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Article

Protonation of P-Stereogenic Phosphiranes: Phospholane Formation via Ring Opening and C−H Activation

Ryan M. Tipker, Jake A. Muldoon, Jacob Jo, Christopher S. Connors, Balazs R. Varga, Russell P. Hughes,* and David S. Glueck*

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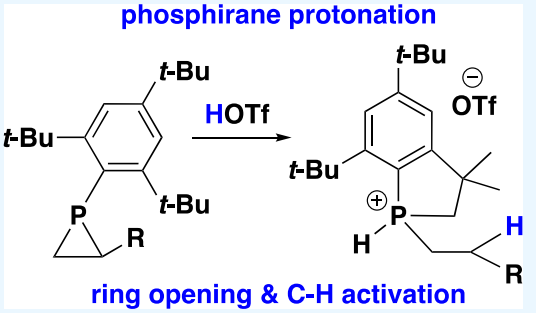
ABSTRACT: Protonation of cyclopropanes and aziridines is well-studied, but reactions of phosphiranes with acids are rare and have not been reported to result in ring opening. Treatment of *syn*-Mes*PCH$_2$CHR (Mes* = 2,4,6-(*t*-Bu)$_3$C$_6$H$_2$, R = Me or Ph, *syn*-**1**-**2**) or *anti*-Mes*PCH$_2$CHPh (*anti*-**2**) with triflic acid resulted in regiospecific *anti*-Markovnikov C-protonation with ring opening and cyclophosphination of a Mes* *ortho*-*t*-Bu group to yield the phospholanium cations [PH(CH$_2$CH$_2$R)(4,6-(*t*-Bu)$_2$-2-CMe$_2$CH$_2$C$_6$H$_2$)][OTf] (R = Me or Ph, **3**−**4**), which were deprotonated with NEt$_3$ to give phospholanes **5**−**6**. Enantioenriched or racemic *syn*-**1** both gave racemic **3**. The byproduct [Mes*PH(CH$_2$CH$_2$Me)(OH)][OTf] (**7**) was formed from *syn*-**1** and HOTf in the presence of water. Density functional theory calculations suggested that P-protonation followed by ring opening and hydride migration to C yields the phosphenium ion, [Mes*P(CH$_2$CH$_2$Me)][OTf], which undergoes C−H oxidative addition of an *o*-*t*-Bu methyl group. This work established a new reactivity pattern for phosphiranes.



INTRODUCTION

Like the isoelectronic epoxides and aziridines,[1] phosphiranes are potentially useful as "spring-loaded" building blocks[2] in organophosphorus chemistry because of their strained three-membered rings. P-quaternization increases the strain further,[3] promoting ring opening, but coordination of Lewis or Brønsted acids to phosphiranes is limited by their low Lewis basicity and proton affinity.[4] In contrast to other phosphines, phosphiranes do not readily form adducts with BH_3,[5] and P-methylation requires the highly reactive electrophile methyl triflate.[6] Similarly, protonation of phosphiranes has until recently only been observed in the gas phase, where the parent P−H phosphiranium cation $[C_2H_4PH_2]^+$ has been observed by mass spectrometry[7] and studied computationally.[8]

As models for possible condensed-phase examples of phosphirane protonation,[9] Scheme 1 shows some reactions of three-membered rings with acids bearing a weakly coordinating anion X^-. Aziridine N-protonation yields aziridinium salts.[10] Cyclopropane protonation usually occurs with Markovnikov selectivity at the least substituted carbon, with C−C cleavage and ring opening generating the most stable carbocation,[11] as shown for 1,1,2-trimethylcyclopropane.[12] Phosphirane P-protonation would yield a P−H phosphiranium cation (route **A**), as with aziridines or in P-methylation with MeOTf (**B**). Alternatively, C-protonation might occur at the carbon with less (**C**) or more (**D**) substitution, yielding branched or linear P-substituents after ring opening with P−C cleavage to yield phosphenium ion intermediates. Instead, C-protonation followed by breaking the C−C bond could form isomeric phosphines with a carbocation substituent (**E** or **F**). However, the relative Pauling electronegativities of P and C (2.19 and 2.55) and the observation that C−C bonds are usually stronger than P−C bonds suggest that these products are unlikely.[13]

Finally, protonation of a phosphirane bearing a good leaving group gave a P−H bond and left the ring intact (**G**),[14] suggesting that acid treatment of a substrate without a leaving group would yield a P−H phosphiranium cation (route **A**, Scheme 1), which might undergo further reactions. To test this hypothesis, we investigated phosphiranes **1**−**2**,[15] which were readily methylated with MeOTf (route **B**, Schemes 1 and 2),[6h] expecting formation of P−H phosphiranium cations (route **A**, Schemes 1 and 2) upon treatment with HOTf.

Although protonation of **1**−**2** with triflic acid occurred under very mild conditions, cations from route **A** were not observed. Instead, in a new type of reaction for this functional group, phosphirane ring opening and C−H activation of a *t*-butyl group resulted in formation of a five-membered phospholane ring in **3**−**4** (Scheme 3). From the results of

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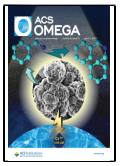
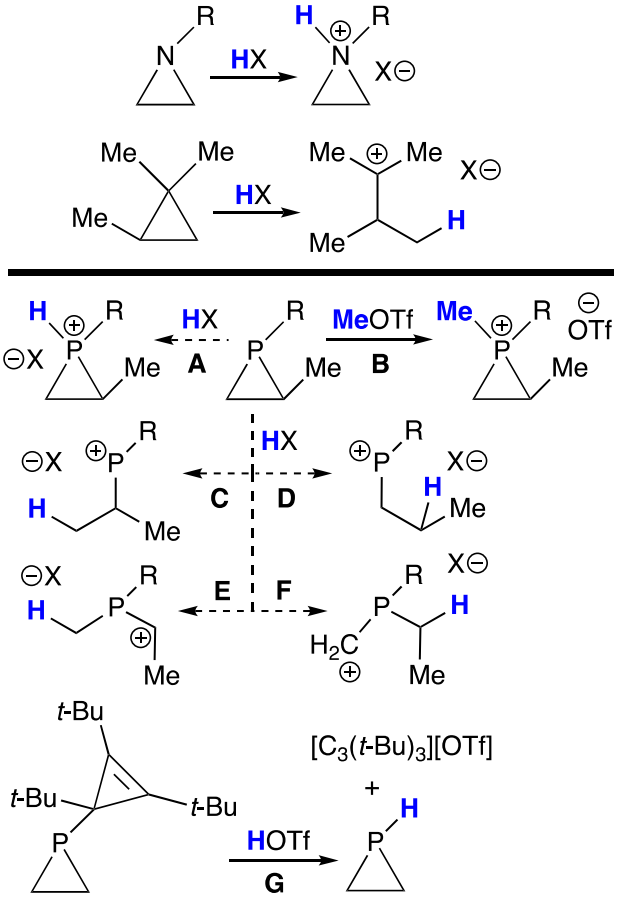
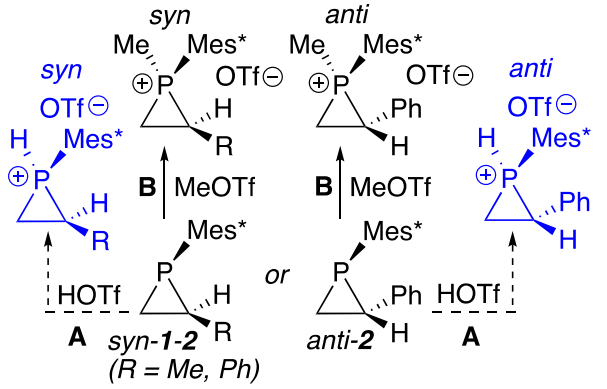


Scheme 1. Protonation of Aziridines and a Cyclopropane, and Possible Pathways for Phosphirane Protonation

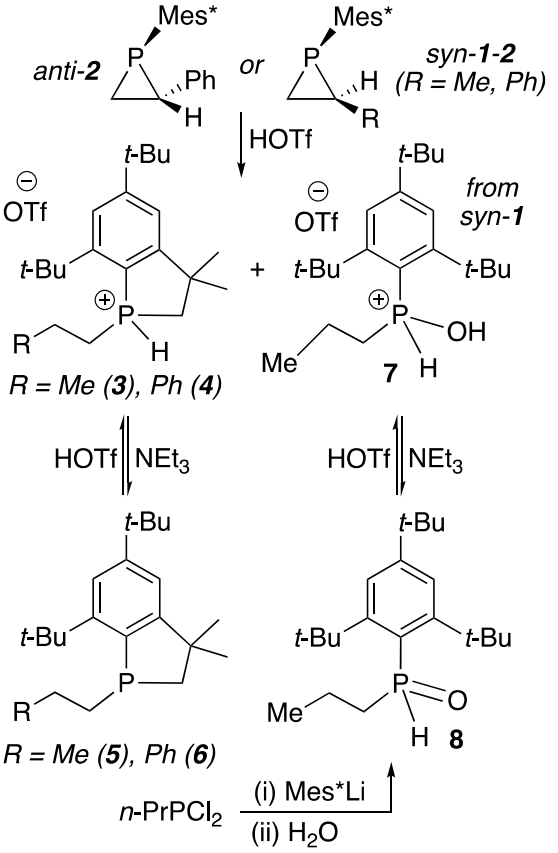


Scheme 2. Methylation of Phosphiranes 1−2 with MeOTf (Route B) Gave P-Me Phosphiranium Cations, So Protonation with HOTf (Route A) Was Expected To Yield P−H Phosphiranium Cations



varying phosphirane regiochemistry (*syn* vs *anti*) and stereochemistry (enantiomerically enriched vs racemic), isotopic labeling, and density functional theory (DFT) calculations, we propose a mechanism for this process via a combination of pathways **A** and **D** (Scheme 1), with initial P-protonation followed by ring opening and hydride migration to the more substituted carbon to yield a highly reactive phosphenium ion intermediate, which undergoes oxidative addition of C−H or O−H bonds.

Scheme 3. Phosphirane Protonation with Triflic Acid Gave Cyclophosphinated Phospholanium Cations 3−4[a]



[a]Reaction of **1** with DOTf gave **3-D** with a P-CH_2CHDMe group. Minor byproduct **7** formed from *syn*-**1** and HOTf in the presence of water and was identified by independent synthesis

RESULTS AND DISCUSSION

Treatment of racemic *syn*-Mes*PCH_2CHMe (*syn*-**1**, Mes* = 2,4,6-$(t\text{-Bu})_3C_6H_2$) or either diastereomer of racemic Mes*PCH_2CHPh (*syn*-**2** and *anti*-**2**) with triflic acid in pentane gave the cyclophosphinated phospholanium cations $[PH(CH_2CH_2R)(4,6\text{-}(t\text{-Bu})_2\text{-}2\text{-}CMe_2CH_2C_6H_2)][OTf]$ (R = Me (**3**); R = Ph (**4**)), resulting from apparent *anti*-Markovnikov protonation at C (route **D**, Scheme 1) and C−H activation of a Mes* *ortho*-*t*-Bu group (Scheme 3). These reactions occurred in minutes at room temperature. Treatment of *syn*-**1** with DOTf gave **3-D** bearing a CH_2CHDMe group, demonstrating deuteration at the CHMe ring carbon. Although **3-D** should exist as a mixture of diastereomers, the same single sets of signals were observed by nuclear magnetic resonance (NMR) spectroscopy when racemic or enantiomerically enriched **1** was used. Because of their high solubility, isolation of pure cations **3**−**4** was difficult, but deprotonation with NEt_3 gave phospholanes **5**−**6**, which could be purified by chromatography on silica.[16] Treatment of **5**−**6** with triflic acid regenerated cations **3**−**4**.

When water was not rigorously excluded, phosphirane protonation gave a minor byproduct, which was identified in the reaction of **1** as the protonated secondary phosphine oxide (SPO)[17] $[Mes^*P(H)(OH)(CH_2CH_2Me)][OTf]$ (**7**, Scheme 3).[18] Treatment of the **3**−**7** mixture with NEt_3 gave phospholane **5** and SPO **8**, which were separated by chromatography on silica.[19] The structure of **8** was confirmed

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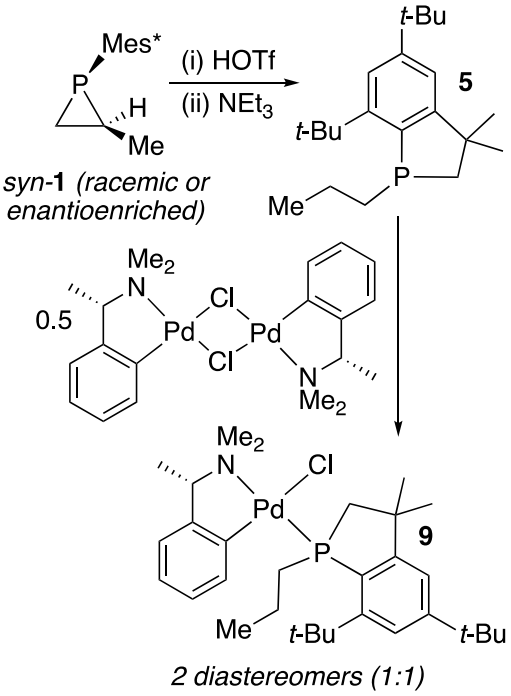
by independent synthesis via hydrolysis of the chlorophosphine Mes*P(*n*-Pr)(Cl). Separate treatment of **8** with triflic acid regenerated cation **7**.

The stereochemistry of phosphirane-to-phospholanium ring expansion was investigated using enantiomerically enriched *syn*-**1**. After deprotonation of **3**, coordination of the resulting phospholane **5** to a chiral Pd-amine complex gave a 1:1 mixture of diastereomeric Pd complexes **9**, as also observed for racemic **1**.[20] Thus, the reaction of phosphirane **1** with triflic acid destroyed both its P- and C-stereocenters to give racemic **5** (via **3**) with no chirality transfer (Scheme 4).

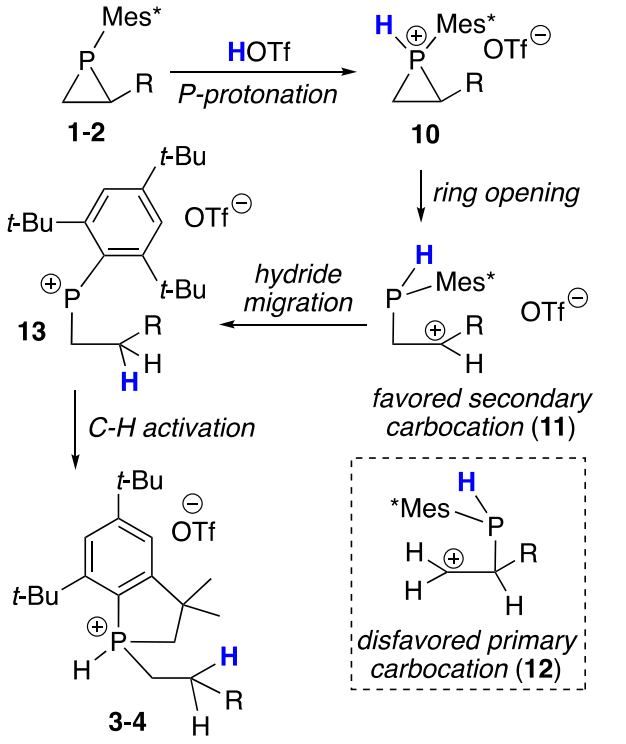
Scheme 4. Protonation of Enantiomerically Enriched or Racemic Phosphirane *syn*-1 Gave Racemic Phospholanium Cation 3, As Shown by Complexation of 5 to a Chiral Pd–Amine Complex



P-stereogenic phosphiranes **1**–**2** and their analogues are potentially useful in asymmetric synthesis because they can be prepared in high enantiomeric purity from commercially available chiral epoxides.[15] Because protonation demolished their valuable stereocenters, applications of this reaction are severely limited, so we did not further investigate its scope. Instead, to better understand why phosphirane methylation and protonation led to different results (routes **A** and **B**, Scheme 2), we investigated potential mechanisms of phosphirane protonation by DFT calculations.

Scheme 5 shows a proposed reaction mechanism, which is consistent with the experimental observations and with DFT calculations. As in the known aziridine N-protonation and phosphirane P-methylation, reaction with acid initially results in P-protonation to yield phosphiranium cation **10**. P–C cleavage and ring opening then yields secondary carbocation **11**, which is preferred over primary carbocation **12**. Hydride migration from the secondary phosphine to the pendant carbocation, which is precedented by intermolecular examples of hydride abstraction from primary or secondary phosphines by the trityl cation or related Lewis acids,[21] then yields

Scheme 5. Proposed Mechanism of Ring Opening and Phospholanium Ion Formation via Phosphirane Protonation



phosphenium ion **13**.[22] This reactive intermediate could undergo intermolecular O–H activation of water to yield byproduct **7**,[18] in competition with intramolecular C–H activation of an *ortho* *t*-Bu group to give cations **3**–**4**. Such cyclophosphination is a common process in Mes*P chemistry, as with the phosphenium ion [Mes*PSMes*]$^+$,[23] and in protonation of the phosphaalkene Mes*P=CH_2, which yielded a phospholanium cation similar to **3**–**4**, via the proposed phosphenium intermediate [Mes*PCH_3][OTf].[24]

We proposed protonated phosphiranes **10** as intermediates in the synthesis of phosphiranes **1**–**2**, where cyclophosphination was not observed.[15] The explanation of this apparent contradiction lies in the anion. In phosphirane synthesis, tosylate can apparently deprotonate **10** to give **1**–**2**. In phosphirane protonation, however, the weaker base triflate cannot deprotonate **10**, enabling formation of **11** and further steps in the sequence.

Notably, we also proposed reversible formation of cations like **11**, which contained PMe(Mes*) instead of PHMes*, in the isomerization of the P-Me phosphiranium cations [Mes*P(Me)CH_2CHPh][OTf], where, again, cyclophosphination did not occur.[6h] This is consistent with a greater migratory aptitude of H over Me in this system,[25] which may help to explain the observation that P-Me phosphiranium cations can be isolated,[6] while P–H analogues like **10** remain unknown in solution.

Since no intermediates could be observed experimentally in these reactions, the free energy landscape was explored using DFT (B3LYP-D3/6-311G**++). Full details of all calculations and structures are provided in the Supporting Information (SI). No solvent correction was utilized since the reactions occur in pentane. The calculated pathways are shown in Scheme 6, starting from P–H phosphiranium cation **10** (R =

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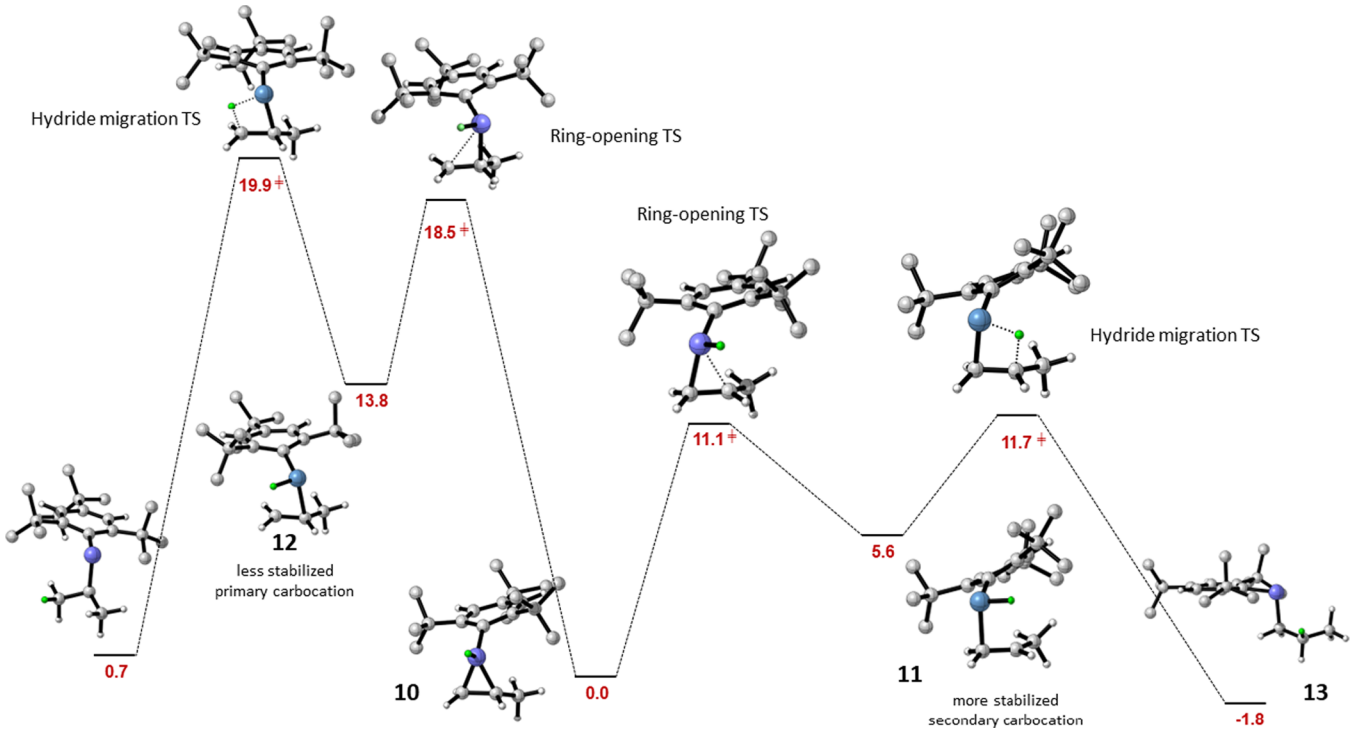
Scheme 6. DFT-Calculated (B3LYP-D3/6-311G++) Free Energy Landscape for Rearrangement of Phosphiranium Cation 10**[a]



[a]H-atoms on *t*-Bu groups are omitted for clarity, and the migrating H is shown in green. Free energies are given in kcal/mol relative to compound **10** (0.0).

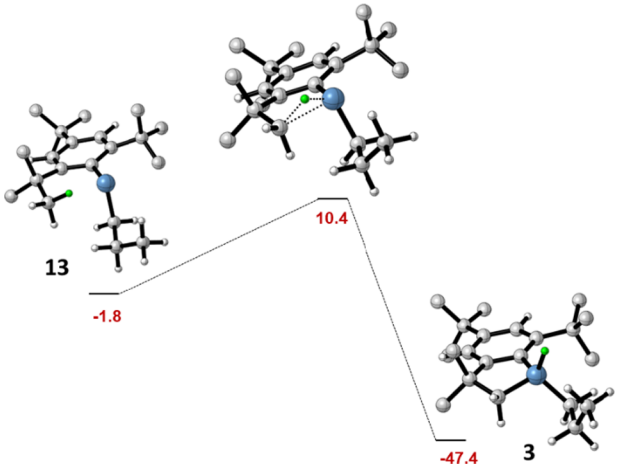
Me) formed by protonation of *syn*-**1**. The pathway **10** → **11** → **13** is strongly favored over the alternative pathway via **12** to give the isopropyl isomer of **13**, consistent with the deuteration experiments and the observed regiospecificity. Intermediates **11** and **12** could be formed directly by edge-protonation of the P−C bonds, but all attempts to model such direct pathways from *syn*-**1** in *silico* led to formation of **10**.

The secondary carbocation **11** is more stable than its primary analogue **12**, as expected, with a significantly lower barrier to its formation. We have shown previously that carbocation **11** and P-methylated analogues are strongly stabilized by hyperconjugation with the β−P−C σ-bond.[6h,15] While the activation free energies for the H-migration steps from **11** and **12** are identical (6.1 kcal/mol), the relative stability of **11** and the lower barrier to its formation from **10** provides the lower energy route to **13** in which the original chirality at P and C has been dismantled.

Once formed, phosphenium ion **13** can undergo activation of one of the C−H bonds of an *o*-*t*-Bu group via a low-energy transition structure shown in Scheme 7.

Finally, since these reactions were carried out in pentane it seems clear that triflate anion must be ion-paired with any of the cations in Schemes 6 and 7. These ion pairs have been modeled, but we find no direct role of a triflate interaction with P in any intermediate or transition structure. While triflate does bind to P in product **13**, its dissociation is required for CH activation to occur, emphasizing the importance of its reduced nucleophilicity and basicity, compared to tosylate, in the observed rearrangement.

Scheme 7. DFT-Calculated (B3LYP-D3/6-311G++) Free Energy Landscape for C−H Activation in Rearrangement of Phosphenium Cation 13**



[a]Most *t*-Bu H-atoms are omitted for clarity, and the migrating H is shown in green. Free energies are given in kcal/mol relative to compound **10** (Scheme 6: 0.0).

CONCLUSIONS

Protonated phosphiranes (P−H phosphiranium cations, route **A** in Schemes 1 and 2) have not yet been observed in the condensed phase, presumably because their combination of ring strain and a reactive P−H bond results in further transformations. Here, we have reported a new type of reaction for the phosphirane functional group, involving ring opening with P−C cleavage and formation of a new P−C bond by

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activation of a *t*-butyl C−H group under mild conditions. These observations emphasize the high reactivity of the strained phosphirane ring in **1**−**2** and in proposed intermediates P−H phosphiranium cations and phosphenium ion **13**[26] and the importance of the nucleophilicity/basicity of the anions in the chemistry of such cations. In comparison to stable N−H aziridinium cations (Scheme 1), the increased P−H phosphiranium cation reactivity may be a consequence of weaker P−H and P−C bonds. As with the cyclopropane protonation in Scheme 1, the proposed mechanism of phosphirane protonation involves formation of the most stable carbocation (**11** vs **12**) by ring opening.

EXPERIMENTAL SECTION

Please see the SI for general experimental methods and details of synthesis, characterization, and computational results. Representative procedures are given below.

Reaction of the Racemic Phosphirane *syn*-Mes*PCH$_2$CHMe (*syn*-1) with Triflic Acid: Synthesis of Phospholanium Cation 3. To a solution of racemic *syn*-**1** (0.050 g, 0.16 mmol, 1.0 equiv) in anhydrous pentane (5 mL, dried with activated molecular sieves), HOTf (11 μL, 19 mg, 0.13 mmol, 0.8 equiv) was added from a freshly opened bottle in a glovebox under anhydrous conditions. The solution became cloudy, and a yellow oil formed. After 18 h, the oil had disappeared; the pentane was decanted, giving a white solid, which was dried under vacuum (55 mg, 93% yield). Note: this procedure minimized the formation of the byproduct [Mes*P(*n*-Pr)(H)(OH)][OTf] (7, $^{31}P\{^1H\}$ NMR δ 37.5; about 4% by integration; see below for independent synthesis and characterization). Additional unidentified impurities were observed by $^{31}P\{^1H\}$ NMR (δ 71.5) and ^1H NMR spectroscopy (δ 6.2) in $CDCl_3$.

HRMS *m*/*z* calcd for $C_{21}H_{36}P$ (M^+): 319.2555. Found: *m*/*z* 319.2550. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 17.8. ^{31}P NMR ($CDCl_3$): δ 17.8 (d, J = 525). $^{19}F\{^1H\}$ NMR ($CDCl_3$): δ −78.3. ^1H NMR ($CDCl_3$): δ 7.94 (br d, J = 522, 1H, PH), 7.61 (dd, J = 6, 2, 1H, Ar), 7.26 (1H, Ar), 3.06−3.00 (m, 1H, phospholane CH_2), 2.78−2.71 (m, 1H, PCH_2), 2.60 (dd, J = 16, 11, 1H, phospholane CH_2), 2.46−2.30 (m, 1H, PCH_2), 1.82−1.71 (m, 1H, PCH_2CH_2), 1.60−1.55 (m, 1H, PCH_2CH_2), 1.51 (3H, Me), 1.48 (3H, Me), 1.46 (9H, *t*-Bu), 1.32 (9H, *t*-Bu), 1.10 (t, J = 7, 3H, $PCH_2CH_2CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.5 (quat Mes*), 161.4 (quat Mes*), 160.2 (d, J = 3, quat Ar), 155.2 (d, J = 9, quat Ar), 125.9 (d, J = 10, Mes* CH), 120.5 (q, J = 319, CF_3), 120.1 (d, J = 14, Mes* CH), 43.7 (quat CMe_2), 37.6 (quat CMe_3), 35.7 (quat CMe_3), 32.5 (Me), 32.4 (Me), 32.3 (*t*-Bu Me), 31.0 (*t*-Bu Me), 30.0 (d, J = 52, phospholane CH_2), 25.8 (d, J = 46, PCH_2), 16.9 (d, J = 3, PCH_2CH_2), 15.1 (d, J = 18, $PCH_2CH_2CH_3$).

Deprotonation of Phospholanium Cation 3 with NEt$_3$: Synthesis of Phospholane 5. To a solution of phospholanium triflate **3** (76 mg, 0.16 mmol, 1 equiv, containing about 8% of the protonated SPO **7**) in CH_2Cl_2 (1 mL), triethylamine (27 μL, 20 mg, 0.19 mmol, 1.2 equiv) was added. Deprotonation was monitored via $^{31}P\{^1H\}$ NMR spectroscopy, which showed formation of phospholane **5** (major product, δ −16.5) and SPO **8** (δ 23.5, see below for independent synthesis and characterization), along with a trace of the known secondary phosphine PHMes*(*n*-Pr) (δ −73.6)[19c] and an unidentified product (δ −35.6). The solution was concentrated under reduced pressure, and the resulting solid was dissolved in hexane (2 mL). The solution was run through a silica pipette column (42 mm × 5 mm) with hexanes as starting eluent and added CH_2Cl_2 in a gradient. The hexane fractions contained PHMes*(*n*-Pr), while the CH_2Cl_2 fraction contained the phospholane with a trace of the secondary phosphine. The CH_2Cl_2 fraction was concentrated under vacuum to yield a colorless oil containing CH_2Cl_2 (21 mg, 41% yield).

Anal. Calcd for $C_{21}H_{35}P$: C, 79.20%; H, 11.08%. Found: C, 79.34%; H, 11.14%. HRMS *m*/*z* calcd for $C_{21}H_{36}P$ (MH^+): 319.2555. Found: *m*/*z* 319.2549. $^{31}P\{^1H\}$ NMR (C_6D_6): δ −16.8. ^{31}P NMR (C_6D_6): δ −16.8. ^1H NMR (C_6D_6): δ 7.52 (dd, J = 4, 2, 1H), 7.19 (d, J = 2, 1H), 4.27 (CH_2Cl_2), 2.00 (dd, J = 19, 14, 1H, phospholane CH), 1.80 (d, J = 14, 1H, phospholane CH), 1.75−1.64 (m, 2H, PCH_2), 1.62 (9H, *t*-Bu), 1.57−1.41 (m, 2H, PCH_2CH_2), 1.37 (3H, Me), 1.32 (9H, *t*-Bu), 1.25 (3H, Me), 0.92 (t, J = 8, 3H, $PCH_2CH_2CH_3$). $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 157.9 (quat Ar), 151.9 (d, J = 14, quat Mes*), 151.7 (quat Mes*), 136.3 (d, J = 22, quat Ar), 121.6 (d, J = 6, Mes* CH), 118.5 (Mes* CH), 46.5 (d, J = 6, quat CMe_2), 37.9 (d, J = 9, phospholane CH_2), 37.1 (quat CMe_3), 34.8 (quat CMe_3), 33.6 (d, J = 3, Me), 33.3 (d, J = 21, PCH_2), 33.3 (Me), 32.3 (d, J = 9, *t*-Bu Me), 31.2 (*t*-Bu Me), 20.6 (d, J = 19, PCH_2CH_2), 15.5 (d, J = 13, $PCH_2CH_2CH_3$).

Synthesis of the SPO Mes*PH(O)(*n*-Pr) (8). A solution of Mes*Br (300 mg, 0.922 mmol, 1 equiv) in dry degassed tetrahydrofuran (THF) (5 mL) was cooled to −78 °C. A solution of *n*-BuLi (0.44 mL, 2.5 M in hexanes, 1.1 mmol, 1.2 equiv) was added at −78 °C, turning the mixture a pale yellow; it was stirred for 2 h at −78 °C. This solution was added via cannula over 30 min to a solution of *n*-PrPCl$_2$ (0.149 mL, 174 mg, 1.2 mmol, 1.3 equiv) in THF (10 mL), with both solutions at −78 °C. After the addition was complete, stirring was continued for 40 min. The mixture was then warmed to room temperature and stirred overnight. The major $^{31}P\{^1H\}$ NMR signal (THF) at δ 84.2 was assigned to Mes*P(*n*-Pr)(Cl), by analogy to related compounds.[27]

To this mixture, 5 mL of degassed H_2O was added. In the air, the solution was extracted with hexanes (20 mL) and the aqueous phase was washed with hexanes (20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude white solid (276 mg, 89% yield). The $^{31}P\{^1H\}$ NMR spectrum showed that the major compound present was the target SPO, Mes*PH(O)(*n*-Pr) (δ 22.4), with a little of the protonated SPO [Mes*PH(OH)(*n*-Pr)][Cl] (δ 38.3), and a trace of the secondary phosphine PHMes*(*n*-Pr) (δ −74.0).

A portion of this material (180 mg) was purified by chromatography on silica, using a pipette column (42 mm × 5 mm) starting with hexanes as eluent, followed by CH_2Cl_2, and then EtOAc. According to $^{31}P\{^1H\}$ NMR spectroscopy, the hexane fractions contained PHMes*(*n*-Pr) (41 mg), the CH_2Cl_2 fraction contained a mixture of the protonated SPO and the SPO (δ 38.2 and 23.4, plus other unidentified materials; 71 mg), and the EtOAc fraction contained the SPO (60 mg, 19% yield, or 30% yield considering only the portion that was purified by chromatography).

Anal. Calcd for $C_{21}H_{37}OP$: C, 74.96%; H, 11.08%. Found: C, 74.87%; H, 11.05%. HRMS *m*/*z* calcd for $C_{21}H_{36}OP$ ($(M-H)^+$): 335.2504. Found: *m*/*z* 335.2507. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 23.3. ^{31}P NMR ($CDCl_3$): δ 23.3 (dt, J = 480, 11). ^1H NMR ($CDCl_3$): δ 7.78 (dt, J = 476, 5, 1H, PH), 7.41 (d, J = 4, 2H, Mes* CH), 2.07−1.98 (m, 1H, P-CH_2), 1.67−1.59 (m, 1H, P-CH_2), 1.54 (18H, *o*-*t*-Bu), 1.41−1.33 (m, 1H,

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CH_2Me), 1.28 (9H, *t*-Bu), 0.97−0.86 (m, 1H, CH_2Me), 0.82 (t, J = 8, 3H, $PCH_2CH_2CH_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.2 (br, quat Ar), 152.7 (d, J = 3, quat Ar), 127.6 (d, J = 93, ipso quat Mes*), 123.5 (d, J = 9, Mes* CH), 38.7 (d, J = 3, quat CMe_3), 35.5 (d, J = 68, PCH_2), 34.9 (quat CMe_3), 33.9 (br, *t*-Bu Me), 31.0 (*t*-Bu Me), 16.7 (PCH_2CH_2), 15.0 (d, J = 15, $PCH_2CH_2CH_3$).

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supplementary Material.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00885.

Experimental procedures, characterization data, NMR spectra, and computational results (PDF)

Coordinates of computed structures and transition states (XYZ)

■ AUTHOR INFORMATION

Corresponding Authors

Russell P. Hughes − *Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States*; Email: russell.p.hughes@dartmouth.edu

David S. Glueck − *Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States*; orcid.org/0000-0002-8438-8166; Email: glueck@dartmouth.edu

Authors

Ryan M. Tipker − *Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States*

Jake A. Muldoon − *Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States*

Jacob Jo − *Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States;* Present Address: Vanderbilt University School of Medicine, 1161 21st Avenue S # D3300, Nashville, Tennessee 37232, United States (J.J.); orcid.org/0000-0002-0424-3507

Christopher S. Connors − *Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States*

Balazs R. Varga − *Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c00885

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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