Phosphine-Catalyzed Intermolecular Acylfluorination of Alkynes via a P(V) Intermediate

Hayato Fujimoto,[1] Takuya Kodama,[1] Masahiro Yamanaka[2] and Mamoru Tobisu*,[1]

[1]Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[2]Department of Chemistry, Faculty of Science, Rikkyo University, 3-34-1 Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan

Supporting Information Placeholder

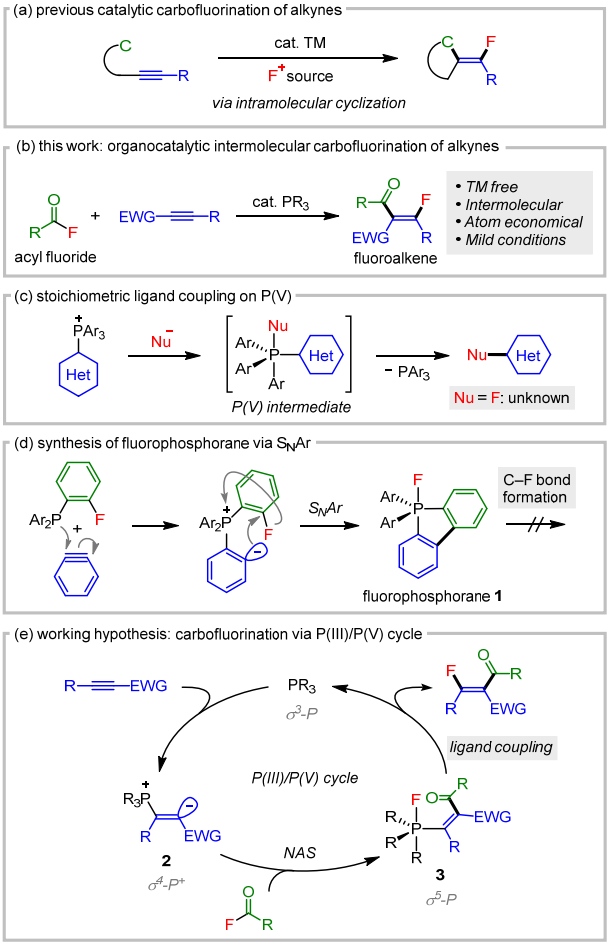
ABSTRACT: We report on the phosphine-catalyzed intermolecular carbofluorination of alkynes using acyl fluorides as fluorinating reagents. This reaction promises to be a useful method for the synthesis of highly substituted monofluoroalkene derivatives, since acyl fluorides can be easily prepared from the corresponding carboxylic acid derivatives and the reaction proceeds under ambient conditions without the need for a transition-metal catalyst. Experimental and computational studies indicate that a five-coordinated fluorophosphorane is involved as the key intermediate in the fluorination step.

Fluorinated molecules occupy an important place in the pharmaceutical, medicinal, agrochemical and material sciences.[1] Among the various fluorinated motifs, monofluoroalkene derivatives are of particular interest, partly because of their utility as a peptide bond isostere.[2] Therefore, novel, straightforward methods for the synthesis of monofluoroalkenes via C–F bond formation are in great demand.[3] The carbofluorination of alkynes, which proceeds via the concomitant formation of C–C and C–F bonds, is a powerful method for the synthesis of monofluoroalkenes. Although some methods for the catalytic carbofluorination of alkynes have recently been developed,[4] these methods are restricted to intramolecular reactions in which transition-metal catalysts and highly electrophilic F^+ reagents, such as Selectfluor and NFSI (Scheme 1a) are used. Herein we report on the phosphine-catalyzed intermolecular carbofluorination of alkynes via the C–F bond-forming ligand coupling of a P(V) intermediate (Scheme 1b).

In recent years, ligand coupling on P(V) species[5] has attracted renewed interest as an alternative to transition-metal mediated cross-coupling reactions. For example, McNally and coworkers reported on the ligand coupling of pyridine derivatives on a P(V) species which was generated by the reaction of heterocyclic phosphonium salts with heteronucleophiles[6] (Scheme 1c) and heterobiaryl synthesis via a P(V) intermediate.[7] Vilotijevic and coworker also reported on the ligand coupling of benzothiazole derivatives on a P(V) species.[8] Despite the significant advances in P(V)-mediated reactions over the past years, a P(V)-mediated C–F bond-formation reaction have not been achieved.[9]

Quite recently, we reported on the first synthesis of a stable tetraarylfluorophosphorane by the reaction of fluorine-substituted phosphines with an aryne via tandem nucleophilic addition and nucleophilic aromatic substitution (Scheme 1d).[10]

Scheme 1. Carbofluorination of Alkynes: Background and Working Hypothesis

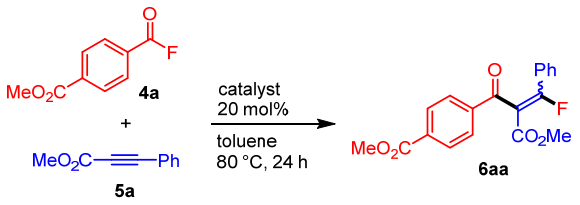


Phosphine-mediated C–F bond formation would be possible if the ligand coupling from the fluorophosphorane **1** were to take place. However, all of our attempts to achieve ligand coupling of **1** were unsuccessful. We envisaged that increasing the electrophilicity of the equatorial ligand in the fluorophosphorane derivative would permit this unprecedented C–F bond forming ligand cou-

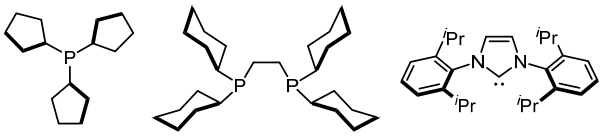
pling on P(V) to be successful. Based on this hypothesis, we designed phosphine-catalyzed carbofluorination of alkynes via a P(III)/P(V) manifold (Scheme 1e). It is well known that phosphines add, not only to an aryne, but also to an electron-deficient alkyne such as an alkynoate to form a carbanion species.[11] If the resulting carbanion **2** is sufficiently nucleophilic to react with an acyl fluoride, the fluorophosphorane **3** would be formed by nucleophilic acyl substitution (NAS). The fluorophosphorane **2** has an equatorial ligand bearing electron-withdrawing groups, which we hypothesized would facilitate ligand coupling to form a C–F bond with the regeneration of the phosphine catalyst.

To verify the feasibility of our hypotheses, we initially examined the reaction between the acyl fluoride **4a** and alkynoate **5a** using different phosphines and NHCs (Table 1). Intensive screening resulted in identifying PCy_3 as a uniquely effective catalyst, whereas other phosphines and *N*-heterocyclic carbenes failed to promote this carbofluorination. Thus, the reaction of **4a** (1.5 equiv) with **5a** in the presence of PCy_3 (30 mol%) in toluene at room temperature afforded the monofluoroalkene **6aa** in 74% isolated yield. A ^{19}F NMR analysis indicated that the carbofluorination product was formed as a 1:1.2 mixture of *E*:*Z* isomers. The isomers interconverted by the reversible addition–elimination of PCy_3 under the catalytic conditions used (see Scheme S1),[12] thus leading to the formation of the thermodynamically more stable *Z* isomer as the major product.[13,14] In addition to the fact that this reaction represents the first intermolecular carbofluorination, it features the use of acyl fluorides both as acylating and fluorinating reagents in an atom-economical manner, which is also unprecedented.

Table 1. Catalyst Optimization for Carbofluorination between 4a and 5a [a]



entry	catalyst	yield (%)
1	PCy_3	52
2[b]	PCy_3	76 (74) *E*:*Z* = 1:1.2
3	P^nBu_3	0
4	P^tBu_3	0
5	PAd_3	0
6	$PAd_2{}^nBu$	0
7	$PPhMe_2$	0
8	$PPhCy_2$	0
9	$PCyp_3$	4
10	DCYPE	6
11	IPr	0



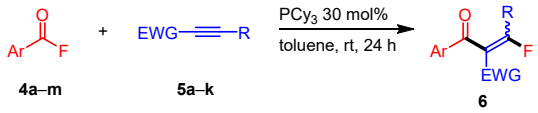
$PCyp_3$ DCYPE IPr

[a] **4a** (0.30 mmol), **5a** (0.20 mmol), PCy_3 (0.04 mmol) and toluene (1.0 mL) in sealed tube at 80 ºC for 24 h. [b] Reaction conducted at room temperature in the presence of PCy_3 (0.06 mmol). Yield of isolated products are shown in parentheses. *E*:*Z* ratios were determined by ^{19}F NMR analysis.

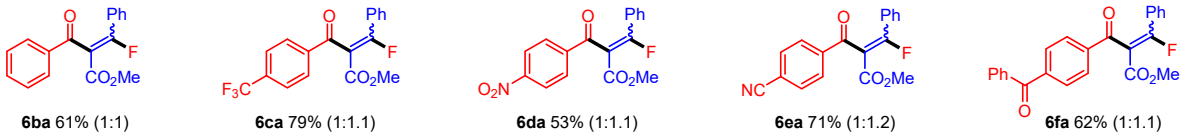
With the optimized reaction conditions in hand, we subsequently examined the scope of the carbofluorination reactions (Scheme 2). Regarding acyl fluorides, electron-neutral (**4b**) as well as electron-deficient substrates bearing trifluoromethyl (**4c**), nitro (**4d**), cyano (**4e**), and benzoyl (**4f**) groups readily participated in this reaction to produce the corresponding monofluoroalkenes. Halogens such as iodo (**4g**), bromo (**4h**) and chloro (**4i**) groups were compatible, allowing the resulting monofluoroalkenes to be amenable to further structural elaboration via common C–X bond functionalization reactions. Acyl fluorides bearing heteroaryl (**4j**) and π-extended aryl (**4k**) groups also underwent the carbofluorination successfully. Alkynoates bearing methyl (**5b**), methoxy (**5c**), fluoro (**5d**), bromo (**5e**), chloro (**5f**) groups reacted to afford the corresponding monofluoroalkenes. Although alkynoates bearing alkyl groups, such as methyl 2-octynoate failed to form the corresponding carbofluorinated product, the 3-thienyl (**5g**) and 2-pyridyl substituted alkynoate (**5h**) were compatible. Interestingly, when **5h** was used, products **6jh**, **6ah** and **6ih** with a high *Z* selectivity were obtained.[15] The structure of **6jh** was confirmed by single-crystal X-ray analysis.[16] This carbofluorination proceeded when alkynes bearing a different electron-withdrawing group such as ethyl ester (**5i**), *t*-butyl ester (**5j**) and benzoyl (**5k**) groups were used instead of the methyl ester **5a**, affording the corresponding coupling products **6ji**–**6jk**. This organocatalyic carbofluorination can be used in the late-stage functionalization of pharmaceuticals containing a carboxylic acid functionality, such as probenecid and febuxostat to form the corresponding monofluoroalkene derivatives **6la** and **6ma**.

To gain additional insights into the reaction mechanism, some control experiments were performed (Scheme 3). Apart from the mechanism shown in Scheme 1e, an alternative pathway that is initiated by the reaction of PCy_3 with the acyl fluoride is also possible. This would lead to the formation of an acylphosphonium fluoride, which could function as a fluoride ion source to induce the subsequent addition to the alkynoate to form the fluoroallenoate **7** as a key intermediate.[17] However, external fluoride sources, such as CsF and tetrabutylammonium difluorotriphenylsilicate (TBAT) failed to promote the carbofluorination of **4a** and **5a**, thus excluding the alternative fluoride-mediated mechanism (Scheme 3a). In an attempt to observe the postulated fluorophosphorane intermediate **3**, the reaction of **4a** and **5a** in toluene-d_8 using 1.0 equiv of PCy_3 was monitored by ^{19}F NMR spectroscopy (Scheme 3b). However, no resonances assignable to P(V) species were observed and **6ba** was formed in 43% yield (*E*:*Z* = 1.6:1), indicating that the rate of ligand coupling of **3** is rapid compared with that of the formation of **3**. When the same reaction was conducted in CD_3CN, instead of toluene-d_6, **6ba** was not formed in an appreciable amount and instead, PCy_3F_2 (**8**) and the hydroacylated product **9** were produced in 28% and 34% yields, respectively. R_4PF-type compounds can exist as both four-coordinate ionic (phosphonium fluoride) and five-coordinate neutral (fluorophosphorane) species, wherein a phosphonium fluoride form is more stable in polar solvents.[18] Therefore, the fluorophosphorane **3** ionizes in CD_3CN thus making it susceptible to undergoing dispropotionation,[19] which would eventually lead to the formation of **8** and **9** via protonation. These results suggest that phosphonium fluoride is not a competent intermediate for C–F bond formation.

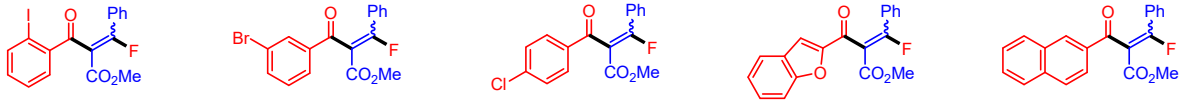
Scheme 2. Scope of the Phosphine-Catalyzed Carbofluorination of Alkynoates [a]



acyl fluorides scope

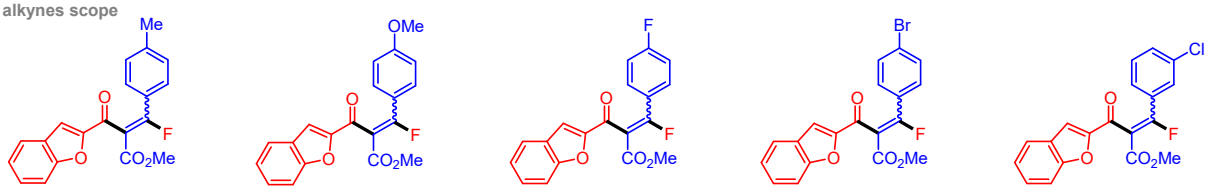


6ba 61% (1:1) **6ca** 79% (1:1.1) **6da** 53% (1:1.1) **6ea** 71% (1:1.2) **6fa** 62% (1:1.1)

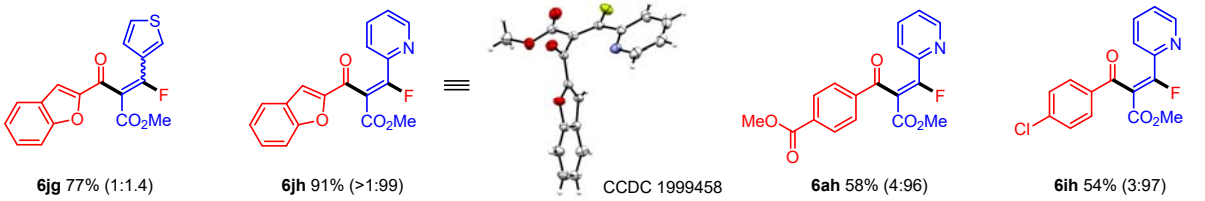


6ga 70% (1:1) **6ha** 75% (1:1.3) **6ia**75% (1:1) **6ja** 81% (1:1.6) **6ka** 83% (1:1.1)

alkynes scope

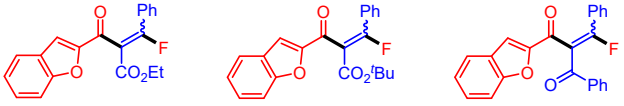


6jb 88% (1:1.6) **6jc** 94% (1:1.4) **6jd** 78% (1:1.3) **6je** 60% (1:1.2) **6jf** 66% (1:1)



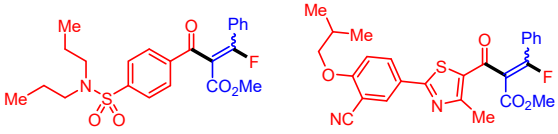
6jg 77% (1:1.4) **6jh** 91% (>1:99) CCDC 1999458 **6ah** 58% (4:96) **6ih** 54% (3:97)

EWGs scope



6ji 79% (1:1.2) **6jj** 30% (1:1) **6jk** 78% (1:1)

pharmaceuticals scope

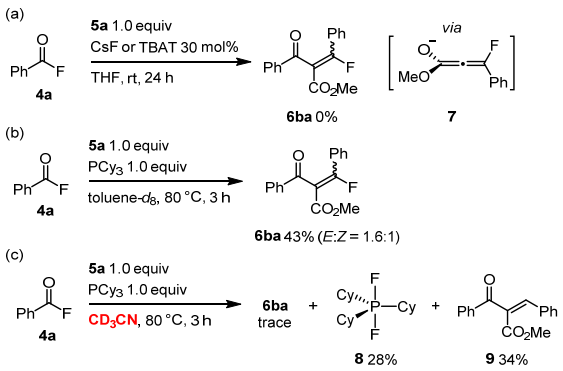


6la 91% (1:1.1) *from Probenecid*

6ma 51%[b] (1:1.4) *from Febuxostat*

[a] Acyl fluoride (0.30 mmol), alkyne (0.20 mmol), PCy_3 (0.06 mmol) and toluene (1.0 mL) in a sealed tube at room temperature for 24 h. Yields of isolated products are shown. *E*:*Z* ratios were determined by ^{19}F NMR analysis and are shown in parentheses. [b] Reaction at 50 ºC.

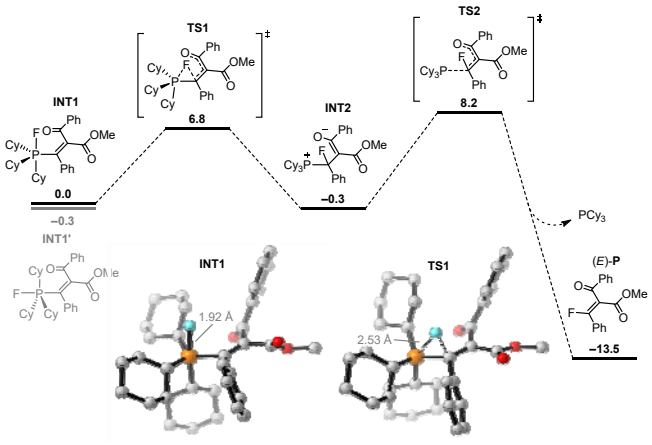
Scheme 3. Control Experiments



To further verify the intermediacy of fuluorophosphorane **3** in the PCy_3-catalyzed carbofluorination, DFT calculations (ωB97X-D/6-31+G(d,p)) were conducted for the C–F bond-forming ligand coupling process (Scheme 4). **INT1** and **INT1'** are the most stable fluorophosphoranes among the suite of isomers, having a trigonal bipyramidal geometry in which fluorine occupies the apical position.[9,10,20] Because **INT1** and **INT1'** have nearly the same energy ($\Delta G = -0.3$ kcal/mol), **INT1** and **INT1'** can be interconverted by a Berry pseudorotation mechanism with a low activation barrier.[21] These phosphorane intermediates were found to be more stable than the corresponding phosphonium forms when toluene was used as a solvent (see Scheme S3). C–F bond formation from the **INT1** occurs in a stepwise fashion, similar to the C–C bond-forming ligand coupling of a P(V) intermediate.[7a] In the C–F bond forming

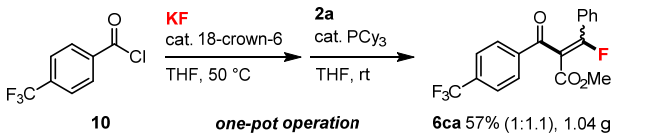
step, an apical P–F bond breaks, allowing the fluorine atom to migrate to the equatorial β-carbon (**TS1**) to form the zwitterionic intermediate **INT2**. In the C–P bond breaking step, fluorinated product (*E*)-**P** is generated by the dissociation of PCy_3. This energy diagram indicates that the process from **INT1** to (*E*)-**P** is a reversible process (highest activation barrier for the reverse reaction: $\Delta G^{\ddagger}$ = 21.7 kcal/mol), which leads to the *E*/*Z* isomerization of the product.[22] Considering that the addition of a phosphine to an alkyne has a high activation barrier (~19 kcal/mol),[13] the ligand coupling process (~8.5 kcal/mol) would be relatively facile. This view is consistent with the failure to observe a fluorophosphorane intermediate, such as **INT1** (Scheme 3b).

Scheme 4. Calculated Energy Diagrams for the Ligand Coupling of a Phosphorane Intermediate



A synthetic advantage of acid fluorides is that they are directly accessible from the corresponding carboxylic acids and acyl chlorides. Phosphine-catalyzed carbofluorination can be performed using an acyl fluoride produced in situ from the acyl chloride **10** with KF to afford monofluoroalkene **6ca** in 57% yield on a gram-scale.

Scheme 5. Gram-Scale Reaction Using an Acyl Chloride with KF



In conclusion, we report on the *first* catalytic intermolecular carbofluorination reaction. This reaction operates under mild conditions and in the absence of metals, thus showing a wide functional group tolerance. DFT calculations revealed that a C–F bond is formed via ligand coupling on a phosphorus, which has not been achieved to date.[9] The development of novel fluorination reactions using the fluorophosphorane platform are currently being investigated in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization of new compounds and computational details (PDF)
Compound **6jh** crystal structure (CIF)

AUTHOR INFORMATION

Corresponding Author

*tobisu@chem.eng.osaka-u.ac.jp

Notes

The authors declare no competing financial interests.

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(14) The *E* isomer is the major product at the initial stage of this reaction (cf. Scheme 3c). This result indicates that the *E* form is preferentially formed and that it isomerizes to the thermodynamically more stable *Z* form under the reaction conditions used.

(15) Computational experiments indicate that the pyridine-substituted *Z* form products are stabilized by stereoelectronic interactions between nitrogen lone pair and an $\pi^*_{C=O}$ orbital (see Scheme S2).

(16) Crystal data for **6jh**, monoclinic, space group $P2_1/c$ (no. 14), a = 6.91739(14) Å, b = 23.4940(4) Å, c = 9.63136(19) Å, β = 104.644(2)º, V = 1514.42(5) Å^3, T = 123 K, Z = 4, R_1 (wR_2) = 0.0379 (0.1075) for 899 parameters and 19566 unique reflections. GOF = 1.048. CCDC 1999458.

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