).

The products of the oxidative dearomatising diamination are richly-functionalised small scaffolds, and we show some illustrative functional group transformations on these products in Scheme 2. Reduction of the alkene function of the enone may be achieved either by conjugate reduction with triethylsilane and Wilkinson's catalyst (to give **7**), or by hydrogenation with $\text{Pd}(\text{OH})_2/\text{C}$ (to give **8** or **9**). Reduction of the resulting ketones could be achieved with LiAlH_4 but was found to be more diastereoselective using NaBH_4 and CeCl_3 at low temperature (e.g. d.r. of 93:7 vs. 100:0 for formation of **10**). Stereoselective installation of an amine group was effected by sequential one-pot imine formation/reduction to give **13**. Highly stereoselective reduction of enone **2c** to an allylic alcohol can be achieved under Luche conditions to give **14**.



Scheme 2 Functional group manipulations. Reagents and conditions: (i) 2% $[\text{Rh}(\text{PPh}_3)\text{Cl}]$, Et_3SiH , THF, r.t. then 1 N HCl; (ii) 20% $\text{Pd}(\text{OH})_2/\text{C}$, H_2 (1 atm), EtOAc, r.t.; (iii) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH, $-78\text{ }^\circ\text{C}$ to r.t.; (iv) MeNH_2 , $\text{Ti}(\text{O}i\text{Pr})_4$, EtOH, then NaBH_4 ; (v) Pd/C , H_2 , MeOH then NaOMe , MeOH.

Finally, cleavage of the *N*-tosyl urea can be achieved by treatment of the saturated ketone **8** with sodium methoxide, giving spirobicyclic product **15**. The stereochemistry of compounds **8**, **14** and a crystalline derivative of **10** was confirmed by X-ray crystallography, while that of **13** was confirmed by nOe experiments (ESI[†]).

In summary we have described and exemplified a new one-pot intramolecular dearomatisation/aza-Michael process that installs a *cis*-1,2-diaminocyclohexane motif that can be readily further functionalized. The rapid generation of structural and stereochemical complexity from simple achiral precursors reinforces the power of dearomatisation reactions in synthesis. The small polycyclic products have the potential to act as scaffolds for the synthesis of putative bioactive compounds: over 400 compounds based on scaffolds such as **13** have been prepared and contributed to the Public Compound Collection of the Joint European Compound Library within the European Lead Factory project,²² and results based on our own exploitation of these scaffolds will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.



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