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Pentacoordinate Phosphoranes as Versatile Reagents in Fluoroalkylation Reactions

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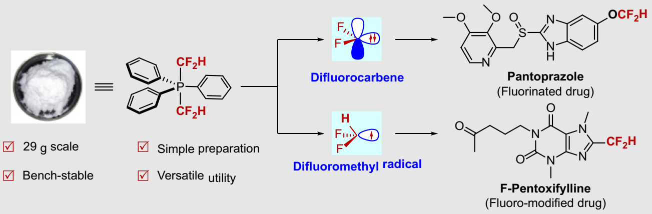
A general method for the synthesis of bench-stable bis(difluoromethyl) pentacoordinate phosphoranes has been developed. The reaction is rapid, operationally simple, and easily scalable. The pentacoordinate phosphoranes can generate both difluoromethyl radical ($\cdot CF_2H$) and difluorocarbene ($:CF_2$) intermediates. Thus, a variety of fluoroalkylation transformations have been achieved by $\cdot CF_2H$, such as oxidative difluoromethylation of electron-deficient heterocycles, nickel/photoredox dual-catalyzed difluoromethylation of aryl bromides, and photoredox difluoromethylation of alkenes, or by $:CF_2$, such as *gem*-difluorocyclopropanation of alkenes, base-promoted difluoromethylation of heteroatom nucleophiles, Pd-catalyzed difluoromethylation of arylboronic acids, and Cu-mediated trifluoromethylation of aryl iodides (via $:CF_2$ and recombined CF_3^-). These fluoroalkylation methods have been successfully applied to late-stage fluoroalkylation of drugs and drug-like molecules.



Keywords: **pentacoordinate phosphorane, difluoromethyl radical, difluorocarbene, difluoromethylation, fluoroalkylation**

Introduction

Fluorinated moieties, ubiquitous in emerging pharmaceuticals and agrochemicals, play an important role in blocking metabolically labile sites and confer these molecules with enhanced lipophilicity, membrane permeability, and binding affinity to the target enzymes compared to their mother compounds (Figure 1a).[1–6] Exquisite installation of fluorine-containing functional groups into molecular scaffolds is a foundation of synthetic organofluorine research.[2–4] Thus, development of new reagents and reactions are highly demanded to tackle the synthetic challenge for organofluorine compounds. To this end, reagents with versatile fluoroalkyl group transfer capacity that are efficient, inexpensive, and operationally simple are extremely popular.[7–15] Because of the advantage of the flexible carbon-heteroatom bond, heteroatom (i.e., Si,[7,8] S,[9–11] P,[12–14] I,[9,15] etc.) tailored motifs are frequently exploited to fabricate fluoroalkylation reagents. This is rationalized due to the following: (i) large electronegativity discrimination between carbon and heteroatoms results in polar carbon–heteroatom bonds; (ii) changes in oxidation state or substituents on heteroatoms may impart the bonds with substantive polarity alteration, which favors the cleavage

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of carbon–heteroatom bonds;[9–11] (iii) the high electron-maintaining capability and stability of heteroatom-containing motifs as leaving group facilitates the transfer of fluoroalkyl groups.[9,12–15] Given the ease of manipulation, a plethora of useful fluoroalkylating agents have been developed by merging fluorinated moieties and heteroatoms with multiple oxidation states.[7–15] In this vein, reaction intermediates are pivotal for exploring applications; for example, the facile generation of difluorocarbene (:CF_2) from trifluoromethyltrimethylsilane (TMSCF_3)[16,17] and (bromodifluoromethyl)trimethylsilane (TMSCF_2Br)[18–23] renders their insertion into carbon/heteroatom–hydrogen (X–H) bonds and *gem*-difluorocyclopropa(e)nation of unsaturated C–C bonds; (difluoromethyl)trimethylsilane (TMSCF_2H)[24] and sodium difluoromethanesulfinate (HCF_2SO_2Na)[25–29] have been frequently applied to radical difluoromethylation of alkenes and arenes. However, bench-stable, operationally simple, and highly efficient fluoroalkylation reagents are still in high demand for addressing current synthetic challenges.

Due to the facile cleavage of carbon–phosphorus bonds, fluorinated organophosphorus compounds have found extensive applications in organofluorine compounds' syntheses. In fact, the most common fluorinated phosphonium salts and phosphorus ylides have been engaged in fluoroalkylation and fluoroolefination reactions.[12,14,30,31] However, these reagents suffer from limited tunability and reaction capacity, and thus exploring new structures would further expand the synthetic utility of organophosphorus compounds. Recently, McNally and coworkers[32] developed a method of phosphorus-mediated 4-fluoroalkylation of pyridines; the reaction was supposed to proceed via intramolecular fluoroalkyl-group migration upon pentacoordinate phosphorane intermediates. In this case, pre-installation of fluoroalkyl group(s) into uncommon tertiary phosphine precursors was required, and the pentacoordinate phosphorane intermediates were not stable enough for isolation and characterization (Figure 1b).[32] Capture of difluorocarbene (:CF_2) with tertiary phosphines facilely generates difluoromethylene ylide, which is in equilibrium with difluoromethyl phosphonium salt in the presence of water.[12] Here, we report a serendipitous discovery that in the presence of water, nucleophilic addition of difluoromethylene ylide (generated in situ via capture of :CF_2 with tertiary phosphine) to difluoromethyl phosphonium followed by reduction furnishes a bench-stable pentacoordinate phosphorane, which was applied as both :CF_2 and difluoromethyl radical (·CF_2H) reagents in difluoromethylation, difluoromethylenation, and trifluoromethylation reactions (Figure 1c).

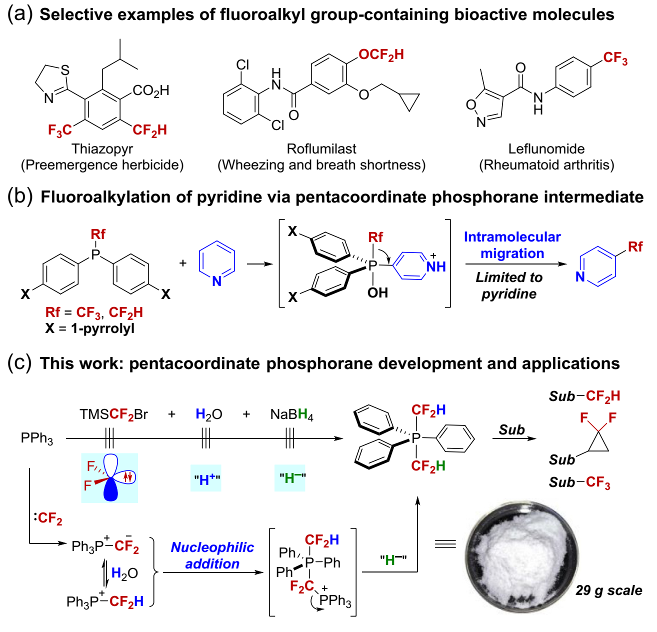

Figure 1 | *Fluoroalkyl group-containing compounds and synthetic methods involving pentacoordinate phosphoranes. sub, substrate.*

Experimental Methods

General procedure for synthesis of pentacoordinate phosphoranes

To an oven-dried 10 mL Schlenk tube were added tertiary phosphine (0.1 mmol, 1.0 equiv), $KHCO_3$ (50 mg, 0.5 mmol, 5.0 equiv), and $NaBH_4$ (11.3 mg, 0.3 mmol, 3.0 equiv), then dichloromethane (DCM, 1 mL, 0.1 M) was added under nitrogen atmosphere; subsequently TMSCF_2Br (45 μL, 0.3 mmol, 3.0 equiv) and H_2O (7.2 μL, 0.4 mmol, 4.0 equiv) were added, and the resulting mixture was stirred at room temperature for 1 h. After the reaction was completed, the solid was filtered off and the solvent was removed under vacuum; the resulting mixture was purified by flash chromatography on silica gel (eluent, petroleum ether:DCM) to afford the corresponding products (**2**).

General procedure for difluoromethylation of heterocycles

To a 15 mL Schlenk tube were added heterocycle (0.1 mmol, 1.0 equiv), $PPh_3(CF_2H)_2$ (73 mg, 0.2 mmol, 2.0 equiv), $K_2S_2O_8$ (54 mg, 0.2 mmol, 2.0 equiv), dimethyl sulfoxide (DMSO, 1 mL), H_2O (300 μL), and trifluoroacetic acid (TFA, 1.0 mmol, 10.0 equiv); the resulting mixture was stirred at 50 °C for 24 h. After the reaction was completed, H_2O (20 mL) and then saturated $NaHCO_3$ (50 mL) were added, and the mixture was extracted with ethyl acetate (4 × 50 mL). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (eluent,

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petroleum ether:ethyl acetate) to afford the corresponding products (**4**).

General procedure for nickel-photoredox-catalyzed difluoromethylation of aryl bromides

Under N_2 atmosphere, to a 15 mL Schlenk tube were added aryl bromide (0.1 mmol, 1.0 equiv), $PPh_3(CF_2H)_2$ (73 mg, 0.2 mmol, 2.0 equiv), $NiBr_2$·glyme (3 mg, 0.01 mmol, 10 mol %), bathophenanthroline (**L1**, 5 mg, 0.015 mmol, 15 mol %), and $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ (1 mg, 0.001 mol, 1 mol %) in a glovebox. The tube was brought to bench top, tetrahydrofuran (THF, 1 mL, 0.1 M) was added, and the reaction mixture was stirred for 24 h under irradiation of blue light-emitting diode (LED) (10 W, 465 nm). After the reaction was completed, the resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate) to afford the corresponding products (**6**).

General procedure for difluoromethylation of alkenes

To a 15 mL Schlenk tube were added alkene (0.3 mmol, 3.0 equiv), $PPh_3(CF_2H)_2$ (36.4 mg, 0.1 mmol, 1.0 equiv), and $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ (1 mg, 0.001 mol, 1 mol %). The tube was evacuated and backfilled with N_2, then MeOH (1 mL) was added, and the resulting mixture was stirred for 24 h under irradiation of blue LED (10 W, 465 nm). After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate) to afford the corresponding products (**8**).

General procedure for *gem*-difluorocyclopropanation of alkenes

Under N_2 atmosphere, to a 15 mL Schlenk tube were added alkene (0.1 mmol, 1.0 equiv), $PPh_3(CF_2H)_2$ (36.4 mg, 0.2 mmol, 2.0 equiv), and *N*,*N*-dimethylformamide (DMF, 1 mL). The resulting mixture was stirred at 110 °C for 12 h, and then 20 mL of ethyl acetate was added. The organic phase was separated and washed with water (3 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate) to afford the corresponding products (**9**).

General procedure for difluoromethylation of heteroatom nucleophiles

Under N_2 atmosphere, to a 15 mL Schlenk tube were added heteroatom nucleophile (0.1 mmol, 1.0 equiv), $PPh_3(CF_2H)_2$ (73 mg, 0.2 mmol, 2.0 equiv), potassium ethoxide (EtOK, 17 mg, 0.2 mmol, 2.0 equiv), and DMF (1.0 mL). The resulting mixture was stirred at room temperature for 12 h, and then 20 mL of EtOAc was added. The organic phase was separated and washed with water (3 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate) to afford the corresponding products (**11**).

General procedure for difluoromethylation of arylboronic acids

In a glovebox, to a 15 mL sealed tube were added arylboronic acid (0.1 mmol, 1.0 equiv), $PPh_3(CF_2H)_2$ (93 mg, 0.25 mmol, 2.5 equiv), $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol, 5 mol %), Xantphos (8.7 mg, 0.015 mmol, 15 mol %), K_3PO_4 (10.6 mg, 0.05 mmol, 50 mol %), and toluene (1 mL). The resulting mixture was stirred at 110 °C for 12 h. Then 20 mL of ethyl acetate was added, the organic phase was separated and washed with water (3 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether:ethyl acetate) to afford the corresponding products (**6**).

General procedure for trifluoromethylation of aryl iodides

In a glovebox, to a 15 mL sealed tube were added aryl iodide (22 mg, 0.1 mmol, 1.0 equiv), $PPh_3(CF_2H)_2$ (73 mg, 0.2 mmol, 2.0 equiv), KF (17 mg, 0.3 mmol, 3.0 equiv), CuBr (43 mg, 0.3 mmol, 3.0 equiv), and THF (1 mL). The resulting mixture was stirred at 100 °C for 12 h. Then 10 mL of ethyl acetate was added, the organic phase was separated and washed with water (3 mL) and brine (3 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (eluent, petroleum ether/ethyl acetate) to afford the corresponding products (**14**).

Results and Discussion

In 1949, Wittig and Rieber synthesized the first stable all-carbon pentacoordinate phosphorane, pentaphenylphosphorane (PPh_5), via the reaction of phenyllithium with tetraphenylphosphonium bromide.[33,34] However, this method could not be extended to alkyl group (with α-hydrogen)-containing all-carbon pentacoordinate phosphorane synthesis, due to the strong basicity of carbanion nucleophiles (e.g., PhLi) that deprotonate rather than add to the phosphoniums.[34,35] Thus, only sporadic all-carbon arylphosphorane analogues have been reported, yet no substantive synthetic utility has been achieved, largely because of poor synthetic accessibility and structural variation.[35] Apparently, lowering the basicity of nucleophiles is crucial for the successful addition to alkyl

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group-containing phosphoniums, otherwise deprotonation takes place.

Due to the strong electron-withdrawing nature of fluorine, fluorinated carbanions possess lower basicity compared to their nonfluorine analogues.[36,37] We envisioned the utilization of fluorine-containing carbanion would circumvent the α-deprotonation of phosphonium. In this regard, Dilman and coworkers[38] reported a cyclopentacoordinate phosphorane; however, no substantive synthetic application has been reported, probably due to the structural limitation. Difluoromethylene phosphorus ylides can be easily prepared in situ from tertiary phosphines and :CF_2 reagents or generated from the deprotonation of difluoromethyl phosphonium salts; in the presence of water, ylides are in equilibrium with phosphonium salt. The addition of ylides to phosphonium salts forms a pentacoordinate phosphorane intermediate; the tailored phosphorus motif can be removed by a reductant. After screening the reaction parameters, $TMSCF_2Br$ was found to be the best choice of :CF_2 reagent. With $KHCO_3$ as initiator and $NaBH_4$ as reductant, the reaction proceeded rapidly to completion in DCM within 1 h (Figure 2, for more details, see Supporting Information Tables S1–S9). When the reaction was performed on 0.1 mol scale, 29.4 g of **2a** was obtained in 79% yield, which guaranteed its further application investigations. Under the optimized conditions, a variety of tertiary phosphines were successfully converted to all-carbon pentacoordinate phosphoranes (Figure 2 and Supporting Information Table S10). When triaryl phosphines bearing electron-donating and electron-withdrawing groups on the aromatic rings and alkylaryl phosphines were used, the reaction proceeded smoothly to afford bis(difluoromethyl) pentacoodinate phosphoranes in moderate to good yields (**2a**–**2f**). To elucidate the role of H_2O and $NaBH_4$, we conducted deuterium labeling experiments, which confirmed our hypothesis that one hydrogen source of difluoromethyl group was H_2O and the other was $NaBH_4$ (see Supporting Information Figure S5).

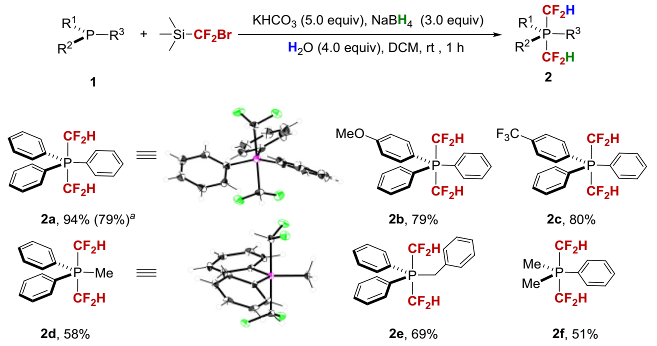

Figure 2 | *Synthesis of bis(difluoromethyl) pentacoordinate phosphoranes. DCM, dichloromethane.* [a]*Yield obtained using 0.1 mol of* PPh_3 *as substrate.*

The structure of compounds **2a** and **2d** were unambiguously confirmed by X-ray crystallography (Figure 2 and Supporting Information Figures S3 and S4 and Tables S11 and S12). Both structures have a trigonal bipyramidal configuration, with two difluoromethyl groups located at the axial position and three nonfluorine groups located at the equatorial position. In the case of **2a**, the axial P–C(CF_2H) bond lengths are 1.987(17) Å and 1.978(17) Å, respectively, and the average length 1.982 Å is shorter than the axial P–C(C_6H_5) bond length (1.987 Å) of previously reported pentaphenyl phosphorane.[39] The equatorial P–C(C_6H_5) bonds have a mean length of 1.835 Å, which is shorter than the equatorial P–C bond length in pentaphenyl phosphorane (1.850 Å), and is of similar length as in triphenyl phosphine (1.828 Å). The average P–C(CF_2H) bond length in **2a** is obviously longer than P –C(CF_2H) in $Ph_3P^+CF_2HBr^-$ (1.862 Å), and likewise, the average P–C(C_6H_5) bond length in **2a** is longer than P–C (C_6H_5) in $Ph_3P^+CF_2HBr^-$ (1.785 Å).[40] The axial P–C(CF_2H) bonds are apparently longer than the equatorial P–C (C_6H_5) bonds (ca. 1.987 to 1.835 Å), indicating that the axial P–C(CF_2H) bond cleavage is easier than equatorial P–C(C_6H_5) bond cleavage, rendering **2a** better "CF_2H" transfer capability.

To study the reactivity of all-carbon pentacoordinate phosphoranes, cyclic voltammetry measurements of compound **2a** was initially conducted, and the redox potential was determined to be 1.82 V (vs Ag/AgCl in CH_3CN) (see Supporting Information Figure S2). Simultaneous thermal analysis (differential scanning calorimetry and thermogravimetry) revealed that the decomposition of **2a** occurred from 152 to 183 °C (see Supporting Information Figure S1). When **2a** was heated in DCM at 110 °C for 7 h in a sealed tube, PPh_3, difluorotriphenylphosphorane (Ph_3PF_2), and difluoromethane (CH_2F_2) were detected as the major products by ^{19}F and ^{31}P NMR; in methanol, besides PPh_3 and CH_2F_2, $MeOCF_2H$ was detected as the major product; in toluene, besides PPh_3 and CH_2F_2, triphenylphosphine oxide (Ph_3PO) and trace amount of difluoromethyltriphenylphosphonium salt ($Ph_3PCF_2H^+$) were observed (see Supporting Information Figures S7–S10). In conjunction with the X-ray data, under heating conditions, the P–C bond dissociation occurred predominantly at the P–CF_2H bond rather than the P–C_6H_5 bond to generate CF_2H^- and then protonation gave CF_2H_2. Residual $Ph_3PCF_2H^+$ motif produced :CF_2 via deprotonation of difluoromethyl group to afford $Ph_3P{=}CF_2$, which then released :CF_2 under high temperatures.[12] However, neither difluoromethybenzene ($PhCF_2H$) nor biphenyl were observed, indicating that the intramolecular migration reaction upon P(V) was less likely occuring.[32]

Considering triphenylphosphine is a readily available and cost efficient starting material, we next explored the reactivity of pentacoordinate phosphoranes by using **2a**

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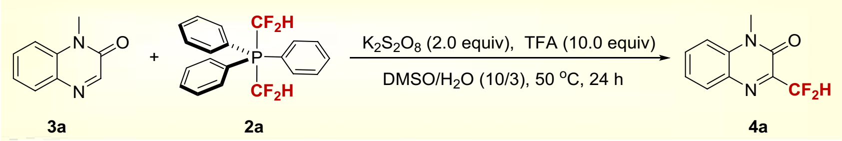
as a model fluorinating agent. At the outset, we attempted to perform difluoromethyl transfer reactions. Difluoromethylated heterocycles are ubiquitous in bioactive molecules; however, the conventional synthetic methods often employ toxic fluorinating agents, harsh reaction conditions, and suffer from limited substrate scope.[41–46] Although in recent years radical-based approaches have proven effective for difluoromethylation of heterocycles, nevertheless, either costly/toxic metal catalysts or strictly inert conditions are required.[12,47–49] Hence, we investigated the difluoromethylation of heterocycles by using 1-methyl quinoxolin-2-one (**3a**) as a model substrate and **2a** as the difluoromethylation reagent. After carefully screening the reaction parameters, we found $K_2S_2O_8$ was the most efficient oxidant compared to *tert*-butyl peroxybenzoate (TBPB), *tert*-butyl hydroperoxide (TBHP), and $Na_2S_2O_8$ (Table 1, entries 1–4). The addition of water improved the yield, probably by increasing the solubility of $K_2S_2O_8$ (Table 1, entries 5–7). When catalytic $AgNO_3$ was used as an additive, the yield significantly improved, while added TFA afforded the best result (Table 1, entries 1 and 8, for more details, see Supporting Information Tables S13 and S14).

Subsequently, we examined the reaction with structurally different pentacoordinate phosphoranes as difluoromethylation reagents to compare the "CF_2H" transfer capability. When an electron-donating group bearing **2b** was used, the yield increased to 91%, whereas the electron-withdrawing group bearing **2c** afforded lower yield of 74% (Table 1, entries 9 and 10). When a phenyl group replaced a methyl (**2d**) or benzyl group (**2e**), 75% and 44% yields were obtained, respectively, and dimethylphenyl phosphorus-based phosphorane (**2f**) afforded 77% yield (Table 1, entries 11–13). Notably, phenylation, methylation or benzylation of quinoxalinone was not observed in these cases. Although the difluoromethylation efficiency of electron-rich phosphorane **2b** was higher than others, given the easy availability and low cost of PPh_3, we chose **2a** as a general reagent for the following studies.

With the optimized conditions in hand, a variety of heterocycles, including quinoxolin-2-one (**3a**–**3f**), 1-benzothiophene (**3g**), and indole (**3h**), were subjected to the oxidative difluoromethylation conditions, and moderate to good yields were obtained (Figure 3a). To our delight, the difluoromethylation occurred selectively on the electron-deficient heterocycles rather than phenyl ring, and the reaction site was generally activated by an adjacent electron-withdrawing group, typically a carbonyl group (C=O). The substituents on phenyl rings, such as chloro, fluoro, and methyl groups, had no remarkable effect on the yield (**4b**, **4c**, and **4e**). To further illustrate the utility of this transformation, commercial drugs and natural products, such as 4-methylumbelliferon (4-MU), Uvadex, caffeine, and pentoxifylline, were successfully difluoromethylated (**4i**–**4l**).

Table 1 | *Optimization of Oxidative Difluoromethylation Conditions*



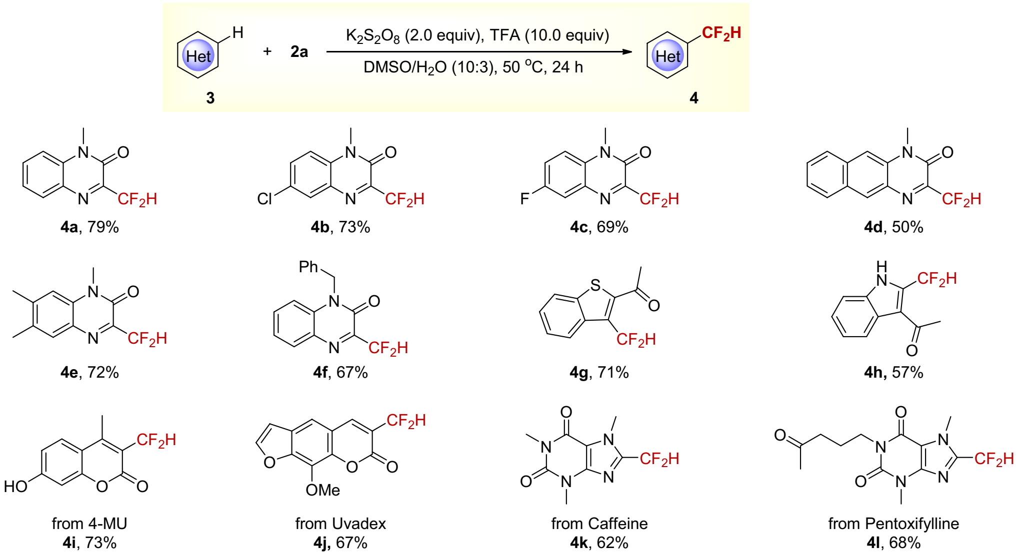
Entry	Variation from Standard Conditions	Yield of (4a %)[a]
1	Standard conditions	82% (79%)[b]
2	TBPB instead of $K_2S_2O_8$	0
3	TBHP instead of $K_2S_2O_8$	0
4	$Na_2S_2O_8$ instead of $K_2S_2O_8$	37%
5	Without H_2O	40%
6	Ratio of DMSO/H_2O = 10/1	47%
7	Ratio of DMSO/H_2O = 10/4	55%
8	20 mol % of $AgNO_3$ was used	71%
9	**2b** was used instead of **2a**	91%
10	**2c** was used instead of **2a**	74%
11	**2d** was used instead of **2a**	75%
12	**2e** was used instead of **2a**	44%
13	**2f** was used instead of **2a**	77%

TFA, trifluoroacetic acid; DMSO, dimethyl sulfoxide; TBPB, *tert*-butyl peroxybenzoate; TBHP, *tert*-butyl hydroperoxide.

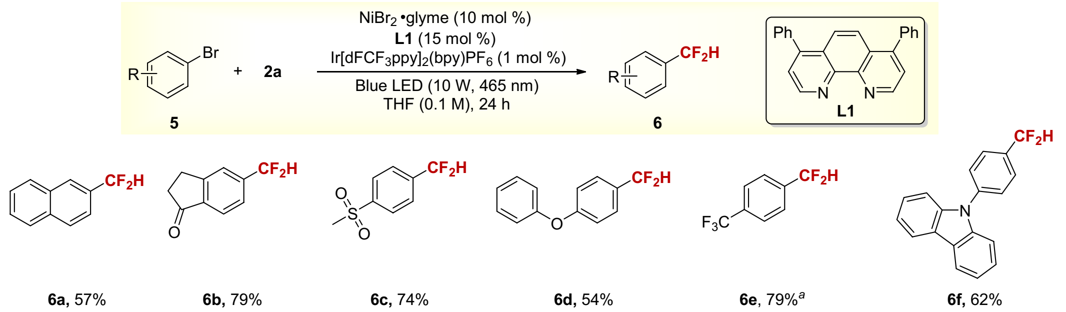
[a] Standard conditions: **3a** (0.1 mmol, 1.0 equiv), **2a** (0.2 mmol, 2.0 equiv), $K_2S_2O_8$ (0.2 mmol, 2.0 equiv), DMSO (1 mL), air, 24 h, 50 °C, TFA (10.0 equiv); for entries 2–4, the reactions were performed at rt; for entries 2–8, TFA was not used.

[b] Yield of isolated product.

(a) **Oxidative difluoromethylation of heterocycles**



(b) **Nickel photoredox dual-catalyzed difluoromethylation of aryl bromides**



(c) **Photoredox-catalyzed difluoromethylation (left) and thermal-promoted *gem*-difluorocyclopropanation of alkenes (right)**

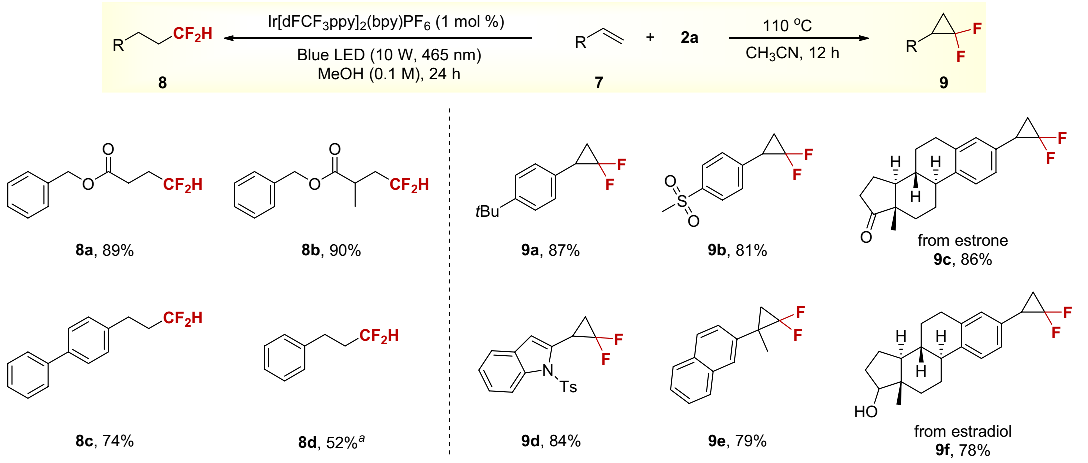


Figure 3 | *Radical difluoromethylation and difluorocarbene (:CF$_2$) gem-difluorocyclopropanation with pentacoordinate phosphorane **2a**.* [a]*Yields were determined by ^{19}F NMR with benzotrifluoride as an internal standard. 4-MU, 4-methylumbelliferon; THF, tetrahydrofuran.*

Copper-mediated difluoromethylation of aryl halides suffers from low efficiency and limited substrate scope, that is, a stoichiometric amount of Cu(I) salt is generally required to achieve high conversion, and only aryl iodides or activated aryl bromides are suitable substrates.[50–53] The merger of transition metal and photocatalysis has proven to be effective in facilitating reactions of non-traditional nucleophilic partners via distinct activation modes.[54–56] In this regard, MacMillan and coworkers succeeded in difluoromethylation of unactivated aryl bromides via

Ni/photoredox dual catalysis by using HCF_2Br as a difluoromethyl source. However, due to the ozone depleting nature of HCF_2Br and stoichiometric amount of tris(trimethylsilyl)silane, the synthetic utility was largely limited.[55,56] Because of the powerful photoredox/nickel dual catalysis, we investigated the difluoromethylation of aryl bromides with **2a** as the difluoromethylation reagent. After briefly screening the Ni-catalyst, ligand, and other parameters (see Supporting Information Tables S15–S17), we found that using 10 mol % of $NiBr_2$·glyme and 1 mol % of $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ as co-catalyst, and 15 mol % of **L1** as ligand, under 465 nm blue LED light irradiation, the reaction proceeded smoothly to furnish the difluoromethylated product in 54–79% yields (Figure 3b). In general, the aryl groups bearing electron-donating substituents (**6d** and **6f**) afforded slightly lower yields than those with electron-withdrawing substituents (**6b**, **6c**, and **6e**), probably because the electron-deficient aryl bromides were of higher reactivity. No nucleophilic difluoromethylation occurred when a ketone group was present, indicating that a difluoromethyl anion (CF_2H^-) was less likely involved (**6b**) The observation of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)-trapped difluoromethyl product indicated that a $\cdot CF_2H$ process was more likely (see Supporting Information Figure S12).

To further illustrate the radical reactivity of pentacoordinate phosphoranes, we conducted the reaction of **2a** with alkenes (see Supporting Information Tables S18 and S19). Gratifyingly, by using the same photocatalyst $Ir[dF(CF_3)ppy]_2(bpy)PF_6$, with methanol as a hydride donor and solvent, the hydrodifluoromethylation of alkenes proceeded uneventfully to give moderate to excellent product yields, which corroborated the radical addition mechanism (Figure 3c, left, for detailed see Supporting Information Figure S13). Notably, the electron-deficient alkenes (**8a** and **8b**) gave better yields than styrenes (**8c** and **8d**), which accords with the previous report that the $\cdot CF_2H$ is an electron-rich radical.[25]

Interestingly, when the reaction of alkenes and **2a** was carried out under heating conditions, *gem*-difluorocyclopropane product was obtained as the main product (see Supporting Information Tables S20 and S21). *gem*-Difluorocyclopropanes are promising building blocks in medicinal chemistry and provide discrepant but complementary possibilities for fundamental functional group interconversions.[57] These compounds are generally synthesized by [2+1] reaction of $:CF_2$ with alkenes, thus, *gem*-difluorocyclopropanation of C=C double bonds is recognized as a typical reaction mode of $:CF_2$.[16,18,58–60] Delightfully, the difluorocyclopropanation with substituted styrenes proceeded smoothly by simply heating to 110 °C in CH_3CN, and both electron-rich and electron-deficient styrenes afforded good to excellent yields of *gem*-difluorocyclopropanes (Figure 3c, right). Furthermore, *gem*-difluorocyclopropanation of estrone and estradiol derived styrenes worked smoothly in good yields (**9c** and **9f**), demonstrating the synthetic prowess of this protocol, yet carbonyl and hydroxy groups remained intact under these conditions, which enabled further manipulation for complicated drug molecules. Compared to *gem*-difluorocyclopropanation with $TMSCF_2Br$, this method is more effective for electron-deficient and hydroxyl group-containing styrenes (**9b** and **9f**).[18]

Heteroatom difluoromethyl compounds often act as lipophilic hydrogen bond donors, which therefore have found broad applications in drug design and functional materials, such as Desflurane (an anesthetic), Riodipine (Ca^{2+} antagonists), and Roflumilast (phosphodiesterase-4 inhibitor).[3,61] Conventional methods to access such structures generally trap the $:CF_2$ with heteroatom nucleophiles. The efficiency of such transformations vastly depends on the reactivity of $:CF_2$ sources, thus operationally simple and environmentally benign $:CF_2$ reagents with broad substrate scope are highly desirable.[18,58,59,61]

To expand the reactivity patterns of all-carbon pentacoordinate phosphoranes, we investigated the $:CF_2$ reaction mode of **2a** with heteroatom nucleophiles. At the outset, the reaction of **2a** with thiophenol (**10a**) was carried out with EtOK as a base to boost the reaction, and difluoromethylation of *O*-, *S*-, *Se*-, *N*-nucleophiles took place readily (Figure 4a, for detailed see Supporting Information Tables S22 and S23). Subsequently, a variety of heteroatom nucleophiles, including arylthiol, phenol, benzeneselenol, and imidazole, were difluoromethylated in moderate to good yields (Figure 4a). The reaction conditions were so mild that a wide range of functional groups were tolerated, such as heterocycles, halides, and amides. In addition, the reaction was only slightly sensitive to steric hindrance (**11f** and **11j**); both electron-rich and -deficient substrates were efficiently difluoromethylated. Notably, the product of **11a** and **11p** were previously successfully applied in difluoro(phenylchalcogen)methylation reactions,[62] while **11b** and **11g** could be easily oxidized and applied as *gem*-difluoroolefination and radical difluoromethylation reactions, respectively.[63,64] The successful synthesis of Pantoprazole (in 25% yield, 71% yield based on recovered starting material) and Roflumilast (in 31% yield, 77% yield based on recovered starting material), and difluoromethylation of Triclosan and Theophylline on oxygen and nitrogen atom, respectively, in 79% yield further elaborated the practical utility of this method (**11l**–**11q**). Notably, the difluoromethylation of *N*-nucleophile Theophylline was achieved under simple heating (**11q**).

Recently, Zhang and coworkers developed a difluoromethylation method of arylboronic acids with $:CF_2$ reagent as the difluoromethyl source; the reaction was proven to proceed via palladium–difluorocarbene ($Pd{=}CF_2$) intermediate.[65–71] The excellent functional group compatibility, mild reaction conditions, and high efficiency endowed the protocol with promising applications in aryl difluoromethylation. However, elaborate

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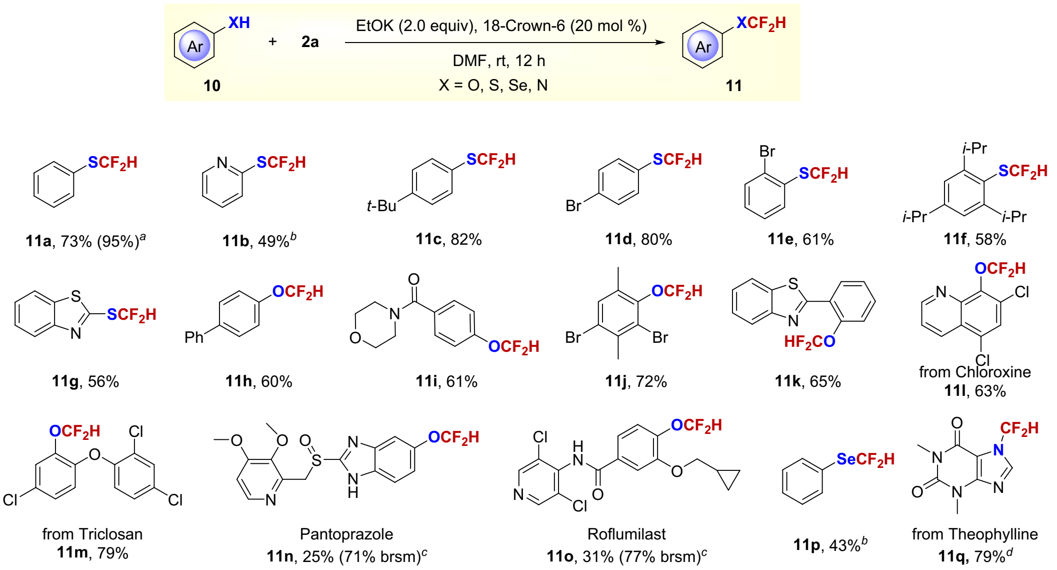
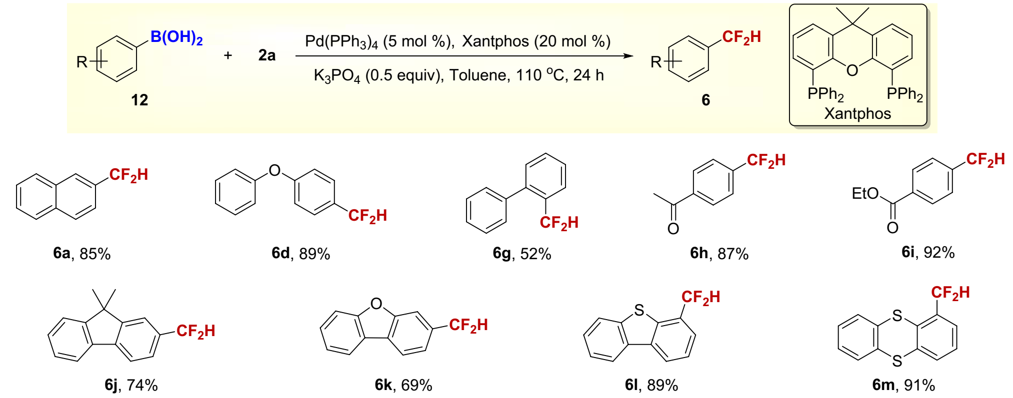
(a) **Base-promoted difluoromethylation of heteroatom nucleophiles**



(b) **Palladium-catalyzed difluoromethylation of boronic acids**



(c) **Copper-mediated trifluoromethylation of aryl iodides**

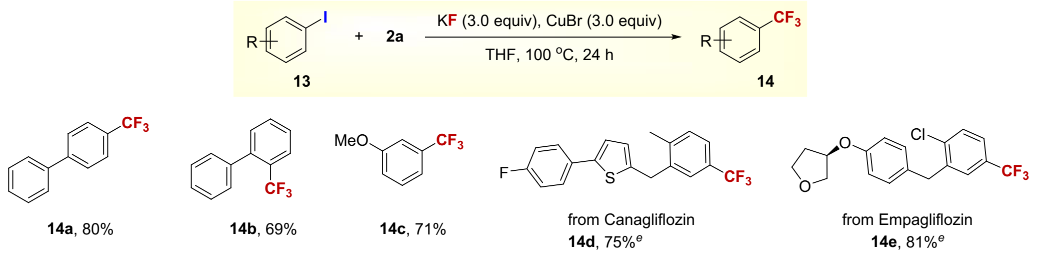


Figure 4 | *Difluorocarbene-involved difluoromethylation and trifluoromethylation with pentacoordinate phosphorane* ***2a****. DMF,* N,N-*dimethylformamide.* [a]*Yield using diphenyl disulfide as starting material.* [b]*Yields were determined by* ^{19}F *NMR with benzotrifluoride as an internal standard.* [c]*Yield based on recovered starting material (brsm).* [d]*The reaction was performed at 110 °C in* CH_3CN *for 12 h, without EtOK and 18-Crown-6.* [e]*The reaction time was 48 h.*

manipulation of additives was requisite for the product selectivity, thus making the reaction conditions complicated. Considering that pentacoordinate phosphorane **2a** can generate :CF_2 simply by heating, we envisioned that the use of **2a** as :CF_2 precursor would simplify the reaction conditions and thus improve the practicality. After a brief screening of the reaction parameters, we found that the reaction proceeded efficiently by using $Pd(PPh_3)_4$ as catalyst, Xantphos as ligand, and K_3PO_4 as base to promote transmetalation of arylboronic acids to palladium (see Supporting Information Tables S24–S29). Of note, the generation of :CF_2 was simply initiated by heating, where heating was also pivotal for reductive elimination. To demonstrate the reaction efficacy, different substituted arylboronic acids were subjected to the established conditions, resulting in aryl difluoromethylation products in moderate to excellent yields (Figure 4b). The reaction was amenable to ketone, ester, diaryl ethers, and thioethers functional groups, indicating that a CF_2H^- or radical intermediate may not be involved in this reaction (**6d**, **6h**, **6i**, **6k**, **6l**, and **6m**). This protocol provided a complementary approach for the synthesis of difluoromethyl arenes (for comparison, see Figures 3a and 4b). In this reaction, **2a** is superior to other $:CF_2$ reagents in practicality, particularly to silicon-based $:CF_2$ reagents that are not compatible with stoichiometric base (used to facilitate transmetalation of boronic acids).

The trifluoromethyl group (CF_3) is one of the most privileged fluorinated moieties in many prescribed drugs or drug candidates. Thus, there are a plethora of trifluoromethylation reagents developed for incorporating CF_3 into target molecules.[7–9,72] The in situ generation of trifluoromethyl anion (CF_3^-) via recombination of $:CF_2$ and fluoride has been judiciously applied to ^{18}F-labelled CF_3 introduction.[73–76] As compound **2a** tends to generate $:CF_2$ under heating, we examined the application in trifluoromethylation. At the outset, 4-phenylbenzyl iodide (**13a**) was chosen as a model substrate, and the reaction was carried out in the presence of Cu(I) salts and fluoride sources. After carefully screening the reaction parameters, we found that using CuBr as a CF_3^- trap, KF as a fluoride anion donor, and a reaction temperature of 100 °C in THF afforded the best results (see Supporting Information Tables S30–S33). When the reaction was conducted with catalytic Cu-catalyst, the reaction could hardly be driven to completion, resulting in low yield (see Supporting Information Table S32). Because of the easy availability and low cost of CuBr, therefore, a stoichiometric amount of CuBr was used to improve the reaction efficiency. Brief substrate scope study revealed that the reaction proceeded smoothly for the trifluoromethylation of aryl iodides, yet it was slightly sensitive towards steric hindrance (Figure 4c, **14a–14c**). Encouragingly, Canagliflozin and Empagliflozin derived iodides were successfully trifluoromethylated by this method in 75% and 81% yields, respectively (**14d** and **14e**). It is interesting that when the reaction was performed at 120 °C for 1 h, 32% trifluoromethylated product was detected by ^{19}F NMR, which demonstrated the promising application of this methodology in ^{18}F-labelled aryl trifluoromethylation (see Supporting Information Table S33).

Conclusion

In summary, we developed a general method for the synthesis of bench-stable bis(difluoromethyl) pentacoordinate phosphoranes. The method is operationally simple and can be easily scaled up. Control experiments revealed that hydrogen atoms on two difluoromethyl groups were from H_2O (a proton source) and $NaBH_4$ (a reductant). By employing bis(difluoromethyl)triphenyl phosphorane (**2a**) as a fluorinating agent, a variety of reactions involving $\cdot CF_2H$, $:CF_2$, and CF_3^- intermediates have been achieved, including oxidative difluoromethylation of electron-deficient heterocycles (via $\cdot CF_2H$), nickel/photoredox dual-catalyzed difluoromethylation of aryl bromides (via $\cdot CF_2H$), photoredox difluoromethylation of alkenes (via $\cdot CF_2H$), *gem*-difluorocyclopropanation of alkenes (via $:CF_2$), base-promoted difluoromethylation of heteroatom nucleophiles (via $:CF_2$), Pd-catalyzed difluoromethylation of arylboronic acids (via $:CF_2$), and Cu-mediated trifluoromethylation of aryl iodides (via $:CF_2$ and CF_3^-). Subsequently, these methods have been applied to late-stage fluoroalkylation of drugs and drug-like molecules. Moreover, the reactions depicted here may provide mechanistic evidence and insights for pentacoordinate phosphorane chemistry. The reagent and methods described herein may have great potential in both drug discovery and manufacture.

Supporting Information

Supporting Information is available and includes details on experimental procedures, reaction optimizations, mechanistic studies, and compound characterization data.

Conflict of Interest

The authors declare no competing interests.

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