Deoxyfluorination of 1°, 2°, and 3° Alcohols by Nonbasic O–H Activation and Lewis Acid-Catalyzed Fluoride Shuttling

Hye Won Moon,[1] Marissa N. Lavagnino,[1] Soohyun Lim,[1] Maximilian D. Palkowitz,[2] Michael D. Mandler,[3] Gregory L. Beutner,[4] Myles J. Drance,[1,‡] Jeffrey M. Lipshultz,[1,#] Paul M. Scola,[2] and Alexander T. Radosevich[1,*]

[1]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

[2]Small Molecule Drug Discovery, Bristol Myers Squibb, 250 Water Street, Cambridge, Massachusetts 02141, United States

[3]Small Molecule Drug Discovery, Bristol Myers Squibb, Princeton, New Jersey 08543, United States

[4]Chemical and Synthetic Development, Bristol Myers Squibb, One Squibb Drive, New Brunswick, New Jersey 08903, United States

ABSTRACT: A method for deoxyfluorination of aliphatic primary, secondary, and tertiary alcohols is reported, employing a nontrigonal phosphorous triamide for base-free alcohol activation in conjunction with an organic soluble fluoride donor and a triarylborane fluoride shuttling catalyst. Mechanistic experiments are consistent with a reaction that proceeds by collapse of an oxyphosphonium fluoroborate ion pair with fluoride transfer. The substrate scope complements existing deoxyfluorination methods and enables preparation of homochiral secondary and tertiary alkyl fluorides by stereoinversion of the substrate alcohol.

1. Introduction

Alcohol deoxyfluorination is a useful approach to valuable organofluorine compounds.[1] Leading methods employ fluorinated sulfur- (e.g. DAST, PyFluor)[2,3,4] or carbon-based (e.g. AlkylFluor, CpFluor)[5] reagents in conjunction with a suitable base to promote alkyl alcohol conversion to an oxynucleofuge followed by *in situ* displacement with fluoride (Fig. 1A).[6,7] In principle, the application of these techniques to homochiral alcohols provides for a synthesis of stereochemically-defined alkylfluorides but in practice the activated intermediate is prone to either β-elimination or stereoablative ionization, especially for tertiary alcohol substrates.[8] Due in part to this synthetic limitation, there are only a small number of pharmaceuticals incorporating fully substituted C–F stereogenic centers.[9]

Advances in main group chemistry are unveiling new approaches to bond activation and functionalization.[10] For instance, the biphilic[11] phosphorus triamide **1** is known to undergo rapid oxidative addition to O–H bonds under mild and neutral conditions, generating an equilibrium mixture of ring-chain tautomers **1**·[H][OR] and **1'**·[OR] (Fig. 1B).[12] We considered the possibility that this O–H activation transformation might be advanced in service of a net deoxyfluorination sequence by further conversion to an alkoxyphosphonium ion, either by hydride abstraction from **1**·[H][OR] or *P*-quaternization of **1'**·[OR]. This line of thinking was informed by the recognition that oxyphosphonium ions are well-known intermediates in Appel deoxyhalogenation,[13,14] although their application to deoxyfluorination is comparatively rare.[15,16] As notable precedent, Ohmori has described the thermal decomposition of electrochemically-generated alkoxytriphenylphosphonium tetrafluoroborates to the corresponding fluoroalkanes.[17] Accordingly, if a suitable trigger for alkoxyphosphonium fluoroborate formation from tautomers **1**·[H][OR] and **1'**·[OR] were identified, then an entry to alcohol deoxyfluorination could be envisioned.

Here, we report the successful realization of this deoxyfluorination design plan within a one-pot method proceeding by: (*i*) alcohol O–H activation under neutral, nonbasic conditions, (*ii*) triggered formation of an alkoxyphosphonium leaving group, and (*iii*) chemoselective nucleophilic fluoride transfer from a weakly basic fluoroborate ion. The mild, nonbasic conditions of both the O–H activation and nucleophilic fluoride transfer reactions suppress undesired elimination in favor of desired deoxyfluorination, enabling the synthesis of stereochemically-enriched tertiary alkyl fluorides.

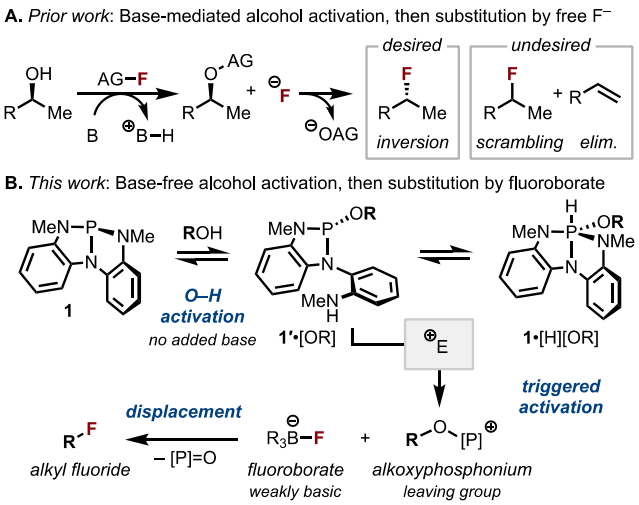


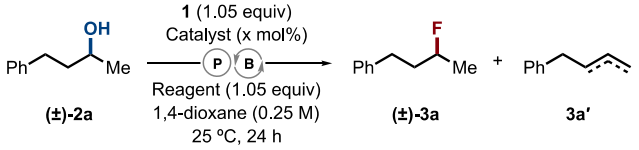
Figure 1. (A) General approach to alcohol deoxyfluorination. AG = activating group. B = base. (B) Deoxyfluorination of aliphatic alcohols via P-mediated alcohol activation through alkoxyphosphonium species.

2. Results

2.1 Impact of Reaction Condition Variables.

Initial investigations were undertaken with 4-phenyl-2-butanol (**(±)-2a**), which was successfully converted to fluorinated product **(±)-3a** in 81% yield (Table 1, entry 1) by treatment with biphilic phosphorus triamide **1** (1.05 equiv) followed by triphenylmethyl tetrafluoroborate (Ph_3CBF_4, 1.05 equiv) in 1,4-dioxane at room temperature. Under these conditions, the desired deoxyfluorination pathway was favored over formation of the combined elimination

Table 1. Discovery and optimization of 2° alcohol deoxyfluorination.



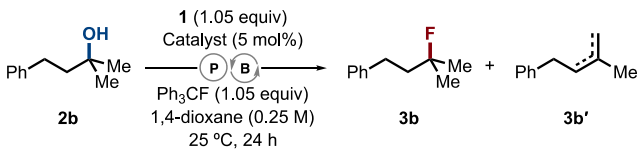
Entry	Reagent	Catalyst	Catalyst (mol%)	Yield **3a** (%)	Ratio (**3a**/**3a′**)[a]
1	Ph_3CBF_4	--	--	81	5.8:1
2	Ph_3CF	$BF_3{\cdot}OEt_2$	5	83	8.3:1
3	Ph_3CF	$BF_3{\cdot}OEt_2$	10	83	7.5:1
4	Ph_3CF	$BF_3{\cdot}OEt_2$	100	81	5.4:1
5	Ph_3CF	$BF_3{\cdot}OEt_2$	150	81	5.8:1

Yields are determined by ^{19}F NMR with internal standard. See SI Section IV for full synthetic details. [a]Yield **3a′** determined by GC.

side-products **3a′** (5.8:1 ratio of **3a**:**3a′**). The product selectivity for deoxyfluorination could be improved if stoichiometric Ph_3CBF_4 was replaced by 1.05 equiv of the soluble fluoride ion donor triphenylmethyl fluoride (Ph_3CF) and a catalytic quantity of $BF_3{\cdot}OEt_2$ (5 mol%), effectively generating the Ph_3C^+ electrophile and BF_4^- nucleophile in situ.[18,19] By this Lewis acid-catalyzed "fluoride shuttling" approach,[20] alkylfluoride **(±)-3a** was formed in 83% yield and 8.3:1 selectivity in favor of deoxyfluorination over elimination (entry 2).[21] Examining the effect of catalyst stoichiometry, the yield of desired deoxyfluorinated product was unaffected across a range of loadings; however, the selectivity between fluorinated and eliminated products decreased with increasing catalyst loading (entries 2-5).

Given known difficulties in tertiary alcohol deoxyfluorination, conversion of tertiary alcohol **2b** to tertiary alkylfluoride **3b** was attempted under the foregoing conditions (1.05 equiv of **1**, 1.05 equiv of Ph_3CF, 5 mol% of $BF_3{\cdot}OEt_2$). In the event, fluorinated product **3b** was indeed isolated, albeit in a modest yield (55%) and with an increase in the formation of elimination side-products **3b′** (Table 2, entry 1). Improvements in yield and selectivity for **3b** were achieved by varying the boron Lewis acid,[24] whereby a qualitative correlation between deoxyfluorination yield and computed fluoride ion affinity (FIA) was observed (see SI Section IX for full details).[25] Namely, it was found that tris(2,4-difluorophenyl)borane (**B1**, FIA = 72 kcal/mol) afforded **3b** in 80% yield and enhanced selectivity (4.2:1) (entry 6). By contrast, the use of either a more fluorophilic (i.e. tris(pentafluorophenyl)borane, FIA=88 kcal/mol, entry 7)[26] or a less fluorophilic (i.e. triphenylborane, FIA=62, entry 4) triarylborane led to diminished yield of **3b**.[27] In the former case, $(F_5C_6)_3B$ presumably binds F^- too avidly and disfavors fluoride transfer to the *tert*-carbon center. In the latter case, Ph_3B binds F^- too poorly and does not activate the Ph_3CF donor. This trend was corroborated experimentally via the Gutmann-Beckett method, in which the shift in ^{31}P NMR resonance ($\Delta\delta$) upon borane complexation with triethylphosphine oxide is correlated to Lewis acidity.[28] However, FIA is not the only determinant of reaction success; cationic phosphacorrole Lewis acids with similar FIA to **B1** did not promote fluorination (see SI Section VII E for full details).[29]

Table 2. Discovery and optimization of 3° alcohol deoxyfluorination.



Entry	Catalyst	Yield 3b	Ratio [a] (**3b**/**3b′**)	$\Delta\delta$ [b] (ppm)	FIA_{solv} [c] (kcal/mol)
1	$BF_3{\cdot}OEt_2$	55	2.2:1	31.8	81
2	$B(O\textit{i}\text{-}Pr)_3$	0	--	0.2	42
3	BEt_3	0	--	25.7	53
4	BPh_3	<1	<1:20	23.9	62
5	$B(4\text{-}F\text{-}C_6H_4)_3$	25	1:1.1	25.7	66
6	$B(2,4\text{-}F_2\text{-}C_6H_3)_3$ (**B1**)	**80**	**4.2:1**	**30.0**	**72**
7	$B(C_6F_5)_3$	2	<1:40	35.0	88

Entry	Catalyst	Reagent	Yield 3b	Ratio [a] (**3b**/**3b′**)
8	--	PyFluor	11	1:3.5
9	--	PBSF	19	1:3.7
10	--	AlkylFluor	44	1.5:1
11[22]	--	TFFH/$Et_3N{\cdot}3HF$	67	2.5:1

Yields are determined by ^{19}F NMR with internal standard. See SI (Sections IV, V) for full synthetic details. [a]Yield **3b′** determined by ^1H NMR. [b]Difference in ^{31}P NMR shift of $Et_3P{=}O$ upon complexation with borane. [c]Fluoride ion affinity (FIA) calculated at DSD-BLYP(D3JB)/Def2-QZVPP level of theory (CPCM with $\varepsilon = 2.21$ for 1,4-dioxane) referenced to COF_2 system.[23]

For comparison, several known protocols for deoxyfluorination were evaluated using the challenging tertiary alcohol **2b** as substrate (Table 2, entries 8-10),[3,4] but each returned the product alkyl fluoride **3b** in lower yield and selectivity. As is evident, the P-mediated, B-catalyzed method presents a useful complement to existing techniques for deoxyfluorination, especially in the case of 3° alcohols.

2.2 NMR Investigations of Reaction Intermediates.

The course of the deoxyfluorination reaction described in Table 2, entry 6 was monitored by in situ ^{31}P NMR spectroscopy (Fig. 2). The spectroscopic data establishes that nontrigonal triamide **1** (δ 159.8 ppm) is rapidly converted by reaction with alcohol **2b** into an equilibrium mixture composed of hydridophosphorane **1**·[H][OR] (δ –37.6 ppm, d, $^1J_{P-H}$ = 588 Hz) as the major component and ring-chain tautomer **1′**·[OR] (δ 117.1 ppm) as the minor component (the minor atropisomer of **1′**·[OR] can also be observed at δ 110.2 ppm). The signals for these species decrease over the ensuing deoxyfluorination reaction timecourse with growth of a new ^{31}P NMR resonance at δ 36.9 ppm (a minor resonance assigned as an atropisomer was also observed δ 35.9 ppm). This latter species was shown to correspond to *P*-tritylated phosphonamide **4** after synthesis and X-ray crystallography of the related **4**·[BF_3]

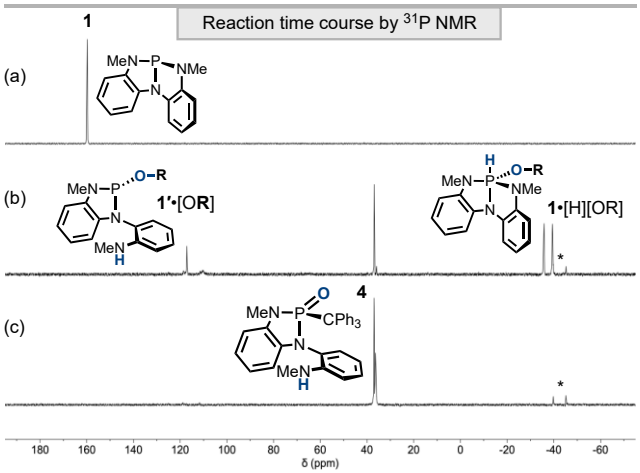


Figure 2. Time-stacked in situ ^{31}P NMR spectra of the deoxyfluorination of **2b** by **1** and **B1** at: (a) 0 min, (b) 30 min, (c) 12 h. **1** (δ 159.8 ppm), **1**·[H][OR] (δ –37.6 ppm, *J*=588 Hz), **1′**·[OR] (δ 117.1 ppm), and **4** (δ 36.9 ppm). *See SI (Section VII A) for assignment of the minor species as **1**·[F][OR] (δ –42.5 ppm, *J*=879 Hz).

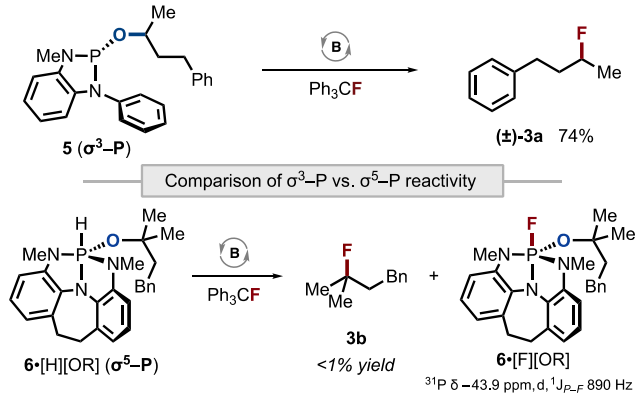


Figure 3. Treatment of σ^3-P compound **5** under standard conditions leads to 74% deoxyfluorination yield, but σ^5-P scaffold **6**, which cannot adopt σ^3-P tautomer, is ineffective at deoxyfluorination.

adduct (see SI Section VII B). This stoichiometric byproduct can be efficiently separated from the fluorinated product by silica gel chromatography.

Evidently, the trityl cation electrophile (generated by fluoride abstraction from Ph_3CF by **B1**) reacts with the σ^3-P tautomer **1'**•[OR] even though present as the minor constituent of the ring-chain equilibrium. In line with this hypothesis, σ^3-P compound **5** (prepared by reaction of **(±)-2a** with chlorodiazaphospholene[30] in the presence of base, see SI Section VII for details) is converted to fluorinated product **(±)-3a** in 74% yield by exposure to 1.05 equiv Ph_3CF and 5 mol% **B1** (Fig. 3).[31] Along complementary lines, utilizing hydridoalkoxyphosphorane **6**·[H][OR] (a structurally constrained analogue of **1** that can only exist as the σ^5-P tautomer)[32] results in no deoxyfluorinated product **3b**; instead, fluoroalkoxyphosphorane **6**·[F][OR] stemming from hydride abstraction and fluoride addition to a cationic P center is observed. Indeed, fluoroalkoxyphosphoranes are the primary alcohol-derived side products observed under the reported synthetic reaction conditions (Figure 2, indicated by *), and the amount observed is inversely correlated to substrate performance under deoxyfluorination conditions.

2.3 Mechanistic Model.

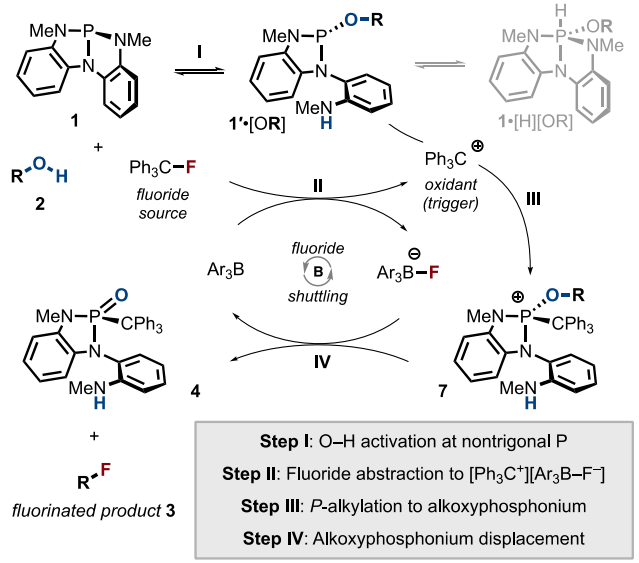


Figure 4. Proposed reaction sequence for deoxyfluorination, proceeding by the following four stages: (I) activation of O–H substrate by nontrigonal compound **1** to give equilibrating tautomers **1'**·[OR] and **1**·[H][OR]; (II) fluoride abstraction from Ar_3C–F by Ar_3B to give ion pair $[Ph_3C^+][Ar_3B–F^–]$; (III) *P*-quaternization of **1'**·[OR] by Ph_3C^+ to give alkoxyphosphonium **7**; (IV) *O*-dealkylation of **7** by fluoride transfer from $Ar_3B–F^–$.

Consistent with the preceding results, a proposed stepwise reaction sequence for the deoxyfluorination reaction is depicted in Figure 4. First, activation of the O–H bond of alcohol **2** by **1** generates an equilibrium mixture of the σ^3-P and σ^5-P tautomers **1'**·[OR] and **1**·[H][OR], respectively (Step I). Simultaneously, the borane catalyst Ar_3B reversibly abstracts fluoride from Ph_3CF, resulting in an ion pair consisting of $[Ar_3B–F]^–$and Ph_3C^+ (Step II), which can quaternize σ^3-P **1'**·[OR] (Step III). This *P*-quaternization step is possibly initiated by single-electron oxidation.[33] The resulting alkoxyphosphonium **7** can undergo *O*-dealkylation by fluoride transfer from $[Ar_3B –F]^–$ to regenerate catalyst Ar_3B,[34] liberate phosphonamide **4**, and deliver fluorinated product **3** (Step IV).

2.4 Reaction Scope and Examples.

Qualitative observations made during study of the substrate scope of this alcohol deoxyfluorination method conform to the foregoing mechanistic picture (Fig. 5). Tertiary alcohols, which establish a significant population of reactive σ^3-P tautomer **1'**·[OR] by virtue of the substrate steric bulk,[12a] are efficiently converted into the corresponding tertiary fluorides **3b**–**3j** in good chemical yield (42–90% yield) by suppression of deleterious elimination, likely owing to the lack of exogenous Brønsted base in the reaction conditions. Of note in this regard is homobenzylic product **3d**, which would be prone to elimination to a stable styrene product. Additionally, differentially halogenated product **3e** is formed in good yield (71%) with preservation of the primary alkyl bromide moiety; trivalent phosphorus triamide **1** is weakly nucleophilic and reacts only slowly with most alkyl halide electrophiles. Saturated amine heterocycles such as Boc-protected azetidine **3g** and piperidine **3h** can be fluorinated efficiently at both endocyclic and exocyclic positions, respectively. Unsaturated moieties such as cyclic olefins (**3i**) and alkynes (**3j**) are well-tolerated in the fluorination protocol. Example **3f** illustrates an instance where the standard Lewis acid catalysis conditions gave only trace deoxyfluorination; we speculate that the presence of Lewis basic functionality inhibits boron Lewis acid turnover. Accordingly, the use of stoichiometric Ph_3CBF_4 in place of Ph_3CF/**B1** (cf. Table 1, entry 1 above) returned the deoxyfluorination product in good yield (53%).

Secondary alcohols are also converted into alkyl fluorides (**3a**, **3k**–**3o**, 52–87% yield). Secondary benzylic product **3k** could be obtained in good yield, despite the propensity for elimination. The reaction conditions are tolerant of sulfones (**3l**, 87% yield), acyclic olefins (**3m**, 62% yield), and dialkyl ethers (**3o**, 57% yield). Fluorination of substrates containing Lewis basic pyridine rings are viable but require increased loading of **B1** on account of acid-base adduct formation (**3n**). Biomolecule scaffolds including protected carbohydrates (**3o**) can also be fluorinated.

Primary alkyl alcohols can also be converted into the corresponding 1° alkylfluorides, although the reactions require heating to 50 °C in these cases (**3p** and **3q**, 50% and 41% yield, respectively). This observation likely stems from the σ^3-P tautomer being relatively disfavored (as compared to that derived from 2° and 3° alcohols), due to diminished destabilizing steric effects in the more crowded σ^5-P tautomer. Consequently, we note the relative reactivity of substrates observed in the present method (3° ≈ 2° > 1°) complements that reported for other thermally stable deoxyfluorination reagents.[2,3,5]

2.5 Stereochemical Studies.

In order to probe the stereochemical outcome of the fluoride transfer step, the deoxyfluorination of homochiral cyclic substrates was investigated (Fig. 6). Deoxyfluorination of *N*-Boc-*anti*-4-hydroxy-L-proline methyl ester provided *syn*-diastereomer **3r** (72%) and *N*-Boc-*syn*-4-hydroxy-L-proline methyl ester provided *anti*-diastereomer **3s** (76%), indicating that neither anchimeric assistance nor stereoelectronic ring effects determine the stereochemical outcome

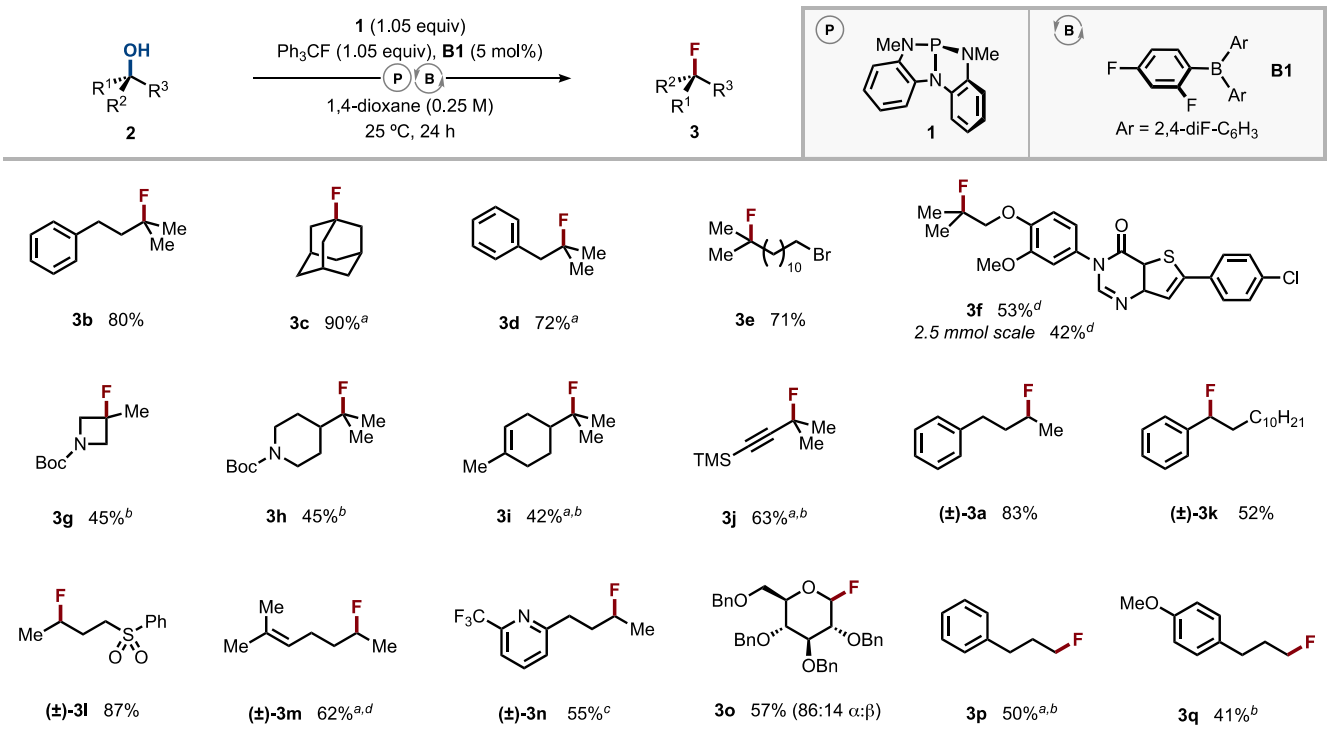


Figure 5. Examples of deoxyfluorination of aliphatic alcohols. Yields isolated on 0.4 mmol scale. See SI Section VI for full synthetic details. [a] Yield determined by ^{19}F NMR with internal standard. [b] 50 °C. [c] 1 equiv of **B1**. [d] Using 1.05 equiv of Ph_3CBF_4 in place of Ph_3CF and **B1**.

in these cases. Evidently, nucleophilic displacement of the activated oxyphosphonium ion by fluoroborate proceeds with inversion of stereochemistry. Indeed, tropane alkaloid **3t** was also obtained by stereospecific invertive deoxyfluorination of *N*-Boc-nortropine **2t**. Correspondingly, the sterol 3β-hydroxy-5α-androstan-17-one (**2u**) under standard conditions afforded 3α-fluorosteroid **3u** as a single diastereomer. The saturated sterol **2v** is fluorinated with retention of stereochemistry, a result we attribute to the homoallylic stabilization of the intermediate nonclassical carbocation.[35]

The preference for stereochemical inversion during deoxyfluorination holds equally for acyclic enantioenriched substrates (Fig. 7). The deoxyfluorination of homochiral secondary alcohol (*S*)-**2a** (>99:1 e.r.) afforded homochiral secondary alkyl fluoride (*R*)-**3a**[36] in 82% chemical yield and with excellent enantiospecificity for inversion (97.5:2.5 e.r.). Notably, deoxyfluorination of homochiral tertiary alcohol (*S*)-**2w** (97.5:2.5 e.r.) similarly afforded enantioenriched tertiary alkyl fluoride (*R*)-**3w** in both good yield (68%) and with good configurational purity (91:9 e.r.). The latter case was also examined under a variety of previously published conditions for alkyl fluorination, and each delivered fluorinated product in diminished yield and selectivity while exhibiting varying stereochemical outcomes (see SI Section VI D for full details).

3. Discussion

The results above illustrate the efficient deoxyfluorination of primary, secondary, and tertiary alcohols employing a phosphorus triamide reagent as alcohol activator and a borane catalyst as fluoride shuttle. This non-basic, dual activation approach is particularly efficient in the activation of tertiary substrates–a substrate class that is traditionally challenging for similar deoxyfluorination protocols–and displays selectivity for inversion of stereochemistry at the alcoholic position. Given the high degree of steric crowding inherent to substitution at 3° carbon electrophiles, it seems reasonable to expect significant C–O dissociation prior to C–F bond formation in net fluoride transfer step. A stereoinvertive stepwise substitution reaction[37] proceeding by rapid collapse of a contact ion pair[38] (composed of an incipient phosphine oxide-stabilized carbocation and fluoroborate anion) before solvent cage escape would account for the observed stereochemistry. This interpretation is consistent with other instances of stereospecific inversion at unactivated hindered tertiary sites,[39] including those mediated by alkoxyphosphonium ions.[40] Furthermore, a cyclopropyl-containing substrate (**2x**) is observed to undergo ring-opening fluorination under the reaction conditions, supporting the putative intermediacy of a carbocation (see SI Section VI for full details). As an aside, we note that both

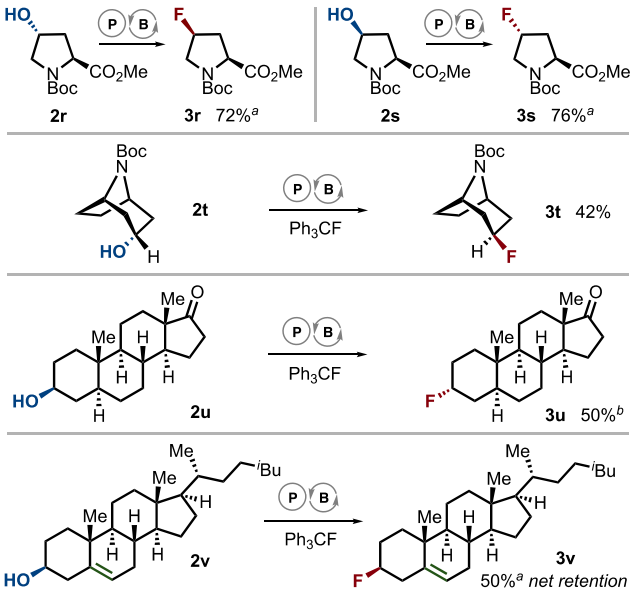


Figure 6. Stereospecificity of deoxyfluorination in cyclic substrates. Yields

isolated on 0.4 mmol scale. See SI Section VI for full synthetic details. Reaction conditions: alcohol substrate (0.4 mmol), **1** (1.05 equiv), Ph_3CF (1.05 equiv), **B1** (5 mol%), 1,4-dioxane (0.25 M), 25 ºC, 24 h. [a] 50 °C. [b] 40 °C

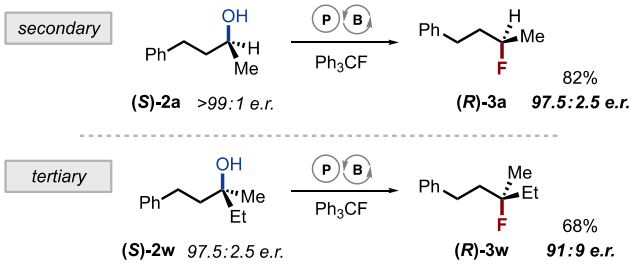


Figure 7. Stereospecific invertive deoxyfluorination of enantiomerically-enriched acyclic 2º and 3º carbinols (S)-**2a** and (S)-**2w**, respectively. Yields isolated on 0.4 mmol scale. See SI (Section VII D) for full synthetic details. Reaction conditions: alcohol substrate (0.4 mmol), **1** (1.05 equiv), Ph_3CF (1.05 equiv), **B1** (5 mol%), 1,4-dioxane (0.25 M), 25 ºC, 24 h.

σ^3-P tautomer **1'**•[OR] and oxyphosphonium **7** are inherently stereogenic at phosphorus. The extent to which that P-stereochemistry is influenced by the chirality of the alcohol substrate or impacts the enantiospecificity of deoxyfluorination remains a matter of ongoing investigation.[41] Nevertheless, our finding establishes a route to difficult-to-access tertiary alkyl C–F stereocenters, especially those devoid of adjacent functional groups such as found in **3w**, by relay of stereochemistry from comparatively easy-to-prepare homochiral tertiary C–O starting materials.

4. Conclusion

In conclusion, we have demonstrated that a base-free deoxyfluorination method can be achieved using a nontrigonal phosphorus compound **1**, triarylborane **B1** as a fluoride shuttling catalyst, and trityl fluoride as a soluble fluoride source and activator. The abasic nature of the reaction conditions suppresses formation of elimination-derived side products, which has historically inhibited the successful fluorination of tertiary alkyl and benzylic alcohols. We anticipate that this stereospecific deoxyfluorination will complement existing deoxyfluorination methods particularly for secondary and tertiary alcohols and provide new strategies for C–F bond formation catalyzed by a Lewis acid. Importantly, the working understanding of the reaction mechanism pathway provides a path forward to further development and optimization of the phosphorus reagent for deoxyfluorination, which is currently underway in our labs.

5. Experimental Section

A full description of the general experimental methods can be found in the Supporting Information.

5.1 Representative Synthetic Procedure. In a nitrogen atmosphere glovebox, a 4 mL vial equipped with magnetic stir bar was charged with alcohol substrate if solid (0.400 mmol), **1** (107.2 mg, 0.4200 mmol, 1.05 equiv), and trityl fluoride (110.2 mg, 0.4200 mmol, 1.05 equiv). The solids were dissolved in dioxane (1.6 mL, 0.25 M), followed by addition of alcohol substrate if liquid (0.400 mmol). Tris(2,4-difluorophenyl) borane (**B1**, 7.0 mg, 20 µmol, 0.050 equiv) was then added to the solution. The resulting mixture was capped, removed from the glovebox, and stirred at ambient temperature with 400 rpm stirring. After 24 hours, the reaction was transferred to a 40 mL vial with washing with ethyl acetate. The crude reaction was concentrated, taken up in a minimal amount of dichloromethane, and then purified by flash column chromatography on silica gel.

5.2 Spectroscopic Investigations. In a nitrogen atmosphere glovebox, a solution of **1** (26.8 mg, 0.105 mmol, 1.05 equiv), trityl fluoride (27.5 mg, 0.105 mmol, 1.05 equiv), and 1-fluoronaphthalene (17.5 mg, 0.120 mmol, 1.20 equiv) in dioxane (0.3 mL) were prepared in a 4 mL vial, and transferred to a J. Young NMR tube. The J. Young tube was capped, removed from the glovebox, and inserted into an NMR probe to obtain ^{31}P and ^{19}F NMR (number of scans = 4, delay = 120 s) spectra (t = 0 min). The J. Young tube was brought back into the glovebox, and a solution of **2b** (17.0 µL, 0.100 mmol, 1.00 equiv) and **B1** (1.8 mg, 5.0 µmol, 0.050 equiv) in dioxane (0.2 mL) was added. The J. Young tube was capped, shaken, removed from the glovebox, and inserted into an NMR probe to obtain ^{31}P and ^{19}F NMR spectra at 30 minutes, 2 hours, 4 hours, and 12 hours. The quantification of product **3b** and trityl fluoride was determined by relative integration between 1-fluoronaphthalene (–123.90 ppm, m, 1F), product **3b** (–138.33 ppm, m, 1F), and trityl fluoride (–126.01 ppm, s, 1F).

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Experimental procedures, ^1H, ^{13}C, and ^{31}P NMR spectra, Cartesian coordinates, computational details, and crystallographic data (PDF)

AUTHOR INFORMATION

Corresponding Author

*radosevich@mit.edu (A.T.R.)

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Funding for this work was provided by NSF and Bristol Myers Squibb. Mechanistic studies of O–H activation and phosphorane speciation were supported under NSF CHE-1900060. Synthetic scope studies were supported by BMS. M.N.L. thanks the National Institute of General Medical Sciences of the National Institutes of Health for support under Award Number F32 GM147996. M. J. D. thanks the Arnold and Mabel Beckman foundation for postdoctoral fellowship support. The authors acknowledge Ming Gu and Robert Langish for HRMS data acquired at BMS Research and Early Development (Cambridge), Drs. S. J. Hwang, A. Tanushi, and G. T. Cleveland for assistance in collecting and processing crystal structure data, Prof. S. Buchwald for access to HPLC equipment, and Dr. Y. Kanda for exploratory studies. Use of the Advanced Photon Source, an Office of Science User Facility operated for the U.S. Department of Energy (DOE) Office of Science by Argonne National Laboratory, was supported by the United States DOE under Contract No. DE-AC02-06CH11357.

PRESENT ADDRESSES

‡M. J. D.: Vassar College, 124 Raymond Avenue, Poughkeepsie, New York 12604, United States

#J.M.L.: Chemistry Department, Stony Brook University, John S. Toll Drive, Stony Brook, New York 11794, United States

REFERENCES

[1] (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (b) Wang, J.; Sánchez-Roselló, M.; Aceña,J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506. (c) Y. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422–518. (d) Richardson, P. Fluorination methods for drug discovery and development. *Expert Opin. Drug Discov.* **2016**, *11*, 983–999. (e) Pirnot, M.; Stone, K.; Wright, T. J.; Lamberto, D. J.; Schoell, J.; Lam, Y.-H.; Zawatzky, K.; Wang, X.; Dalby, S. M.; Fine, A. J.; McMullen, J. P. Manufacturing Process Development for Belzutifan, Part 6: Ensuring Scalability for a Deoxyfluorination Reaction. *Org. Process Res. Dev.* **2022**, *26*, 551–559. (f) Britton, R.; Gouverneur, V.; Lin, J.-H.; Meanwell, M.; Ni, C.; Pupo, G.; Xiao, J.-C.; Hu, J. Contemporary synthetic strategies in organofluorine chemistry. *Nat. Rev. Methods Primers* **2021**, *1*, 47.

[2] For deoxyfluorination of alkyl alcohols with S(IV)–F reagents, see: (a) Middleton, W. J. New fluorinating reagents. Dialkylaminosulfur fluorides. *J. Org. Chem.* **1975**, *40*, 574–578. (b) Singh, R. P.; Shreeve, J. M. Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds Using Deoxofluor and DAST. *Synthesis* **2002**, 2561–2578. (c) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; L'Heureux, A. Aminodifluorosulfinium Tetrafluoroborate Salts as Stable and Crystalline Deoxofluorinating Reagents. *Org. Lett.* **2009**, *11*, 5050–5053. (d) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; LaFlamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. Aminodifluorosulfinium Salts: Selective Fluorination Reagents with Enhanced Thermal Stability and Ease of Handling. *J. Org. Chem.* **2010**, *75*, 3401–3411. (e) Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N. Discovery of 4-*tert*-Butyl-2,6-Dimethylphenylsulfur Trifluoride as a Deoxofluorinating Agent with High Thermal Stability as well as Unusual Resistance to Aqueous Hydrolysis, and its Diverse Fluorination Capabilities Including Deoxofluoro-Arylsulfinylation with High Stereoselectivity. *J. Am. Chem. Soc.* **2010**, *132*, 18199–18205.

[3] For deoxyfluorination of alkyl alcohols with S(VI)–F reagents, see: (a) Nielsen, M. K.; Ugaz, C. R.; Li, W.; Doyle, A. G. PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent. *J. Am. Chem. Soc.* **2015**, *137*, 9571–9574. (b) Nielsen, M. K.; Ahneman, D. T.; Riera, O.; Doyle, A. G. Deoxyfluorination with Sulfonyl Fluorides: Navigating Reaction Space with Machine Learning. *J. Am. Chem. Soc.* **2018**, *140*, 5004–5008. (c) Guo, J.; Kuang, C.; Rong, J.; Li, L.; Ni, C.; Hu, J. Rapid Deoxyfluorination of Alcohols with *N*-Tosyl-4-chlorobenzenesulfonimidoyl Fluoride (SulfoxFluor) at Room Temperature. *Chem. Eur. J.* **2019**, *25*, 7529–7264. (d) Wang, X.; Zhou, M.; Liu, Q.; Ni, C.; Fei, Z.; Li, W.; Hu, J. Deoxyfluorination of alcohols with aryl fluorosulfonates. *Chem. Commun.* **2021**, *57*, 8170–8173. (e) Melvin, P. R.; Ferguson, D. M.; Schimler, S. D.; Bland, D. C.; Sanford, M. S. Room Temperature Deoxyfluorination of Benzaldehydes and α-Ketoesters with Sulfuryl Fluoride and Tetramethylammonium Fluoride. *Org. Lett.* **2019**, *21*, 1350–1353.

[4] Rapp, M.; Bilska, M.; Koroniak, H. Fluorination of tertiary alcohols derived from di-*O*-isopropylidenehexofuranose and *O*-isopropylidenepentofuranose. *J. Fluor. Chem.* **2011**, *132*, 1232–1240.

[5] (a) Goldberg, N. W.; Shen, X.; Li, J.; Ritter, T. AlkylFluor: Deoxyfluorination of Alcohols. *Org. Lett.* **2016**, *18*, 6102–6104. (b) Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. Late-Stage Deoxyfluorination of Alcohols with Phenofluor. *J. Am. Chem. Soc.* **2013**, *135*, 2470–2473. (c) Li, L.; Na, C.; Wang, F.; Hu, J. Deoxyfluorination of alcohols with 3,3-difluoro-1,2-diarylcyclopropenes. *Nature Commun.* **2016**, *7*, 13320. (d) Sood, D. E.; Champion, S.; Dawson, D.; Chabbra, S.; Bode, B.; Sutherland, A.; Watson, A. J. B. Deoxyfluorination using CuF_2 enabled by a Lewis base activating group strategy. *Angew. Chem. Int. Ed.* **2020**, *59*, 8460–8463.

[6] For aryl alcohol deoxyfluorination with PhenoFluor and related reagents, see: (a) Tang, P.; Wang, W.; Ritter, T. Deoxyfluorination of Phenols. *J. Am. Chem. Soc.* **2011**, *133*, 11482–11484. (b) Fujimoto, T.; Becker, F.; Ritter, T. PhenoFluor: Practical Synthesis, New Formulation, and Deoxyfluorination of Heteroaromatics. *Org. Proc. Res. Dev.* **2014**, *18*, 1041–1044. (c) Fujimoto, T.; Ritter, T. PhenoFluorMix: Practical Chemoselective Deoxyfluorination of Phenols. *Org. Lett.* **2015**, *17*, 544–547. (d) Neumann, C.; Ritter, T. Facile C–F Bond Formation through a Concerted Nucleophilic Aromatic Substitution Mediated by the PhenoFluor Reagent. *Acc. Chem. Res.* **2017**, *50*, 2822–2833.

[7] For aryl alcohol deoxyfluorination with sulfuryl fluoride, see: (a) Schimler, S. D.; Cismesia, M. A.; Hanley, P. S.; Froese, R. D. J.; Jansma, M. J.; Bland, D. C.; Sanford, M. S. Nucleophilic Deoxyfluorination of Phenols via Aryl Fluorosulfonate Intermediates. *J. Am. Chem. Soc.* **2017**, *139*, 1452–1455. (b) See, Y. Y.; Morales-Colón, M. T.; Bland, D. C.; Sanford, M. S. Development of S_NAr Nucleophilic Fluorination: A Fruitful Academia-Industry Collaboration. *Acc. Chem. Res.* **2020**, *53*, 2372–2383.

[8] For tertiary alkanol deoxyfluorination, stereoablative strategies dominate, see: (a) Brioche, J. One-pot synthesis of tertiary alkyl fluorides from methyl oxalates by radical deoxyfluorination under photoredox catalysis. *Tetrahedron Lett.* **2018**, *59*, 4387−4391. (b) Aguilar Troyano, F. J.; Ballaschk, F.; Jaschinski, M.; Ozkaya,Y.; Gomez-Suarez, A. Light-Mediated Formal Radical Deoxyfluorination of Tertiary Alcohols through Selective Single-Electron Oxidation with $TEDA^{2+}$. *Chem. Eur. J.* **2019**, *25*, 14054−14058. (c) González-Esguevillas, M.; Miró, J.; Jeffrey, J. L.; MacMillan, D. W. C. Photoredox-catalyzed deoxyfluorination of activated alcohols with Selectfluor®. *Tetrahedron* **2019**, *75*, 4222–4227. (d) Lovett, G. H.; Chen, S.; Xue, X.-S.; Houk, K. N.; MacMillan, D. W. C. Open-Shell Fluorination of Alkyl Bromides: Unexpected Selectivity in a Silyl Radical-Mediated Chain Process. *J. Am. Chem. Soc.* **2019**, *141*, 20031–20036. (e) Zhang, W.; Gu, Y.-C.; Lin, J.-H.; Xiao, J.-C. Dehydroxylative Fluorination of Tertiary Alcohols. *Org. Lett.* **2020**, *22*, 6642–6646.

[9] Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon–Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887–3964.

[10] (a) Abbenseth, J.; Goicoechea, J. M. Recent developments in the chemistry of non-trigonal pnictogen pincer compounds: From bonding to catalysis. *Chem. Sci.* **2020**, *11*, 9728–9740. (b) McCarthy, S. M.; Lin, Y.-C.; Devarajan, D.; Chang, J. W.; Yennawar, H. P.; Rioux, R. M.; Ess, D. H.; Radosevich, A. T. Intermolecular N–H Oxidative Addition of Ammonia, Alkylamines, and Arylamines to a Planar σ^3-Phosphorus Compound via an Entropy-Controlled Electrophilic Mechanism. *J. Am. Chem. Soc.* **2014**, *136*, 4640–4650. (c) Arduengo, A. J.; Stewart, C. A.; Davidson, F.; Dixon, D. A.; Becker, J. Y.; Culley, S. A.; Mizen, M. B. The Synthesis, Structure, and Chemistry of 10-Pn-3 Systems: Tricoordinate Hypervalent Pnicogen Compounds. *J. Am. Chem. Soc.* **1987**, *109*, 627–647.

[11] Lee, K.; Blake, A. V.; Tanushi, A.; McCarthy, S. M.; Kim, D.; Loria, S. M.; Donahue, C. M.; Spielvogel, K. D.; Keith, J. M.; Daly, S. R.; Radosevich, A. T. Validating the Biphilic Hypothesis of Nontrigonal Phosphorus(III) Compounds. *Angew. Chem. Int. Ed.* **2019**, *58*, 6993–6998.

[12] (a) Zhao, W.; McCarthy, S. M.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. Reversible Intermolecular E–H Oxidative Addition to a Geometrically Deformed and Structurally Dynamic Phosphorous Triamide. *J. Am. Chem. Soc.* **2014**, *136*, 17634–17644. (b) Robinson, T. P.; De Rosa, D. M.; Aldridge, S.; Goicoechea, J. M. E–H Bond Activation of Ammonia and Water by a Geometrically Constrained Phosphorus(III) Compound. *Angew. Chem. Int. Ed.* **2015**, *54*, 13758–13763.

[13] (a) Appel, R. Tertiary Phosphane/Tetrachloromethane, a Versatile Reagent for Chlorination, Dehydration, and P-N Linkage. *Angew. Chem. Int. Ed.* **1975**, *14*, 801–811. (b) Arbusow, B. A. Michaelis-Arbusow- und Perkow-Reaktionen. *Pure Appl. Chem.* **1964**, *9*, 307–335. (c) Oyo, M.; Masaaki, Y. Preparation of Esters of Carboxylic and Phosphoric Acid via Quaternary Phosphonium Salts. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382. (d) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products. *Synthesis* **1981**, *1981*, 1–28.

[14] (a) Lewis, E. S.; Colle, K. S. Alkoxyphosphonium Salts. 3. Kinetics and Thermodynamics in Alkylation by Alkoxyphosphonium Salts. *J. Org. Chem.* **1981**, *46*, 4369–4372. (b) Castro, B. R. Replacement of Alcoholic Hydroxyl Groups by Halogens and Other Nucleophiles via Oxyphosphonium Intermediates. *Org. React.* **1983**, *29*, 1–162.

[15] (a) Kunz, H.; Sager, W. 33. Stereoselective glycosylation of Alcohols and Silyl Ethers Using Glycosyl Fluorides and Boron Trifluoride Etherate. *Helv. Chim. Acta* **1985**, *68*, 283–287. (b) Bandgar, B. P.; Kamble, V. T.; Biradar, A. V. Practical and General Method for Direct Synthesis of Alkyl Fluorides from Alcohols under Mild Conditions. *Monatsh. Chem.* **2005**, *136*, 1579–1582. (c) Chen, J.; Lin, J.-H.; Xiao, J.-C. Halogenation through Deoxygenation of Alcohols and Aldehydes *Org. Lett.* **2018**, *20*, 3061–3064.

[16] Fluorophosphoranes are known to perform alkanol deoxyfluorination under relatively forcing conditions, see: (a) Yang, Z., Shen, X. Fluorophosphorane Deoxofluorination. In: *Fluorination. Synthetic Organofluorine Chemistry*; Hu, J., Umemoto, T., Eds;. Springer, Singapore, 2020; pp 297–304. (b) Eljo, J.; Carle, M. S.; Murphy, G. K. Hypervalent Iodine-Based Activation of Triphenylphosphine for the Functionalization of Alcohols. *Synlett* **2017**, *28*, 2871–1875.

[17] (a) Maeda, H.; Koide, T.; Maki, T.; Ohmori, H. Electrochemical Preparation and Some Reactions of Alkoxy Triphenylphosphonium Ions. *Chem. Pharm. Bull.* **1995**, *43*, 1076–1080. (b) Maeda, H.; Koide, T.; Matsumoto, S.; Ohmori, H. Fluorination of Secondary and Primary Alcohols by Thermal Decomposition of Electrochemically Generated Alkoxy Triphenylphosphonium Tetrafluoroborates. *Chem. Pharm. Bull.* **1996**, *44*, 1480–1483. (c) Maeda, H.; Matsumoto, S.; Koide, T.; Ohmori, H. Dehydroxy Substitution Reactions of the Anomeric Hydroxy Groups in Some Protected Sugars Initiated by Anodic Oxidation of Triphenylphosphine. *Chem. Pharm. Bull.* **1998**, *46*, 939–943.

[18] (a) Cresswell, A. J.; Davies, S. G.; Roberts, P. M.; Thomson, J. E. Beyond the Balz–Schiemann Reaction: The Utility of Tetrafluoroborates and Boron Trifluoride as Nucleophilic Fluoride Sources. *Chem. Rev.* **2015**, *115*, 566–611. (b) Swain, C. G.; Rogers, R. J. Mechanism of formation of aryl fluorides from arenediazonium fluoborates. *J. Am. Chem. Soc.* **1975**, *97*, 799–800.

[19] (a) Henne, A. L.; Arnold, R. C. Hydrofluorination in the Presence of Boron Fluoride. *J. Am. Chem. Soc.* **1948**, *70*, 758–760. (b) Nakanishi, S.; Myers, T.C.; Jensen, E. V. Acid-catalyzed Decomposition of Chloro- and Fluoroformates. *J. Am. Chem. Soc.* **1955**, *77*, 5033–5034. (c) Smith, W. C. The Chemistry of Sulfur Tetrafluoride. *Angew. Chem. Int. Ed.* **1962**, *1*, 467–475. (d) Cantacuzène, J.; Atlani, M. Synthèse stéréospécifique et récurrente des cis et trans difluoro-2,6 cyclohexanones: Etude physicochimique. *Tetrahedron* **1970**, *26*, 2447–2468. (e) Shackelford, S. A.; McGuire, R. R.; Pflug, J. L. Xenon difluoride fluorination. I. Aliphatic alkenes fluorinated by a convenient benchtop procedure. *Tetrahedron Lett.* **1977**, *18*, 363–366. (f) Stavber, S.; Zupan, M. Regiospecific BF_3 catalysed fluorine addition to fluoro-substituted benzene derivatives using xenon difluoride. *J. Chem. Soc., Chem. Commun.* **1978**, 969–970. (g) Stavber, S.; Zupan, M. Fluorination with cesium fluoroxysulfate. Room temperature fluorination of benzene and naphthalene derivatives. *J. Org. Chem.* **1985**, *50*, 3609–3612. (h) Patrick, T. B.; Darling, D. L. Fluorination of activated aromatic systems with cesium fluoroxysulfate. *J. Org. Chem.* **1986**, *51*, 3242–3244. (i) Petrov, V. A.; Krespan, C. G. Conjugate Electrophilic Iodofluorination of Fluoroolefins. *J. Org. Chem.* **1996**, *61*, 9605–9607.

[20] (a) Levin, M. D.; Chen, T. Q.; Neubig, M. E.; Hong, C. M.; Theulier, C. A.; Kobylianskii, I. J.; Janabi, M.; O'Neil, J. P.; Toste, F. D. A catalytic fluoride-rebound mechanism for $C(sp^3)$-CF_3 bond formation. *Science* **2017**, *356*, 1272–1276. (b) Sati, G. C.; Martin, J. L.; Xu, Y.; Malakar, T.; Zimmerman, P. M.; Montgomery, J. Fluoride Migration Catalysis Enables Simple, Stereoselective, and Iterative Glycosylation. *J. Am. Chem. Soc.* **2020**, *142*, 7235–7242.

[21] Kirschner, S.; Peters, M.; Yuan, K.; Uzelac, M.; Ingleson, M. J. Developing organoboranes as phase transfer catalysts for nucleophilic fluorination using CsF. *Chem. Sci.* **2022**, *13*, 2661–2668.

[22] Bellavance, G.; Dubé, P.; Nguyen, B. Tetramethylfluoroformamidium Hexafluorophosphate (TFFH) as a Mild Deoxofluorination Reagent. *Synlett* **2012**, *23*, 569–572.

[23] Christe, K. O.; Dixon, D. A.; McLemore, D.; Wilson, W. W.; Sheehy, J. A.; Boatz, J. A. On a quantitative scale for Lewis acidity and recent progress in polynitrogen chemistry. *J. Fluor. Chem.* **2000**, *101*, 151–153.

[24] Nicasio, J. A.; Steinberg, S.; Inés, B.; Alcarazo, M. Tuning the Lewis Acidity of Boranes in Frustrated Lewis Pair Chemistry: Implications for the Hydrogenation of Electron-Poor Alkenes. *Chem. Eur. J.* **2013**, *19*, 11016–11020.

[25] (a) Myers, E. L.; Butts, C. P.; Aggarwal, V. K. $BF_3{\cdot}OEt_2$ and TMSOTf: A synergistic combination of Lewis acids. *Chem. Commun.* **2006**, 4434–4436. (b) Santi, M.; Ould, D. M. C.; Wenz, J.; Soltani, Y.; Melen, R. L.; Wirth, T. Metal-Free Tandem Rearrangement/Lactonization: Access to 3,3-Disubstituted Benzofuran-2-(3*H*)-ones. *Angew. Chem. Int. Ed.* **2019**, *58*, 7861–7865.

[26] Massey, A. G.; Park, A. J. Perfluorophenyl derivatives of the elements: I. Tris(pentafluorophenyl)boron. *J. Organomet. Chem.* **1964**, *2*, 245–250.

[27] (a) Carden, J. L.; Dasgupta, A.; Melen, R. L. Halogenated triarylboranes: synthesis, properties and applications in catalysis. *Chem Sci.* **2020**, *49*, 1706–1725. (b) Lawson, J. R.; Melen, R. L. Tris(pentafluorophenyl)borane and Beyond: Modern Advances in Borylation Chemistry. *Inorg. Chem.* **2017**, *56*, 8627–8643. (c) Piers, W. E. The Chemistry of Perfluoroaryl Boranes. *Adv. Organomet. Chem.* **2004**, *52*, 1−76. (d) Piers, W. E.; Chivers, T. Pentafluorophenylboranes: from obscurity to applications. *Chem. Soc. Rev.* **1997**, *26*, 345–354.

[28] Erdmann, P.; Leitner, J.; Schwarz, J.; Greb, L. An Extensive Set of Accurate Fluoride Ion Affinities for *p*-Block Element Lewis Acids and Basic Design Principles for Strong Fluoride Ion Acceptors. *ChemPhysChem* **2020**, *21*, 987–994.

[29] Gilhula, J. C.; Radosevich, A. T. Tetragonal phosphorus(V) cations as tunable and robust catalytic Lewis acids. *Chem. Sci.* **2019**, *10*, 7177–7182.

[30] Lipshultz, J. M.; Fu, Y.; Liu, P.; Radosevich, A. T. Organophosphorus-catalyzed relay oxidation of H-Bpin: electrophilic C–H borylation of heteroarenes. *Chem. Sci.* **2021**, *12*, 1031–1037.

[31] (a) Mukaiyama, T.; Ikegai, K.; Aoki, H.; Pluempanupat, W.; Masutani, K. New methods for carbon–nitrogen, carbon–sulfur, and carbon–carbon bond formations by quinone-mediated oxidation–reduction condensation using alkyl diphenylphosphinites. *Bull. Chem. Soc. Jpn.* **2005**, *81*, 103–109. (b) Mukaiyama, T.; Yamabe, H. Alkyl Phosphinites: Versatile Synthetic Intermediates for Dehydration Condensation Reactions. *Chem. Lett.* **2007**, *36*, 2–7. (c) Ochmann, L.; Kessler, M. L.; Schreiner, P. R. Alkylphosphinites as Synthons for Stabilized Carbocations. *Org. Lett.* **2022**, *24*, 1460–1464.

[32] Moon, H. W.; Maity, A.; Radosevich, A. T. Ancillary Tethering Influences σ^3-P vs σ^5-P Speciation and Enables Intermolecular S–H Oxidative Addition to Nontrigonal Phosphorus Compounds. *Organometallics* **2021,** *40*, 2785–2791.

[33] The *P*-quaternization step possibly occurs by single-electron oxidations, see: (a) Cheng, J.; Handoo, K. L.; Parker, V. D. Hydride Affinities of Carbenium Ions in Acetonitrile and Dimethyl Sulfoxide Solution. *J. Am. Chem. Soc.* **1993**, *115*, 2655–2660. (b) Yanilkin, V. Y.; Morozov, V. I.; Nigmadzyanov, F. F.; Gryaznova, T. V.; Kibardin, A. M. Electrooxidation of 2,3-dihydro-1*H*-1,3,2-diazaphospholes. *Russ. Chem. Bull.* **1998**, *47*, 1478–1480. (c) Yanilkin, V. Y.; Zverev, V. V. Total reorganization energy and its components in processes of one-electron oxidation of phosphorus compounds in acetonitrile. *Russ. Chem. Bull.* **1999**, *48*, 677–685.

[34] Chen, T.; Mei, Y.; Liu, L. L.; Zhao, Y.; Wu, Y.; Stephan, D. W. Alkoxyphosphorane/Borane Cooperative Alkylations: A Frustrated Lewis Pair Version of the Mitsunobu Reaction. *Chem. Eur. J.* **2023**, *29*, e2023002.

[35] (a) Shoppee, C. W.; Summers, G. H. R. Steroids and Walden Inversion. Part VII The Stereochemistry and the Mechanism of the i-Steroid Rearrangement. *J. Chem. Soc.* **1952**, 3361–3374. (b) Kosower, E. M.; Winstein, S. Neighboring Carbon and Hydrogen. XXII. Homoallylic Systems. The Preparation and Behavior of Certain 3,5-Cyclosteroids. *J. Am. Chem. Soc.* **1956**, *78*, 4347–4354. (c) Winstein, S. Kosower, E. M. Neighboring Carbon and Hydrogen. XXXIII. Reactivities of 3,5-Cyclocholestan-6-yl Derivatives. Strain and Reactivity in Homoallylic Systems. *J. Am. Chem. Soc.* **1959**, *81*, 4399–4408.

[36] Sandford, C.; Rasappan, R.; Aggarwal, V. K. Synthesis of Enantioenriched Alkylfluorides by the Fluorination of Boronate Complexes. *J. Am. Chem. Soc.* **2015**, *137*, 10100–10103.

[37] Zhang, X.; Tan, C.-H. Stereospecific and stereoconvergent nucleophilic substitution reactions at tertiary carbon centers. *Chem* **2021,** *7*, 1451-1486.

[38] (a) Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. Salt Effects and Ion Pairs in Solvolysis and Related Reactions. III. Common Ion Rate Depression and Exchange of Anions during Acetolysis. *J. Am. Chem. Soc.* **1956**, *78*, 328–335. (b) Peters, K. S. Nature of Dynamic Processes Associated with the S_N1 Reaction Mechanism. *Chem. Rev.* **2007**, *107*, 859–873.

[39] (a) Lanke, V.; Marek, I. Stereospecific nucleophilic substitution at tertiary and quaternary stereocentres. *Chem. Sci.* **2020**, *11*, 9378–9385. (b) Pronin, S. V.; Shenvi, R. A. Synthesis of a Potent Antimalarial Amphilectene. *J. Am. Chem. Soc.* **2012**, *134*, 19604–19606. (c) Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. Stereoinversion of tertiary alcohols to tertiary-alkyl isonitriles and amines. *Nature* **2013**, *501*, 195–199. (d) Marcyk, P. T.; Jefferies, L. R.; AbuSalim, D. I.; Pink, M.; Baik, M.-H.; Cook, S, P. Stereoinversion of Unactivated Alcohols by Tethered Sulfonamides. *Angew. Chem. Int. Ed.* **2019**, *58*, 1727–1731. (e) Watile, R. A.; Bunrit, A.; Margalef, J.; Akkarasamiyo, S.; Ayub, R.; Lagerspets, E.; Biswas, S.; Repo, T.; Samec, J. S. M. Intramolecular substitutions of secondary and tertiary alcohols with chirality transfer by an iron(III) catalyst. *Nature Commun.* **2019**, *10*, 3826. (f) Lanke, V.; Marek, I. Nucleophilic Substitution at Quaternary Carbon Stereocenters. *J. Am. Chem. Soc.* **2020**, *142*, 5543–5548.

[40] (a) Shi, Y.-J.; Hughes, D. L.; McNamara, J. M. Stereospecific synthesis of chiral tertiary alkyl-aryl ethers via Mitsunobu reaction with complete inversion of configuration. *Tetrahedron Lett.* **2003**, *44*, 3609–3611. (b) Mukaiyama, T.; Shintou, T.; Fukumoto, K. A Convenient Method for the Preparation of Inverted tert-Alkyl Carboxylates from Chiral tert-Alcohols by a New Type of Oxidation−Reduction Condensation Using 2,6-Dimethyl-1,4-benzoquinone. *J. Am. Chem. Soc.* **2003**, *125*, 10538–10539. (c) Shintou, T.; Fukumoto, K.; Mukaiyama, T. Efficient Method for the Preparation of Inverted Alkyl Carboxylates and Phenyl Carboxylates via Oxidation–Reduction Condensation Using 2,6-Dimethyl-1,4-benzoquinone or Simple 1,4-Benzoquinone. *Bull. Chem. Sci. Jpn.* **2004**, *77*, 1569–1579. (d) Kuroda, K.; Kaneko, N.; Hayashi, Y.; Mukaiyama, T. Preparation of *tert*-Alkyl Azides from Tertiary Alcohols by Way of Benzoquinone-mediated Oxidation–Reduction Condensation. *Chem. Lett.* **2006**, *35*, 1432–1433. (e) Green, J. E.; Bender, D. M.; Jackson, S.; O'Donnell, M. J.; McCarthy, J. R. Mitsunobu Approach to the Synthesis of Optically Active α,α-Disubstituted Amino Acids. *Org. Lett.* **2009**, *11*, 807–810.

[41] (a) Bergin, E.; O'Connor, C. T.; Robinson, S. B.; McGarrigle, E. M.; O'Mahony, C. P.; Gilheany, D. G. Synthesis of P-Stereogenic Phosphorus Compounds. Asymmetric Oxidation of Phosphines under Appel Conditions. *J. Am. Chem. Soc.* **2007**, *129*, 9566–9567. (b) Rajendran, K. V.; Nikitin, K. V.; Gilheany, D. G. Hammond Postulate Mirroring Enables Enantiomeric Enrichment of Phosphorus Compounds via Two Thermodynamically Interconnected Sequential Stereoselective Processes. *J. Am. Chem. Soc.* **2015**, *137*, 9375–9381.

TOC Graphic