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

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ABSTRACT: We report 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-coordinate fluorophosphorane is involved as the key intermediate in the fluorination step.

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Fluorinated molecules occupy an important place in the pharmaceutical, medicinal, agrochemical, and materials sciences.[1] Among the various fluorinated motifs, monofluoroalkene derivatives are of particular interest, partly because of their utility as peptide bond isosteres.[2] Therefore, novel, straightforward methods for the synthesis of monofluoroalkenes via C−F bond formation are in great demand.[3] 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 the phosphine-catalyzed intermolecular carbofluorination of alkynes via C−F bond-forming ligand coupling on 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 co-workers reported the ligand coupling of pyridine derivatives on a P(V) species that was generated by the reaction of heterocyclic phosphonium salts with heteronucleophiles[6] (Scheme 1c) and heterobiaryl synthesis[7] via a P(V) intermediate. Vilotijevic and co-workers also reported a related phosphine-mediated C2-functionalization of benzothiazole derivatives.[8] Despite the significant advances in P(V)-mediated reactions over the past years, a P(V)-mediated C−F bond-formation reaction has not been achieved to date.[9]

Quite recently, we reported 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] Phosphine-mediated C−F bond formation would be possible if ligand coupling on fluorophosphorane **1** were to take place. However, all of our attempts to achieve ligand coupling on **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 coupling on P(V) to be successful. On the basis of this hypothesis, we designed a phosphine-catalyzed carbofluorination of alkynes via a P(III)/P(V) manifold (Scheme 1e). It is well-known that phosphines can 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, fluorophosphorane **3** would be formed by nucleophilic acyl substitution (NAS). Fluorophosphorane **3** has an equatorial ligand bearing electron-withdrawing groups, which we hypothesized would facilitate ligand coupling to form a C−F bond with regeneration of the phosphine catalyst.

To verify the feasibility of our hypotheses, we initially examined the reaction between acyl fluoride **4a** and alkynoate **5a** using different phosphines (Table 1). Intensive screening resulted in the identification of PCy_3 as a uniquely effective catalyst, whereas other phosphines, amines (DMAP and DABCO), and N-heterocyclic carbenes failed to promote this carbofluorination. The reaction of **4a** (1.5 equiv) with **5a** in the presence of PCy_3 (30 mol %) in toluene at room temperature afforded monofluoroalkene **6aa** in 74% isolated yield. ^{19}F NMR analysis indicated that the carbofluorination product was formed as a 1:1.2 mixture of the *E* and *Z* isomers. The isomers interconverted by reversible addition−elimination of PCy_3 under the catalytic conditions used (see Scheme S1),[12] and therefore, the ratio of isomers was determined under thermodynamic control.[13−15] In addition to the fact that this reaction represents the first catalytic intermolecular carbofluorination, it features the use of acyl fluorides both as

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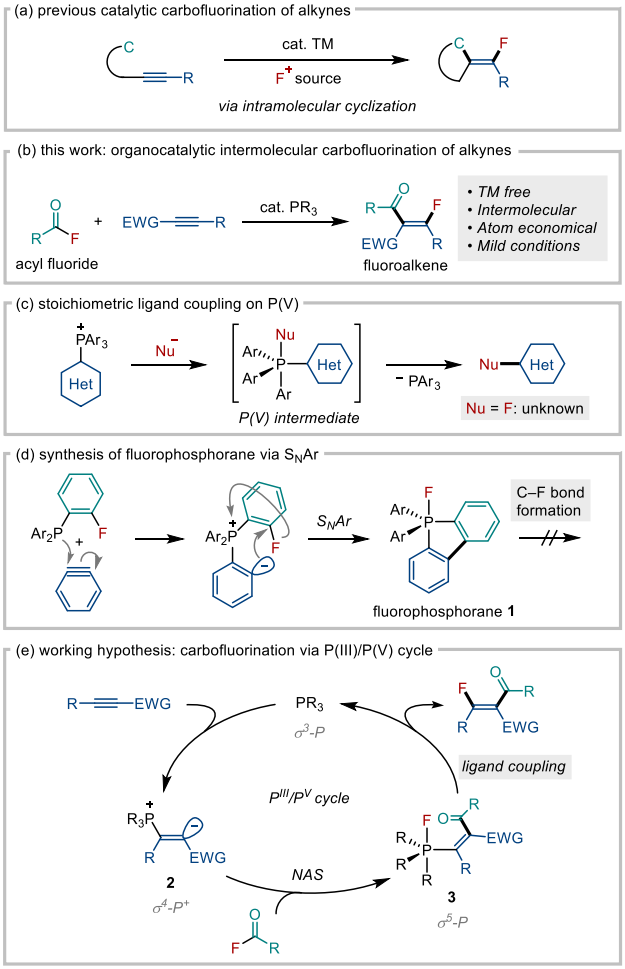
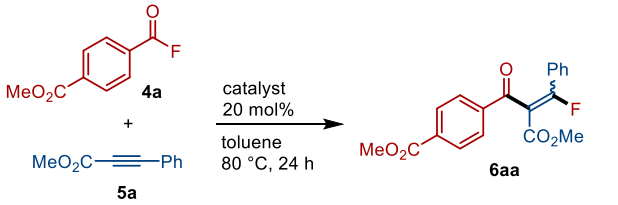
Scheme 1. Carbofluorination of Alkynes: Background and Working Hypothesis



acylating and fluorinating reagents in an atom-economical manner, which is also unprecedented.

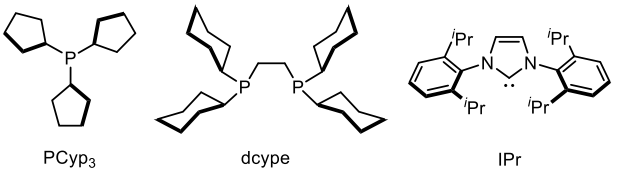
With the optimized reaction conditions in hand, we subsequently examined the scope of the carbofluorination reaction (Scheme 2). With regard to acyl fluorides, electron-neutral (**4b**) as well as electron-deficient substrates bearing trifluoromethyl (**4c**), nitro (**4d**), cyano (**4e**), and benzoyl (**4f**) groups readily participated in this reaction to produce the corresponding monofluoroalkenes. Halogen groups such as *p*-chloro (**4g**), *o*-iodo (**4h**), and *m*-bromo (**4i**) were compatible, allowing the resulting monofluoroalkenes to be amenable to further structural elaboration via common C−X bond functionalization reactions. The electron-rich substrate **4j** also participated in this reaction, although it required a longer reaction time (72 h). Acyl fluorides bearing a heteroaryl (**4k**) or π-extended aryl (**4l**) group also underwent the carbofluorination successfully. Aromatic alkynoates bearing a methyl (**5b**), methoxy (**5c**), fluoro (**5d**), bromo (**5e**), or chloro (**5f**) group reacted to afford the corresponding monofluoroalkenes. Although aliphatic alkynoates bearing alkyl groups such as *n*-pentyl, cyclopropyl, and *tert*-butyl failed to form the corresponding carbofluorinated products, 3-thienyl- and 2-pyridyl-substituted alkynoates (**5g**, **5h**) were compatible. Interestingly, when **5h** was used, products **6kh**, **6ah**, and **6gh** were obtained with high *Z* selectivity.[16] The structure of **6kh** was confirmed by single-crystal X-ray analysis.[17] This

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



entry	catalyst	yield (%)[b]	*E*:*Z*[c]
1	PCy_3	52	1:1.2
2[d]	PCy_3	76 (74[e])	1:1.2
3	$PCyp_3$[f]	4	
4	dcype[f]	6	
5	P^nBu_3, P^tBu_3, PAd_3, $PAd_2{}^nBu$, $PPhMe_2$, $PPhCy_2$	0	
6	DMAP, DABCO	0	
7	IPr[f]	0	

[a]Reaction conditions: **4a** (0.30 mmol), **5a** (0.20 mmol), catalyst (0.04 mmol), and toluene (1.0 mL) in a sealed tube at 80 °C for 24 h. [b]^{1}H NMR yields. [c]Determined by ^{19}F NMR analysis. [d]The reaction was conducted at room temperature in the presence of PCy_3 (0.06 mmol). [e]Yield of the isolated product. [f]Catalyst structures:



carbofluorination proceeded when alkynes bearing a different electron-withdrawing group such as an ethyl ester (**5i**), *tert*-butyl ester (**5j**), or benzoyl (**5k**) group were used instead of methyl ester **5a**, affording the corresponding coupling products **6ki**−**kk**. This organocatalyic carbofluorination can be used in the late-stage functionalization of pharmaceuticals containing a carboxylic acid functionality, as shown by the reactions of probenecid and febuxostat to form the corresponding monofluoroalkene derivatives **6ma** and **6na**.

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 fluoroallenoate **7** as a key intermediate.[18] However, external fluoride sources such as CsF and tetrabutylammonium difluorotriphenylsilicate (TBAT) failed to promote the carbofluorination of **4b** and **5a**, thus excluding the alternative fluoride-mediated mechanism (Scheme 3a). In an attempt to observe the postulated fluorophosphorane intermediate **3**, the reaction of **4b** 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 ligand coupling on **3** is rapid compared with the formation of **3**. When the same reaction was conducted in CD_3CN instead of toluene-d_8, **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% yield, respectively. R_4PF-type compounds can exist as both four-coordinate ionic (phosphonium fluoride) and five-coordinate neutral (fluorophosphor-

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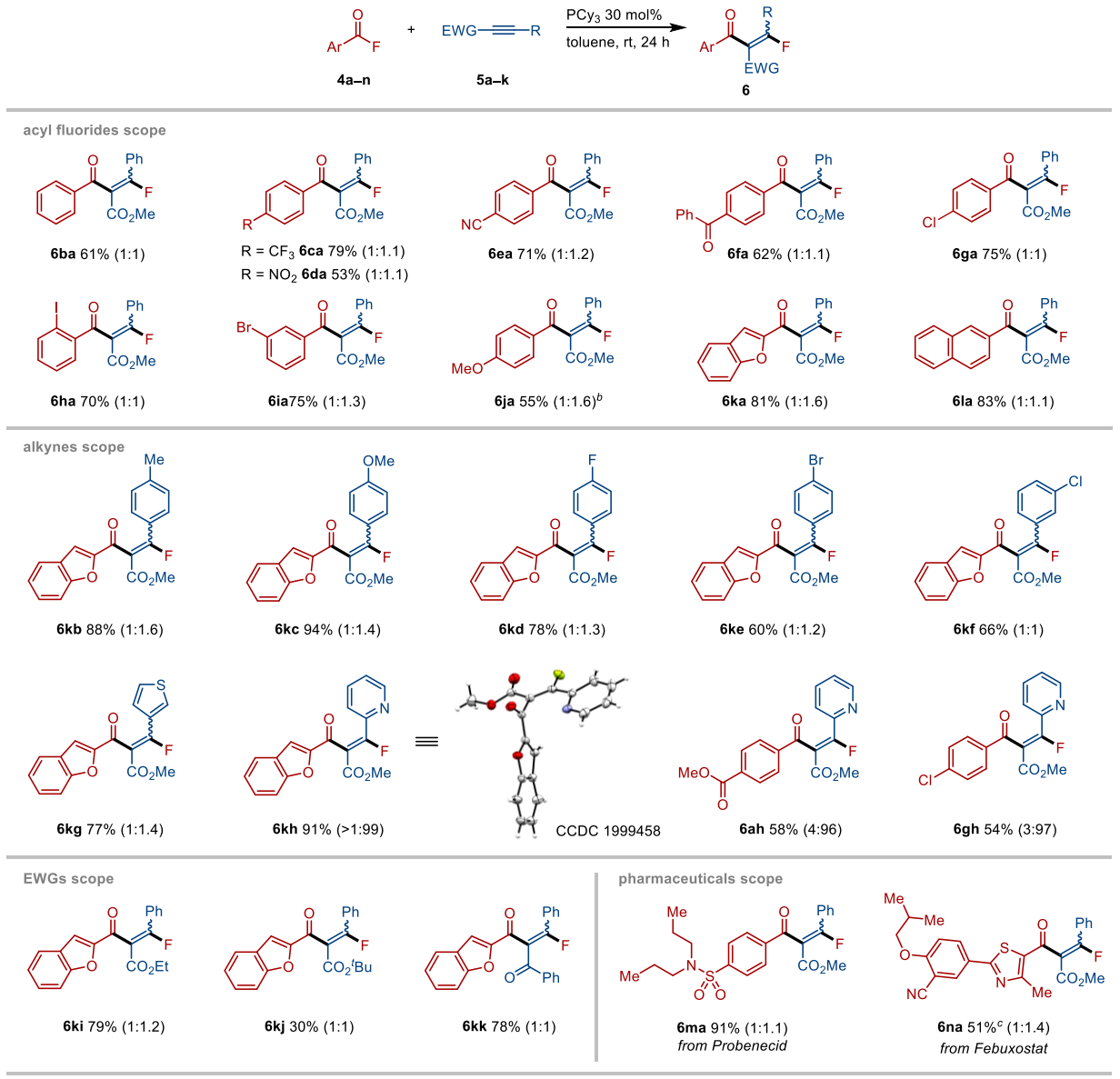
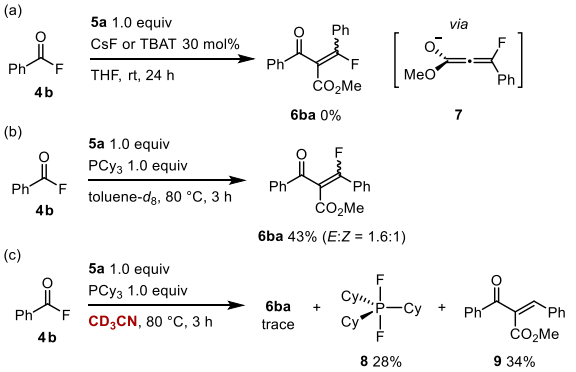
Scheme 2. Scope of the Phosphine-Catalyzed Carbofluorination of Alkynoates[a]



[a]Reaction conditions: 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]The reaction was run for 72 h. [c]The reaction was run at 50 °C.

Scheme 3. Control Experiments



ane) species, with the phosphonium fluoride form being more stable in polar solvents.[19] Therefore, fluorophosphorane **3** ionizes in CD_3CN, thus making it susceptible to undergoing decomposition,[9,20] which would eventually lead to the formation of **8** and **9** via protonation.[21] These results suggest that the phosphonium fluoride is not a competent intermediate for C–F bond formation.[22]

To further verify the intermediacy of fluorophosphorane **3** in the PCy_3-catalyzed carbofluorination, density functional theory (DFT) calculations (ωB97X-D/6-31+G(d,p) with PCM (toluene)) 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.[9,10,23] Since **INT1** and **INT1′** have nearly the same free energy (ΔG = −0.3 kcal/mol), they can be interconverted. C–F bond formation from **INT1** occurs in a

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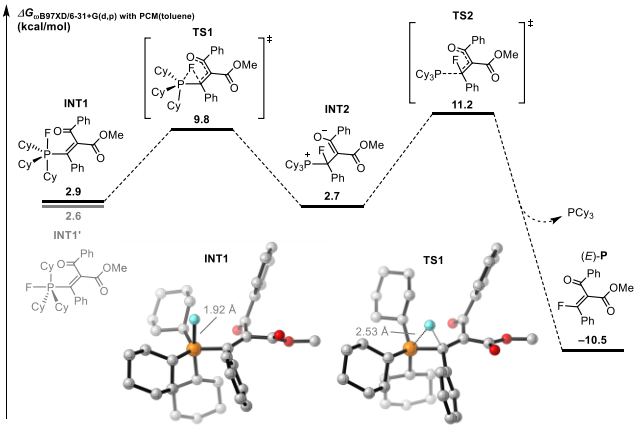
Scheme 4. Calculated Energy Diagram for the Ligand Coupling on a Phosphorane Intermediate[a]



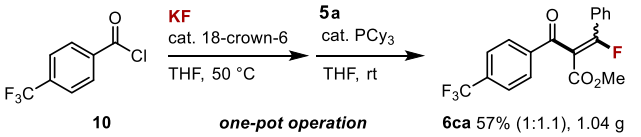
[a]The Gibbs free energies of intermediates and transition states relative to the sum of the free energies of the starting materials are presented.

stepwise fashion, similar to C−C bond-forming ligand coupling on 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, the 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 (the highest activation barrier for the reverse reaction is $\Delta G^{\ddagger}$ = 21.7 kcal/mol), which leads to the *E*/*Z* isomerization of the product.[24] Considering that the addition of a phosphine to an alkyne has a high activation barrier (~19 kcal/mol),[14] the ligand coupling process (~8.5 kcal/mol) would be relatively facile.[25] This view is consistent with the failure to observe a fluorophosphorane intermediate, such as **INT1** (Scheme 3b). To investigate the steric effect of the phosphine catalyst, the energy diagram using PMe_3 as a model of a relatively small catalyst was calculated. The results indicated that the process is less favored than that using PCy_3 both in terms of kinetics ($\Delta G^{\ddagger}$ = 16.7 kcal/mol) and thermodynamics (ΔG = −3.6 kcal/mol). The steric bulk of PCy_3 is particularly effective in facilitating the C−P bond cleavage step (**INT2** → (*E*)-**P**) in comparison with PMe_3, as evidenced by the longer P−C_β bond in **INT2** (Scheme S4).[26]

Another mechanistic possibility involves the formation of **INT2** by outer-sphere attack of fluoride to a four-coordinate phosphonium intermediate. However, no stable phosphonium fluoride ion pair structures were formed in our calculations. Instead, a stable pentavalent geometry was formed for the fluorophosphorane. Indeed, a four-coordinate phosphonium intermediate was found to be considerably more unstable than the corresponding phosphorane form in toluene solution (see Scheme S3).[27] Therefore, there is no energetic benefit for an outer-sphere mechanism compared with the inner-sphere ligand coupling mechanism shown in Scheme 4. In fact, all of our calculations that were intended to explore an outer-sphere fluorination pathway converged on **TS1**.[28]

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 acyl chloride **10** and KF to afford monofluoroalkene **6ca** in 57% yield on a gram scale (Scheme 5).

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



In conclusion, we have reported 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 is currently being investigated in our laboratory.[29]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c08928.

Detailed experimental procedures, characterization of new compounds, and computational details (PDF)
Crystallographic data for **6kh** (CIF)
Crystallographic data for **8** (CIF)

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Notes

The authors declare no competing financial interest.

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(13) The *E* isomer is the major product at the initial stage of this reaction, and the *E*:*Z* ratio converges to 1:1 as the reaction proceeds (Figure S1).

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(15) The fluoroalkene products can be made *Z*-rich by photoisomerization. See the Supporting Information for details.

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

(17) Crystal data for **6kh** (CCDC 1999458): 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)°, 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.

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(21) Although the actual source of the hydrogen incorporated into **9** remains elusive, a residual water (via nucleophilic attack onto phosphonium[12]) or a cyclohexyl group (via *β*-hydrogen elimination[20b]) are potential candidates.

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(22) For a similar discussion regarding the effect of the solvent in discriminating between inner- and outer-sphere mechanisms in palladium-catalyzed allylic alkylation reactions, see: (a) Trost, B. M.; Xu, J. Palladium-Catalyzed Asymmetric Allylic α-Alkylation of Acyclic Ketones. *J. Am. Chem. Soc.* **2005**, *127*, 17180−17181. (b) Trost, B. M.; Xu, J.; Schmidt, T. Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of Enol Carbonates. *J. Am. Chem. Soc.* **2009**, *131*, 18343−18357.

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(24) The activation barrier for the addition of PCy_3 to (*Z*)-**P** is 22.7 kcal/mol, which also makes its isomerization energetically feasible under the reaction conditions used. The energy difference between (*E*)-**P** and (*Z*)-**P** is small, which is consistent with the *E*:*Z* ratio of the products obtained experimentally (see the Supporting Information for details).

(25) (a) Compared with the related heteroaryl-substituted fluorophosphoranes reported by McNally,[9] the C−F bond-forming ligand coupling from **INT1** is facile, presumably because this process does not require dearomatization. (b) We also calculated a pathway from the hypothetical fluorophosphorane **INT5**, which contains only one electron-withdrawing group on the alkene moiety (Scheme S5), to obtain insight into the effect of the electrophilicity of the ligand on the P(V) ligand coupling process. Interestingly, the ligand coupling from **INT5** could proceed with an activation barrier similar to that for **INT1** (6.9 kcal/mol), indicating that two electron-withdrawing groups are not essential for the ligand coupling to occur. **INT1** and **INT5** would be expected to have similar electrophilicities since the C═O bonds in **INT1** are twisted from the C═C bond plane, possibly as a result of steric repulsion with cyclohexyl groups, which inhibits efficient electron withdrawal by a resonance effect.

(26) The steric bulk of PCy_3 might also be effective in facilitating the C−F bond formation step (**INT1** → **INT2**) because the Wiberg bond order of the P−F bond in **INT1** was calculated to be 0.31, which is actually smaller than that for a related tetraorganofluorophosphorane that has a shorter P−F bond (∼1.8 Å).[9,10] The extended P−F bond in **INT1** could be attributed to steric repulsion induced by the bulky cyclohexyl groups, which facilitates the C−F bond formation step.

(27) We also carried out relaxed-scan calculations, and the results suggested that the free energy of fluorophosphorane **INT1** increases as the P−F bond distance increases (Figure S3). In contrast, a phosphonium form is more stable than the five-coordinate phosphorane in the case of the corresponding chloride (see the Supporting Information for details). These results are in agreement with McNally's work on related heteroaryl-substituted phosphorus compounds (see ref 9).

(28) Moreover, no other intermediates were found along the reaction pathway between **INT1** and **INT2** on the basis of an intrinsic reaction coordinate (IRC) analysis starting from **TS1** (Figure S4).

(29) A prior version of the present article was deposited as a preprint on ChemRxiv. See: Fujimoto, H.; Kodama, T.; Yamanaka, M.; Tobisu, M. Phosphine-Catalyzed Intermolecular Acylfluorination of Alkynes via a P(V) Intermediate. *ChemRxiv* **2020**, DOI: 10.26434/chemrxiv.12471665.

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