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# Unlocking the C-centered ring-opening of phosphiranium ions for a straightforward entry to functionalized phosphines

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Phosphorus chemistry occupies a pivotal position in contemporary organic chemistry but significant synthetic challenges still endure. In this report, a class of electrophilic phosphiranium salts, bearing fluorinated benzyl quaternizing groups, is introduced for the direct synthesis of diversely  $\beta$ -functionalized phosphines. We show that, in comparison with regular quaternary phosphiranium salts, these species display the sought balance of excellent stability and high electrophilic reactivity that allow the unlocking of the C-centered ring-opening reactions with different classes of weak nitrogen-, sulfur- and oxygen protic nucleophiles.

Developing new synthetic tools is a significant challenge in modern organic chemistry. In the field of phosphine synthesis, halogenophosphines have long been considered the most suitable chemical reagents for the electrophilic introduction of a phosphorus atom into organic molecules through C-P bond formation. By contrast, electrophilic P-containing building blocks able at creating C-Nu bonds in reactions with nucleophiles Nu to forge functionalized phosphines have been overlooked for a long time.

Neutral<sup>1,2</sup> and cationic<sup>3–13</sup> 3-membered heterocyclic rings offer an uncommon combination of stability<sup>1</sup>, synthetic flexibility, regioselective reactivity, atom economy, and very often stereospecificity across their ring-opening transformations. Those heterocycles that are prone to easy ring opening are referred to as spring-loaded rings<sup>14</sup>, whose reactivity is governed by a synergy of ring-strain<sup>15</sup> and C-heteroatom bond polarity to provide the suitable level of electrophilicity<sup>16</sup> for easy ring opening into small open-chain heteroelement-containing target molecules or polymers<sup>17,18</sup>.

In this arena of strained heterocyclic chemistry, phosphacycles as appealing electrophilic P-containing building blocks are underestimated and this may be considered an anomaly given the longstanding importance of phosphorus in chemical sciences and the

related need to propose new approaches and connectivities in the construction of P-containing molecules. This deficiency is primarily due to prohibitive ring-strain energy of only 19.9 kcal.mol<sup>-1</sup> far below oxiranes and aziridines (RSE  $\approx$  27 kcal.mol<sup>-1</sup>)<sup>4,19</sup>. Additionally, the phosphorus element has some unfavorable characteristics, such as low electronegativity ( $E_P = 2.19 < E_C = 2.55 < E_N = 3.04$ ), and susceptibility for hypervalency, alongside beliefs (recently dispelled in phosphiranes)<sup>20</sup> about oxidation sensitivity.

Phosphiranes have been comprehensively studied as complexes coordinated with metal carbonyls<sup>21,22</sup>. Curiously the opening reactions of these yet electrophilically boosted species<sup>5,23</sup> by nucleophiles have been largely ignored<sup>21,22</sup>. In the rarely reported examples, only attacks at phosphorus were described despite the steric bias on the heteroatom brought by metal complexations, leading to exotic P-containing products of little synthetic utility<sup>24</sup>. Those results therefore highlight the difficulty in controlling a synthetically more useful C-centered ring opening transformation of these electrophilically ambident and inadequately polarized phosphacycles<sup>25–27</sup>.

Quaternization of the pnictogen atom in group 15 three-membered heterocycles is known to increase ring strain<sup>23</sup> and electrophilicity<sup>16</sup> to a greater extent than the formation of metal

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complexes. This arguably makes phosphiranium salts the best option for C-selective ring opening in 3-atom phosphacycles chemistry. Curiously the latter species have so far garnered very little curiosity<sup>28–30</sup> since their discovery about 60 years ago<sup>31</sup>. Until recently, the only attempts devoted to their opening were made on a P-phenyl, P-methyl triflate salt<sup>32</sup>. Rapid conversions ensued, thus validating the notion that ring strain drives phosphiraniums to reactivity but again<sup>24</sup> nucleophilic attacks did occur on phosphorus<sup>32</sup>. Increasing the steric bulk of the aryl P-substituent was found instrumental in providing steric protection against nucleophilic attack at phosphorus, as demonstrated by the successful polymerization of a set of tri-*t*-butylphenylphosphiranes through C-centered ring-opening of transiently formed phosphiraniums<sup>33,34</sup>. Related to this, it is clear that the two P-substituents in phosphiranium salts provide a steric bias that can control the ring opening selectivity.

By implementing these concepts, previous investigations in our laboratories had established that simple, readily prepared quaternary phosphiranium salts (QPrS)<sup>35,36</sup> of type **A**, derived from the bulky mesityl phosphine enabled facile intermolecular ring-openings with good chemical efficiency and complete carbon selectivity using anilines as nucleophile component, thus establishing a route to functionalized phosphines. In contrast, protic nucleophiles weaker than anilines proved fruitless.

Aware that the nature of the substituents on P also has significant potential for adjusting the electrophilic properties of phosphiraniums, we next sought for alternative EPrS candidates of type **B** integrating a proper electron-withdrawing group to overcome these limitations while being conducive to a set of original phosphines.

Drawing upon recent research on fluorinated phosphonium salts as highly effective organocatalysts<sup>37,38</sup>, particularly in the realm of

Lewis super acid chemistry<sup>39</sup>, we surmised that phosphiranium salts resulting from quaternization by polyfluorinated alkylating agents would optimally meet our objectives, and thus enable us to successfully approach ring-opening reactions with weak protic nucleophiles and thus expand opportunities for the synthesis of structurally functionalized phosphines (Fig. 1).

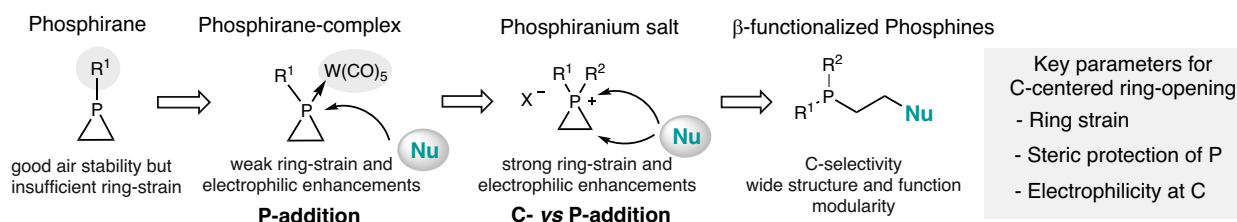
Herein, we report the success of this strategy with the preparation of fluorinated phosphiranium substrates and their effective C-centered ring-opening reactions with an extended range of weak nitrogen-, sulfur- and oxygen nucleophiles. The experimental results are convincingly supported by computational data. As a whole, we believe this study definitively grants phosphiranium ions the status of synthetically useful spring-loaded heterocycles.

## Results

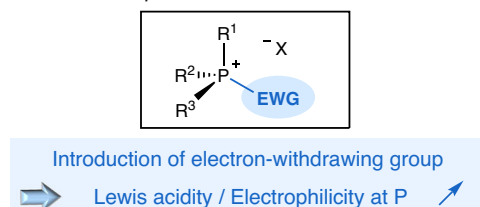
To support our assumption and ascertain that the introduction of fluorinated benzyl groups would increase electrophilicity, we first compared computationally the reactivity indexes of some representative species. Both the global electrophilicity parameter  $\omega$  and the energies of the LUMO orbitals for the different optimized model and known<sup>35,36</sup> QPrS of type **A** and targeted EPrS of type **B** (Fig. 2) were evaluated (for more details, see Supplementary Fig. 4)<sup>40</sup>. Population analyses were carried out on the optimized structures (optimized in the absence of constraints, at the (PCM:chloroform)  $\omega$ B97XD/6-31+G(d,p) level). They were computed at the  $\omega$ B97XD/6-31+G(d,p) level. Natural Bond Orbital analysis was computed using NBO keyword (version 3 by default)<sup>41</sup>.

Starting from the simplest P-Me, Me QPrS **A1**, the substitution of one methyl group by a benzyl group leads to a marginally more electrophilic QPrS **A2**. In contrast, its replacement by an aromatic group

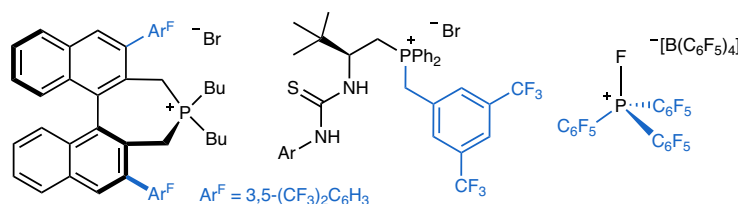
### a General statements: 3-membered phosphorus heterocycles ring-opening



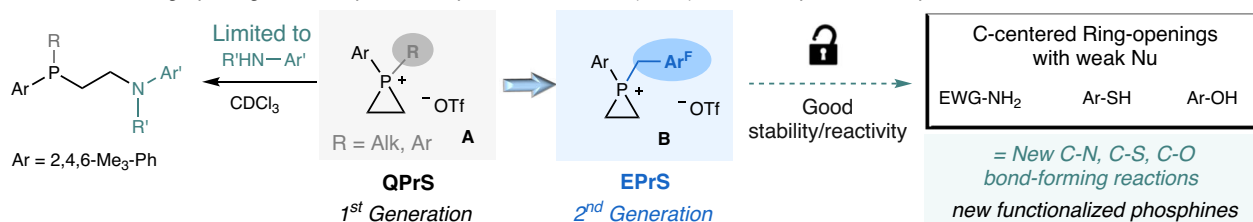
### b Electrophilic phosphonium cations (EPC) as source of inspiration



### c Representative examples of polyfluorinated organocatalysts refs 36–38



### d This work: Ring-opening of Electrophilic Phosphiranium Cations (EPrS) with weak protic nucleophiles



**Fig. 1 | Nucleophilic ring opening of 3-membered phosphorus heterocycles.**

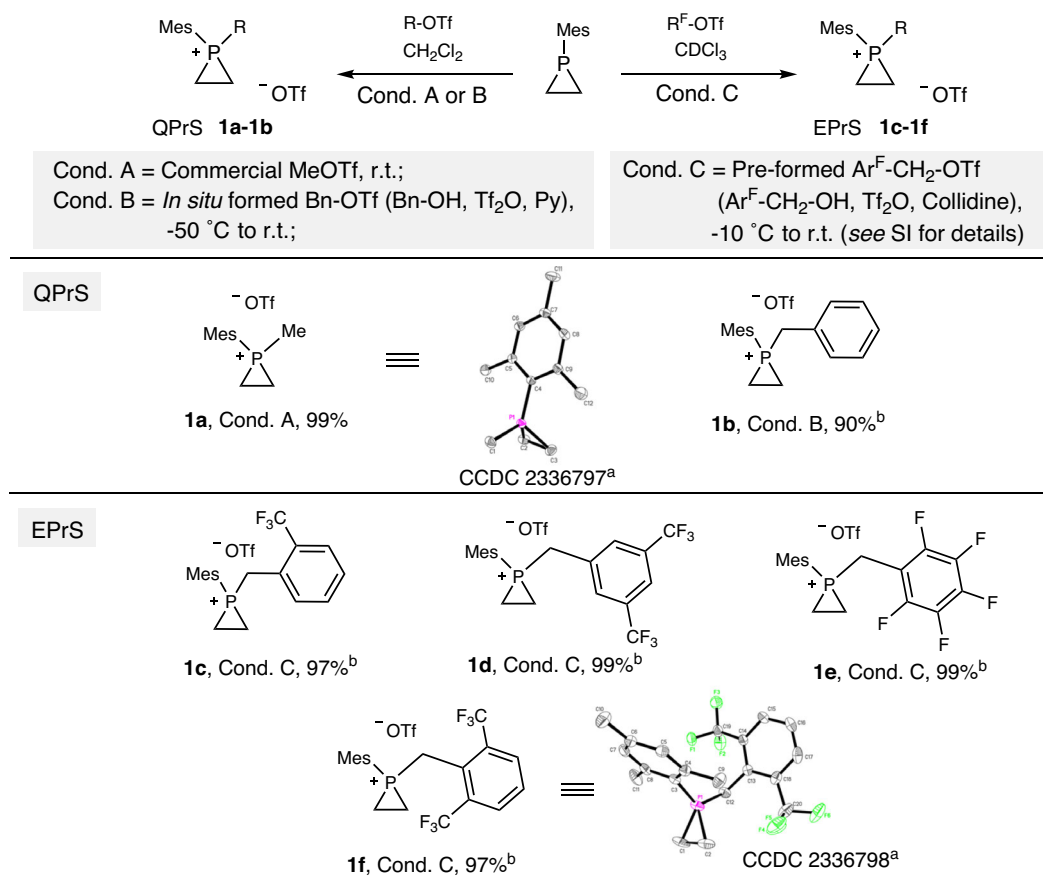
**a** General statements: 3-membered phosphorus heterocycles ring-opening;

**b** Electrophilic phosphonium cations (EPC) as source of inspiration;

**c** Representative examples of polyfluorinated organocatalysts refs. 36–38; **d** This work: Ring-opening of Electrophilic Phosphiranium Cations (EPrS) with weak protic nucleophiles.

	<b>A1</b>	<b>A2</b>	<b>A3</b>	<b>B1</b>	<b>B2</b>
$E_{\text{LUMO}}$ (eV)	0.18	-0.03	-0.44	-0.58	-0.99
$\omega$	1.01	1.08	1.24	1.31	1.47

**Fig. 2 | Energy of the LUMO (in eV) and global electrophilicity parameter  $\omega$  for optimized QPrS and EPrS.** MO calculated at the  $\omega$ B97X-D/6-31+G(d,p) level, considering the optimized structures calculated at the  $\omega$ B97X-D/6-31+G(d,p) (PCM: CHCl<sub>3</sub>) level.



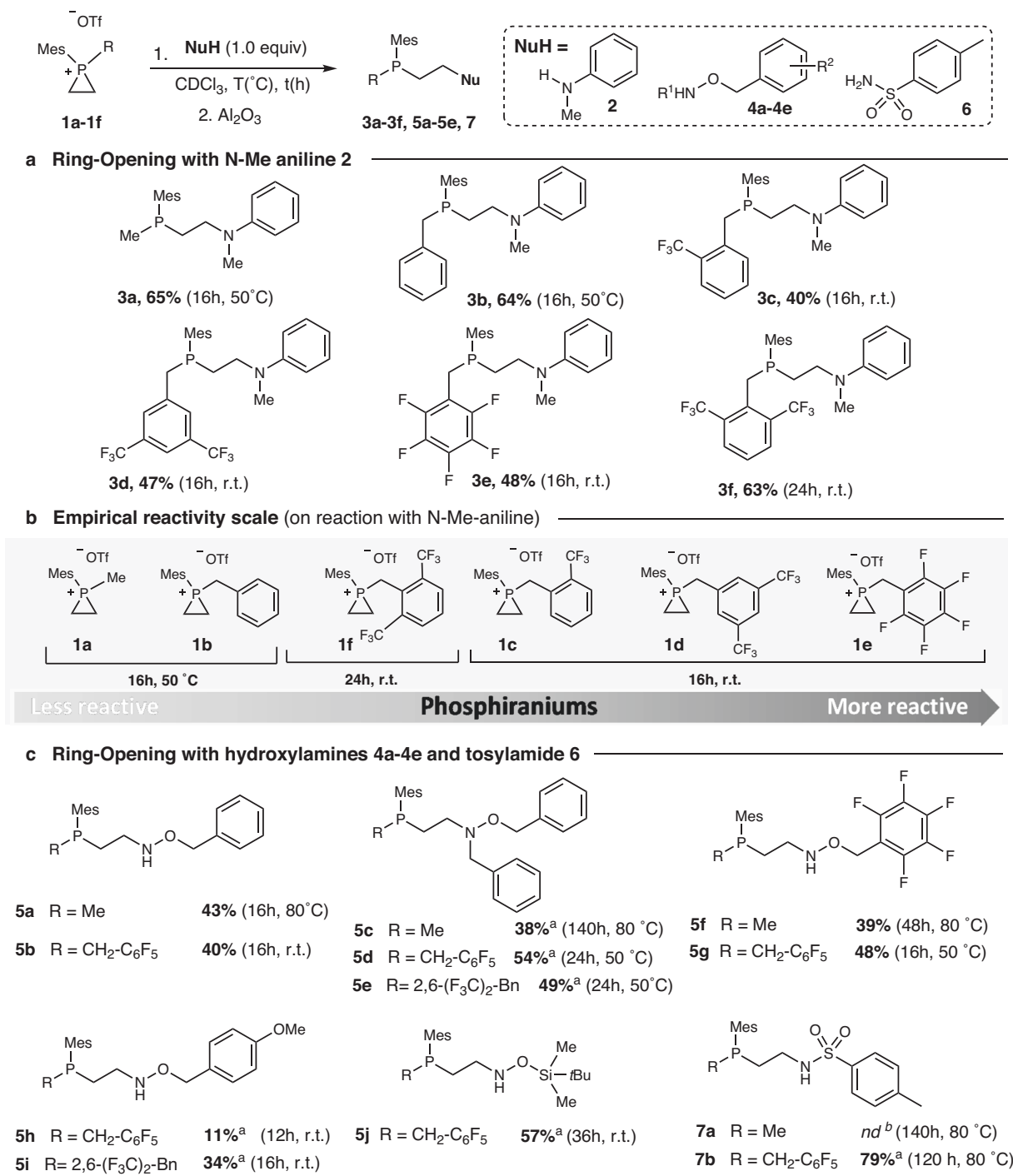
**Fig. 3 | Synthesis of QPrS 1a-1b and EPrS 1c-1f from 1-mesitylphosphirane.** The crude isolated yields were given.<sup>a</sup> TfO<sup>-</sup> anion omitted for clarity.<sup>b</sup> Crude yield estimated (2 steps, from Ar-CH<sub>2</sub>-OH).

such as a mesityl in QPrS **A3** is more impactful ( $E_{\text{LUMO}}$  decreased by 0.62 eV,  $\omega$  increased by 0.23 unit). As anticipated, fluorinated benzyl substituted EPrS **B1** has indeed a low-lying LUMO orbital (-0.58 eV) and higher global electrophilicity ( $\omega = 1.31$ ). Its analog EPrS **B2** with one bis-trifluoromethylated benzyl group is the most electrophilic of the series with a low-lying LUMO orbital (at -0.99 eV) and a strong electrophilicity ( $\omega = 1.47$ ).

The **A1** EPrS LUMO orbital is centered on the phosphiranium cycle when considering the cation alone, while LUMO+1 orbital has to be considered in the presence of the triflate counter anion. The empty orbital localized on the phosphiranium carbon atoms also depend on the substitution of the phosphiranium (from LUMO to LUMO+4). Thus, in addition to the exclusive LUMO orbital, we have also considered an orbital-weighted orbital scheme ( $E_{\text{LUMO-mix}}$ ), mixing the five lowest empty orbitals, with equal contributions, as proposed by

Tiznado et al.<sup>42</sup> This latter leads to different values with respect to  $E_{\text{LUMO}}$ , but a similar trend (See Supplementary Fig. 4 for details).

To assess the relative reactivity of QPrS and EPrS on an experimental basis, we then prepared some representative examples of each type. P-methylation (Cond. A) and benzylation (Cond. B) of 1-mesitylphosphirane were easily performed as previously reported and outlined in Fig. 3<sup>35</sup>. After adapting reaction conditions for the triflation step of the fluorinated benzyl alcohols, the corresponding triflates were obtained in excellent yields (95-98%) with small amounts (*ca* 2-11%) of the unreacted benzyl alcohol and the corresponding dibenzyl ether, resulting from condensation of the parent alcohol on the *in situ* formed triflate (ratio determined by <sup>1</sup>H NMR). Due to their sensitivity, the triflates were directly used in the quaternization step with the parent phosphirane which turned out to be very facile and provided the desired, new EPrS **1c-1f** almost quantitatively (95-99%, estimated to be 85-93% pure by <sup>1</sup>H NMR, Cond. C).



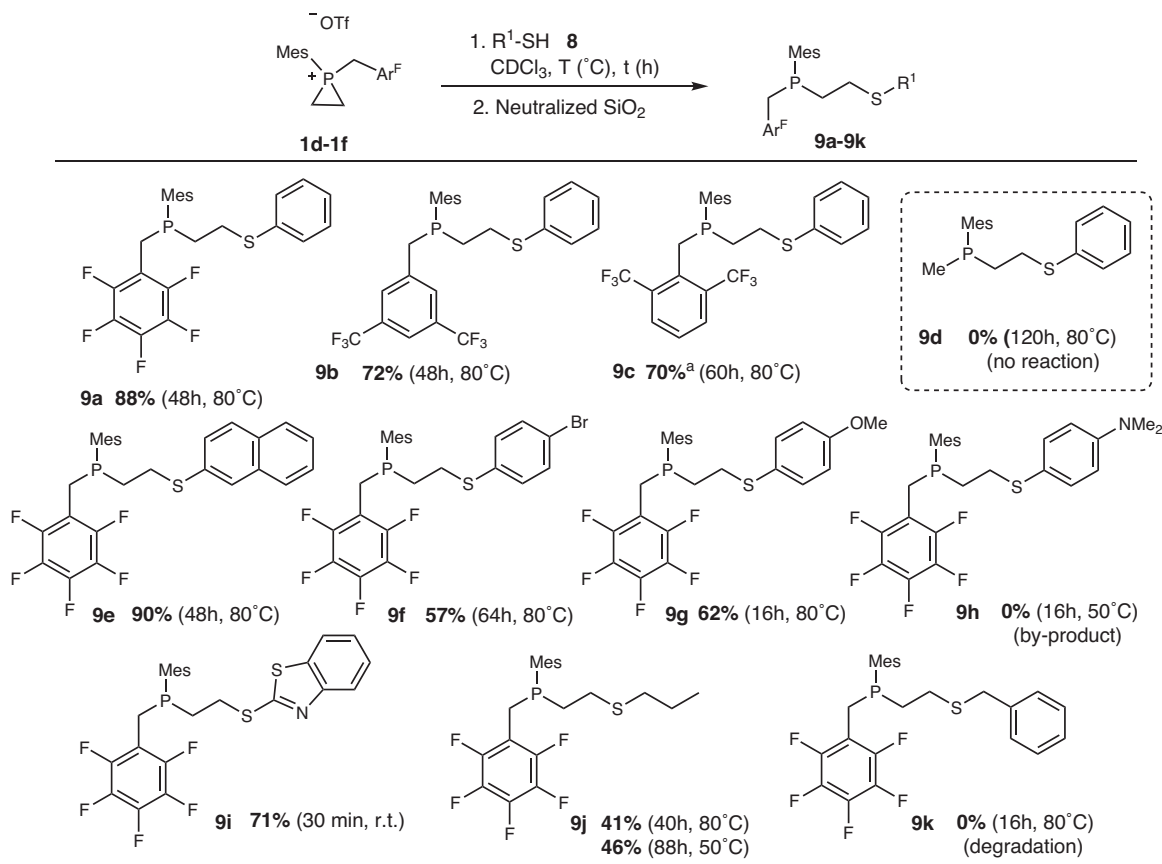
**Fig. 4 | Ring-opening of QPrS and EPrS 1a–1f with protic nitrogen nucleophiles. a** Ring-opening with N-Me aniline **2**. **b** Empirical reactivity scale of QPrS and EPrS 1a–1f. **c** Ring-opening with hydroxylamines 4a–4e and tosylamide **6**. The isolated

yields were given.<sup>a</sup> Product isolated as the corresponding phosphine oxide, after treatment of the crude with H<sub>2</sub>O<sub>2</sub>; <sup>b</sup> nd not detected - although full conversion of the phosphiranium substrate was observed.

Similar to QPrS **1a–1b**, EPrS **1c–1f** appeared to be stable and can be stored neat for months at –20 °C, in the absence of air and water. Likewise, periodic NMR monitoring of CDCl<sub>3</sub> solutions of samples of **1c–1f** at room temperature showed no signs of decomposition over a week. These are very important observations that demonstrate phosphiranium salts, including the most electrophilic versions to be remarkably stable compounds that should rapidly find wider use in organic synthesis. Crystals suitable for X-ray analysis were obtained for QPrS **1a** and EPrS **1f**, enabling a comparison of their structural

properties. This solid-state analysis revealed two longer C–P bonds of the ring in **1f** (1.799(6) Å and 1.784(6) Å) than in **1a** (1.779(2) Å and 1.773(3) Å). Compression of the CPC angle (50.5(3)° for **1f** vs 51.4(1)° for **1a**) was also observed (Fig. 3) suggesting a higher ring strain for the fluorinated salt **1f** that is consistent with its stronger electrophilic index (Fig. 2) and greater reactivity (Fig. 4).

The reactivity of QPrS **1a–1b** and EPrS **1c–1f** was then assessed using N-Me aniline **2** as a benchmark nucleophile (Fig. 4a). In all cases, the reactions were conducted in CDCl<sub>3</sub> for monitoring by <sup>1</sup>H and <sup>31</sup>P



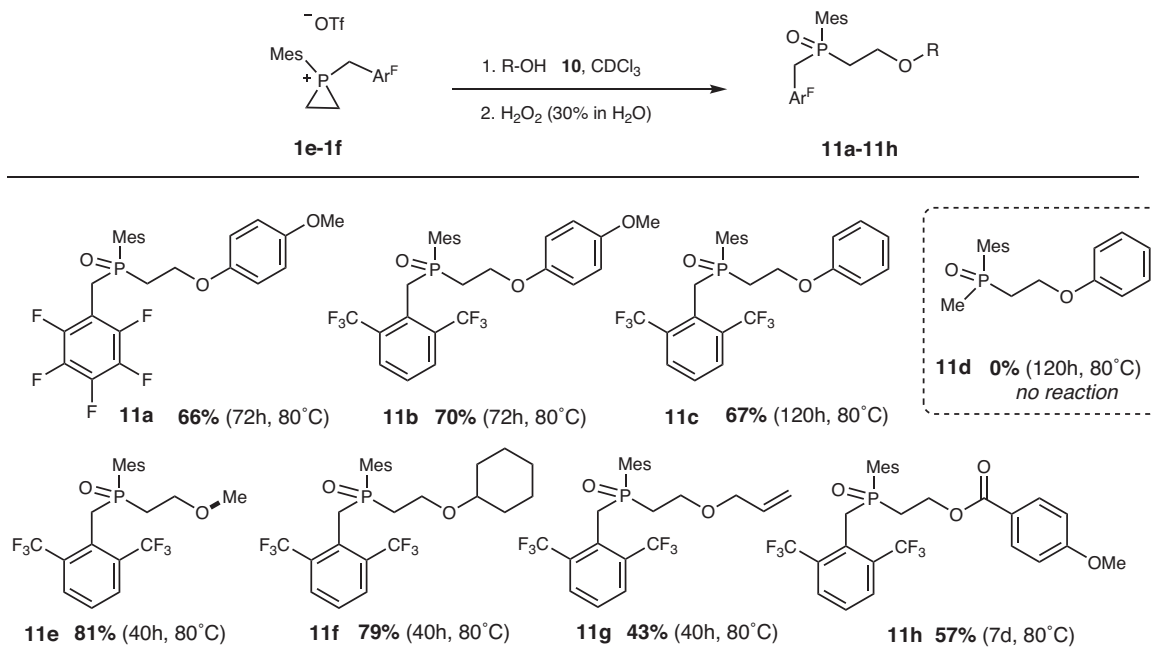
**Fig. 5 | Ring-opening of EPrS **1d-1f** with protic sulfur nucleophiles.** The isolated yields were given. <sup>a</sup> Product isolated as the corresponding phosphine oxide, after treatment of the crude with H<sub>2</sub>O<sub>2</sub>.

NMR and continued until complete conversion. Reactions of phosphiraniums **1a** and **1b** both proceed at 50 °C, affording the corresponding ring-opened products **3a** and **3b** in comparable yields of 65% and 64% respectively. Remarkably, in all cases, conversions of the fluorinated phosphiranium substrates **1c-1f** were observed at room temperature, validating their high reactivity. This strong reactivity is nevertheless accompanied by a slight drop in yields (40–63%) due to the competitive formation of an opened tertiary phosphine oxide side-product (most likely resulting from reaction with residual traces of water)<sup>36</sup>. As expected, the best yield (63%), with no visible detection of by-product formation, was obtained with phosphiranium **1f** with a 2,6-diCF<sub>3</sub>-benzyl group, thus confirming the importance of steric protection around phosphorus. It should be mentioned that ring-opening reactions of model substrates **1a** and **1e** were also tested with water alone. While the reaction was shown to be very slow with **1a** at 80 °C, comparatively the reaction of the P-F<sub>5</sub>-benzyl **1e** proceeded faster at rt. In both cases, only the corresponding opened tertiary phosphine oxides were obtained, with no traces of the C-centered ring-opened products with water (i.e. the corresponding β-hydroxyphosphines) being observed.

This set of results maps the reactivity of phosphiraniums **1a-1f** with respect to their ring-opening (see Empirical scale established from experimental data that are reaction rates and reaction temperature, Fig. 4b) which is mostly in line with our initial, then computed-supported predictions. Only an inversion of the two most reactive species **1e** and **1f** is observed, most likely resulting from a combination of steric and electronic factors. Our results clearly show that **1e** is the most reactive species of this set of phosphiraniums, while the more congested **1f** offers the best compromise between reactivity and selectivity.

After establishing experimental evidence that EPrS are superior electrophilic members, we aimed to expand the range of usable nucleophiles. We first investigated hydroxylamine derivatives as another class of weak aza-nucleophiles (Fig. 4c) based on some similarities with aniline (close nucleophilicity parameter and pK<sub>a</sub> value). An initial attempt with model P-Me QPrS **1a** and O-benzylhydroxylamine **4a** validated the potential of this class of nucleophile, with the formation of the expected opened product **5a** in 43% yield under relatively harsh reaction conditions (80 °C for 16 h). According to our predictive reactivity scale and in full line with our preliminary results with N-Me aniline, the transformation of F<sub>5</sub>-benzyl EPrS **1e** by **4a** appeared much easier, again proceeding at room temperature and giving reaction product **5b** in ~50% yield due to the formation of P-oxidized degradation products during the reaction. A very close 42% yield was obtained when performing oxidation of the crude mixture, thus showing that the oxidized side-products were not formed during isolation. Use of the sterically more demanding N-benzyl hydroxylamine **4b** logically decreased reactivity, with no conversion of both EPrS **1e** and **1f** observed at room temperature. However, the desired β-aminophosphines were obtained upon heating at 50 °C for 24 h, in milder conditions and better isolated yields (54% and 49% yields) compared to the analog **5c** resulting from reactions with the P-methyl QPrS **1a** (38% yield at 80 °C for 140 h). Two additional illustrations of the distinct advantage harnessed by EPrS are the ring openings with hydroxylamine **4c** strongly deactivated by a F<sub>5</sub>-benzyl group and with the O-silylated hydroxylamine **4e**, giving the corresponding adducts **5g** in 48% yield and **5j** in 57% yield after oxidation. In comparison, slightly lower yields of the corresponding phosphines were obtained using the usual work-up. In the latter case, the high reactivity of **1e** allowing a room temperature reaction proved decisive for the retention of the





**Fig. 6** | Ring-opening of EPrS **1e-1f** with protic oxygen nucleophiles. The isolated yields were given.

sensitive TBDMS group. It is however important to note that the opening products with hydroxylamines proved to be more unstable than in the other series, especially during chromatographic purification. As a result, the open products, whether phosphines or their oxidized form, could not be isolated in completely pure forms.

Remarkably, the ring-opening of **1e**, but not of QPrS **1a**, readily occurred on reaction with the strongly deactivated tosylamide **6** at 80 °C to afford good yield (79%) of the corresponding adduct **7b**, and thus highlights another facet of the synthetic potential of EPrS. Besides the result itself, this experiment is important as additional evidence of the robustness of EPrS, which shows good stability at relatively high temperatures.

Encouraged by this first set of results with nitrogen-based nucleophiles, we were next eager to confront our highly electrophilic EPrS **1d-1f** with an extended range of less reactive heteronucleophiles that previously failed to react with the QPrS analogs. As an entry point, we chose thiol derivatives as soft nucleophilic partners (Fig. 5).

As just mentioned above, the first-generation P-Me QPrS **1a** proved inert toward thiophenol at 80 °C even after extended reaction times, somehow expectedly, and only slow degradation of substrate **1a** was observed. By contrast, engaging F<sub>5</sub>-benzyl EPrS **1e** at gradually increasing temperatures allowed us to establish 80 °C as a threshold temperature for reactivity. To our delight, <sup>31</sup>P NMR monitoring revealed complete conversion and appearance of a single diagnostic signal characteristic for a protiophosphonium (i.e. protonated phosphine) adduct after 48 h. An adaptation of the isolation protocol using SiO<sub>2</sub> pre-treated with 10%TEA/EtOAc instead of neutral alumina (to deprotonate the protiophosphonium intermediate directly resulting from the ring opening into phosphine - see Fig. 7b for the proposed mechanism) resulted in a facile and high-yielding (88%) isolation of thiophosphine **9a**.

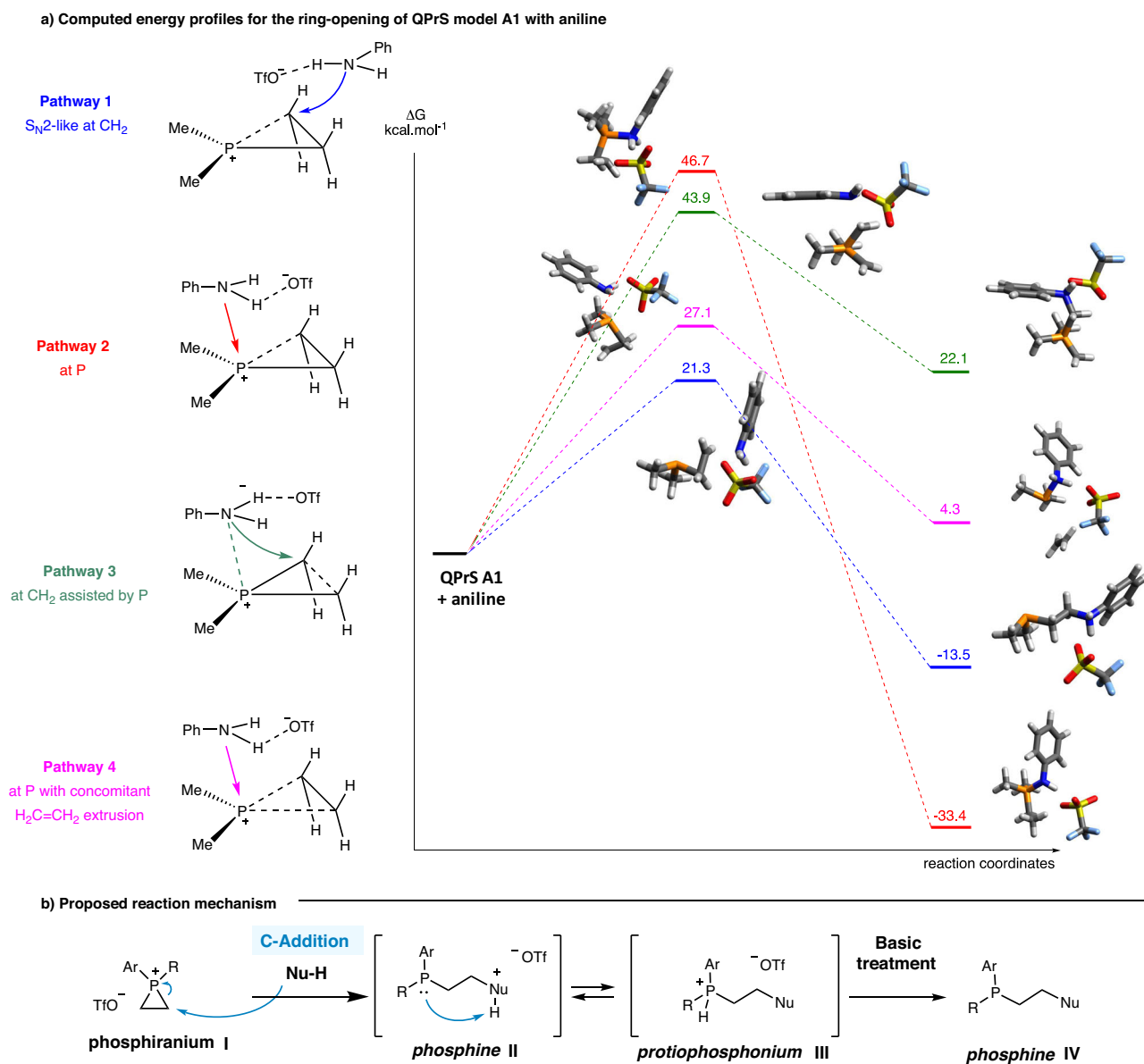
With an optimal protocol established for this transformation, we next probed the substrate scope. Opening of 3,5-diCF<sub>3</sub>-, and 2,6-diCF<sub>3</sub>-EPrS **1d** and **1f** proceeded equally well but only phosphines **9b** could be obtained in 72% yield while subsequent oxidation was found essential to get the bis-2,6-diCF<sub>3</sub> product **9c** in its P = O form (70%). Gratifyingly, the reaction expanded nicely to naphthyl thiol and diversely substituted thiophenols, except for the dimethylamino thiophenol, which only led to side-products formation. 2-Mercaptobenzothiazole has

recently demonstrated high reactivity in various organocatalytic enantioselective opening reactions of strained rings<sup>43</sup>, and was thus next tested. As we had hoped on these grounds, this nucleophile exhibited a high reactivity substantiated by complete conversion of EPrS **1e** within 30 min at room temperature to give the opened phosphine **9i** in 71% yield. Aliphatic thiols were found to be more reactive but less selective than their aromatic analogs with the ring-opening reaction of propanethiol occurring at 50 °C and providing thiophosphine **9j** in 46% yield. Running the reaction under our standard conditions at 80 °C markedly increased the reaction rate and maintained the reaction profile (40 h at 80 °C *vs* 88 h at 50 °C, 41% yield). In stark contrast, reaction with benzyl thiol only resulted in decomposition with no trace of adduct **9k** being obtained, possibly due to post-reaction cleavage of the sensitive benzylic C-S bond.

To challenge the reactivity of EPrS even more deeply and continue our progressive efforts towards expanding bond creation and molecular diversity through their ring opening, we finally turned our attention to the specific case of oxygenated nucleophiles (Fig. 6). The latter represent the most striking challenge due to both the weak nucleophilicity of alcohols and natural O- to P- affinity.

Preliminary tests with pentafluorobenzyl phosphiranium **1e** and *p*-methoxyphenol rapidly demonstrated the feasibility of the supposedly difficult ring-opening at 80 °C for 72 h. However, the resulting β-alkoxy phosphine turned out to be highly unstable to various isolation protocols and could not be isolated. Oxidation of the reaction crude was then directly performed using standard conditions (H<sub>2</sub>O<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt), allowing formation and isolation of the stable phosphine oxide **11a** in a very satisfactory 66% yield.

The bulkier 2,6-diCF<sub>3</sub>-EPrS **1f** converted at the same rate and afforded the phosphine oxide product **11b** in a slightly augmented yield of 70%. The study was then pursued with substrate **1f** which satisfyingly led to a similar result with the non-activated phenol, albeit with an expected slower rate (120 h, 67% in **11c**). In these three examples, <sup>31</sup>P NMR monitoring of the reaction showed that the reaction was very selective as evidenced by the appearance of a very major diagnostic signal. Given the obstacles concerning the use of alcohols as nucleophiles mentioned above, these results arguably are important in phosphiranium chemistry. Logically, we confirmed a complete lack of reactivity with the Me-QPrS substrate **1a**.



**Fig. 7 | Ring-opening mechanism.** **a** Computed energy profiles for the nucleophilic addition of aniline on QPrS model **A1** calculated at the  $\omega$ B97X-D/6-31+G(d,p) (PCM:  $\text{CHCl}_3$ ) level; **b** Proposed reaction mechanism.

This optimal protocol was then used to probe the reaction of **1f** with aliphatic alcohols. Similarly to thiols, the latter exhibited increased reactivity, with reactions of methanol and cyclohexanol proceeding faster (40 h vs 72 h with phenol derivatives) and providing the corresponding phosphine oxides in high yields (81% and 79% respectively). Allylic alcohol displayed a similar reactivity but only 43% of the corresponding adduct was obtained due to partial decomposition of the adduct.

Last but not least, even *p*-methoxy benzoic acid which is by far the poorest nucleophile that we have examined, demonstrated a good reactivity profile to deliver after oxidative work-up of the  $\text{P}=\text{O}$  product **11h** in 57% yield. This result was obtained after 7 days of reaction at 80 °C, and therefore definitively establishes a robustness of these perfluorobenzyl EPrS.

With the scope of the reaction established over three distinct classes of nucleophiles, we then turned our attention to the ring-opening mechanism.

Based on the products obtained and our earlier preliminary mechanistic experiments<sup>36</sup>, it is reasonable to assume that the

reaction proceeds through an  $\text{S}_{\text{N}}2$ -type mechanism with the direct addition of the nucleophile on a ring carbon atom. However, since phosphiranium salts display two electrophilic competing reaction sites and are prone to fragmentations due to their ring strain, other scenarios cannot be precluded<sup>44,45</sup>. A DFT study was thus performed to get insights into the reaction pathway (Fig. 7). Considering the size of fluorinated QPrS used experimentally, we first confirmed that the computationally less demanding dimethyl substituted **A1** constituted a good model for these studies (see Supplementary Table 2 for details).

Four different paths were examined for the interaction between EPrS **A1** and aniline chosen as model partners. Our first and preferred approach involves attack of the aniline nucleophile at the  $\text{CH}_2$  center of the phosphiranium from the back-side of the  $\text{CH}_2\text{-P}$  bond in an  $\text{S}_{\text{N}}2$ -like process (Pathway 1, blue). The second one involves the approach of the nucleophile at the cationic P center (Pathway 2, red), when a third path considers the first formation of an aniline-phosphonium complex followed by addition at the  $\text{CH}_2$  position in an indirect way (Pathway 3, green)<sup>44,45</sup>. The last approach deals with an





**Fig. 8 | Competition experiments with 2-mercaptobenzothiazole **8f** as reference nucleophile. a** Competition experiment of EPrS **1f** vs. QPrS **1a**. **b** Competition experiment of EPrS **1e** vs. QPrS **1a**.

attack on the positively charged P center with concomitant ethylene extrusion (Pathway 4, pink).

In agreement with our assumptions, the direct addition at carbon was found to be the most favored of the four considered and is highly exergonic (Fig. 7a, Pathway 1). The calculations also show that pathway 2 lies very high in energy and even if leading to a stable adduct, is not feasible considering the reaction conditions. In contrast, pathway 3<sup>44,45</sup> turned out to be highly kinetically and thermodynamically disfavored. Last, pathway 4, which involves P-addition with simultaneous extrusion of ethylene<sup>32</sup>, is more kinetically favorable but thermodynamically disfavored and is therefore not competitive compared to pathway 1. ( $\Delta\Delta G^\ddagger = 5.8 \text{ kcal.mol}^{-1}$ ). It is important to note that similar energy profiles apply over the reactions of models QPrS **B** and EPrS **A** differently substituted on P with the range of heteronucleophiles used in this study (see Supplementary Table 5 for additional computed values). This supports a uniform reaction mechanism driven by the preferential addition of protic nucleophiles at carbon atom as illustrated in Fig. 7b.

In addition, if the proposed mechanism primarily results in the formation of phosphines of type **II**, it is important to highlight that monitoring of the QPrS reactions by <sup>31</sup>P NMR always shows the formation of protiophosphoniums **III** resulting from N- to P-proton exchange, even in reactions with the most basic anilines. A basic treatment was thus applied to release the corresponding free phosphines **IV**. Significant differences in <sup>31</sup>P resonances were observed for the protonated-**III** and free phosphines **IV**. While in most cases, we assume that the proton is most likely shared between the phosphorus atom and the nucleophile's heteroatom in **III**, a clear signal splitting by coupled <sup>31</sup>P-<sup>1</sup>H NMR was detected with the less basic nucleophiles (in particular electron-poor anilines) consistent with protonation at P (with coupling constants <sup>1</sup>J<sub>P-H</sub> measured in the 500–540 Hz range).

By contrast, introduction of fluorinated groups in EPrS decreases the basicity of the corresponding phosphines significantly. Consequently, in reactions involving basic nitrogen nucleophiles and

fluorinated EPrS, we only observed formation of type **II** phosphine intermediates, while species **III** prevail in the case of F<sub>5</sub>-aniline, tosylamide, S- and O-nucleophiles. These differing observations are also consistent with the need to adapt the basic treatment depending on the nature and the basicity of the nucleophile used (*vide supra*).

To complete this study, we elected to take advantage of the high reactivity of 2-mercaptobenzothiazole **8f** to perform competition experiments to estimate the relative electrophilicity of phosphiraniums **1f** and **1a** to gain a quantitative assessment of the observed electrophilicity/reactivity ranking (Fig. 8)<sup>46</sup>. As outlined in Fig. 8 the experiment was performed with an excess of the two competing electrophiles **1f** and **1a** and the reference nucleophile **8f**. Once the latter was fully consumed, the reaction mixture was analyzed by <sup>1</sup>H NMR spectroscopy to determine the relative ratios of the remaining electrophiles **1f** and **1a** as well as the respective protonated ring-opened products **12a** and **12b**. A competition constant *k* of 27 was then determined for **1f** (*vs.* **1a**) according to equation 1 (eq. 1). In full correlation with the proposed reactivity scale established from our experimental results (see Fig. 4b), a similar experiment performed to assess the reactivity of EPrS **1e** in competition with **1a**, revealed a superior competition constant of 44 (eq. 2) that complies with our reactivity scale (Fig. 3).

In summary, we present a class of designer electrophilic phosphiranium salts (EPrS) incorporating fluorinated quaternizing groups. A thorough computational-structural-experimental investigation of their properties has demonstrated their higher electrophilic reactivity over previously described quaternary phosphiranium salts (QPrS). This was substantiated by a much better reactivity in the C-centered ring-opening with nucleophiles, enabling faster processes with previously effective anilines and expansion to a range of heretofore unsuccessful partners, including hydroxylamines, tosylamide, thiols, and alcohols. Besides fundamental aspects, the developed methodology offers an original alternative route to functionalized tertiary phosphines, which have already proved valuable as nonsymmetrical ligands or

organocatalysts<sup>47–49</sup>. In comparison to classical approaches which generally exploit either the nucleophilic reactivity of phosphines (mostly through their anions) or the electrophilic reactivity of halogenophosphines, the developed sequence moreover constitutes a convergent synthetic method with possible late-stage diversification (via the quaternization step) and easy deviation from routine diaryl P-substitutions.

Calculations helped for a better understanding of phosphiraniums chemistry and notably demonstrated a uniform C-centered SN<sub>2</sub>-type mechanism of the ring-opening process. Work is currently underway in our laboratories to further evaluate these fluoro EPRs and to explore the design and reactivity of new highly reactive analogs.

## Methods

See Supplementary Information for synthetic details, spectra, computational details and crystallographic data.

### General procedure for ring opening reactions

To a solution of phosphiranium salt in CDCl<sub>3</sub> (0.075 mmol/mL) was added the nucleophile derivative at room temperature. The mixture was stirred and eventually heated when necessary (see reaction time and temperature specified for each compound). Conversion of the starting material was monitored by <sup>31</sup>P NMR. After cooling down to room temperature, the product was isolated using one of the following procedures, depending on the stability of the resulting tertiary phosphine (specified for each compound in the Supplementary Information).

**Isolation Procedure A:** The crude was filtered through a short pad of basic Al<sub>2</sub>O<sub>3</sub> using EtOAc as eluent, concentrated under reduced pressure and then purified by flash chromatography on silica gel (eluent: Cyclohexane/EtOAc) when necessary.

**Isolation Procedure B:** The crude was filtered through a short pad of Silica gel (neutralized with 10% Et<sub>3</sub>N and dried prior to use) using EtOAc or CH<sub>2</sub>Cl<sub>2</sub> as eluent, concentrated under reduced pressure and then purified by flash chromatography on silica gel (eluent: Cyclohexane/EtOAc) when necessary.

**Isolation Procedure C:** The crude was filtered through a short pad of silica gel (neutralized with 10% Et<sub>3</sub>N and dried prior to use) using CH<sub>2</sub>Cl<sub>2</sub> as eluent. The filtrate was concentrated to ca 1 mL and then H<sub>2</sub>O<sub>2</sub> (30 % in H<sub>2</sub>O, 5 equiv) was added. The mixture was stirred for 0.5 h at room temperature and then a saturated solution of NaHSO<sub>3</sub> (10 mL/mmol) was added to quench the reaction. After decantation, the aqueous phase was extracted with EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure and then purified by flash chromatography on silica gel (eluent: Cyclohexane/EtOAc) when necessary.

## Data availability

All data supporting the findings of this study are available within the paper and its Supplementary Information (experimental procedures, DFT calculations and characterization data). All data are available upon request from the corresponding authors. All the cartesian coordinates of intermediates and transition states are available as a Source Data file. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 2336797 (**1a**) and CCDC 2336798 (**1f**). Copies of the data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>. Source data are provided with this paper.

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## Author contributions

V.D. and C.T. conceived the study and supervised the research. M.A. and M.-J.T. performed the experiments and analyzed the data. N.S.M. performed the crystallographic studies. S.C. and S.L. helped in preparing the manuscript and provided constructive advice. I.C. performed the density functional theory (DFT) calculations. J.P. helped in DFT calculations. V.D. and C.T. wrote the manuscript. All the authors discussed the results and commented on the manuscript.

## Competing interests

The authors declare no competing interests.

## Additional information

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