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Article

Monodefluorinative Halogenation of Perfluoroalkyl Ketones via Organophosphorus-Mediated Selective C−F Activation

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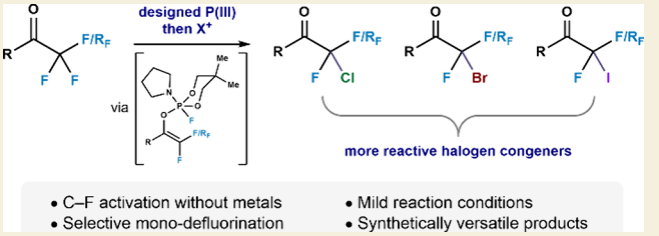
ABSTRACT: Through the prosperity of organofluorine chemistry in modern organic synthesis, perfluorinated organic compounds are now abundant and widely available. Consequently, these substances become attractive starting materials for the production of complex, multifunctional fluorinated molecules. However, the inherent challenges associated with the activation and discrimination of the C−F bonds typically lead to overdefluorination as well as functional group incompatibility. To address these problems, our group utilized a rationally designed organophosphorus reagent that promoted mild and selective manipulation of a single C−F bond in trifluoromethyl and pentafluoroethyl ketones via an interrupted Perkow-type reaction, which allowed the replacement of fluorine with more labile and synthetically versatile congeners such as chlorine, bromine, and iodine. The resulting α-haloperfluoroketones have two reactive units with orthogonal properties that would be suitable for the subsequent structural diversification. DFT calculations identified the favorable P−F interaction as the crucial factor from both thermodynamic and kinetic viewpoints.



KEYWORDS: *C−F activation, perfluoroalkyl ketone, organophosphorus, defluorination, halogenation*

Perfluorinated alkyl groups are versatile moieties that can instill unique physical and chemical properties in organic molecules.[1] In particular, the strong and unreactive nature of the C−F bond makes these organofluorine structures suitable for replacing biologically labile functional groups such as methylene, alcohols, and carbonyl compounds (Figure 1A).[2] The short length and high polarization of the C−F bond enable the substitution of C−H and C−O bonds with minimal conformational alteration while maintaining the physical and chemical characteristics (e.g., H-bond-accepting ability), which has been serving as a well-known strategy to increase bioactivity and metabolic stability. Moreover, such bioisosteric modifications can be extended to two adjacent carbons. Therefore, the installation of perfluoroalkyl groups has been an intensely studied research area of organic synthesis that has reached an impressive level of sophistication.[3] One step further, if the C−F bonds of now widely available trifluoromethyl or pentafluoroethyl groups can be selectively manipulated, much more elaborated organofluorine structures will be accessed with enormous diversification (Figure 1B). A conventional approach to the functionalized difluoromethyl[4] and tetrafluoroethyl[5] moieties is the combination of a preconstructed perfluoroalkyl nucleophile and a carbon electrophile. However, these methods suffer from the high cost and uneasy handling of the di/tetrafluoroalkyl anion reagents, which often decompose to a carbene species via the extrusion of a geminal fluoride. On the other hand, the defluorinative functionalization of abundant, fully fluorinated alkyl groups has recently garnered attention as an economical alternative although the challenge lies in the effective and also selective activation of one among many robust C−F bonds.[6] The reaction conditions must be forcing enough to activate the strong C−F bond but also sufficiently mild to tolerate the newly incorporated functional groups (e.g., Cl, Br, and I). Furthermore, because the C−F bond strength decreases with fewer geminal fluorine substituents (Figure 1C),[7] the product may undergo unwanted overdefluorination, which turned out difficult to avoid in recent synthetic methods even though the C−F cleavage was achieved effectively via chemical activation with strong Lewis acids,[8] transition metals,[9] or reducing metals[10] as well as photo/electrochemical stimulations[6a,11] (Figure 1D).

Our group envisioned that selective transformations of single fluorine in perfluoroalkyl groups to other chemically versatile halogens would impart enormous synthetic potential. In particular, perfluoroalkyl ketones were regarded as suitable substrates considering their abundance and the utility of the additional carbonyl function, which would enable the ready generation of various unsymmetrical gem-difluorides and perfluorides through the orthogonal manipulation of each

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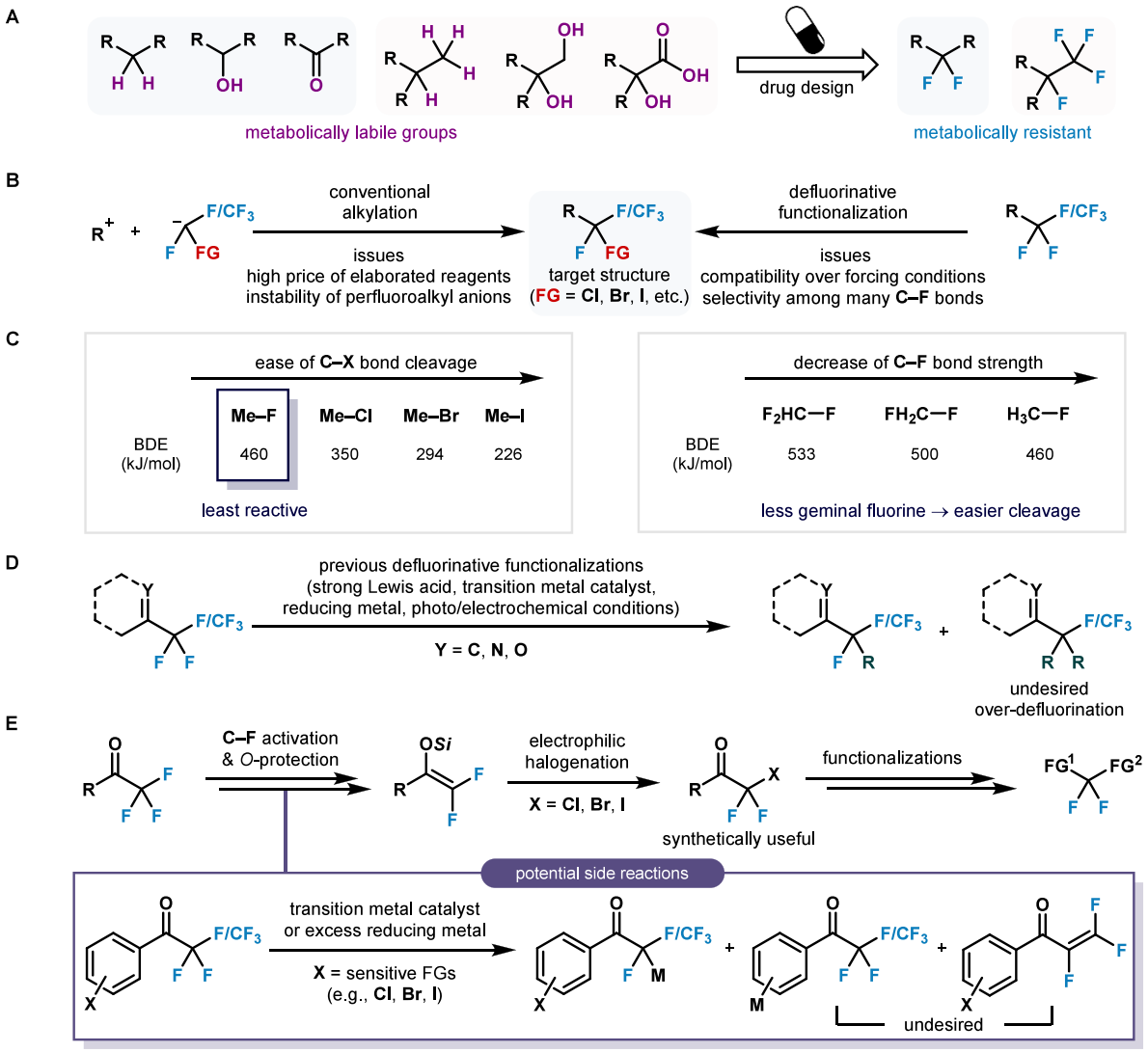

Figure 1. Importance of functionalized perfluoroalkyl groups and difficulty in selective mono C−F activation. (A) Difluoromethylene and tetrafluoroethyl groups as useful bioisosteres. (B) Approaches to functionalized perfluoroalkyl structures. (C) Comparison of C−F bond strengths. (D) Overdefluorination problem in previous activation methods. (E) Metal-mediated defluorinative halogenation of perfluoroalkyl ketones and potential side reactions.

side. Whereas the synthetic applicability of halodifluoromethylcarbonyl compounds has been examined,[11h−l,12] their preparation from the trifluoromethylcarbonyl analogs relies on multistep synthesis involving metal-mediated defluorination, *O*-silylation, and electrophilic halogenation (Figure 1E).[11l,12,13] The presence of reactive transition metal or excess reducing metal limits the use of sensitive functional groups and thus hampers the formulation of a one-pot protocol for the halogen exchange toward more labile congeners.[14] Furthermore, in the case of perfluoroalkyl substrates, *β*-fluoride elimination often takes place in the anionic enolate intermediate, necessitating the *O*-silyl protection step.[15] Therefore, the development of a metal-free, single-operation process is desirable for efficient *α*-defluorinative halogenation of perfluoroalkyl ketones.

To address the above-mentioned problems, we investigated an organophosphorus-mediated, interrupted Perkow reaction for mild and facile C−F functionalization of perfluoroalkyl ketones. The traditional Perkow reaction of *α*-perchloro/bromo ketones with trialkyl phosphite proceeds through an unstable cationic enoxyphosphonium intermediate that is prone to an Arbuzov-type dealkylation, forming a poorly reactive enoxyphosphate (Figure 2A).[16] The examples of *α*-fluorine activation are rare, and a more electron-donating aminophosphorus reagent is needed to promote the nucleofugal dissociation of fluoride. However, the greatly enhanced reactivity of the intermediate by three nitrogen substituents leads to unproductive consumption of the starting ketone via aldol-type reaction.[17] For the prevention of these side reactions, the phosphorus reagent should be resistant to nucleophilic dealkylation and also have a properly modulated electron-donating ability. A suitable candidate can be found in our previous works on deoxygenative geminal difunctionalizations of 1,2-dicarbonyl compounds via dioxaphospholene, in which a similar dealkylation issue was successfully resolved by the rational phosphorus reagent design (Figure 2B).[18] Phosphoramidite **1** has a sterically bulky neopentyl glycolyl unit that is generally inert to nucleophilic attack, and the presence of one amino moiety is expected to provide an appropriately balanced reactivity for the current purpose.

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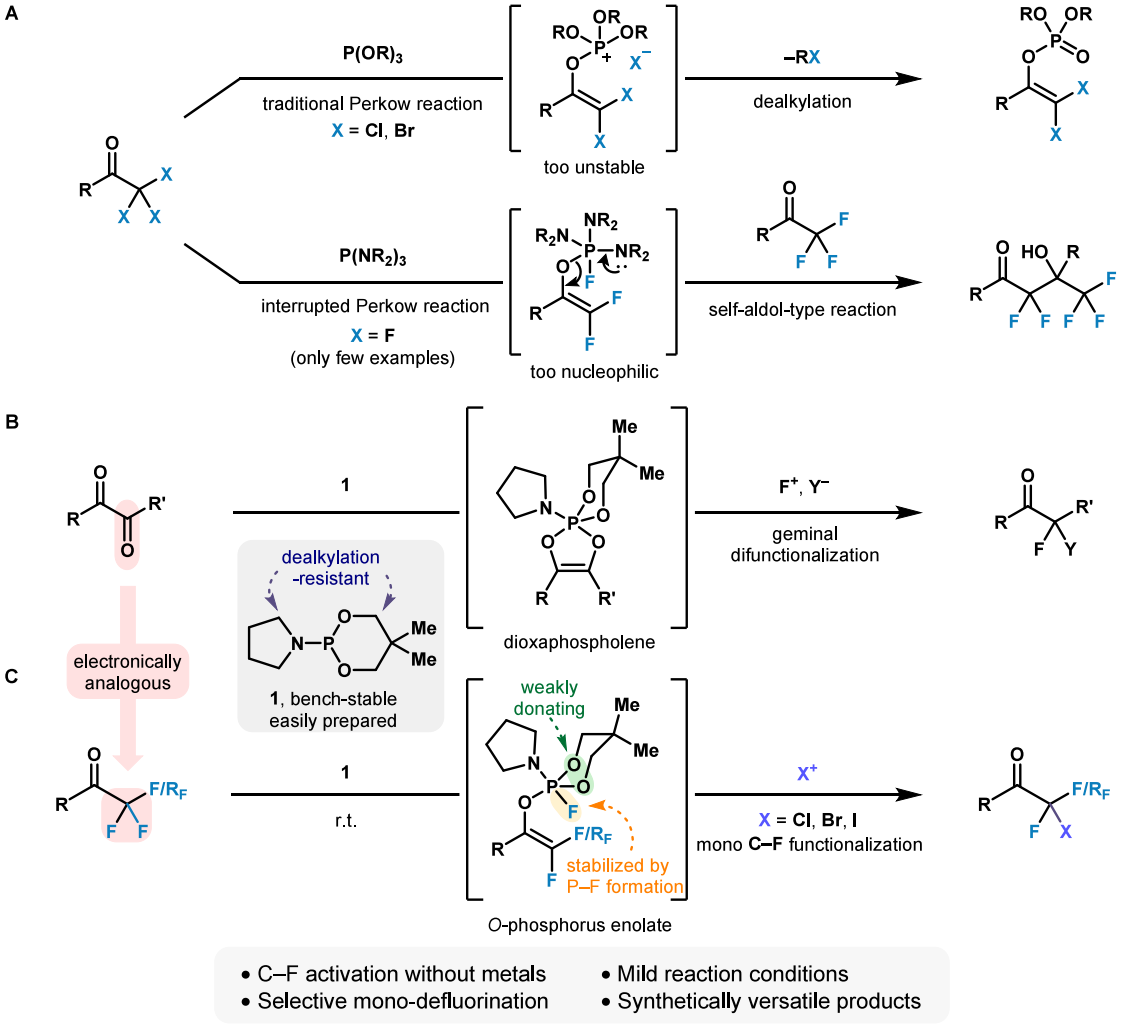

Figure 2. Our research outline. (A) Problems in traditional C−X activation of α-perhaloketones via the Perkow reaction. (B) Our previous works on phosphorus-mediated geminal difunctionalizations of 1,2-dicarbonyl compounds. (C) This work: monoselective defluorinative halogenation of perfluoroalkyl ketones via metal-free C−F activation.

Moreover, the electronically analogous structures of carbonyl and difluoromethylene as well as the strong affinity between phosphorus and fluorine prompted us to apply compound **1** to the activation of perfluoroalkyl ketones (Figure 2C). Gratifyingly, after monodefluorination, *O*-phosphorus enolate was generated without dealkylation, self-aldol-type reaction, or β-fluoride elimination. Furthermore, it reacted with various electrophilic halogenating reagents to selectively give monofunctionalized α-chloro-, bromo-, and iodo-perfluoroalkyl ketones via a single-operation process. In addition, the mildness of our metal-free conditions was demonstrated with several previously challenging substrates containing sensitive functional groups.

At the outset, α,α,α-trifluoroacetophenone (**2a**) was employed as a representative substrate for optimization of the reaction conditions, and the reaction progress was monitored by ^{19}F NMR spectroscopy. The defluorination step was examined first (Table 1). In CH_2Cl_2 with 1.2 equiv of phosphoramidite **1**, the desired *O*-phosphorus difluoroenolate **3a** was formed in a moderate yield, but the rest of the starting material **2a** was consumed by aldol-type reaction to **4a** (entry 1). The use of 1.5 equiv of **1** resulted in a slightly increased selectivity for **3a** over **4a** (entry 2), but no further improvement was observed with a higher loading (entry 3). The aldol-type reaction took place predominantly when THF was employed (entry 4). On the other hand, in other polar aprotic solvents such as MeCN, DMF, and DMSO, the aldol-type reaction was attenuated, and DMSO provided the best outcome (entries 5−7). Although both the yield and the selectivity were satisfactory, it was necessary to decrease the amount of DMSO as it would react with most of the common electrophilic halogenating reagents in the following step, especially when present in an excess amount. Gratifyingly, the use of 1 equiv of DMSO was similarly effective in CH_2Cl_2 solvent with only marginal loss of selectivity (entry 8). Brief variations of DMSO loading revealed 1.5 equiv being optimal (entries 9 and 10). In addition, diphenyl sulfoxide (DPSO), which is less reactive toward halogenating reagents, showed comparable reactivity (entry 11). When $P(NMe_2)_3$ was used instead of **1**, the reaction gave a complex mixture containing only small amounts of **3a** and **4a** (entry 12). As alluded to before, phosphite is much less efficient, and only a trace amount of dealkylated phosphate enolate was detected (entry 13). Additionally, other amino derivatives of **1** were evaluated, but there was no improvement (see the SI).

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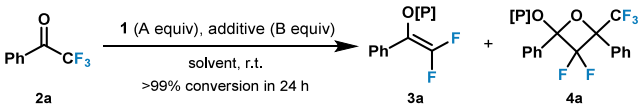
Table 1. Optimization of Phosphorus-Mediated Defluorination of α,α,α-Trifluoroacetophenone[a]

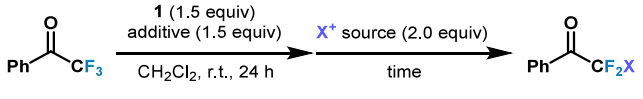


entry	solvent	A	additive	B	3a (%)[b]	4a (%)[b]
1	CH_2Cl_2	1.2			48	47
2	CH_2Cl_2	1.5			56	40
3	CH_2Cl_2	1.8			54	39
4	THF	1.5			5	89
5	MeCN	1.5			66	29
6	DMF	1.5			63	37
7	DMSO	1.5			90	10
8	CH_2Cl_2	1.5	DMSO	1.0	82	19
9	CH_2Cl_2	1.5	DMSO	1.5	86	15
10	CH_2Cl_2	1.5	DMSO	1.8	82	17
11	CH_2Cl_2	1.5	DPSO	1.5	84	19
12[c]	CH_2Cl_2	1.5	DMSO	1.5	6	20
13[d]	CH_2Cl_2	1.5	DPSO	1.5	N/A	N/A

[a]Reaction conditions: **2a** (0.71 mmol), **1** (A equiv), and additive (B equiv) in solvent (3.6 mL). [b]Yields based on ^{19}F NMR analysis of the crude mixture with $PhCF_3$ (0.81 mmol) as an internal standard. [c]HMPT was used instead of **1**. [d]$P(OEt)_3$ was used instead of **1**. See Figure 2 for the precise structure of the phosphorus fragment [P]. (THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; DPSO, diphenyl sulfoxide; HMPT, hexamethylphosphorus triamide; N/A, not applicable)

Subsequently, one-pot halogenation of **3a** was investigated (Table 2) after the most effective defluorinations (Table 1, entries 9 or 11). In the presence of DMSO as an additive, α-chlorination was performed by employing *N*-chlorosuccinimide (NCS; entry 1) and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH; entry 2), but low reactivity was observed in both cases. With trichloroisocyanuric acid (TCICA), both rate and yield were improved despite its reactivity with DMSO (entry 3). When more compatible DPSO was used instead, the yield was increased, and the chromatographic purification of **5a-Cl** afforded a 73% isolated yield on a 1.00 mmol scale (entry 4). On the other hand, unlike the chlorine counterpart, α-bromination with *N*-bromosuccinimide (NBS) and DMSO proceeded with a much higher efficiency (entry 5). Furthermore, upon treatment with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), the *O*-phosphorus difluoroenolate was quantitatively transformed to the chromatographically stable product **5a-Br** in 79% isolated yield (entry 6). In contrast to chlorination, DPSO was less competent (entry 7). Then, α-iodination was examined in a similar manner (entries 8−10), and the combination of 1,3-diiodo-5,5-dimethylhydantoin (DIDMH) and DPSO was found to be the most appropriate (entry 10). Although the product **5a-I** was somewhat unstable on silica gel, it could be isolated in 62% yield without a significant compromise.

Table 2. Optimization of Electrophilic α-Halogenation of *O*-Phosphorus Difluoroenolate[a]



entry	additive	X	X^+ source	time (h)	5a-X (%)[b]
1	DMSO	Cl	NCS	25	16
2	DMSO	Cl	DCDMH	25	6
3	DMSO	Cl	TCICA	10	67
4	DPSO	Cl	TCICA	8	77 (73)[c]
5	DMSO	Br	NBS	1	67
6	DMSO	Br	DBDMH	1	85 (79)[c]
7	DPSO	Br	DBDMH	1	51
8	DPSO	I	NIS	24	56
9	DMSO	I	DIDMH	24	61
10	DPSO	I	DIDMH	24	73 (62)[c]

[a]Reaction conditions: **2a** (0.71 mmol), **1** (1.07 mmol), and additive (1.07 mmol) in CH_2Cl_2 (3.6 mL). [b]Yields based on ^{19}F NMR analysis of the crude mixture with $PhCF_3$ (0.81 mmol) as an internal standard. [c]On a 1.00 mmol scale. Isolated yields after column chromatography. (NCS, *N*-chlorosuccinimide; DCDMH, 1,3-dichloro-5,5-dimethylhydantoin; TCICA, trichloroisocyanuric acid; NBS, *N*-bromosuccinimide; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin; NIS, *N*-iodosuccinimide; DIDMH, 1,3-diiodo-5,5-dimethylhydantoin).

With the optimized halogenating conditions in hand (Table 2, entries 4, 6, and 10), a wide range of perfluoroalkyl ketones were surveyed (Scheme 1). Electron-deficient *p*-halophenyl derivatives (**2b** and **2c**) were suitable for defluorinative chlorination (**5b-Cl** and **5c-Cl**). The tolerance of *p*-bromine substituent was notable (**5c-Cl**) as it was incompatible with transition/reducing metals in previous studies.[13,14] In the case of an electron-rich substrate containing a *p*-methoxy group (**2d**), the defluorination was slow, and only an aldol-type reaction took place with a stoichiometric amount of DMSO in CH_2Cl_2. The desired *O*-phosphorus enolate formation could be promoted to some degree by applying DMSO as a sole solvent, but full conversion was not achieved even after several days, which was detrimental to chromatographic purification because the removal of the unreacted starting material was problematic. Fortunately, after a brief optimization, the reactant could be completely consumed in DMF at 50 °C with a slight excess of **1**, and the chlorination was conducted by utilizing DCDMH to avoid side-reactions at the anisyl group, affording the product (**5d-Cl**) in a pure form. Gratifyingly, pentafluoroethyl derivatives (**2e−g**) were suitable substrates that could be employed without β-fluoride elimination (**5e-Cl−g-Cl**). The defluorination was significantly faster and complete within 10 min, presumably because the highly electron-withdrawing α-trifluoromethyl group effectively stabilized the developing electron density on the enolate moiety. Notably, another trifluoromethyl group at a distal position (**2f**) was uninfluenced (**5f-Cl**) as our C−F activation process operates through the carbonyl group. Then, to demonstrate the feasibility of late-stage functionalization, the defluorinative chlorination was performed with a pharmaceutically relevant adapalene derivative (**2h**), and only mono-α-chlorinated product (**5h-Cl**) could be selectively obtained when 0.5 equiv of TCICA was used to prevent over-chlorination at the nucleophilic arene moieties. Subsequently, the defluorinative bromination was examined with DBDMH and a stoichiometric amount of DMSO. *p*-Haloaryl substrates (**2i** and **2b**) were transformed smoothly to the corresponding bromodifluorides (**5i-Br** and **5b-Br**). Similarly to the chlorination, the electron-rich *p*-anisyl substrate (**2d**) had to be treated with 2 equiv of **1** in DMF at 50 °C to afford a pure product (**5d-Br**). Our reaction tolerated sterically hindering *o*-substituents including sensitive bromine and iodine (**2j**, **2k**, and **2l**) to give the bromodifluoride products (**5j-Br**, **5k-Br**,

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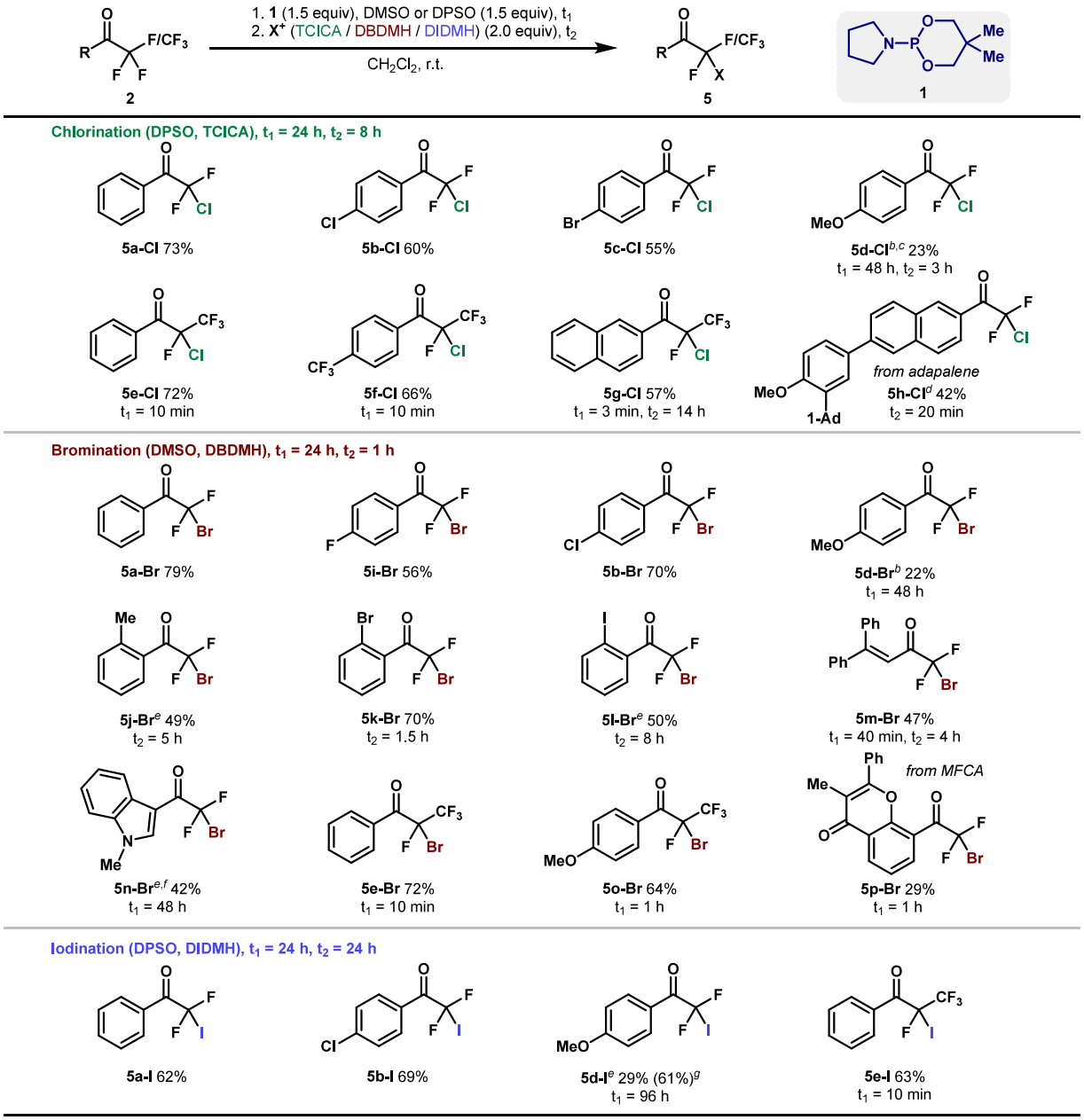
JACS Au 2025, 5, 1007−1015

Scheme 1. Substrate Scope of Defluorinative Halogenation of Perfluoroalkyl Ketones[a]



[a]Reaction conditions: **2** (1.00 mmol), **1** (1.50 mmol), DMSO/DPSO (1.50 mmol), and TCICA/DBDMH/DIDMH (2.00 mmol) in CH_2Cl_2 (5 mL). Isolated yields after column chromatography. [b]In DMF at 50 °C with 2.0 equiv of **1**. [c]With 2.0 equiv of DCDMH. [d]With 0.5 equiv of TCICA. [e]In DMSO solvent without additive. [f]At 50 °C with 5.0 equiv of **1**. [g]On a 0.71 mmol scale. Yields based on ^{19}F NMR analysis of the crude mixture with $PhCF_3$ (0.81 mmol) as an internal standard.

and **5l-Br**) in good yields. Furthermore, an alkenyl substrate (**2m**) was found to be amenable. The defluorination was markedly facile, and α-bromination proceeded in a comparable yield (**5m-Br**). Notably, an electron-rich azaaromatic indolyl group (**2n**) that is often incompatible under electrophilic halogenating conditions could also be employed.[13,14] Although the defluorination was slow, the use of 5.0 equiv of **1** at 50 °C in DMSO solvent provided the product (**5n-Br**) in a useful yield. Again, pentafluoroethyl ketones (**2e** and **2o**) were converted to bromodifluorides (**5e-Br** and **5o-Br**) with high efficiency. Even the relatively unreactive electron-rich substrate (**2o**) was substantially more susceptible to defluorination than the trifluoromethyl analogues. The current protocol was applicable to a bioactive 3-methylflavone-8-carboxylic acid (MFCA) derivative (**2p**), furnishing the α-brominated product (**5p-Br**) albeit in an attenuated yield resulting from unexpectedly uncontrollable reactant dimerization. Finally, defluorinative iodination was evaluated, and both electron-withdrawing (**5b-I**) and -donating (**5d-I**) groups were tolerated. In this case, the anisyl derivative (**2d**) was iodinated in DMSO without losing efficiency. However, the instability of the electron-rich product (**5d-I**) led to a diminished isolated yield. Again, high reactivity was observed for a pentafluoroethyl derivative (**5e-I**).

In the case of alkyl ketone substrate **2q**, even though defluorination proceeded, no halogenation was detected.

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JACS Au 2025, 5, 1007−1015

Instead, α-protonation partially took place, which had not been seen with the aryl ketone substrates. Thus, defluorinative protonation was targeted to demonstrate the extended utility of our method (Figure 3A). Gratifyingly, in the presence of

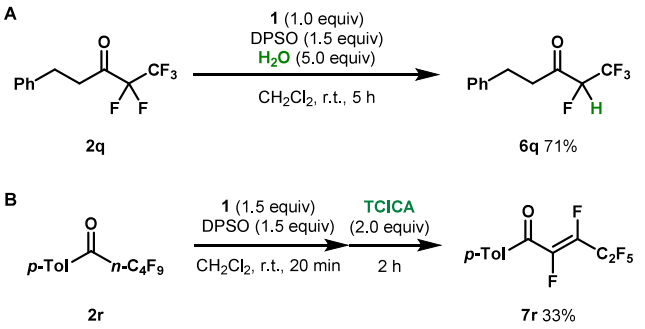

Figure 3. Evaluation of reaction scope expansion. (A) Proton as an electrophile. (B) Substrate with a longer fluoroalkyl chain.

water, the product **6q** was afforded in a 71% isolated yield. An analogous transformation could also be performed with aryl ketone **2a** albeit with moderate efficiency (see the SI). Furthermore, a substrate with a longer perfluoroalkyl chain (**2r**) was evaluated given that pentafluoroethyl ketones generally outperform trifluoromethyl analogues (Figure 3B). Unfortunately, after facile defluorination, β-F-elimination took place predominantly with the n-C_4H_9 group to give perfluoroenone (**7r**).

To gain insights into the mechanism of our α-defluorinative halogenation of perfluoroalkyl ketones, DFT calculation was performed at the M06-2X-D3/6-31+G(d,p)/SMD(CH_2Cl_2 and/or DMSO) level of theory (Figure 4).[19] First, the elementary steps of the phosphorus-mediated defluorination process were analyzed (Figure 4A). At the initial stage, the nucleophilic phosphoramidite **1** attacks the carbonyl group of **2a** in a stepwise manner to form a three-membered oxaphosphirane **Int-II**. Then, it is converted to an ionic tetravalent phosphonium **Int-III** via concerted P−C bond cleavage/fluoride elimination, which goes over the highest point **TS-III** (27.1 kcal/mol) of the potential energy curve. Spontaneously, the facile combination of the phosphonium cation and the fluoride anion provides stable, neutral pentavalent phosphorus **3a**, which had been observed by NMR spectroscopies. The strong P−F bond formation renders the overall defluorination process slightly exergonic. Because a dramatic selectivity change between **3a** and aldol-type product **4a** was observed during solvent optimization (Table 1), the solvation effect was further evaluated by modifying the SMD parameters (Figure 4B). It appeared that the activation energy of the rate-determining step decreases in polar DMSO, which would effectively stabilize the separated partial charges in **TS-III**. In contrast, virtually no solvent effect was found for the formation of **4a** (see the SI). Because both steps share the same starting material, the fast production of **3a** will lead to the fast consumption of **2a**, thereby depleting the reactant for the subsequent aldol-type side reaction. Lastly, the halogenation step was calculated with TCICA (Figure 4C). In transition state **TS-V**, TCICA comes from the opposite side of the large pentavalent phosphorus group with a low energy barrier (16.6 kcal/mol) to form desired product **5a-Cl** with a large driving force.

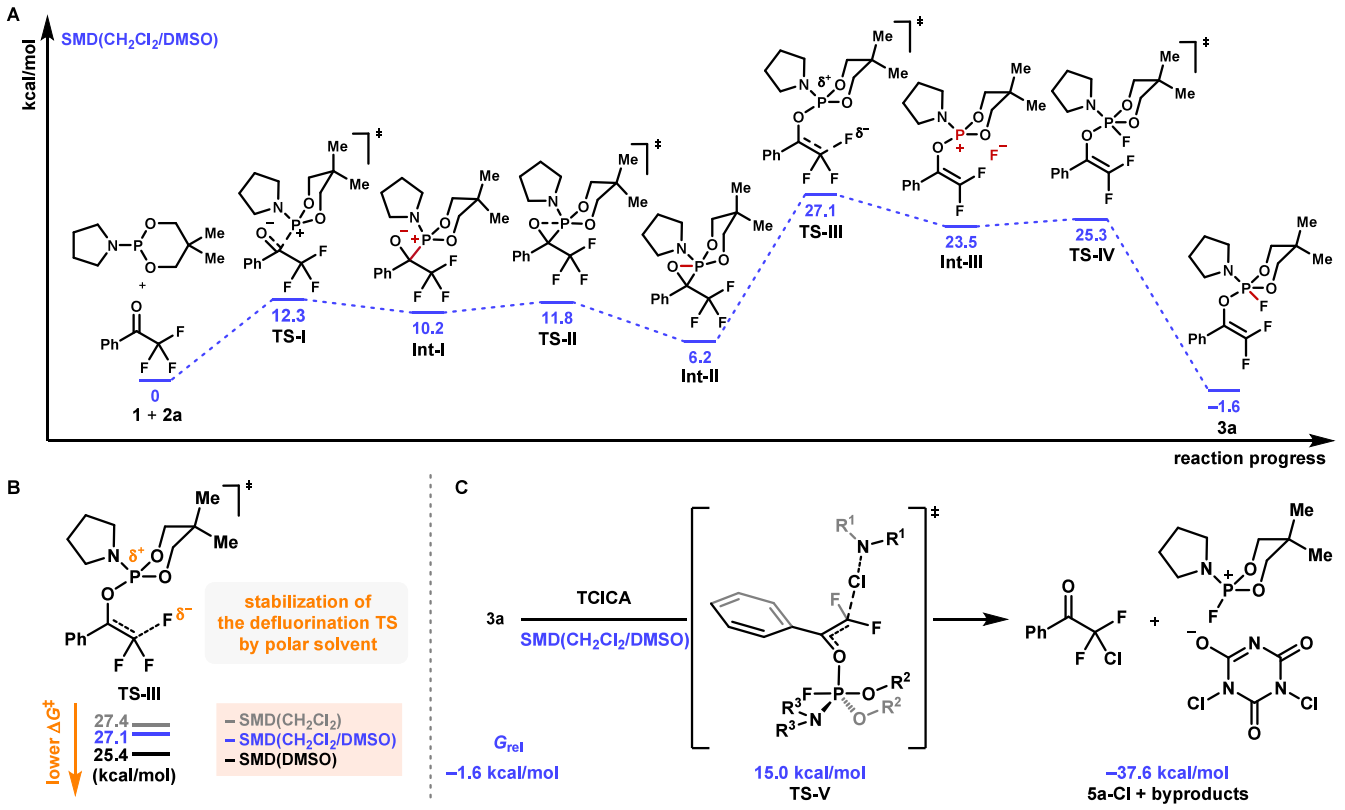

Figure 4. Computational analysis of the reaction mechanism at M06-2X-D3/6-31+G(d,p)/SMD. (A) Gibbs free energy profile of the defluorination process. (B) Solvent effect on the rate-determining step. (C) Chlorination of the *O*-phosphorus difluoroenolate by TCICA.

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In conclusion, we have developed a mild synthetic method for the selective transformation of one C−F bond in perfluoroalkyl ketones into more reactive and thus versatile halogen congeners via an interrupted Perkow reaction. The properly modulated steric and electronic properties of our rationally designed phosphorus reagent as well as the identification of suitable sulfoxide additives allowed the prevention of traditional side reactions and, thereby, effective formation of the *O*-phosphorus perfluoroenolate species. Then, chlorine, bromine, and iodine could be installed in place of fluorine without compatibility issues because of the absence of highly reactive activators such as transition/reducing metals. Computational analysis of the reaction mechanism suggests the strong P−F interaction as the critical thermodynamic driving force, and the consequent charge neutralization is likely responsible for the enhanced nucleophilicity of the enolate intermediate. This single-operation process employing readily accessible trifluoromethyl and pentafluoroethyl substrates provides a convenient and practical means to form valuable products with two useful synthetic handles, halogen and ketone, which can serve as precursors to a variety of functionalized organofluorines.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01242.

Experimental details, characterization data, copies of NMR spectra for all new compounds, and DFT calculation data (PDF)

Computation output files (ZIP)

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Notes

The authors declare no competing financial interest.

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