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# Organophosphorus-Catalyzed Deoxygenation of Sulfonyl Chlorides: Electrophilic (Fluoroalkyl)sulfenylation by $P^{III}/P^{V}$=O Redox Cycling

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## Abstract

A method for electrophilic sulfenylation by organophosphorus-catalyzed deoxygenative *O*-atom transfer from sulfonyl chlorides is reported. This C–S bond-forming reaction is catalyzed by a readily available small-ring phosphine (phosphetane) in conjunction with a hydrosilane terminal reductant to afford a general entry to sulfenyl electrophiles including valuable trifluoromethyl-, perfluoroalkyl-, and heteroaryl derivatives that are otherwise difficult to access. Mechanistic investigations indicate that the twofold deoxygenation of the sulfonyl substrate proceeds via the intervention of an off-cycle resting state thiophosphonium ion. The catalytic method represents an operationally simple protocol using a stable phosphine oxide as precatalyst and exhibits broad functional group tolerance.

### Keywords

Redox chemistry; Oxygen Atom Transfer; Organocatalysis; Phosphetane; Sulfenylation

Organosulfur compounds display versatile redox reactivity, making them archetypal substrates for the development of catalytic *O*-atom transfer (OAT) methods.[1, 2] Historically, the *oxygenative* OAT to S (II) substrates has been the primary focus of synthetic efforts; indeed early transition metal-catalyzed sulfoxidation is now established as a preeminent route for the synthesis of S(IV) and S(VI) compounds, especially in stereoselective fashion (Figure 1A).[3] By contrast, the complementary *deoxygenative* OAT from high-valent organosulfur oxides has generally been viewed with less strategic synthetic importance.[4] One exception in this regard concerns the deoxygenation of sulfonyl derivatives; Sharpless recognized that transient organosulfur intermediates from the phosphine-mediated deoxygenation of sulfonyl chlorides can be trapped by external nucleophiles to effect desirable synthetic chemistry (Figure 1B, X =Cl).[5] In this vein, recent work by Shibata and Cahard,[6] Liu,[7] and Zhao[8] reflects the synthetic potential of this approach *via* the use of phosphorus derivatives as oxygen acceptors, allowing access to valuable and reactive

Dedicated to Prof. Scott E. Denmark on the occasion of his 65th birthday sulfenyl electrophiles from the more readily handled sulfonyl congener. [9] The conceptual appeal of stoichiometric deoxygenative OAT by phosphine-mediated reduction of sulfonyl electrophiles is offset, though, by poor atom economy and low mass efficiency. These undesirable characteristics are exacerbated by the fact that the P(III) reagent, itself a potent nucleophile, consumes the electrophilic sulfenyl donor in competition with the target substrate to give undesired thiophosphonium ions (Figure 1B). In principle, a phosphine-*catalyzed* redox system for sulfonyl deoxygenation operating in the $P^{III}/P^{V}$=O redox couple (Figure 1C) might improve the reaction mass efficiency and simultaneously limit the concentration of phosphine in solution available for unproductive capture of reactive sulfenylation intermediates. Further, the structural attributes enabling *in situ* reduction of a tetracoordinate phosphine oxide (i.e. catalyst turnover) might also permit conversion of structurally-related tetracoordinate thiophosphonium ions into catalytically active tricoordinate phosphines.

Catalytic chemistry driven by reversible interconversion of phosphines ($R_3P^{III}$) and phosphine oxides ($R_3P^{V}$=O) is a developing modality in organophosphorus catalysis.[10,11] In this context, we have shown that a four-membered phosphacycloalkane (*i.e.* phosphetane **2**, Table 1) in combination with a hydrosilane terminal reductant provides an efficient organocatalytic platform for OAT reactions. Such a phosphacatalytic system has been shown to promote efficient reductive OAT from carbonyl[12] and nitro groups[13] by cycling in the $P^{III}/P^{V}$=O redox couple to reveal carbon- and nitrogen-based reactive intermediates, respectively. We envisioned advancing this biphilic organophosphorus-catalyzed OAT concept to encompass deoxygenative processing of sulfonyl moieties to furnish reactive sulfur(II)-based electrophilic intermediates.[14]

In this context, we elected to focus first on the development of a catalytic method for trifluoromethylsulfenylation by deoxygenation of trifluoromethylsulfonyl chloride ($CF_3SO_2Cl$) due to the well-established importance of fluoroalkylthioethers, especially trifluoromethylthioethers (R–$SCF_3$), in agrichemical and pharmaceutical candidates.[15] With the aforementioned biphilic phosphetane-based catalytic system (20 mol% of phosphetane oxide **2**•[O], 2 equiv of $PhSiH_3$), the catalytic deoxygenation of $CF_3SO_2Cl$ in 1,4-dioxane containing indole **1** resulted in regioselective C3-trifluoromethylsulfenylation product **12** in quantitative yield (Table 1, entry 1). Employing tricoordinate phosphine **2** as the catalyst (in lieu of phosphine oxide **2**•[O]) provided product in comparable yield suggesting involvement of $P^{III}$ species in the catalytic cycle (entry 2). Other commercially available $CF_3SO_2$-based reagents (sulfinate **9**, sulfonate **10,** sulfonic acid **11**) proved ineffective (entries 3–5). Alteration of the identity of the exocyclic *P*-substituent of the four-membered ring catalyst from methyl to phenyl, benzyl, -NHBn or pyrrolidino moieties (entries 6–9) gives serviceable albeit inferior yields of **12**. An attempt to use triphenylphosphine oxide **7**•[O] as precatalyst resulted in only 17% product formation (entry 10). Conducting the reaction in absence of either phosphine oxide precatalyst **2**•[O] or phenylsilane yielded no conversion to the product (entries 11,12), thus confirming the requirement of both phosphine oxide and silane reductant in these reactions. In the absence of indole, phosphetane oxide **2**•[O] catalyzes reductive dimerization of $CF_3SO_2Cl$ to the disulfide $F_3CS–SCF_3$.

The results of experiments to probe the scope of the catalytic sulfenylation reaction are shown in Table 2. Substitution throughout the indole core is well-tolerated, and electron-withdrawing as well as electron-donating groups could be used (**12–28**, Table 2A). Indoles with both free −NH **12** and *N*-Me substitution **13** are good substrates for the trifluoromethylsulfenylation reaction. Both 2-Me-indole (**14**) and 2-Ph-indole (**15**) were suitable substrates; sterically demanding **15** necessitated longer reaction time (12 h) compared to **14** (1 h). Electron-rich indoles with methoxy substitution at 4, 5, 6 or 7-positions are highly reactive substrates that formed the -$SCF_3$ products (**17–20**) in 82–92% yield in 1 h of reaction time, while electron-deficient indoles (**21–28**) demanded longer reaction times (4–15 h), and in select cases slightly higher catalyst loading to form $SCF_3$ products in 52–98% yield. Substrates with functional handles amenable to derivatization by cross-coupling reactions are well-represented (5-Bpin (**16**), 6-Cl (**22**), 4-Br (**23**), and 5-Br (**24**). Additionally, substrates containing a range of reducible functionalities including aldehyde (**25**), ester (**26**), nitro (**27**) and nitrile (**28**) groups, all yielded $SCF_3$-products without incident. Apart from $CF_3SO_2Cl$, the catalytic deoxygenative transformation could be extended to perfluoroalkylsulfonyl chlorides including $C_4F_9SO_2Cl$ and $C_8F_{17}SO_2Cl$ to form the corresponding perfluoroalkylsulfenylated indoles in good yields (**29** and **30**, Table 2B).

This mild catalytic deoxygenative protocol could also be applied to a range of aryl (**31–38**) and alkyl (**42**) sulfonyl chlorides, thus establishing a simple and straightforward catalytic sulfenylation strategy (Table 2C, D). In general, the electron-deficient sulfonyl chlorides demonstrated higher reactivity towards catalytic deoxygenation (**34**–**38**) compared to electron-neutral (**31, 33**) and electron-rich sulfonyl chlorides (**32**). The catalytic protocol was similarly also compatible with a range of heteroarylsulfonyl chlorides containing thiophene **39**, pyrazole **40** and oxazole rings **41** (Table 2E).

In order to gain insight into the reaction mechanism, *in situ* spectral monitoring of the catalytic reaction was performed. $^{31}P$ NMR spectra (162 MHz, 25 °C) of a catalytic reaction (1.0 equiv of **1**, 15 mol% of **2**·[O], 2.0 equiv of $PhSiH_3$, 1.8 equiv $PhSO_2Cl$, 0.25 M in 1,4-dioxane) showed that phosphetane oxide *anti*- **2**·[O] (δ 56.4 ppm) was consumed with concomitant generation of new resonances at δ 87.3 (major) and δ 94.4 ppm (minor) (Figure 2, A to B). Complete conversion of **2**·[O] was observed around the 90 min mark, at which point the catalytic conversion of **1** continues and the resonances at δ 87.3 (major) and δ 94.4 ppm (minor) remain the only observable phosphorus-containing signals in solution. At an intermediate timepoint ($t$ = 60 min), a small amount of epimer *syn*-**2**·[O] (δ 62.8 ppm) is noted; however, tricoordinated phosphorus species **2** was not observed at anytime during the reaction.

In a separate experiment, *in situ* spectral monitoring ($^{31}P$ NMR, Figure 3) of a catalytic reaction with 15 mol% of tricoordinate *anti*-**2** as precatalyst but conditions otherwise identical as above (1.0 equiv of **1**, 2.0 equiv of $PhSiH_3$, 1.8 equiv $PhSO_2Cl$, 0.25 M in 1,4-dioxane at 25 °C) was performed. Complete conversion of *anti*-**2** (δ 28.8 ppm) to a mixture of **2**·[O] and the unknown species δ 87.3 ppm was observed immediately ($t$ = 1 min) after

$PhSO_2Cl$ addition. After additional 70 min, unknown resonances at δ 87.3 (major) and δ 94.4 ppm (minor) were the only observable P-containing species in solution.

The identity of the unknown species giving rise to the resonances at δ 87.3 (major) and δ 94.4 ppm (minor) was established to be phenylthiophosphetanium cation **2**·$[SPh]^+$ by independent synthesis from reaction of **2** with freshly prepared PhSCl. We thus inferred that **2**·$[SPh]^+$ might represent the active species responsible for direct sulfenyl transfer to the indole nucleophile. However, no reaction was observed between **2**·$[SPh]^+$ and indole **1** after 16 h of heating in 1,4-dioxane at 40 °C (Scheme 1, A). Evidently, **2**·$[SPh]^+$ is not a competent sulfenyl donor and must not be an "on-cycle" catalytic intermediate. Instead, data indicates that **2**·$[SPh]^+$ is an "off-cycle" resting state that can reenter the catalytic cycle by reaction with other catalytic components. Specifically, the treatment of **2**·$[SPh]^+$ with $PhSiH_3$ converts quickly ($t_{1/2}$<10 min) into tricoordinate phosphetane **2** (Scheme 1, B). Moreover, phenylthiophosphetanium cation **2**·$[SPh]^+$ was shown to be a catalytically competent precatalyst under standard conditions, quantitatively forming sulfenylindole **36** (Scheme 1, C).

Based on these experimental observations, we suggest a plausible reaction mechanism for phosphacatalytic deoxygenation/sulfenylation of indoles as illustrated in Figure 4. The reaction initiates with reduction of the precatalyst **2**·[O] with phenylsilane to the active tricoordinate phosphetane **2** (step A), a step facilitated kinetically by the small ring size of the four-membered phosphacycle.[16] In accord with precedent, phosphetane **2** then operates on $RSO_2Cl$ to effect double deoxygenation, proceeding in a stepwise fashion *via* RSOCl by the accepted halophilic displacement pathway (step B-C).[17] We suggest that the identity of the active sulfenyl donor in the catalytic manifold may be **I**, formed from collapse of halophilic substitution intermediates $RSO^-$ and **2**·$[Cl]^+$. Indeed, *in situ* DART-MS analysis of a catalytic reaction with $PhSO_2Cl$ shows a peak at m/z = 283.13 amu consistent with a cation formulated as **I**, and the same cation is observed by DART-MS when **2**·[O] is treated with PhSCl. In effect, cationic intermediate **I** may be viewed as a phosphine oxide Lewis base adduct of a sulfenium fragment. The enhancement of reactivity by Lewis base activation of electrophilic reagents ($n\rightarrow\sigma^*$) is known; [18] specifically, the work of Denmark provides precedent for Lewis base catalysis of sulfenyl transfer.[19] In this vein, reaction of **I** with an indole nucleophile would form product with cogeneration of HCl and regeneration of **2**·[O] to close the catalytic cycle (step D). Alternatively, formation of the resting state thiophosphetanuim ion **II** may proceed directly from **I** (step E) or *via* sulfenyl chloride RSCl in an "off-cycle" pathway (step F), upon which **II** can rejoin the catalytic cycle by reduction with the terminal phenylsilane reductant (step G).

In summary, we have developed a catalytic deoxygenative protocol for general sulfenylation of indoles from readily available alkyl, aryl and heteroaryl sulfonyl chlorides including trifluoromethyl- and perfluoroalkylsulfonyl chlorides. This work represents a phosphacatalytic approach to double deoxygenation of sulfonyl chlorides that operates *via* $P^{III}/P^{V}$=O redox cycling in the presence of a terminal hydrosilane reductant. While phosphetane **2** is most likely the active catalyst in the reaction, our mechanistic investigations have identified a novel thiophosphetanium cation **II** as the off-cycle catalyst resting state. The application of this phosphacatalytic sulfenylation system for other nucleophiles is currently in progress.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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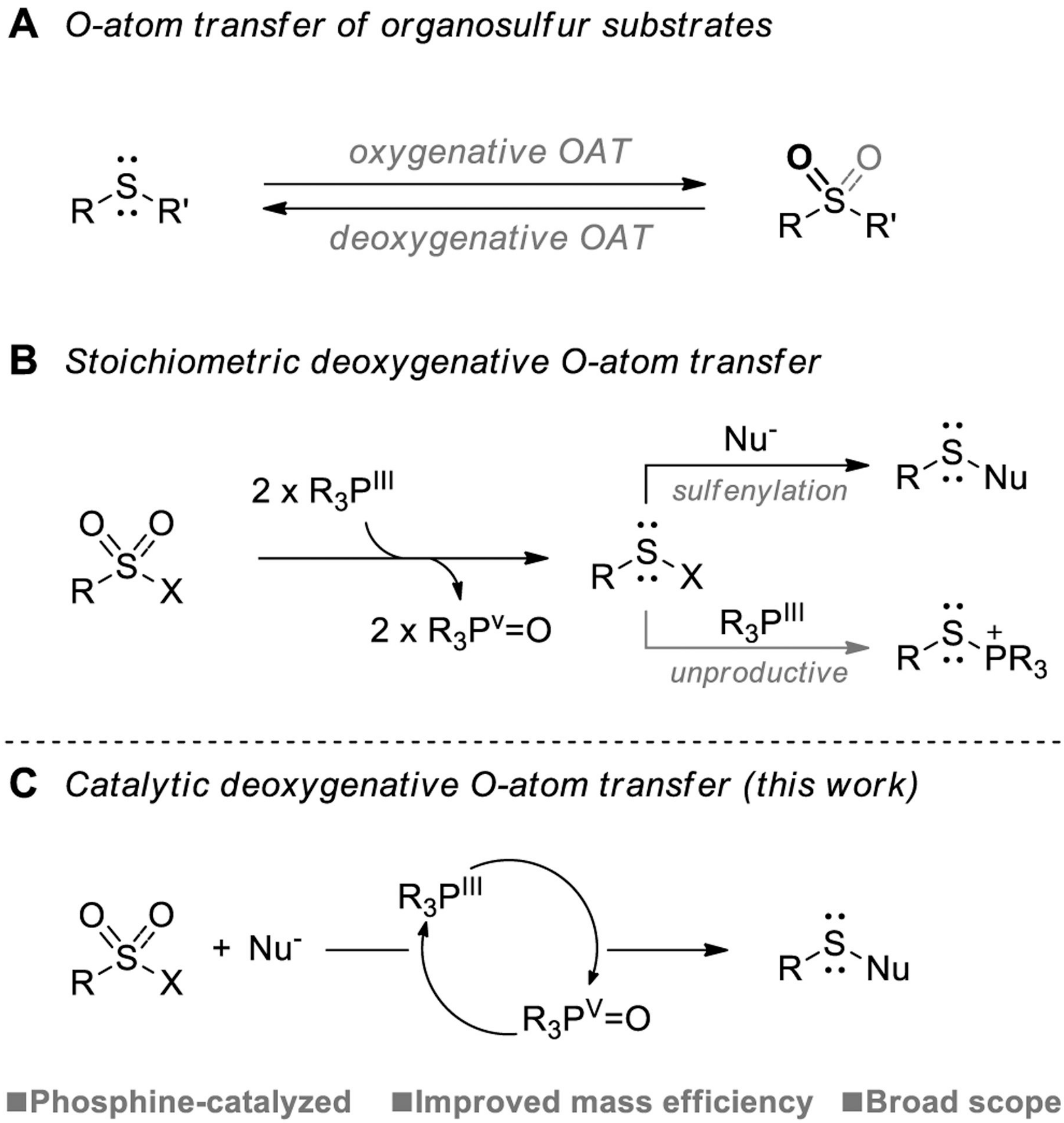



**Figure 1.**

(A) General oxygenative and deoxygenative *O*-atom transfer. (B) Stoichiometric deoxygenative *O*-atom transfer by using phosphines. (C) Novel phosphacatalytic deoxygenation of sulfonyl chlorides *via* $P^{III}/P^{V}$=O redox cycling.

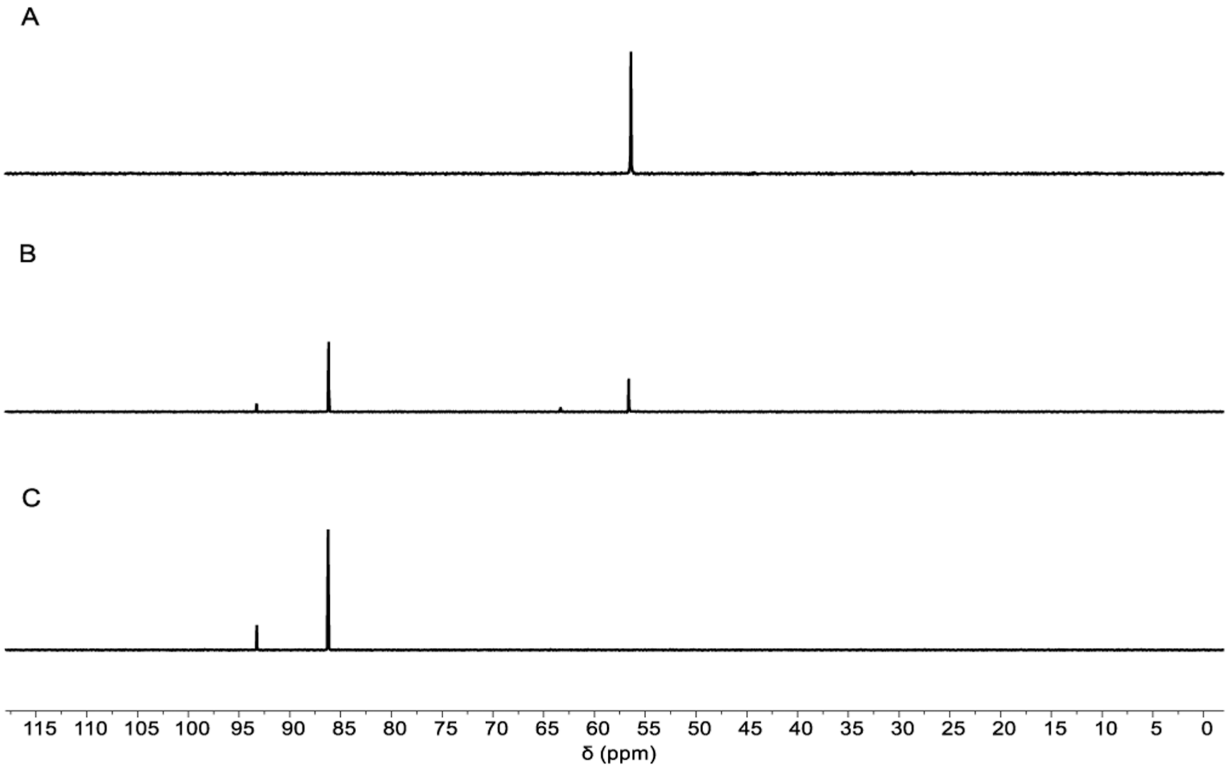



**Figure 2.**
Time-stacked *in situ* $^{31}$P NMR spectra during catalysis ($T$ = 25 °C, 1,4-dioxane). (A) $t$ = 0 min; (B) $t$ = 60 min; (C) $t$ = 90 min. Chemical shifts (δ): *anti*-**2**·[O], 56.4 ppm; 'unknown' peaks at 87.3 and 94.4 ppm.

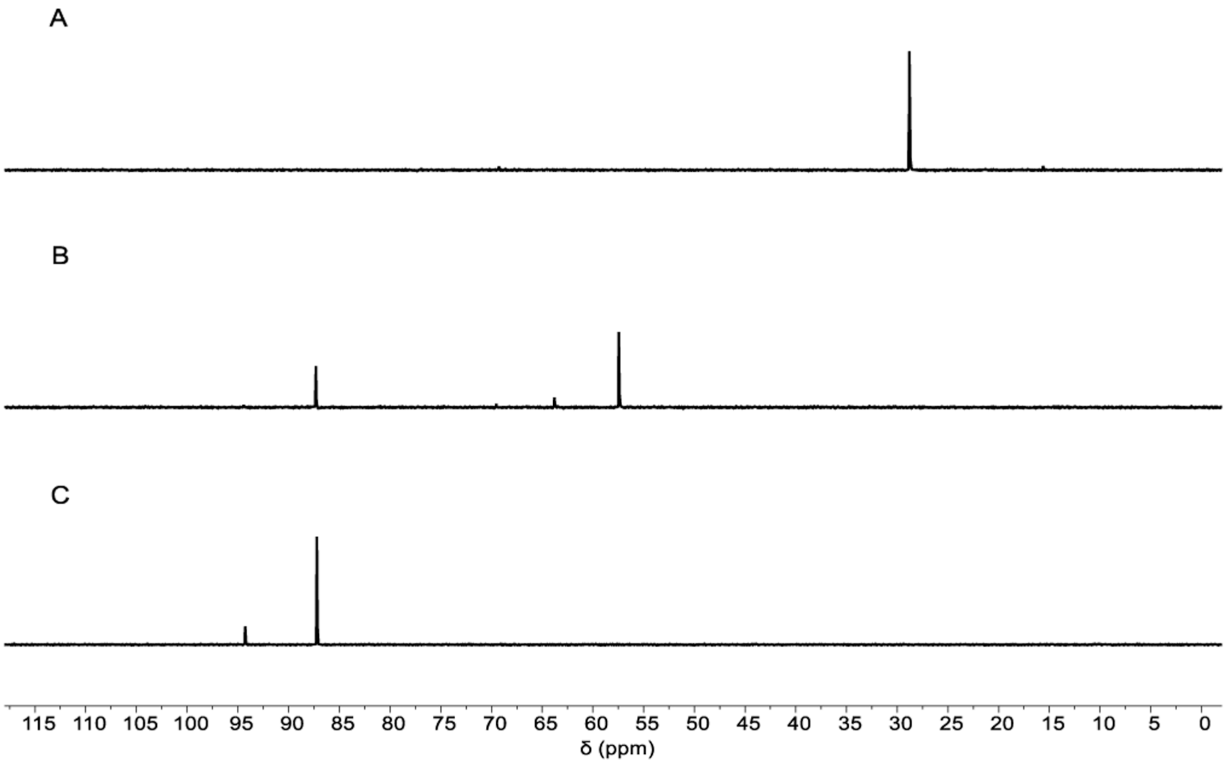



**Figure 3.**

Time-stacked in situ $^{31}$P NMR spectra during catalysis (*T* = 25 °C, 1,4-dioxane). (A) **2**; *t* = 0 min; (B) $PhSiH_3$, $PhSO_2Cl$; *t* = 1 min; (C) *t* = 70 min. Chemical shifts (δ): *anti*-**2**·[O], 56.4 ppm; *anti*-**2**, 28.8 ppm; ‘unknown’ peaks at 87.3 and 94.4 ppm.

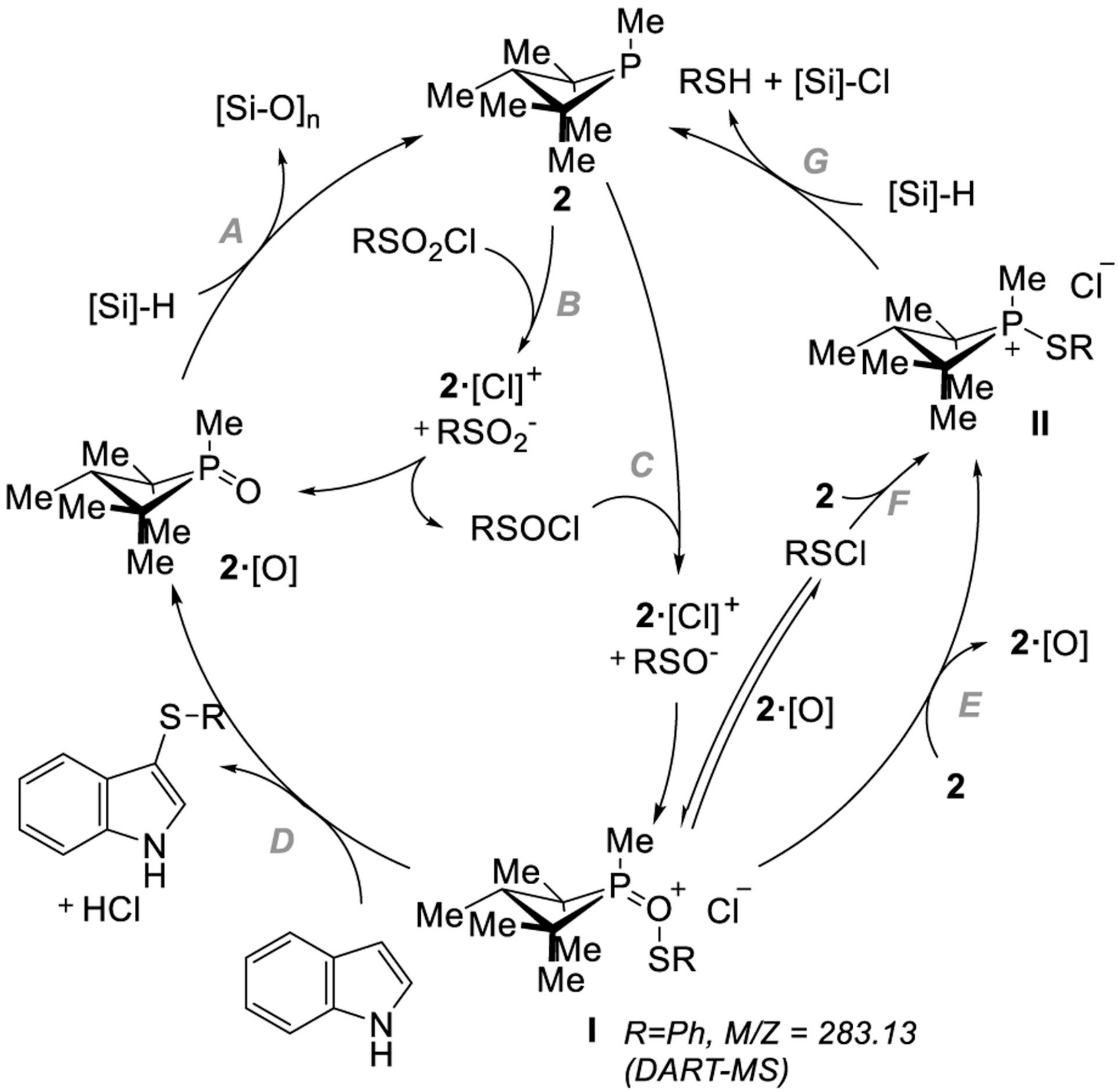
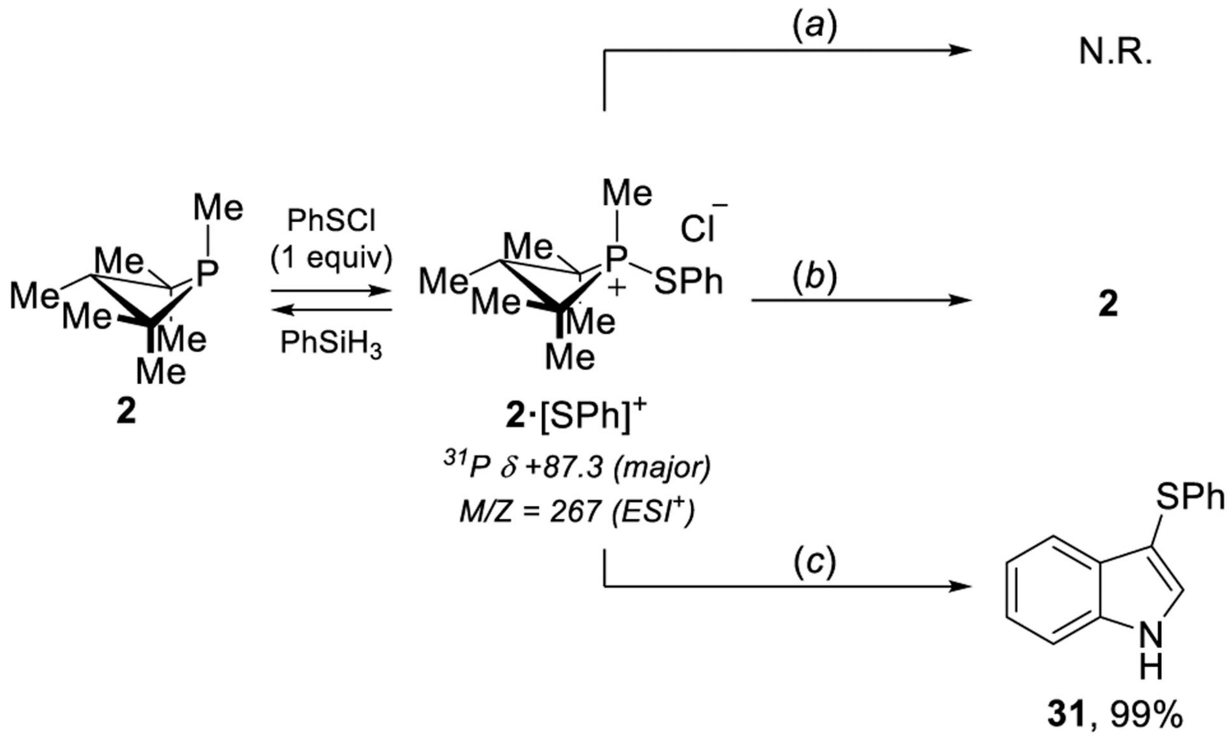



**Figure 4.**
Mechanistic proposal for phosphetane-catalyzed sulfenylation.

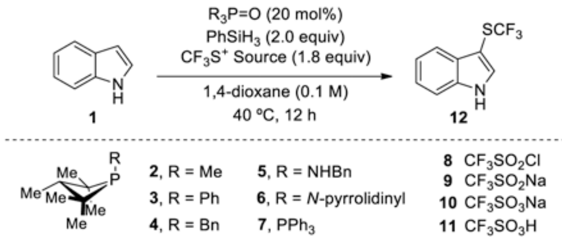



**Scheme 1.**

Synthesis and reactivity of "off-cycle" phenylthiophosphetanium salt **2**·[SPh]$^+$. Reaction conditions: (*a*) indole (**1**, 1.0 equiv), dioxane, rt; (*b*) indole (**1**, 1.0 equiv), $PhSiH_3$ (2.0 equiv), dioxane, rt; (*c*) indole (**1**, 1.0 equiv), $PhSiH_3$ (2.0 equiv), $PhSO_2Cl$ (1.8 equiv), dioxane, rt.

**Table 1.**

Phosphacycles as catalysts for deoxygenative trifluoromethylthiolation of Indole **1**.[a]

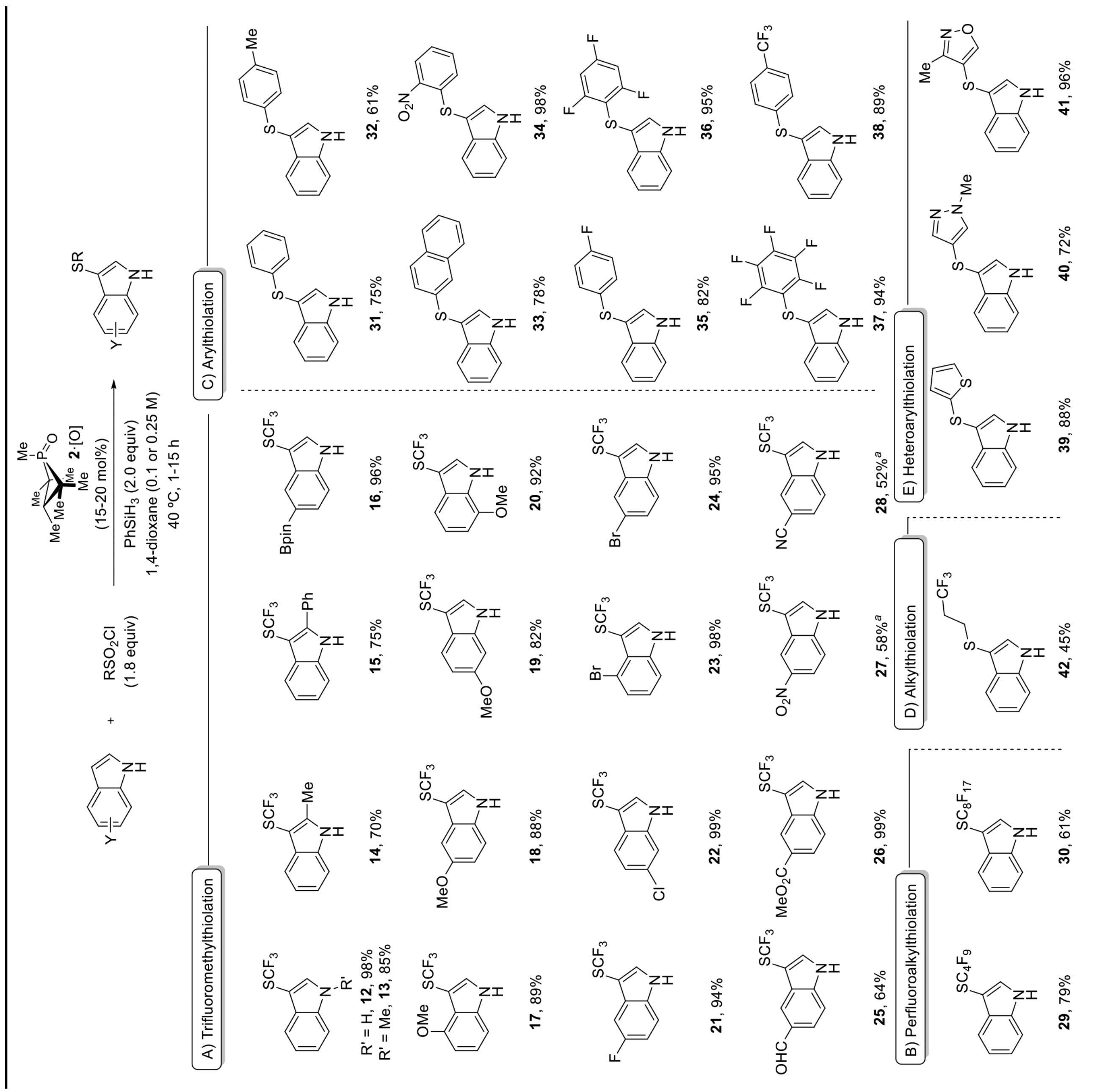



| Entry | $R_3P=O$ | $CF_3S^+$ Source | Silane | Yield (%) |
|---|---|---|---|---|
| 1 | **2**•[O] | **8** | $PhSiH_3$ | 99 |
| 2 | **2** | **8** | $PhSiH_3$ | 99 |
| 3 | **2**•[O] | **9** | $PhSiH_3$ | 0 |
| 4 | **2**•[O] | **10** | $PhSiH_3$ | 0 |
| 5 | **2**•[O] | **11** | $PhSiH_3$ | 0 |
| 6 | **3**•[O] | **8** | $PhSiH_3$ | 80 |
| 7 | **4**•[O] | **8** | $PhSiH_3$ | 85 |
| 8 | **5**•[O] | **8** | $PhSiH_3$ | 90 |
| 9 | **6**•[O] | **8** | $PhSiH_3$ | 55 |
| 10 | **7**•[O] | **8** | PhSiHs | 17 |
| 11 | **2**•[O] | **8** | none | 0 |
| 12 | none | **8** | $PhSiH_3$ | 0 |

[a]Yield determined by $^{19}F$ NMR spectroscopy of crude reaction mixture using α,α,α-trifluorotoluene as internal standard.

**Table 2.**

Scope of catalytic double deoxygenation of sulfonyl chlorides for the synthesis of sulfenylindole derivatives.



[a]25 mol% of catalyst loading was used.