Regioselective Fluoroalkylphosphorylation of Unactivated Alkenes via Radical–Mediated Alkoxylphosphane Rearrangement

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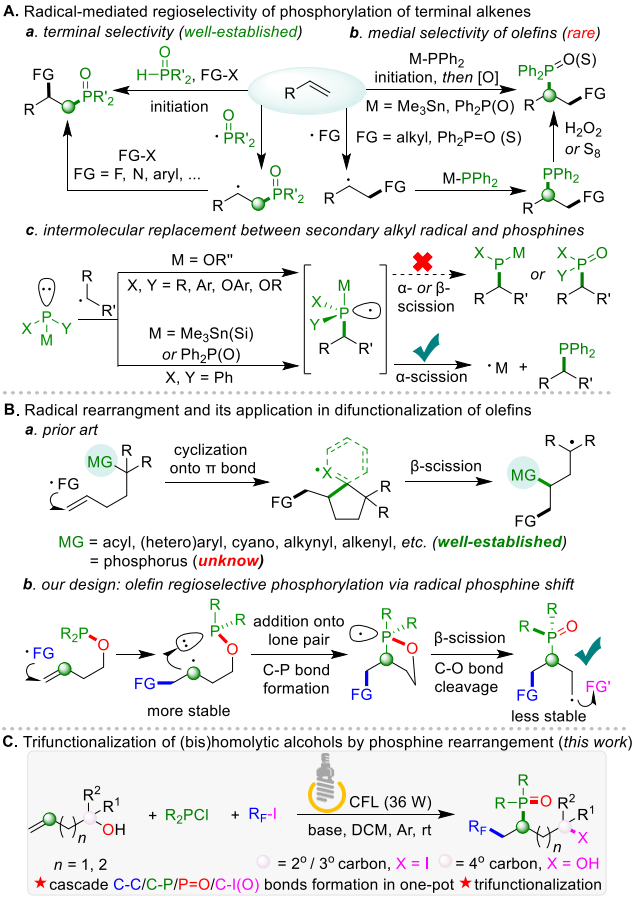
Supporting Information Placeholder

ABSTRACT: A regioselective radical fluoroalkyl-phosphorylation of unactivated alkenes has been developed by a one-pot twosteps reaction of (bis)homoallylic alcohols, organophosphine chlorides (R_2PCl), and fluoroalkyl iodides (R_FI) under visible light irradiation. This protocol employs the radical rearrangement of the in situ formed alkoxyphosphane for the first time to regiospecific installing a phosphonyl group onto the inner carbon of terminal olefins in alkene difunctionalization via C-P bond formation and C-O bond homolytic cleavage. Consequently, a series of high value-added fluoroalkylphosphorylated alkyl iodides and alcohols are easily and efficiently synthesized by subsequent iodination and hydroxylation of the generated carbon-centered radicals.

Organophosphoryl compounds have found wide applications in various fields such as medicinal molecules,[1] functional materials,[2] and catalysis,[3] due to their picturesque physical and chemical properties. Thus, many strategies have been developed for the incorporation of phosphoryl group into organic molecules including ionic,[4] radical,[5] and transition metal-catalyzed[6] C-P bond formations. Among them, phosphoryl radical-mediated difunctionalization of olefins represents an extraordinary valuable and versatile toolbox to introduce both phosphoryl as well as other useful functional groups in the molecules simultaneously.[7] However, the regioselectivity of such difunctionalization is always reflected in the formation of the terminal-selective phosphorylation products since phosphonyl radical as a highly active attacking species is intrinsically attached to the end side of the terminal olefins (Scheme 1Aa). In contrast, the assembly of phosphoryl onto the internal side of terminal olefins is hard to obtain. One possible tactic is to use radical replacement reaction between phosphines and the alkyl radicals derived from alkenes to realize C-P bond construction, followed by the conversion of P^{III} to P^{V} by treating with extra oxidants[8] (Scheme 1Ab). However, common phosphines such as alkyl/aryl/alkoxy/aryloxy phosphines cannot undergo such transformation by forming corresponding phosphoranyl radicals due to their low reactivity[9] (Scheme 1Ac). Thus, a few successful cases have had to use presynthesized highly reactive phosphines Me_3X-PPh_2 (X = Sn or Si)[8a-8c] and $Ph_2P(O)$-PPh_2[8d-8e] to enable the substitution by delivering sufficient α-scission driven forces.

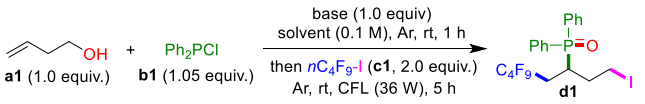
Scheme 1. Regioselective Phosphorylation of Alkenes



Rearrangement reaction, as one of the most significant transformations, has been widely applied to improve synthetic efficiency and molecular complexity.[10] Recently, radical-mediated functional group rearrangement has proven to be an efficient and elegant mean for olefin difunctionalization. By combing the intermolecular radical addition onto olefin and subsequent radical cyclization and β-fragmentation, this protocol realizes olefin difunctionalization by migrating functional groups bearing π bonds from the distal position of molecules to the medial carbon of terminal olefin[11] (Scheme 1Ba). Unfortunately, this strategy is rarely used for the migration of functional groups with lone pair electrons[12] such

as alkoxy phosphine.[13] Despite the intermolecular substitution between alkyl radical and alkoxyphosphine has shown to be fail (Scheme 1Ac), we envisioned its intramolecular mode may be feasible and can be used as the key link to realize the regioselective phosphorylation of olefins. We hypothesized that if a radical is added onto the alkene moiety of alkoxy phosphine adduct formed in situ from homoallylic alcohol and diphenyl phosphine chloride, and the resulting secondary alkyl radical may further cyclize onto the tethered phosphine to produce phosphoranyl radical. If so, by taking advantage of the subsequent β-scission of C-O bond and further functionalization of the formed primary carbon-centered radical, it is possible to achieve the regioselective introduction of phosphoryl at the internal side of terminal alkenes without utilizing special phosphines and extra oxidants; meanwhile, the dehydroxylative trifunctionalization of homoallylic alcohols can be also realized (Scheme 1Bb). Although such rearrangement involves the generation of unstable primary carbon radical and the homolysis of strong C-O bond, the generation of C-P σ bond and P=O π bond may compensate for this endothermic enthalpy and facilitate the reaction. Herein, we demonstrate realization of this goal in the case of regioselective fluoroalkyl phosphorylation of unactivated olefines by a one-pot multi-component reaction of commercially available (bis)homoallylic alcohols, R_2PCl, and fluoroalkyl iodides under visible light irradiation (Scheme 1C). Consequently, a series of vicinal fluoroalkylphosphorylated

Table 1. Optimization of the Reaction Conditions[a]



entry	base	solvent	yield (%)[b]
1	NEt_3	DCM	70
2	-	DCM	0
3	**$HNEt_2$**	**DCM**	**75**
4	nBu_2NH	DCM	61
5	DABCO	DCM	38
6	DBU	DCM	64
7	TMEDA	DCM	44
8	DIPEA	DCM	8
9	NaOAc	DCM	29
10	K_3PO_4	DCM	5
11	$HNEt_2$	DCE	73
12	$HNEt_2$	CH_3CN	53
13	$HNEt_2$	THF	21
14	$HNEt_2$	PhMe	12
15	$HNEt_2$	DMF	0
16[c]	$HNEt_2$	DCM	25
17[d]	$HNEt_2$	DCM	68

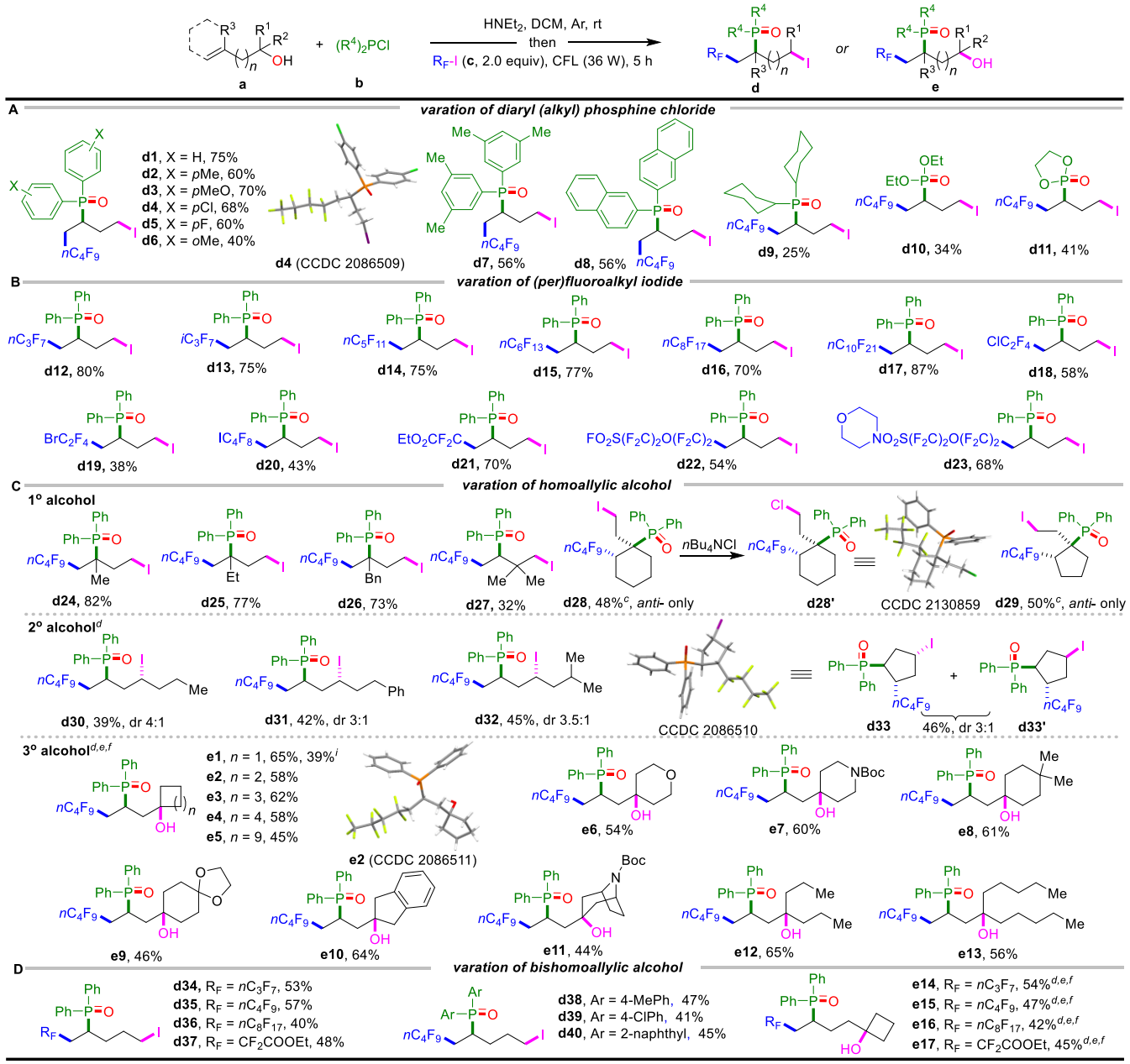
[a]Reaction was conducted on 0.2 mmol scale. [b]Isolated yield. [c]Without light irradiation. [d]Blue LEDs (460 nm, 24 W) was used instead of CFL. DABCO = triethylenediamine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMEDA = *N,N,N',N'*-tetramethylethylenediamine, DIPEA = N,N-diisopropylethylamine, DCM = dichloromethane, DCE = dichloroethane, THF = tetrahydrofuran, DMF = *N,N*-dimethylformamide.

alkyl iodides and alcohols are conveniently synthesized. As the introduction of fluorine into bioactive molecules can significantly enhance their metabolic stability, solubility, permeability, and lipophilicity,[14] incorporating fluorine or fluorine-containing groups into organic phosphonyls are exceptionally meaningful.[15] In this context, our study represents the first example for the synthesis of such compounds by the regioselective incorporation of fluoroalkyl and phosphoryl simultaneously into olefins.

Our studies were commenced with a one-pot twosteps model reaction of homoallylic alcohol (**a1**), Ph_2PCl (**b1**), base, and nC_4F_9I (**c1**) in DCM (dichloromethane) under argon atmosphere at room temperature, followed by the irradiation with CFL (compact fluorescence light, 36 W) as shown in Table 1. Delightedly, the desired phosphorous rearrangement took place smoothly and gave the regioselective trifunctionalized product fluoroalkylphosphorylated alkyl iodide **d1** in 70% yield when triethylamine was used as base; whereas no product **d1** was produced under base-free conditions (Table 1, entries 1 and 2). The yield of **d1** increased to 75 % when $HNEt_2$ was employed instead of triethylamine, (Table 1, entry 3). Other organic and inorganic bases such as nBu_2NH, DABCO, DBU, TMEDA, DIPEA, NaOAc, and K_3PO_4 could also promote this conversion but gave **d1** in unsatisfactory yields (Table 1, entries 4-10). The results of solvents investigation for CH_3CN, THF, toluene, and DMF showed that no better yield was obtained (Table 1, entries 12-15). Light irradiation was essential for an efficient reaction since **d1** was only formed in 25% yield without light; replacing the light source from CFL to blue LEDs (light-emitting diodes, 460 nm, 24 W) led to a slightly lower yield (Table 1, entries 16 and 17).

With the optimum reaction conditions established (entry 2 in Table 1), we set about to evaluate the generality of this method, and the results are illustrated in Scheme 2. The scope of R_2PCl was firstly explored (Scheme 2A). Diphenylchlorophosphines bearing a variety of substituents with different electronical properties such as MeO, Me, Cl, and F on phenyl ring at para-position participated very well in the reaction, providing the desired products **d2-d5** in good yields. The structure of trifunctionalized product **d4** was further confirmed by X-ray crystallographic analysis. 2-Methyl and 3,5-dimethyl substituted Ar_2PCl were also performed well, giving rise to the products **d6** and **d7** in 40% and 56% yields, respectively. In addition, the reaction was compatible with dinaphthyl chlorophosphines, as demonstrated in the case of **d8**. Notably, besides Ar_2PCl, dialkyl and dialkoxy substituted chlorophosphines were also good candidates for this transformation, furnishing the desired products **d9-d11**, albeit in slightly lower yields. Next, a variety of fluoroalkyl iodides were examined as depicted in Scheme 2B. A wide array of linear and branched perfluoroalkyl iodides with different length reacted smoothly in this tactic, giving products **d12-d17** in excellent yields. Other hybrid fluoroalkyl iodides involving Cl, Br, I, ester, sulfonyl fluoride, and sulfamide were all suitable to the conversion by chemoselective cleavage of C-I bond to give the corresponding products **d18-d23**. After that, we examined the scope of the homoallylic alcohols as illustrated in Scheme 3B. Primary homoallylic alcohols bearing methyl, ethyl, and benzyl substituents on the terminal alkene moiety were all compatible with this way, affording the corresponding *α*-tertiary phosphoryl products **d24-d26** in excellent yields. When inner alkenes such as cyclopentenyl and cyclohexenyl

Scheme 2. Exploration of Substrate Scope[a,b]



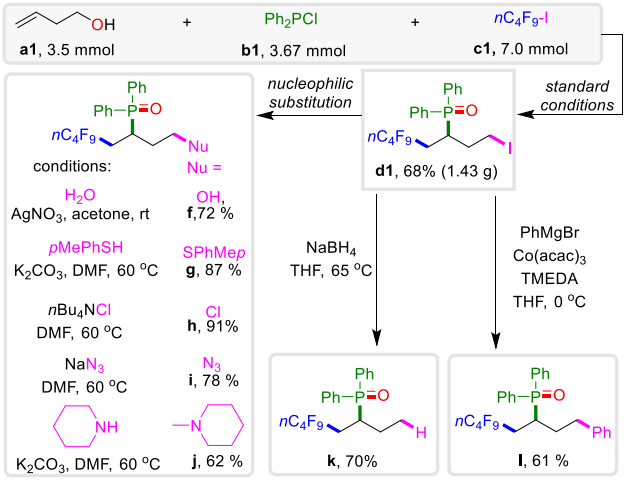
[a]A mixture of **a** (0.2 mmol, 1.0 equiv.), **b** (1.05 equiv.), and $HNEt_2$ (1.0 equiv.) in DCM (2 mL) was stirred at rt under Ar till the substitution was complete. Then R_FI (2.0 equiv.) was added and the mixture was stirred for additional 5 h under CFL irradiation (36 W) at rt under Ar. [b]Isolated yields. [c]For optimal conversion, the adduct of **a** and **b** was first isolated and then being subjected to the photoreaction conditions. [d]Dimethylaminopyridine (0.06 mmol, 30 mol%) was added to promote substitution reaction. [e] NEt_3 (1.5 equiv.) was used instead of $HNEt_2$. [f]H_2O (1.0 equiv.) was added along with R_F-I. [i]Without extra H_2O.

were merged in primary homoallylic alcohols, the reaction also converted well to provide regio- and stereospecific *anti*-fluoroalkylphosphorylation products **d28** and **d29** in moderate yields. The *anti*-configuration was confirmed by X-ray crystallographic analysis of its derivative **d28'** of **d28**. Terminal alkene incorporated secondary homoallylic alcohols with different structures could also be applied to the agreement and gave products **d30-d32** in moderate yields with 4:1-3:1 diastereoselectivity. Significantly, when cyclic secondary homoallylic alcohols like cyclopent-3-en-1-ol was involved in the reaction, trifunctionalized cyclopentanes **d33** and **d33'** were generated as the epimers in a combined yield of 46% with 3:1 stereoselectivity. The structure of major epimer **d33** was determined by X-ray crystallographic analysis. Notably, tertiary homoallylic alcohols were also compatible with this regioselective fluoroalkylphosphorylation by affording products in form of aliphatic alcohols rather than alkyl iodides. Apparently, the newly introduced hydroxyl group was derived from the trace amount of water in extra dry DCM. Indeed, the addition of 1.0 equivalent water could further increase the yields of products. As a result, a variety of cyclic tertiary homoallylic alcohols with different cycloalkyl ring sizes were transformed to the fluoroalkylphosphorylated alcohols **e1-e5** in good yields. The alcohol structure was also

confirmed by X-ray crystallographic analysis of **e2**. Heteroatoms such as O- /N-atom embedded and *gem*-dimethyl substituted homoallylic cycloalcohols were converted to the corresponding products **e6-e8** in high yields. In addition, the conversion of spiro, fused, and bridged homoallylic cycloalcohols to the desired products **e9-e11** was also successful. On the other hand, tertiary alcohols of open chain could also react efficiently under our system, as demonstrated in the cases of **e12** and **e13**. It is noteworthy that this approach worked very well for bishomoallylic alcohols too, yielding the corresponding trifunctionalized products **d34-d40** and **e14-e17** through a radical 6-membered ring phosphorous intermediate rearrangement.

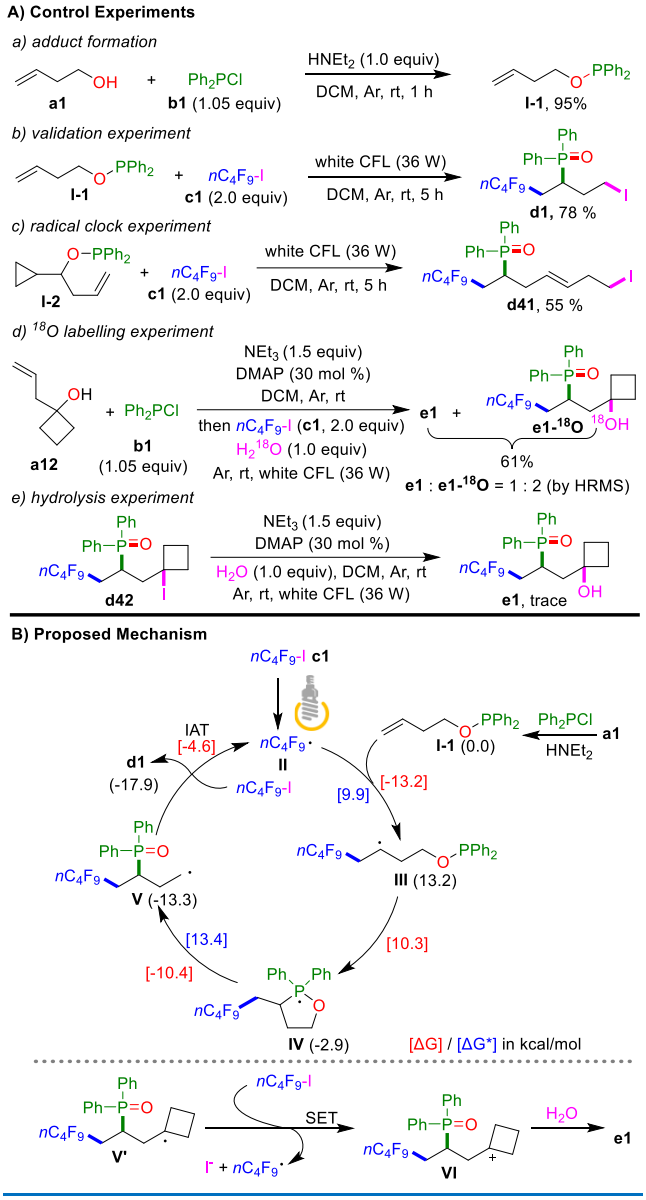
The synthetic practicality of this strategy and the versatility of products are proved as shown in Scheme 3. A gram-scale synthesis of **d1** (1.43 g, 68% yield) was successfully proceeded on 3.5 mmol scale. The follow-up derivatization of **d1** was performed by the nucleophilic substitution, reduction, and arylation of C-I bond, affording the corresponding derivatives **f-l** in good yields.

Scheme 3. Practicality and Follow-up Transformations



To account for the mechanism of this reaction, a series of control experiments were carried out as depicted in Scheme 4A. The reaction of **a1** with **b1** under the conditions of $NHEt_2$ gave the adduct **I-1** in nearly quantitative yield (Scheme 4Aa). When **I-1** was used as the substrate to react with nC_4F_9I without $HNEt_2$, the reaction took place very well under visible light irradiation and gave **d1** in 78% yield (Scheme 4Ab). These results not only confirm that $HNEt_2$ serves as base to promote the reaction of homoallylic alcohols and phosphines to form adduct **I-1** but also reveals that **I-1** is the key intermediate to react with nC_4F_9I to take place phosphorous rearrangement-mediated trifuntionalization. When cyclopropyl incorporated adduct **I-2** was employed to react with nC_4F_9I, the cyclopropyl ring-opening product **d41** was obtained in 55% yield (Scheme 4Ac). This "radical clock" experiment[16] clearly indicates that a radical-mediated phosphorous rearrangement process is involved in the reaction. In addition, isotope-labeling experiment by utilizing $H_2{}^{18}O$ clearly verifies that the newly introduced hydroxyl in products **e** came from

Scheme 4. Mechanistic Studies and Proposed Mechanism



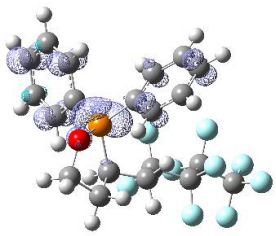


Figure 1. Spin density (B3LYP/6-311+G (d,p), isosurface value = 0.006) of radical **IV**.

water (Scheme 4Ad). However, **e** does not come from alkaline hydrolysis of its corresponding tertiary alkyl iodide **d** since almost no hydrolysis occurred when **d** was treated under the standard base conditions. Thus, the production of **e** can be attributed to the fact that tertiary radicals derived from tertiary alcohols are easily oxidized by fluoroalkyl iodides to form carbocations, which incline to react with water to produce alcohols rather than iodide anion to yield aliphatic iodides.

On the basis of our experimental observation, a proposed mechanism is delineated by a representative sample in Scheme

4B. A base-promoted nucleophilic substitution of Ph_2PCl **b1** and homoallylic alcohol **a1** occurs first to provide the adduct **I-1**. Then C_4F_9 radical **II** which is initiated by the irradiation of C_4F_9-I under visible light,[17] adds onto the alkene moiety of adduct **I-1** to yield the C-centered radical intermediate **III** through a 9.9 kcal/mol reaction energy barrier (see the Supporting Information for the details of DFT (density functional theory) calculations). Despite it is not a main process in our reaction, the generation of C_4F_9 radical can also be obtained from an EDA (electron donor-acceptor) complex of the electron-rich phosphine adduct **I-1** and electron-deficient C_4F_9I.[18] **III** experiences a fast radical cyclization onto the lone electron pairs of phosphine to yield phosphoranyl radical intermediate **IV**, which subsequently undergoes C-O bond β-fragmentation across an energy barrier of 13.4 kcal/mol to form the C-radical intermediate **V**. The calculated Gibbs free energy change of this radical phosphine rearrangement is only -0.1 kcal/mol, which is almost enthalpy neutral. Finally, product **d1** is formed by the reaction of **V** and C_4F_9I via an iodine-atom transfer (IAT) process. When the reaction involves tertiary alcohol, as in the case of **e1**, the formed tertiary radical **V'** tends to undergo a single-electron transfer (SET) process rather than an IAT process to react with C_4F_9I,[18a,19] providing carbocation **VI**, C_4F_9 radical, and iodide anion. The hydroxylation of **VI** by water affords **e1**.

The calculated spin density map of intermediate **IV** clearly indicates that the spin is delocalized on P-atom (0.68) and the tethered two phenyl rings (0.33) (Figure 1), manifesting the formation of phosphoranyl radical. EPR (electronic paramagnetic resonance) experiments also detected the signals of PBN (phenyl *N*-tert-butylnitrone) trapped P^V-centered radical[20] **IV** and C_4F_9 radical **II**, respectively, which further confirmed that this reaction involves a radical-mediated phosphine rearrangement process (see the Supporting Information for the details of EPR experiments).

In summary, we have successfully developed a novel, facile, and efficient approach for the regioselective fluoroalkyl phosphorylation of unactivated alkenes by a one-pot twosteps reaction of readily accessible (bis)homoallylic alcohols, organophosphine chlorides, and fluoroalkyl iodides under visible light irradiation. The protocol employs radical phosphine rearrangement as the key step to realize the unusual installing phosphoryl in the inner side of the terminal olefins by using commercially available common organic chloro-phosphines without extra oxidants. This tactic not only provides remarkable opportunities for the regioselective introducing fluoroalkyl and phosphoryl simultaneously in olefins and the trifunctionalizing (bis)homoallylic alcohols, but also broadens new boundaries of radical rearrangement modes of phosphines and their synthetic application. The further exploration of such radical rearrangement for synthetic purposes are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral characterization, crystallographic data, and DFT calculations (PDF).

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Notes

The authors declare no competing financial interests.

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