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Biphilic Organophosphorus Catalysis: Regioselective Reductive Transposition of Allylic Bromides via P^{III}/P^{V} Redox Cycling

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Abstract

We report that a regioselective reductive transposition of primary allylic bromides is catalyzed by a biphilic organophosphorus (phosphetane) catalyst. Spectroscopic evidence supports the formation of a pentacoordinate (σ^5-P) hydridophosphorane as a key reactive intermediate. Kinetics experiments and computational modeling are consistent with a unimolecular decomposition of the σ^5-P hydridophosphorane via a concerted cyclic transition structure that delivers the observed allylic transposition and completes a novel P^{III}/P^{V} redox catalytic cycle. These results broaden the growing repertoire of reactions catalyzed within the P^{III}/P^{V} redox couple and suggest additional opportunities for organophosphorus catalysis in a biphilic mode.

Phosphorus-based compounds figure prominently in a range of catalytic applications. Apart from their role as supporting ligands in transition metal chemistry,[1] tricoordinate phosphorus compounds comprise a well-known class of *nucleophilic* catalysts,[2] wherein neutral tricoordinate (σ^3-P) phosphines (Figure 1A) behave as electron-pair donors with respect to electron-deficient substrates to elicit catalysis via tetracoordinate (σ^4-P^+) phosphonium intermediates. More recently, the potential of Lewis acidic σ^4-P^+ cations themselves to behave as catalysts in an *electrophilic* mode via intermediate pentacoordinate (σ^5-P) phosphoranes has been demonstrated (Figure 1B).[3–5] Herein, we demonstrate a *biphilic*[6] mode of organophosphorus catalysis that unifies both nucleophilic (donor) and electrophilic (acceptor) reactivities at a single phosphorus center. Specifically, we show that a small-ring phosphacycle catalyzes the regioselective transpositive reduction of allylic bromides in a manner that involves interconversion of well-characterized σ^3-P, σ^4-P^+, and σ^5-P species (Figure 1C). Taken together with ongoing work in the area of phosphine oxide redox catalysis,[7] these results further solidify the viability of the P^{III}/P^{V} oxidation state couple in catalytic chemistry[8] and portend new developments in biphilic organophosphorus catalysis that leverage the unique reactivities of σ^5-P phosphoranes.[9]

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ASSOCIATED CONTENT

Supporting Information

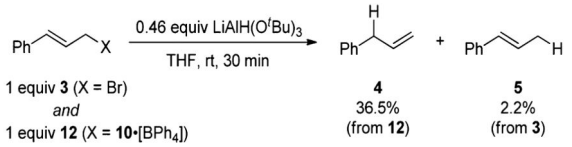
Synthetic procedures, spectral characterization data, kinetics data, Cartesian coordinates for stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

It is known from the work of van Tamelen[10] and Nojima[11] that stoichiometric reaction of allylic phosphonium cations (e.g., **1**, Figure 1C, bottom) with metal hydrides results in reductive deallylation of the σ^4-P^+ cation to the corresponding σ^3-P phosphine.[12] With respect to the allylic moiety, the reduction is regiospecific; alkenes **2** resulting from allylic transposition (i.e., γ-reduction) are the sole products observed under these stoichiometric conditions.[13] On account of this regiochemical outcome (and by analogy to reduction of related σ^4-P^+ cations[14]), the possible intervention of σ^5-P hydridophosphorane intermediates was posited by Gallagher,[15] although direct experimental evidence for this proposed pathway has not been reported.

On the basis of the aforementioned stoichiometric precedent, this allylic reduction presented itself as an appealing platform by which to test emerging hypotheses regarding the design features requisite for biphilic organophosphorus catalysis.[16] In contrast to the regiospecific transposition of the corresponding stoichiometric reduction (Figure 1C), catalytic loading (10 mol %) of triphenylphosphine-derived ion **6**[17] in the reduction of cinnamyl bromide (**3**) with $LiAlH(O^tBu)_3$ delivers products **4**:**5** in a 18:82 ratio (Table 1, entry 2); this γ/α-selectivity ratio deviates only marginally from an uncatalyzed control reduction (entry 1). Evidently, direct uncatalyzed reduction of **3** with $LiAlH(O^tBu)_3$ outcompetes notional biphilic catalysis by triphenylphosphine. Following on Gallagher's hypothesis and abundant precedent demonstrating enhanced electrophilic reactivity of cyclic phosphorus-based compounds compared to their acyclic congeners,[18] the conversion σ^4-$P^+ \rightarrow \sigma^5$-P was targeted for acceleration. While neither dibenzophosphole **8** nor phospholane **9** derivatives (proven catalyst motifs in several catalytic P^{III}/P^V=O redox methods)[19] satisfactorily alter the reduction outcome, catalytic loading of phosphonium salt derived from a four-membered phosphetane **10**[20,21] delivers reduction products with excellent γ/α-selectivity. Specifically, dropwise addition of $LiAlH(O^tBu)_3$ (2.5 equiv, 0.42 M in THF) to a 90 °C mixture of **3** and 10 mol % of allylated **10** in toluene over 15 h results in a combined 96% yield of reduction products as a 94:6 ratio in favor of the γ-reduction product **4**. Use of neutral trivalent phosphetane **10** provides similarly high selectivity (entry 7), while the corresponding HBF_4 salt results in a slightly diminished **4**:**5** ratio (entry 8).The identity of the exocyclic *P*-substituent has only a minor effect on the observed product ratio (compare entries 6 and 9), indicating the dominant role of the phosphetane moiety in controlling the reactivity.

Stoichiometric competition experiments confirm the enhanced reactivity of the strained phosphonium salts derived from four-member phosphacycle **10** toward hydridic reduction. In the reaction of an equimolar mixture of cinnamylphosphetanium salt **12** and cinnamyl bromide **3** with limiting $LiAlH(O^tBu)_3$ (eq 1), it is **12** that is preferentially reduced as inferred from the product distribution determined by GC. Similarly, by monitoring the ^{31}P NMR spectra of the reaction of an equimolar mixture of **14** and acyclic phosphonium **13** (eq 2), we estimate a rate difference of >20 in favor of the phosphetanium **14**. Qualitatively, these outcomes conform to strain/acceleration arguments advanced in organophosphorus



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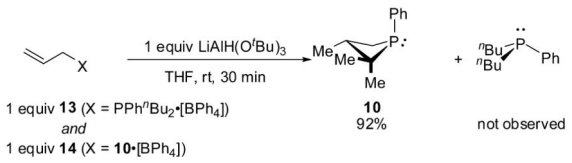
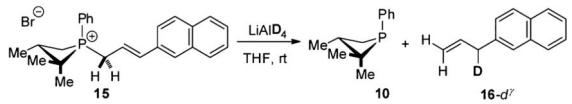


(2)

chemistry by Westheimer[22] and Hudson;[23] namely, the strain accrued to the σ^4-P$^+$ phosphetanium **12** minimizes the geometric reorganization (and by consequence the free energy) necessary to access a presumed σ^5-P hydridophosphorane. As has been noted by Hoz,[24] molecular orbital electronic effects may also play a significant role in the rate accelerations in small-ring systems.

Assessment of the phosphetane-catalyzed allylic reduction with respect to a panel of sterically and electronically varied allylic bromides are collected in Table 2. On a 1 mmol scale, good yield and selectivity for the transposed reduction product is observed for γ-alkyl substituted substrates (Table 2A). Regioselective reductive transposition also deconjugates styrenyl and dienyl substrates with high selectivity (Table 2B). Similarly, sterically encumbered allylic bromides are converted with high selectivity to the contrasteric γ reduction products (Table 2C). Additional examples can be found in the Supporting Information (SI) (Table S3). In all instances, control reductions conducted in the absence of the phosphetane catalyst favored direct α-reduction products, confirming that the γ selectivities reported in Table 2 are in fact due to the action of the catalyst.

Stoichiometric isotopic labeling experiments designed to establish the provenance of the newly formed γ-allylic C–H were conducted. Treatment of **15** with $LiAlD_4$ results in formation of **16**-d^γ (eq 3), where deuterium is incorporated



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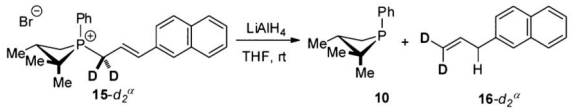
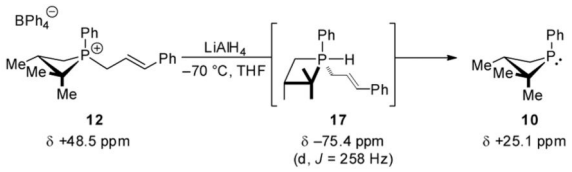


(4)

exclusively at the γ-position.[11] Complementarily, treatment of **15**-d_2^{α} with $LiAlH_4$ results in formation of **16**-d_2^{α} without loss or scrambling of the geminal deuterium labels (eq 4), indicating the phosphetanium salt is not deprotonated during the course of the reaction.

In accord with Gallagher's proposal and consistent with the notion of biphilic catalysis in this system, *in situ* spectral data reveal the intermediacy of a σ^5-P hydridophosphorane species in the reductive deallylation of σ^4-P^+ cinammylphosphetanium ion **12** to σ^3-P phosphetane **10** (eq 5).[25] When monitored by ^{31}P



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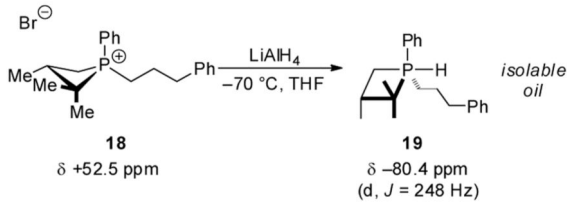
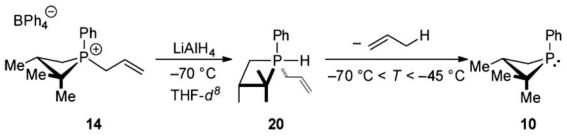


(6)

NMR, reaction of **12** (δ +48.5 ppm, Figure 2A) with $LiAlH_4$ at −70 °C results in formation of a new phosphorus species **17** (δ −75.4 ppm, d, J = 258 Hz, Figure 2B), whose chemical shift and multiplicity are consistent with formulation as a σ^5-P hydridophosphorane.[26] This assignment is further supported by the observation that treatment of the saturated σ^4-P^+ hydrocinammylphosphetanium ion **18** with $LiAlH_4$ (eq 6) yields an isolable species (**19**) with similar spectral characteristics (δ −80.4 ppm, d, J = 248 Hz). Subsequent warming of the NMR solution containing **17** results in clean conversion to σ^3-P phosphetane **10** (δ +25.1 ppm, Figure 2C) without the intervention of any observable intermediates. Overall, the conversion of **12** → **10** proceeds with retention of configuration at phosphorus. We tentatively assign a trigonal bipyramidal stereochemistry depicted as **17** that minimizes both repulsive steric interactions (i.e., the large *gem*-dimethyl group is equatorial and the small

hydride is apical) and phosphetane ring strain; this assignment conforms to the results of DFT modeling (see Figure S2 in SI).

The kinetics of the process σ^5-P → σ^3-P (i.e., **20** → **10**) were monitored by VT-NMR over the temperature range −70 °C < *T* < −45 °C for the parent allyl system (eq 7), permitting extraction



14 20 10

(7)

of the activation parameters by Eyring analysis ($\Delta H^{\ddagger}$ = +15.2(8) kcal·mol^{-1}, $\Delta S^{\ddagger}$ = −3(4) cal·mol^{-1} K^{-1}). DFT calculations (M06-2X/6-311++G(2d,2p)) provide further data regarding the conversion **20** → **10**. Structure **21** (Figure 3) represents the global minimum for the suite of polytopal isomers of the σ^5-P hydridophosphorane in which the phosphetane ring spans one apical and one equatorial site of a phosphorus-centered trigonal bipyramid.[27] The lowest energy pathway connecting hydridophosphorane **21** and phosphetane **22** transits via a single first-order saddle point, whose structure (**TS**) involves concomitant P–Cα bond cleavage (2.29 Å) and direct transferal of H from P to Cγ (*d*(P–H) 1.64 Å, *d*(H–Cγ) 1.62 Å). With respect to geometry, **TS** is best described as a distorted square pyramid about phosphorus with the P-phenyl moiety occupying the apical site, and both the four-membered phosphetane and five-membered envelope-like cycle spanning *cis*-basal positions. The computed $\Delta H^{\ddagger}$ (11.9 kcal/mol) is in good agreement with the experimental value, and the cyclic nature of transition structure **TS** is consistent with the negative value of the experimentally determined activation entropy. We note that this proposed mechanism via the five-center, six-electron transition structure of **TS** bears a formal orbital equivalency with well-known hydrocarbon-based pericyclic group transfer reactions[28] (e.g., ene/retro-ene reactions[29]).

In summary, we have demonstrated a regioselective reductive transposition of allylic bromides catalyzed by a small-ring phosphacycle. The experimental and computational results implicate the operation of a P^{III}/P^{V} mechanistic pathway that involves the interconversion of discrete, observable σ^3-P, σ^4-P$^+$, and σ^5-P species. We note that the phosphetane-catalyzed allylic reduction represents a phosphacatalytic complement to known stoichiometric diazene-mediated[30] and catalytic Pd π-allyl[31] reduction protocols. The biphilic organophosphorus catalysis demonstrated here presents reactivity that merges archetypal nucleophilic and electrophilic manifolds; additional studies, both synthetic and mechanistic, that probe this reactivity are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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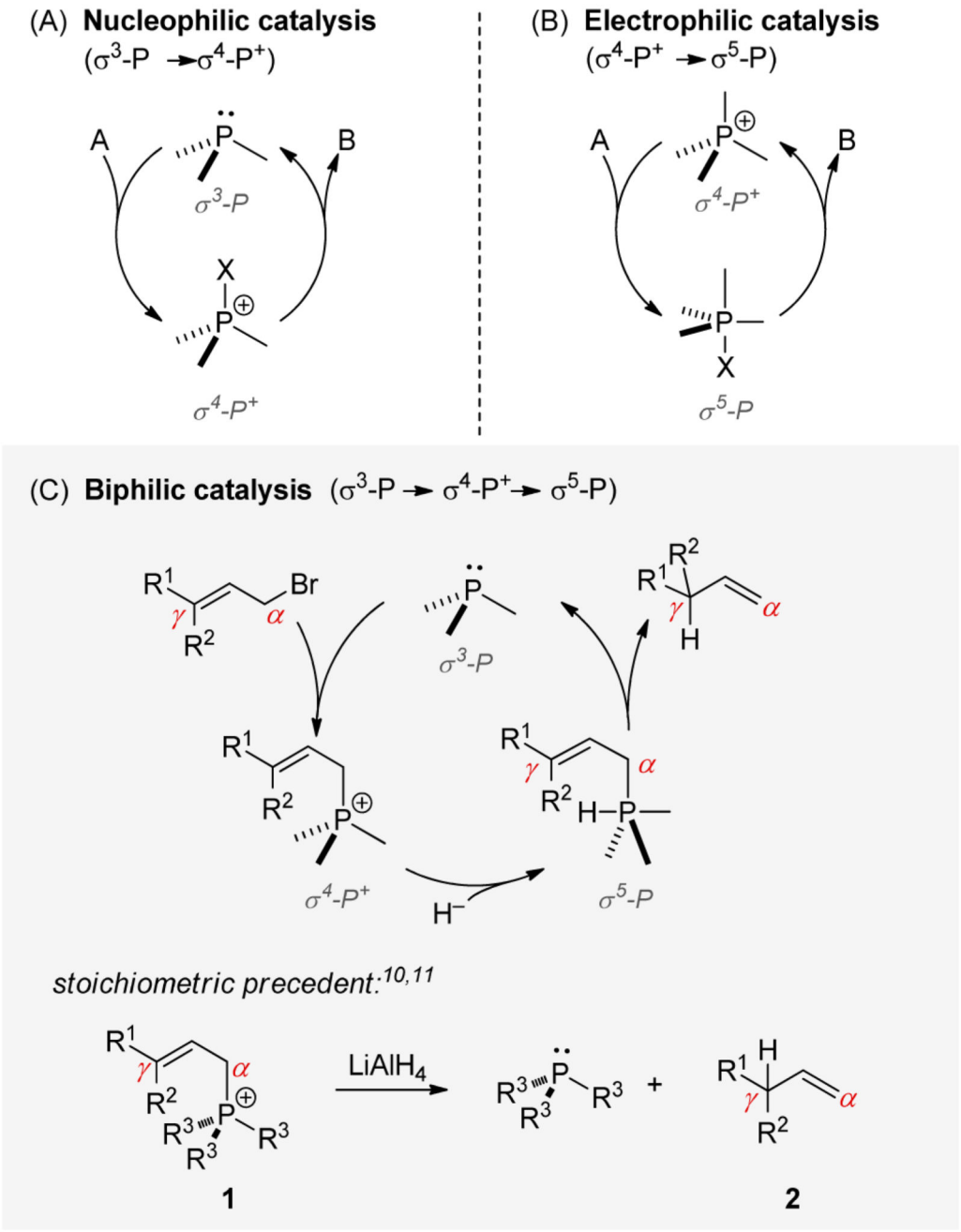


Figure 1.
Modes of organophosphorus catalysis.

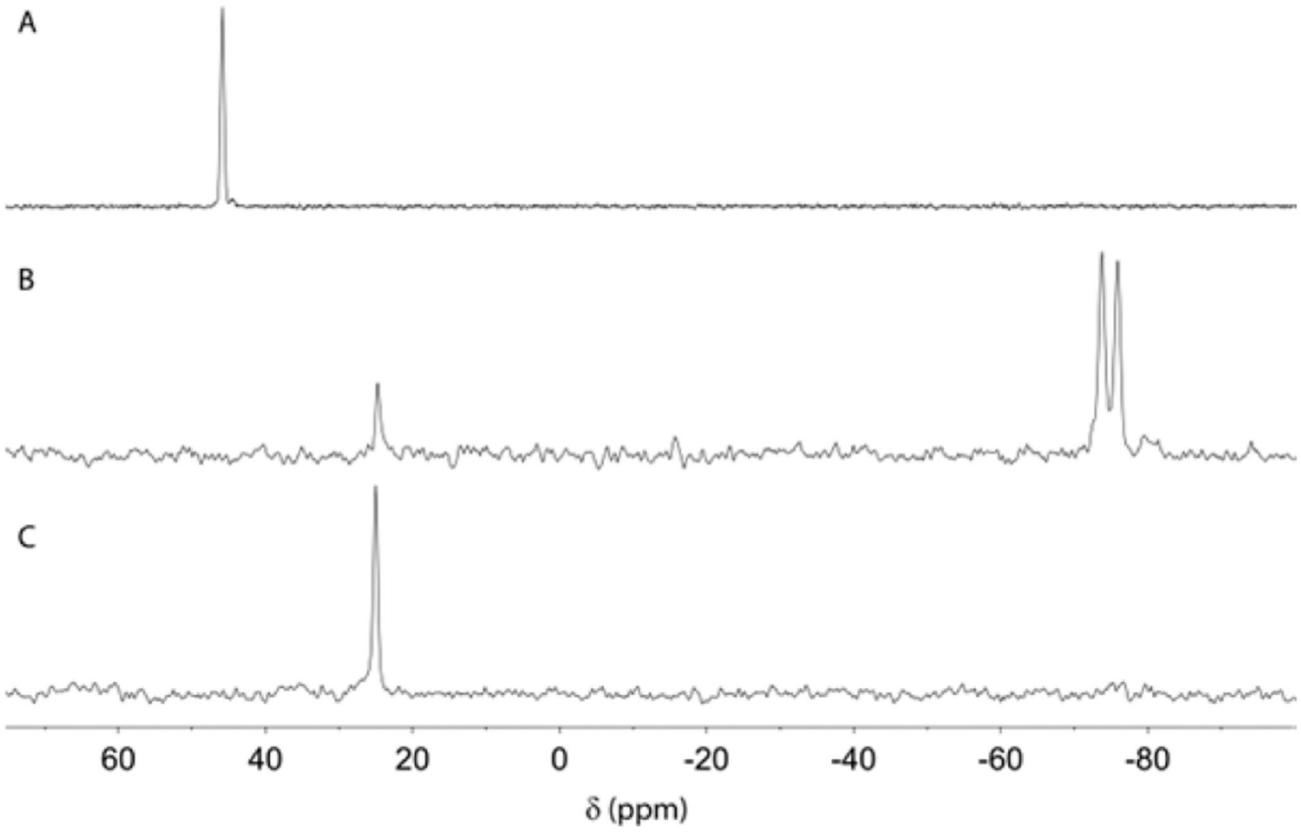


Figure 2.

In situ ^{31}P NMR spectra for the reaction shown in eq 5. (A) Initial spectrum of phosphetanium **12**. (B) Spectrum recorded at −70 °C immediately following addition of $LiAlH_4$ showing formation of **17**. (C) Spectrum recorded after warming reaction to −30 °C showing formation of **10**. Units are ppm relative to 85% H_3PO_4 external standard.

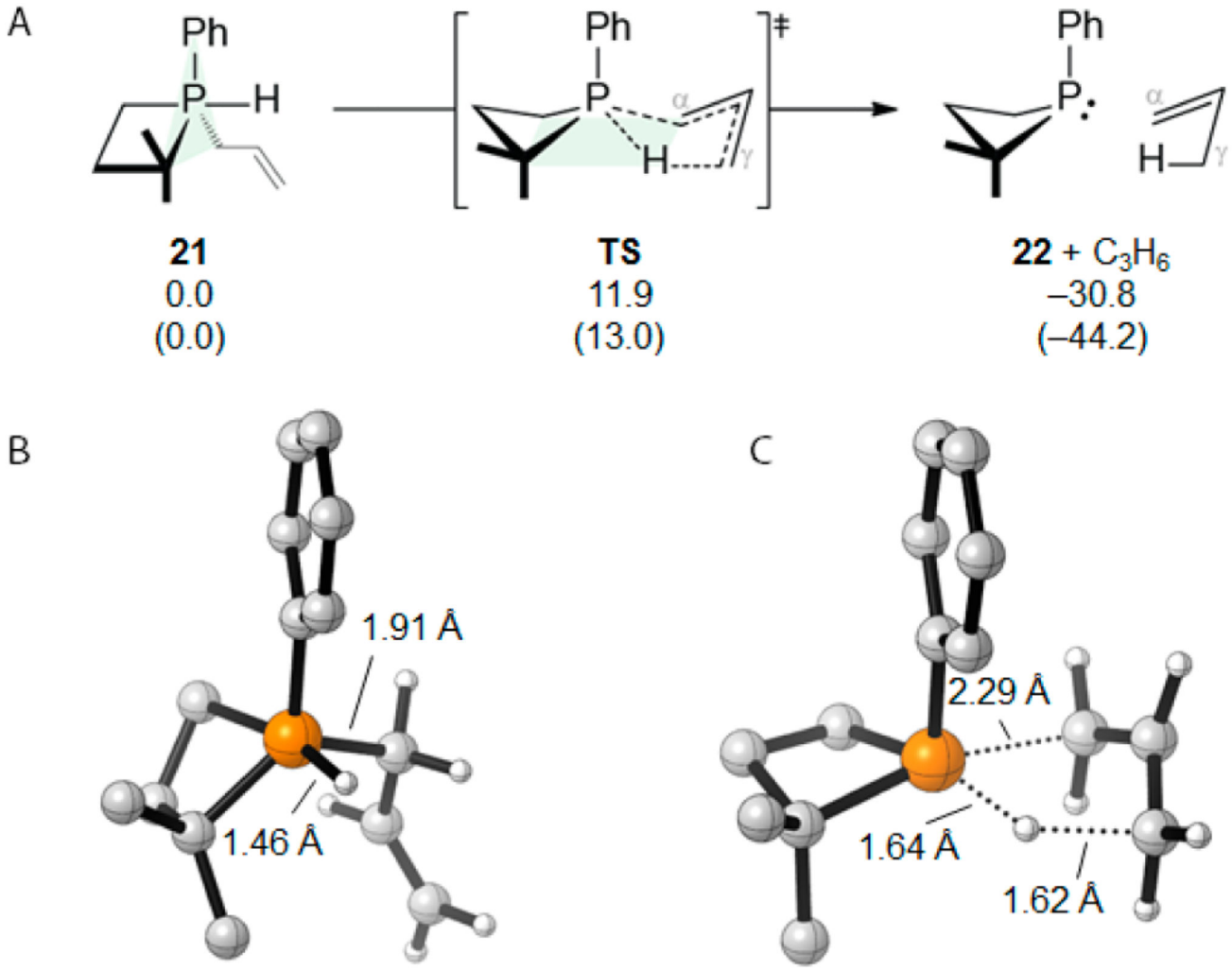
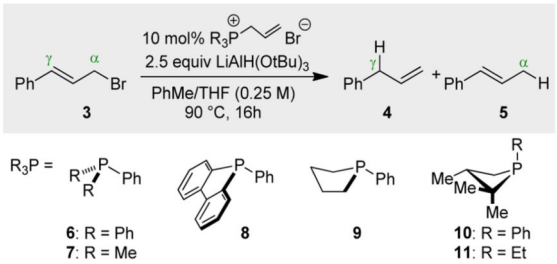


Figure 3.

Computational modeling of the conversion σ^5-P → σ^3-P [M06-2*X*/6-311++G(2d,2p)]. (A) Enthalpy (free energy) for pathway in kcal/mol. (B) Optimized σ^5-P hydridophosphorane structure **21**. (C) Optimized transition state structure **TS**.

Table 1

Effect of Organophosphorus Catalyst on Regioselectivity of Transpositive Allylic Reduction[a]



entry	R_3P[b]	yield[c]	ratio[c] (4:5)
1	none	80	9:91
2	**6**	78	18:82
3	**7**	85	11:89
4	**8**	95	19:81
5	**9**	95	54:46
6	**10**	96	94:6
7	**10** [d]	100	98:2
8	**10** [e]	81	88:12
9	**11**	96	91:9

[a] See Supporting Information for full experimental details.

[b] See ref 17.

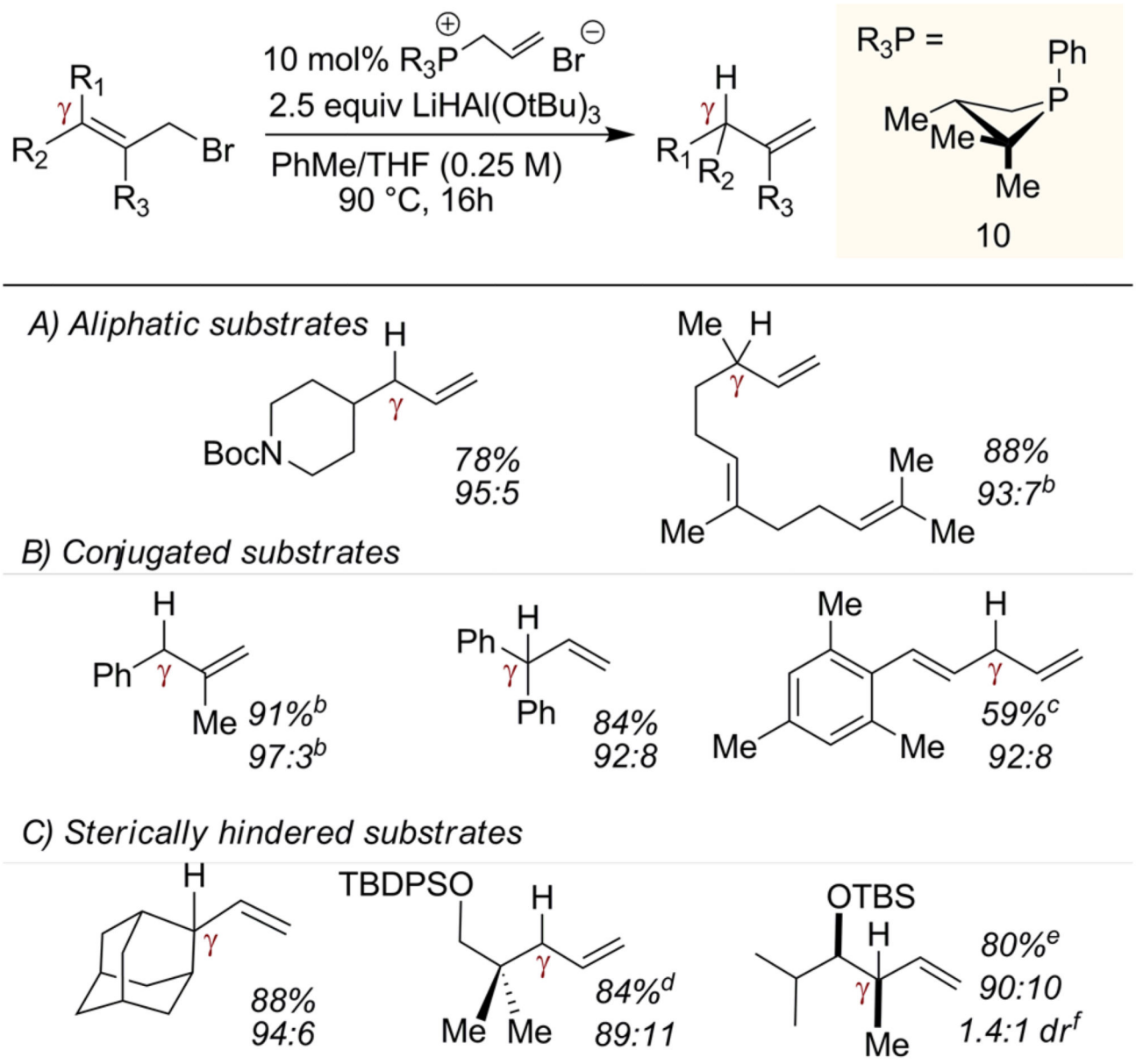
[c] The combined yield and ratio of **4** and **5** were determined by GC analysis (dodecane internal standard).

[d] Neutral trivalent **10** as catalyst.

[e] **10**·HBF_4 salt as precatalyst.

Table 2

Assessment of Phosphetane-Catalyzed Allylic Reduction[a]



[a] See Supporting Information for full experimental details. Isolated yields are reported unless otherwise stated. Ratios (γ:α) determined by ^{1}H NMR integration unless otherwise stated.

[b] Determined by GC analysis.

[c] Reaction time 10 h due to thermal instability of substrate.

[d] TBDPS = *tert*-butyldiphenylsilyl.

[e] TBS = *tert*-butyldimethylsilyl.

[f] *d.r.* and relative stereochemistry of major isomer determined after TBS deprotection.