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A series of ring expansion reactions of P=O-containing molecules have been developed for the synthesis of medium-sized ring cyclic phosphonate esters and phosphonamidates. The reactivity trends initially appear to be counter-intuitive, compared with more well established ring expansion reactions of lactam derivatives, but are explained by considering the differences in heteroatom bonding to P and C respectively.

Molecules containing P=O bonds (*e.g.* DNA, RNA and ATP) are essential to all life on earth.¹ Organophosphorus compounds are also important in medicinal chemistry and agrochemistry, with various biologically active P=O-containing molecules known (*e.g.* 1–3, Scheme 1A).² Their potential to be used as therapeutic and crop protection agents has therefore been well studied, often using prodrug approaches.³

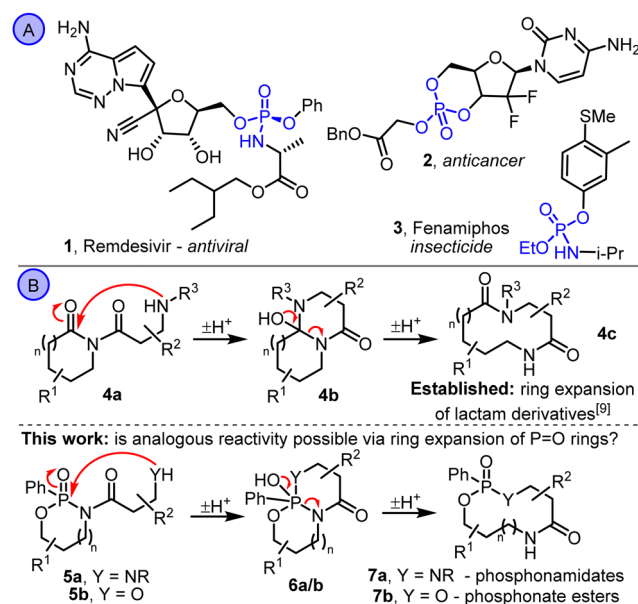
Cyclic P=O-containing molecules are routinely used in prodrug-based medicinal chemistry studies, but almost always as 5- or 6-membered ring derivatives (*e.g.* the recently reported anti-tumor candidate 2).⁴ In view of this, and interest in medium-sized rings and macrocycles in medicinal chemistry more generally,⁵ our aim in this study was to develop new methods to synthesise P=O-containing medium-sized rings using ring expansion reactions (Scheme 1B).^{6,7} Synthetic methods to make medium-sized ring P=O compounds are rare,⁸ and to the best of our knowledge there are no published examples that make use of ring expansion reactions. We therefore set out to explore whether strategies similar to those able to promote the ring expansion of lactam derivatives (*e.g.* 4a → 4b → 4c, Scheme 1B)^{9,10} can be applied to phosphonamidate derivatives of the type 5. By testing amine (5a) and alcohol (5b) tethered substrates, a reactivity trend was revealed that contrasts that seen in the established lactam ring

Ring expansion reactions of P=O-containing molecules†

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expansions; the more nucleophilic amine derivatives 5a rearrange less easily (or not at all), while less nucleophilic alcohol derivatives 5b rearrange well to form cyclic phosphonate esters 7b. Calculated Gibbs free energy data for the isomeric intermediates 5, 6 and 7 indicate that while both reaction series are exergonic, there is a much stronger thermodynamic force for ring expansion, and a lower kinetic barrier, in alcohol derivatives 5b compared with the analogous amine substrates 5a.

Synthetic studies started by exploring amine-based substrates of the type 5a; our previous work showed that related ring expansions are generally faster, more exergonic and higher yielding using amine side chains compared with alcohol¹¹ or thiol-based systems.¹² A Conjugate Addition/Ring Expansion (CARE)¹³ cascade was devised, with phosphonamidate derivative 9 reacted with different nucleophilic primary amines



Scheme 1 (A) Bioactive P=O containing small organic molecules. (B) Ring expansion reactions of lactams vs cyclic phosphonamidates.

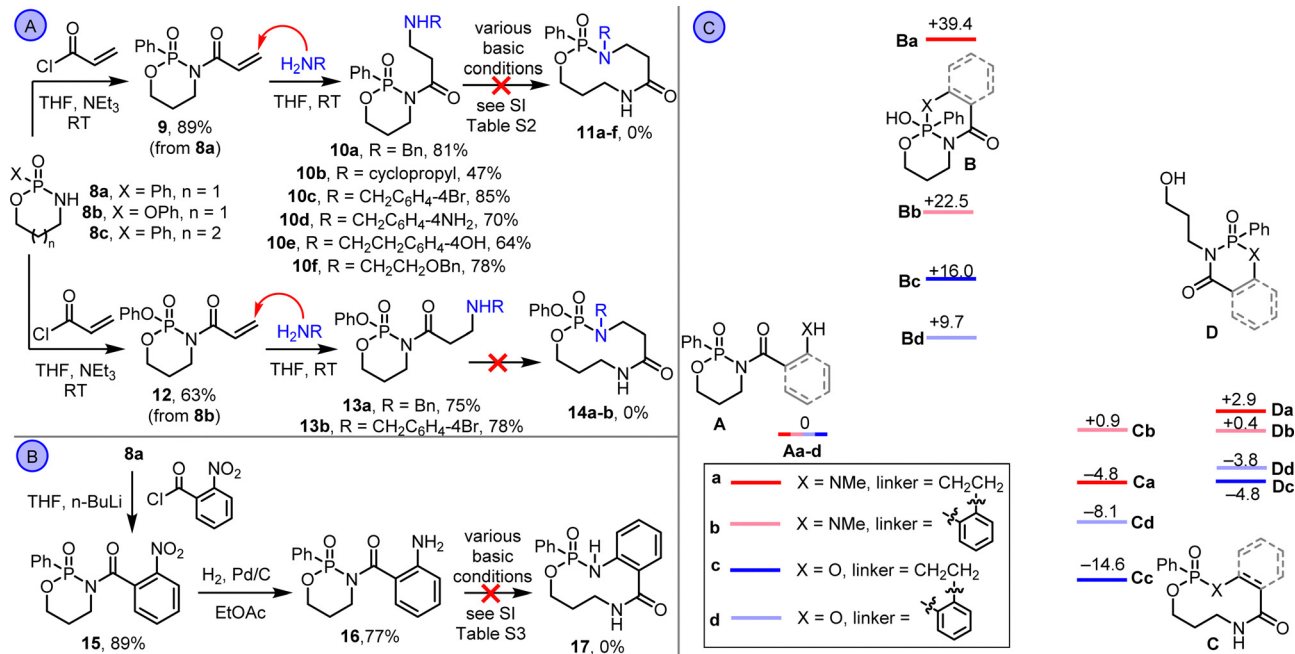
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Scheme 2 (A) Unsuccessful ring expansion of *N*-acyl phosphoramidates with tethered aliphatic amines. (B) Unsuccessful ring expansion of **16**. (C) Relative energies of isomeric species in ring expansion of *N*-acyl phosphoramidates using a DFT/B3LYP/6-31G* approach. $\Delta G^\circ_{\text{rel}}$ values at 298 K are given in kcal mol⁻¹.

(Scheme 2A). The first part of the CARE cascade reaction proceeded as expected, with amine conjugate addition taking place in each case to form amines **10a-f** in good yields.¹⁴ However, no evidence of rearrangement to ring expanded products **11a-f** was obtained under any of the basic reaction conditions screened (see ESI,† Table S2). Similar results were obtained starting from phosphoramidate derivative **12**, with conjugate addition products (**13a,b**) isolated. Aniline derivative **16** was also prepared *via* reduction of nitrobenzene **15** but this substrate also failed to undergo ring expansion (Scheme 2B).

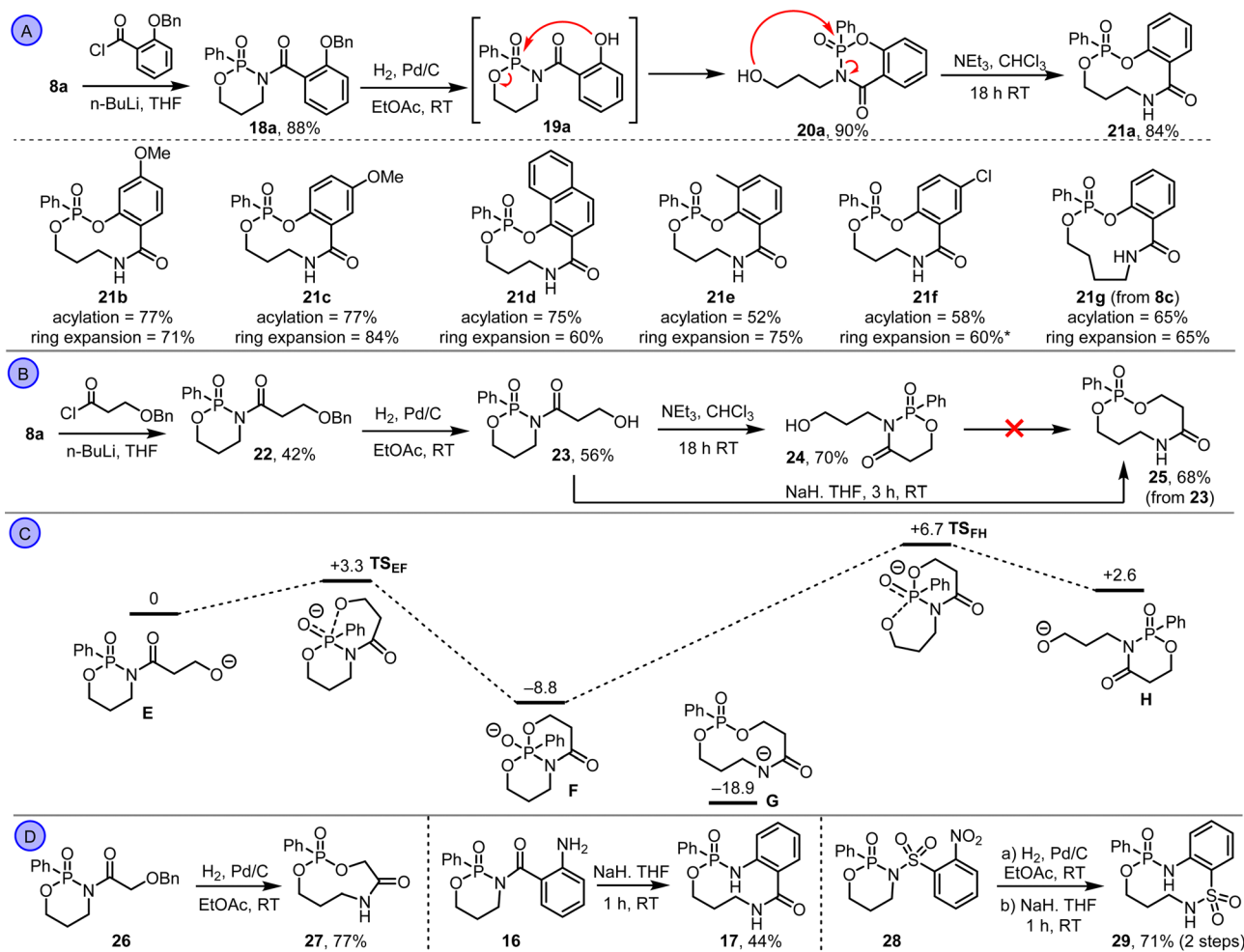
At this point, with the planned ring expansion reactions not proceeding as hoped, their viability was assessed using Density Functional Theory (DFT), using a method that was established and benchmarked for lactam ring expansion reactions in our previous work (Scheme 2C).¹⁵ Thus, the ground state energy of the free amine isomer (A), ring-closed (B) and ring-expanded isomer (C) were calculated for a representative aliphatic amine (analogous to compounds **10a-f**, labelled with 'a' and highlighted in red) and aniline systems (compound **16**, labelled with 'b' and highlighted in pink). The energy of a fourth isomer (D), accessible *via* an alternative fragmentation of the endocyclic P-O bond, was also calculated, in addition to analogous calculations for aliphatic alcohol (labelled with 'c', highlighted in dark blue) and phenol (labelled with 'a', highlighted in pale blue) for comparison. The energies are in kcal/mol and relative to reference states A.

Several observations emerge from the calculations. First, ring expanded isomer (C) was calculated to be the lowest energy in three out of the four series, and borderline for the aniline system (**Ab**, **Cb**, **Db** all have similar energy). Notably, the unwanted isomer **D** was significantly higher in energy than C

in three out of four cases. The isomer with the highest calculated energy in all systems was ring-closed isomer **B**, with this especially marked for the aliphatic amine series (isomer **Ba**). With the caveat that these data are calculated for intermediates and not transition states, this may be indicative of a high kinetic barrier to cyclisation being the reason for the failure of **10a-f** and **16** to rearrange. Finally, the energies of states **B-D** were all significantly lower relative to the reference state for the analogous alcohol and phenol systems compared to the analogous amines; this is best visualised in Scheme 2C by comparing the alcohol states depicted in dark/pale blue (**c** and **d**) to the amines depicted in red/pink (**a** and **b**).

These data provide three key learnings that informed subsequent synthetic studies: (1) the ring expansion reactions are thermodynamically viable based on the calculated energy of states **Ca-d**; (2) there appears to be a significant kinetic barrier to ring expansion, in contrast to our previous work on lactam systems which are under thermodynamic control;¹⁵ (3) alcohol-based substrates should work better than the analogous amines, based on their calculated thermodynamic profiles. At this point, we switched attention to alcohol-based substrates, starting with protected-phenol derivative **18a**, which was synthesised *via* the *N*-acylation of phosphoramidate **8a** (Scheme 3A). Hydrogenolysis of **18a** followed, to form phenol **19a**, which rearranged spontaneously *in situ*. However, rather than rearrange *via* ring expansion, we instead isolated product **20a**, *via* fragmentation of the endocyclic P-O bond. This observation was surprising, considering that this isomer was calculated to be higher in energy than ring expanded product **21a** (compare **Cd** and **Dd** in Scheme 2C). But pleasingly, stirring **20a** with triethylamine in chloroform at RT promoted further





Scheme 3 (A) The ring expansion of *N*-acyl phosphonamidates with tethered phenols. (B) The ring expansion of *N*-acyl phosphonamidates **23**. (C) Relative energies of isomeric species in an anionic ring expansion manifold, using a DFT/B3LYP/6-31+G* approach. ΔG^\ddagger rel values at 298 K are given in kcal mol⁻¹. (D) Other ring expansion reactions of P=O containing molecules. *Contaminated with $\approx 10\%$ **21a**, presumably as a result of hydrogenolysis of the C–Cl bond.

rearrangement into the thermodynamic product **21a**, which was isolated in 84% yield. The same sequence (*N*-acylation, hydrogenolysis and ring expansion under basic conditions) was also used to form medium-sized ring phosphonate esters **21b–g** (Scheme 3A).¹⁶ The structure of compound **21d** was confirmed by X-ray crystallography.¹⁷

Attention then turned to aliphatic alcohol derivative **22** (Scheme 3B). Hydrogenolysis of **22** was performed as before, but there was no evidence of spontaneous rearrangement, with alcohol **23** the only product isolated. This suggests a higher kinetic barrier compared to the phenol systems, which aligns with the calculated energies for **Bc** and **Bd** in Scheme 2C. In an attempt to overcome the kinetic barrier, alcohol **23** was reacted with triethylamine in chloroform at RT; this did promote rearrangement, but again led to the formation of unwanted isomer **24**. Sodium hydride was therefore tested as base in place of triethylamine, and pleasingly this enabled the smooth conversion of **23** into ring-expanded product **25** in 68% yield. It is likely that the use of this stronger base enables an anionic

reaction manifold to be accessed that allows the kinetic barrier to ring expansion to be overcome; notably, in the case of the phenol substrates (e.g. **19a**) their lower pK_a presumably enables a similar anionic pathway to be accessed when using triethylamine. Calculations performed for the aliphatic alcohol system (Scheme 3C) reinforce the notion that accessing an anionic pathway is important, with the five-coordinate phosphorus intermediate **F** calculated to be lower in energy than its corresponding precursor **E**, in stark contrast to the neutral pathway (Scheme 2C). A transition state (**TS_{EF}**) for the conversion of **E** into **F** was found at just 3.3 kcal mol⁻¹, consistent with a facile reaction at RT, and a low energy transition state (**TS_{FH}**) linking isomers **F** and **H** was also found, indicating that the conversion of **H** back into **F** is also viable if any **H** forms. We were unable to find a transition state linking **F** to the ring expanded isomer **G**, but notably **G** was comfortably the lowest energy isomer on the potential energy surface, in line with the formation of **25** as the reaction product.¹⁸

We ended by testing two new reaction systems and revisiting one that had previously failed. First, hydrogenolysis



of **26** enabled its direct conversion into 9-membered ring phosphonate ester **27** in 77% yield. In this 3-atom ring expansion, the fact that it proceeds *via* 5-membered ring cyclisation as opposed to 6-, likely leads to a lower kinetic barrier and hence precludes the need to add base to promote ring expansion. We also found that by using sodium hydride as base, aniline **16** could be converted into **17** in 44% yield. Notably this reaction failed using the less basic condition tested previously and confirms that ring expansion *via* amine nucleophiles is viable provided the kinetic barrier can be overcome. Finally, an alternative aniline-based ring expansion was achieved successfully from sulfonamide derivative **28**; nitro reduction followed by treatment with sodium hydride in THF promoted its conversion into 10-membered ring phosphonamide **29** in 71% yield over two steps.

In summary, ring expansion reactions of P=O-containing starting materials have been developed, allowing access to medium-sized ring cyclic phosphonate ester and phosphonamides. Compared to more well-established ring expansion reactions at C=O bonds (e.g. lactam derivatives **4**, Scheme 1B), two key differences emerged. First is the greater reactivity of alcohol-tethered systems than the analogous amines. This contrasts to reactivity at C=O, where amines generally react faster and in higher yields, and is likely due to the change in relative bond strengths on switching from C to P, in particular the high P–O bond strength. The second key difference is the higher kinetic barriers, which in most cases can be overcome by using either a more acidic substrate (e.g. phenol **19a**) or more basic reaction conditions to access an anionic rearrangement pathway. An advantage to the higher kinetic barriers is the ability to isolate isomeric species (e.g. **23**, **24** and **25**, in Scheme 3C) in high yields under appropriate kinetically controlled conditions.

The synthetic chemistry featured in the manuscript was done by Z. Y., with guidance from W. P. U. The computational chemistry was done by J. K. F. T. and J. M. W., with guidance from J. M. L. The manuscript was written through contributions from all authors. The project was directed and managed by W. P. U. and J. M. L. The authors are grateful for funding from the China Scholarship Council (Z. Y.), the University of York Wild Fund (J. K. F. T.), GSK (J. M. W.) and the Royal Society (J. M. L.) for an Industry Fellowship (INF/R1/221057).

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 F. H. Westheimer, *Science*, 1987, **235**, 1173–1178.
- 2 (a) M. O. Fabrício, *RSC Adv.*, 2014, **4**, 18998–19012; (b) Y.-Y. Zhu, T. Zhang, L. Zhou and S.-D. Yang, *Green Chem.*, 2021, **23**, 9417–9421; (c) F. Bouchareb and M. Berredjem, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2022, **197**, 711–731.
- 3 (a) K.-M. Huttunen, N. Mähönen, J. Leppänen, J. Vepsäläinen, R. O. Juvonen, H. Raunio, H. Kumpulainen, T. Järvinen and J. Rautio, *Pharm. Res.*, 2007, **24**, 679–687; (b) M. Slusarczyk, M. Seppi and F. Pertusati, *Antiviral Chem. Chemother.*, 2018, **26**, 1–31; (c) R. L. Mackman, *ACS Med. Chem. Lett.*, 2022, **13**, 338–347; (d) M. Krečmerová, P. Mayer, R. Rais and B. S. Slusher, *Front. Chem.*, 2022, **10**, 889737.
- 4 L. Zhang, K. Qi, J. Xu, Y. Xing, X. Wang, L. Tong, Z. He, W. Xu, X. Li and Y. Jiang, *J. Med. Chem.*, 2023, **66**, 4150–4166.
- 5 For medium-sized rings and macrocycles in medicinal chemistry, see: (a) F. Kopp, C. F. Stratton, L. B. Akella and D. S. Tan, *Nat. Chem. Biol.*, 2012, **8**, 358; (b) C. Zhao, Z. Ye, Z.-X. Ma, S. A. Wildman, S. A. Blaszczyk, L. Hu, I. A. Guizei and W. Tang, *Nat. Commun.*, 2019, **10**, 4015; (c) E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discovery*, 2008, **7**, 608; (d) E. Marsault and M. L. Peterson, *J. Med. Chem.*, 2011, **54**, 1961; (e) F. Giordanetto and J. Kihlberg, *J. Med. Chem.*, 2014, **57**, 278; (f) A. K. Yudin, *Chem. Sci.*, 2015, **6**, 30.
- 6 For reviews of ring expansion chemistry, see: (a) M. Hesse, *Ring Enlargement in Organic Chemistry*, Wiley-VCH, Weinheim, 1991; (b) W. P. Unsworth and J. R. Donald, *Chem. – Eur. J.*, 2017, **23**, 8780; (c) K. Prantz and J. Mulzer, *Chem. Rev.*, 2010, **110**, 3741; (d) T. C. Stephens and W. P. Unsworth, *Synlett*, 2020, 133; (e) A. K. Clarke and W. P. Unsworth, *Chem. Sci.*, 2020, **11**, 2876; (f) B. Biletskiy, P. Colonna, K. Masson, J.-L. Parrain, L. Commeiras and G. Chouraqui, *Chem. Soc. Rev.*, 2021, **50**, 7513–7538.
- 7 For selected recent examples relevant to this study, see: (a) L. Li, Z.-L. Li, F.-L. Wang, Z. Guo, Y.-F. Cheng, N. Wang, X.-W. Dong, C. Fang, J. Liu, C. Hou, B. Tan and X.-Y. Liu, *Nat. Commun.*, 2016, **7**, 13852, DOI: [10.1038/ncomms13852](https://doi.org/10.1038/ncomms13852); (b) R. Costil, Q. Lefebvre and J. Clayden, *Angew. Chem., Int. Ed.*, 2017, **56**, 14602; (c) A. Lawer, J. A. Rossi-Ashton, T. C. Stephens, B. J. Challis, R. G. Epton, J. M. Lynam and W. P. Unsworth, *Angew. Chem., Int. Ed.*, 2019, **58**, 13942.
- 8 (a) A.-M. Caminade and J. P. Majoral, *Chem. Rev.*, 1994, **94**, 1183–1213; (b) K. C. Majumdar, R. K. Nandi and S. Ganai, *Tetrahedron Lett.*, 2014, **55**, 1247–1250.
- 9 For relevant lactam ring expansion methods, see: (a) T. C. Stephens, M. Lodi, A. Steer, Y. Lin, M. Gill and W. P. Unsworth, *Chem. – Eur. J.*, 2017, **23**, 13314; (b) R. Mendoza-Sanchez, V. B. Corless, Q. N. Nguyen, M. Bergeron-Brlek, J. Frost, S. Adachi, D. J. Tantillo and A. K. Yudin, *Chem. – Eur. J.*, 2017, **23**, 13319; (c) J. Shang, V. J. Thombare, C. L. Charron, U. Wille and C. Hutton, *Chem. – Eur. J.*, 2021, **26**, 1620–1625; (d) Z. Yang, C. R. B. Swanson and W. P. Unsworth, *Synlett*, DOI: [10.1055/a-1932-9717](https://doi.org/10.1055/a-1932-9717).
- 10 For conceptually related ring expansion reactions of non-lactam substrates, see: (a) C. Kitsiou, J. J. Hindes, P. l'Anson, P. Jackson, T. C. Wilson, E. K. Daly, H. R. Felstead, P. Hearnshaw and W. P. Unsworth, *Angew. Chem., Int. Ed.*, 2015, **54**, 15794; (b) L. G. Baud, M. A. Manning, H. L. Arkless, T. C. Stephens and W. P. Unsworth, *Chem. – Eur. J.*, 2017, **23**, 2225; (c) D. R. Loya, A. Jean, M. Cormier, C. Fressigné, S. Nejtrotti, J. Blanchet, J. Maddaluno and M. De Paolis, *Chem. – Eur. J.*, 2018, **24**, 2080.
- 11 T. C. Stephens, A. Lawer, T. French and W. P. Unsworth, *Chem. – Eur. J.*, 2018, **24**, 13947–13953.
- 12 K. Y. Palate, R. G. Epton, A. C. Whitwood, J. M. Lynam and W. P. Unsworth, *Org. Biomol. Chem.*, 2021, **19**, 1404–1411.
- 13 (a) K. Y. Palate, Z. Yang, A. C. Whitwood and W. P. Unsworth, *RSC Chem. Biol.*, 2022, **3**, 334–340; (b) Z. Yang, I. Zalessky, R. G. Epton, A. C. Whitwood, J. M. Lynam and W. P. Unsworth, *Angew. Chem., Int. Ed.*, 2023, e202217178.
- 14 The same reaction was also attempted using NH₃ (delivered as a 7 N solution in methanol) but failed, with only unreacted starting material **19a** recovered.
- 15 A. Lawer, R. G. Epton, T. C. Stephens, K. Y. Palate, M. Lodi, E. Marotte, K. J. Lamb, J. K. Sangha, J. Lynam and W. P. Unsworth, *Chem. – Eur. J.*, 2020, **26**, 12674–12683. See also ref. 11, 13a and 13b.
- 16 The analogous thiol-based system (c.f. **18a** but OBn = SBn) was also tested, but the benzyl cleavage step failed (see ESI[†]).
- 17 CCDC 2260255[†] (**21d**) contains the crystallographic data see: www.ccdc.cam.ac.uk/data_request/cif.
- 18 For all novel products synthesised in this manuscript, the reliable assignment of isomeric species was aided by the observation of ¹³C–³¹P coupling in their ¹³C NMR spectra. This allowed the proximity of different carbon atoms to phosphorus to be easily observed and hence provide a simple method to map the progress of the rearrangement (e.g. to distinguish **23**, **24** and **25**). See ESI[†] Tables S6 and S7 for additional detail.

