Phosphorus-Mediated sp^2-sp^3 Couplings for Selective C–H Fluoroalkylation of Complex Azines

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Abstract

Fluoroalkyl groups profoundly affect the physical properties of pharmaceuticals and influence virtually all metrics associated with their pharmacokinetic and pharmacodynamic profile.[1-4] Drug candidates increasingly contain CF_3 and CF_2H groups, and the same trend in agrochemical development shows that the effect of fluoroalkylation translates across human, insect, and plant life.[5,6] New fluoroalkylation reactions have undoubtedly stimulated this uptake; however, methods that directly convert C–H bonds into C–CF_2X (X = F or H) groups in complex drug-like molecules are rare.[7-13] For pyridine, the most common aromatic heterocycle in pharmaceuticals,[14] only one approach, via fluoroalkyl radicals, is viable for pyridyl C–H fluoroalkylation in the elaborate structures encountered during drug development.[15-17] Here, we have developed a new set of bench-stable fluoroalkylphosphines that directly convert the C–H bonds in pyridine building blocks, drug-like fragments, and pharmaceuticals into fluoroalkyl derivatives. No pre-installed functional groups or directing groups are required; the reaction tolerates a variety of sterically and electronically distinct pyridines and is exclusively selective for the 4-position in most cases. The reaction proceeds via

initial phosphonium salt formation followed by sp^2-sp^3 phosphorus ligand-coupling, an underdeveloped manifold for C–C bond formation.

Fluoroalkyl groups' impact on structure-activity relationship (SAR) studies and the prevalence of pyridines in drugs and agrochemicals has resulted in numerous candidates and marketed compounds (Fig. 1a).[1-3] Strategically installing fluoroalkyl groups can increase hydrophobic binding contacts, improve cell membrane permeability, and limit metabolic susceptibility; difluoromethyl groups also have specific roles as surrogates of hydroxyl, thiol, and amine derivatives.[4] Furthermore, the inductive withdrawing effects of fluoroalkyl groups reduce pyridine basicity and offset excessive binding to cytochrome P450 enzymes, an off-target effect that can result in numerous adverse consequences including unwanted drug-drug interactions.[18,19]

Synthesizing fluoroalkyl pyridines from acyclic precursors provides simple building block compounds.[6] However, in discovery campaigns, it is preferable to transform existing pyridines into fluoroalkyl derivatives because of the large variability in candidate structures that cannot be currently addressed by de novo synthesis. To that end, metal-catalyzed cross-couplings and C–H functionalization reactions are the most common ways to make pyridyl C–CF_2X bonds.[7-13] The latter is advantageous for complex substrates as they do not typically contain pre-installed functional groups, such as (pseudo)halides and boronic acids, required to generate organometallic intermediates, but instead exploit ubiquitous C–H bonds. Surprisingly, the only viable strategy for this endeavor is a Minisci-type radical process, including recent advances from Baran, MacMillan, and Stephenson (Fig. 1b).[15-17] As the C–C bond-forming step in these reactions occurs via the same mechanism, the amenable set of pyridine inputs is bounded and the regiochemical outcomes are a function of the reaction conditions and

pyridine substituents.[20] Kanai reported a process to fluoroalkylate azines where trifluoromethyl anions add to preformed borane adducts. An overall three-stage procedure is required, and the reaction is moderately selective for the 4-position of pyridines. Limited evidence of the reaction's capacity to fluoroalkylate drug-like molecules again reinforces the need for new reactions that can impact drug discovery.[21] Our goal was to design a mechanistically distinct process for pyridine C–H fluoroalkylation via phosphorus ligand-coupling reactions using fluoroalkylphosphines as reagents. The reaction has a unique regiochemical profile and functions on complex pyridine-containing substrates, resulting in access to new chemical space is accessible for pharmaceutical and agrochemical discovery. (Fig. 1c).

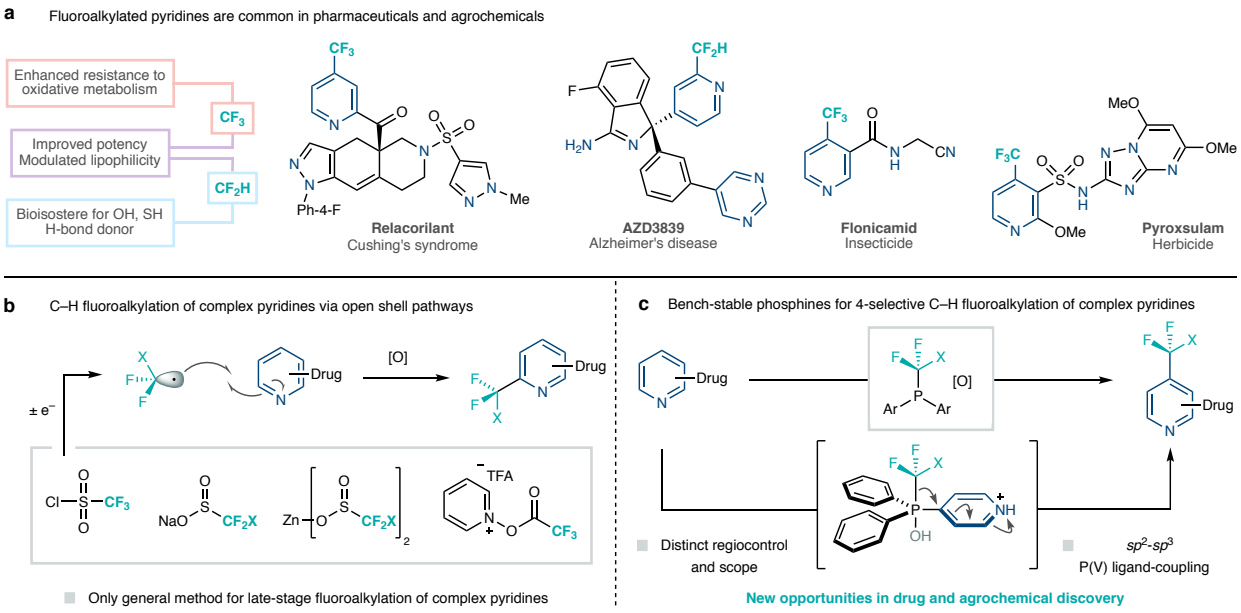
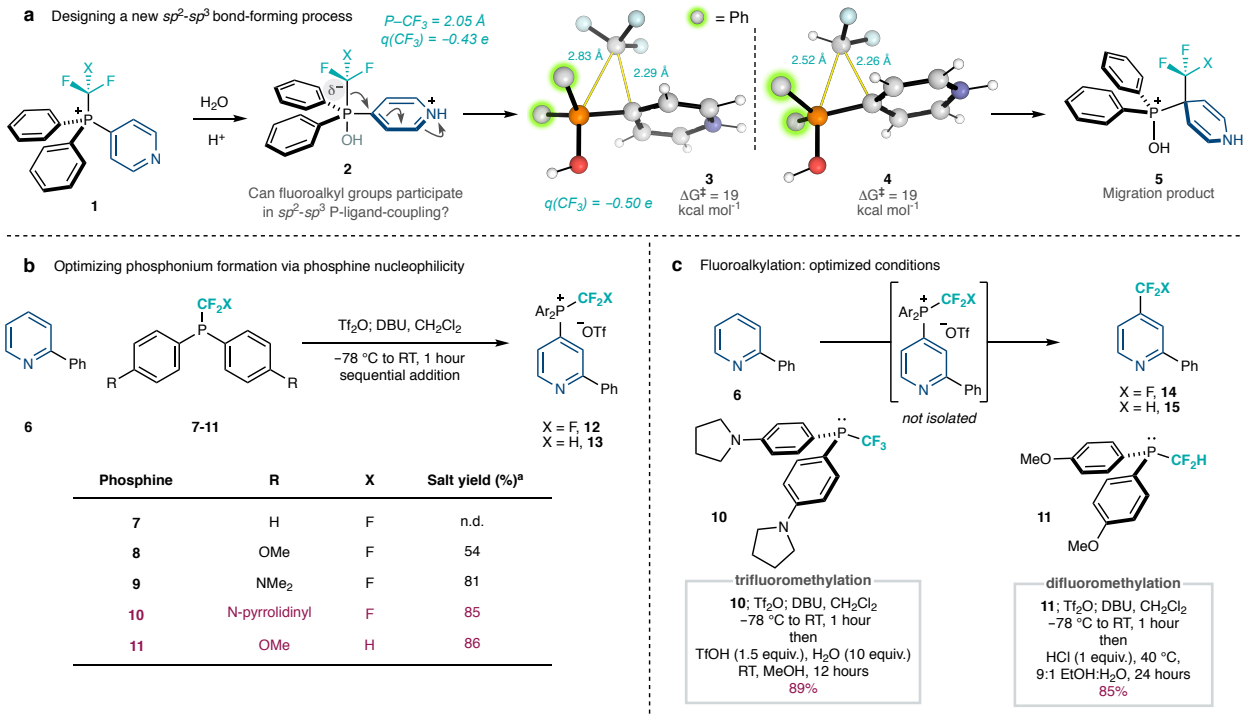


Fig. 1. Importance of fluoroalkylated pyridines and methods to make C–CF_2X bonds (X = F or H). a, Examples of fluoroalkylated pyridines in pharmaceuticals and agrochemicals. **b,** Minisci-type methods for C–CF_2X bond formation. **c**, New phosphine reagents for C–H fluoroalkylation of pyridines via phosphorus ligand-coupling.

We hypothesized that synthesizing fluoroalkyl phosphonium salts and triggering 'contractive' or 'ligand-coupling' processes with oxygen nucleophiles would form C–

CF_2X bonds (Fig. 2a). These reactions ostensibly resemble reductive eliminations at late transition metal centers and have been previously leveraged for Csp^2–Csp^2 bond-formation.[22] However, Csp^2-Csp^3 coupling via this manifold is virtually unknown. In 1989, Uchida reported that benzyl Grignard reagents react with tris(2-pyridyl)phosphine oxides to give low yields of 2-benzylpyridines.[23] The inaccessibility of the phosphine oxide starting materials, the elevated temperatures employed and the lack of control of ligand-coupling selectivity make this reaction impractical for pyridine alkylation. Also, a lack of mechanistic clarity potentially explains why no further studies occurred. Recently, a more substantive understanding of sp^2-sp^2 phosphorus ligand-coupling has emerged, and we reasoned that the apicophilic effects that result in selective pyridine-pyridine coupling were translatable to pyridine fluoroalkylation, further supported by DFT calculations (Tables S6 & S7 and Figs. S15 & S17).[24,25] We anticipated that water would add to fluoroalkylphophonium salt **1** and result in P(V) intermediate **2** (Fig. 2a). A pronounced lengthening of the apical C–P bond (by 0.2 Å to 2.1 Å, Table S10) and accumulation of negative charge on the apical ligand (–0.43 e) preempt ligand-coupling with the pyridinium ring in the equatorial plane. Therefore, fluoroalkyl groups are good candidates for selective coupling due to their ability to stabilize an α-anionic charge on the sp^3 carbon through inductive electron-withdrawal. The lowest energy transition state structures calculated for trifluoromethyl and difluoromethyl coupling (**3** & **4**) suggest these reactions would be facile at ambient temperature ($\Delta G^{\ddagger}$ = 19 kcal·mol^{-1}). Furthermore, the structures resemble the proposed model for ligand-coupling with the fluoroalkyl group migrating from an apical position and continuing to accumulate negative charge in the transition state. Subsequent elimination of diarylphosphine oxide from Meisenheimer-like intermediate **5** completes the process (Fig. S15).



Phosphine	R	X	Salt yield (%)[a]
7	H	F	n.d.
8	OMe	F	54
9	NMe_2	F	81
10	N-pyrrolidinyl	F	85
11	OMe	H	86

Fig. 2. Design and optimization of a phosphorus-mediated process for azine fluoroalkylation. a, Exploiting the apicophilic effect for sp^2-sp^3 ligand-coupling. Counterions omitted for clarity. **b,** Aryl substitution was used to optimize phosphonium salt formation. **c,** A one-pot direct C–H fluoroalkylation reaction. [a]Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. n.d. = not detected.

Fig. 2b shows how a series of diarylfluoroalkyl phosphines (**7-11**) performed in phosphonium salt-forming reactions using 2-phenylpyridine **6** as a model substrate. Notably, these phosphines are straightforward to prepare on a multigram scale using $TMSCF_3$ as both a CF_3 and CF_2H source;[26] two or three steps are required depending on phosphine structure, and the reagents are bench-stable (see the Supplementary Information). Salt formation occurs by sequentially adding Tf_2O, and DBU to a mixture of pyridine **6** and the phosphine. The study clearly shows the yield of the product correlates with the donating capacity of the phosphine's aryl substituents.[27,28] Salt **12** was not detected using diphenyltrifluoromethylphosphine **7**, presumably because the CF_3 group

reduces its nucleophilicity to the extent that reaction with the N-Tf pyridinium intermediate (not shown) is unproductive. However, introducing electron-donating groups at para-positions of the aryl rings (**8-10**) overcomes this problem with pyrrolidine substituents (**10**) proving optimal. We observed a similar trend in CF_2H-substituted phosphines, and methoxy substituted analog **11** was most effective at forming salt **13** (see the Supplementary Information for full details). Notably, the process is exclusively 4-selective and in line with our previous studies on pyridyl phosphonium salt formation.[24,25,28]

Using our optimized conditions, we directly obtained fluoroalkyl derivatives of **6** without isolating the intermediate phosphonium salts (Fig. 2c). During the study in Fig. 2b, we observed minor amounts of tri- and difluoromethylated pyridine products after washing the crude reaction mixture with water and suspected that the fluoroalkylphosphonium salts were particularly prone to ligand-coupling. We rationalized that after forming salts **12** and **13**, adding acid and water would trigger ligand-coupling and enable a one-pot fluoroalkylation process. Previously, in sp^2-sp^2 coupling, we established that nucleophilic attack of alcohols to phosphonium salts is rate-determining, and the withdrawing effect of the fluoroalkyl groups in **11** and **12** should make this step more facile.[24] Salt formation is complete within one hour using **10** then adding TfOH, methanol, and water directly to the reaction mixture and stirring for 12 hours at room temperature results in good yield of the trifluoromethylated product **14**. Removing water from the reaction mixture results in no product indicating its essential role in ligand-coupling. Difluoromethylation (**15**) follows a similar protocol using **11**, except that the ligand-coupling stage occurs at 40 °C reflecting the relative electrophilicity of salts **13** and **14**.

We then applied the trifluoromethylation protocol to a series of building block azines (Fig. 3a). In general, ligand coupling occurs in a range between room temperature and 40 °C for these substrates. Using **10**, both 2,2- and 2,3-bipyridines were directly and selectively trifluoromethylated (**16** & **17**). The reaction is less efficient when a 2-amino substituent is present (**18**), but 3-phenoxy substituted pyridine **19** formed in high yield. Despite the precedent for amides reacting with Tf_2O, we obtained **20** in moderate yield.[29] A series of 2,5-disubstituted pyridines worked well under this protocol including functional groups such as alkynes, imides, and esters (**21-26**). Under standard conditions, the 3-position ester in **23** begins to hydrolyze; changing the conditions to $NaHCO_3$ in THF with 10 equivalents of water alleviates this problem. Under these conditions, we propose that the carbonate nucleophile adds to the phosphonium salt and triggers ligand-coupling without requiring protonation of the pyridine; calculations support the feasibility of this pathway (see the Supplementary Information for computational studies). We did not observe hydrolysis when an ester was in the 2-position and a 2-chloro group was similarly unaffected (**24** & **25**). A set of 2,3-disubstituted pyridines were successfully trifluoromethylated (**27** & **28**) as well as 3,5-disubstituted example **29**. The reaction also tolerates fused aromatic systems **30-32**, and preliminary examples of diazines are promising, including pyridazines and pyrimidines **33** and **34**.

Fig. 3b shows that a similar set of azines are amenable to difluoromethylation. Notable examples within monosubstituted pyridines include bipyridine **38** that was successively difluoromethylated from **17**. Substituents such as 2-Br are compatible (**35**) but require modified basic reaction media to trigger ligand-coupling. Under acidic conditions, no coupling occurred, and the difluoroalkyl phosphonium salt persisted in the reaction mixture even at 80 °C. We hypothesize that the withdrawing effect of the bromo substituent prevents sufficient activation of the pyridine nitrogen atom under acidic

conditions, such that the salt is not electrophilic enough to react with water. The reaction tolerates acid-sensitive functional groups such as 2-esters and *tert*-butoxycarbonyl protected amines (**36** & **42**). The acetal in **39** partially hydrolyzed under standard

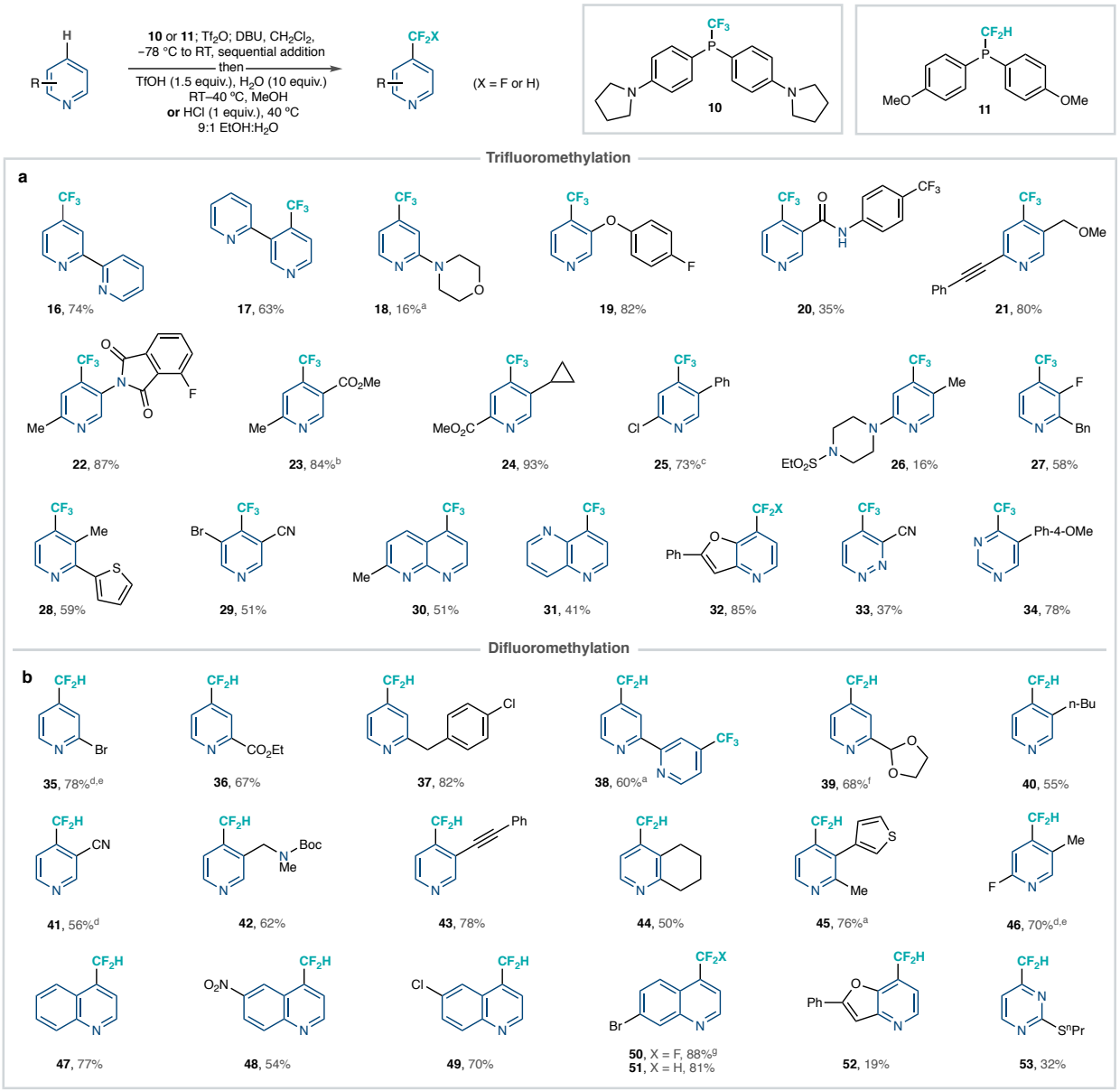


Fig. 3. a, Scope of building block azines amenable to trifluoromethylation using **10**. **b,** Difluoromethylation scope using **11**. [a]Run at 60 °C. [b]$NaHCO_3$ (3 equiv.), H_2O (10 equiv.), THF, RT used for coupling. [c]Run at 80 °C. [d]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [e]K_2CO_3 (1 equiv.), H_2O/THF 1:1, RT used for

coupling. [f]HCl (1 equiv.), TBAF (1 equiv.), 60 °C used for coupling. [g]17:1 regiomeric mixture 4-position vs 2-position.

conditions, but modifying the conditions to a mixture of TBAF and HCl eliminated this pathway; we presume that ligand-coupling occurs either via a P(V) fluorophosphorane or from residual amounts of water in the reaction mixture.[30-32] A notable limitation is 3-halopyridines, where we obtained low yields of difluoromethylated products and observed protiodephosphination as the major product (see the Supplementary Information for further details of the reaction limitations). As above, 2,3- and 2,5-disubstituted pyridines are effective (**44-46**), as are substituted quinolines, a furopyridine, and a pyrimidine (**47-53**).

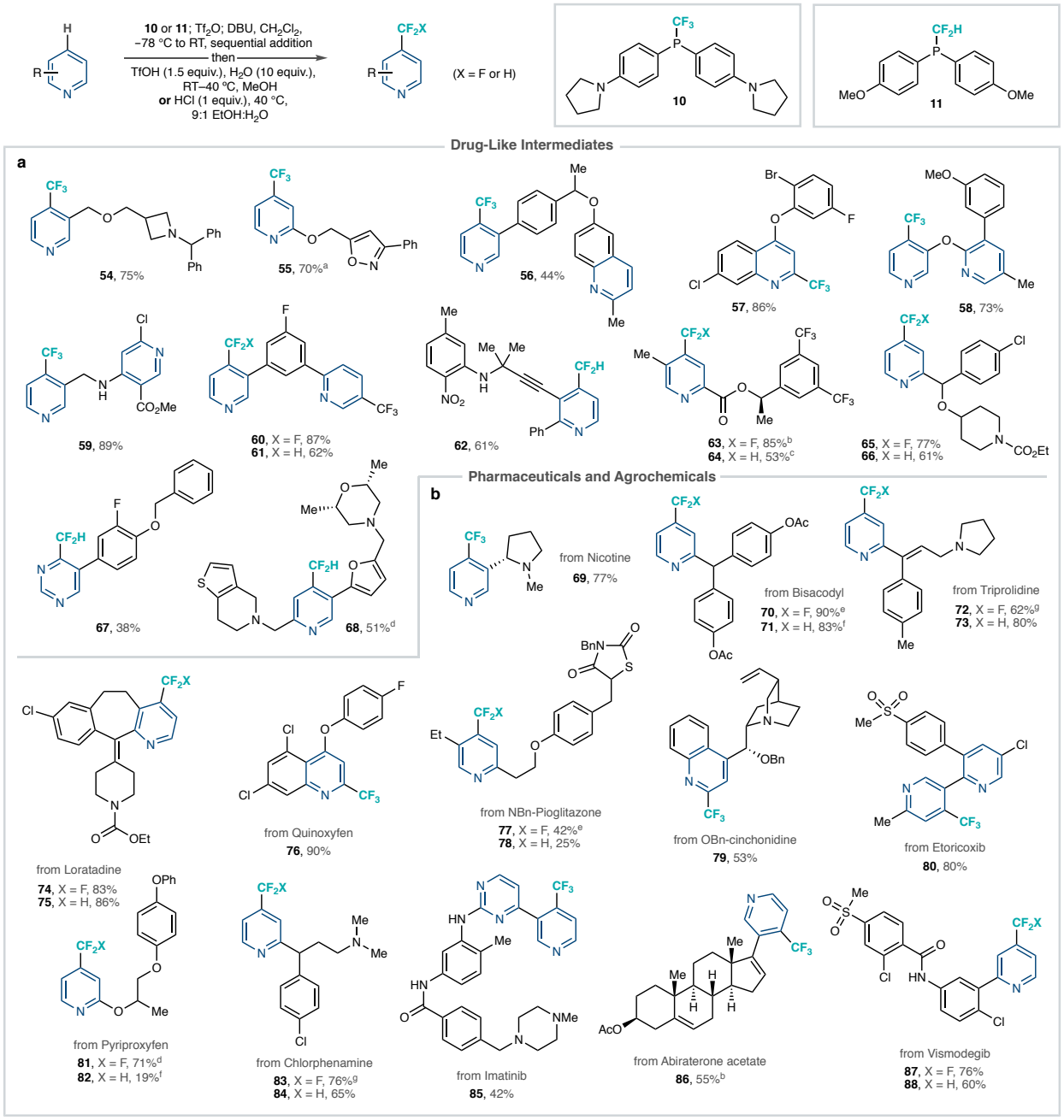


Fig. 4. **a,** Direct fluoroalkylation of complex drug-like intermediates. **b,** Late-stage fluoroalkylation of pharmaceuticals and agrochemicals. [a]Run at 80 °C. [b]TfOH (1 equiv.), TBAF (1 equiv.), RT used for coupling. [c]HCl (1 equiv.), TBAF (1 equiv.), 60 °C used for coupling. [d]Run at 60 °C. [e]$NaHCO_3$ (3 equiv.), H_2O (10 equiv.), THF, RT used for coupling.

[f]K_2CO_3 (1 equiv.), H_2O/THF 1:1, RT used for coupling. [g]1.0 equiv. of TfOH added prior to **10**.

Next, we turned our attention to molecules representing drug-like intermediates and lead compounds (Fig. 4a). Such compounds are structurally diverse and contain multiple functional groups that can potentially interfere with the C–P and C–C bond-forming processes. Furthermore, they are generally devoid of preinstalled functional groups for cross-coupling reactions or biases towards selective outcomes for radical-based fluoroalkylation reactions. Forming trifluoromethylated derivatives **54-56** was straightforward despite the presence of multiple Lewis basic atoms and sites of reactivity (Fig. 4a). Quinolines **57**, **76**, and **79** show that trifluoromethylation occurs at the 2-position when the 4-position is blocked. Phosphines **10** and **11** successfully formed fluoroalkyl pyridines **58-66**; the site-selectivity in **58-61** results from selective N-Tf formation of the 3-substituted pyridines over the 2-substituted pyridines during the salt-forming step.[33] Fig. S10 shows examples of how site selectivity can be switched in complex polyazines. We also obtained difluoroalkyl azines **67** and **68** in reasonable yields.

Late-stage fluoroalkylation reactions enable medicinal and agrochemists to rapidly modify advanced candidates and identify compounds with superior biological properties.[10,13,15-17] This strategy avoids the costly and time-consuming recourse to synthesis from simpler precursors. Furthermore, new methods with distinct regioselectivity provide an entry to new drug candidates that were previously inaccessible. In Fig. 4b, we converted 11 different pharmaceuticals and two agrochemicals into fluoroalkyl derivatives **69-88** using phosphines **10** and **11**. Notably, all products formed as single regioisomers, and given the logic reported for predicting the outcome of Minisci-type fluoroalkylation reactions, we assert that this scope and

regioselectivity would differ significantly from those radical processes.[20] For example, Baran's sulfinate salts selectively fluoroalkylate nicotine at the 2-position, whereas we obtained 4-position CF_3-derivatve **69** using phosphine **10**.[34,35] Further comparisons between this phosphine-mediated approach and radical-based fluoroalkylation are described in Fig. S11.

In summary, we have developed a new process for C–H pyridine fluoroalkylation proceeding via phosphorus sp^2-sp^3 ligand-coupling reactions. Bench-stable fluoroalkyl phosphines first convert pyridines into phosphonium salts, and then adding an aqueous acidic solution forms the C–CF_2X bond in a one-pot process. Fluoroalkyl groups undergo facile ligand-coupling because of their capacity to stabilize anionic charge at the apical positions of P(V) intermediates. This platform reliably fluoroalkylates pyridine building blocks, drug and agrochemical intermediates, and is also a viable method for the late-stage functionalization of complex molecules. The scope of pyridines and the regioselectivity profile is distinct from other common fluoroalkylation methods. We believe this phosphorus-mediated approach will be widely applicable in the pharmaceutical and agrochemical sciences.

References

1 Muller, K., Faeh, C. & Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **317**, 1881-1886, doi:10.1126/science.1131943 (2007).

2 Hagmann, W. K. The many roles for fluorine in medicinal chemistry. *J. Med. Chem.* **51**, 4359-4369, doi:10.1021/jm800219f (2008).

3 Zhou, Y., Wang, J., Gu, Z., Wang, S., Zhu, W., Acena, J. L., Soloshonok, V. A., Izawa, K. & Liu, H. Next generation of fluorine-containing pharmaceuticals, compounds currently in Phase II-III clinical trials of major pharmaceutical companies: new structural trends and therapeutic areas. *Chem. Rev.* **116**, 422-518, doi:10.1021/acs.chemrev.5b00392 (2016).

4 Zafrani, Y., Yeffet, D., Sod-Moriah, G., Berliner, A., Amir, D., Marciano, D., Gershonov, E. & Saphier, S. Difluoromethyl bioisostere: examining the "lipophilic hydrogen bond donor" concept. *J. Med. Chem.* **60**, 797-804, doi:10.1021/acs.jmedchem.6b01691 (2017).

5 Jeschke, P. The unique role of fluorine in the design of active ingredients for modern crop protection. *ChemBioChem.* **5**, 571-589, doi:10.1002/cbic.200300833 (2004).

6 Burriss, A., Edmunds, A. J., Emery, D., Hall, R. G., Jacob, O. & Schaetzer, J. The importance of trifluoromethyl pyridines in crop protection. *Pest. Manag. Sci.* **74**, 1228-1238, doi:10.1002/ps.4806 (2018).
7 Alonso, C., de Marigorta, E. M., Rubiales, G. & Palacios, F. Carbon trifluoromethylation reactions of hydrocarbon derivatives and heteroarenes. *Chem. Rev.* **115**, 1847-1935, doi:10.1021/cr500368h (2015).
8 Barata-Vallejo, S., Lantano, B. & Postigo, A. Recent advances in trifluoromethylation reactions with electrophilic trifluoromethylating reagents. *Chemistry* **20**, 16806-16829, doi:10.1002/chem.201404005 (2014).
9 Yerien, D. E., Barata-Vallejo, S. & Postigo, A. Difluoromethylation reactions of organic compounds. *Chem. Eur. J.* **23**, 14676-14701, doi:10.1002/chem.201702311 (2017).
10 Postigo, A. Difluoromethylation of bioactive compounds. *Late-Stage Fluorination of Bioactive Molecules and Biologically-Relevant Substrates*, 243-285, doi:10.1016/B978-0-12-812958-6.00008-2 (2019).
11 Barata-Vallejo, S. & Postigo, A. Photocatalytic difluoromethylation reactions of aromatic compounds and aliphatic multiple C-C bonds. *Molecules* **24**, doi:10.3390/molecules24244483 (2019).
12 Lemos, A., Lemaire, C. & Luxen, A. Progress in difluoroalkylation of organic substrates by visible light photoredox catalysis. *Adv. Synth. Catal.* **361**, 1500-1537, doi:10.1002/adsc.201801121 (2019).
13 Ye, F., Berger, F., Jia, H., Ford, J., Wortman, A., Borgel, J., Genicot, C. & Ritter, T. Aryl sulfonium salts for site-selective late-stage trifluoromethylation. *Angew. Chem. Int. Ed.* **58**, 14615-14619, doi:10.1002/anie.201906672 (2019).
14 Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **57**, 10257-10274, doi:10.1021/jm501100b (2014).
15 Nagib, D. A. & MacMillan, D. W. C. Trifluoromethylation of arenes and heteroarenes by means of photoredox catalysis. *Nature* **480**, 224-228, doi:10.1038/nature10647 (2011).
16 Fujiwara, Y., Dixon, J. A., O'Hara, F., Funder, E. D., Dixon, D. D., Rodriguez, R. A., Baxter, R. D., Herle, B., Sach, N., Collins, M. R., Ishihara, Y. & Baran, P. S. Practical and innate carbon-hydrogen functionalization of heterocycles. *Nature* **492**, 95-99, doi:10.1038/nature11680 (2012).
17 Beatty, J. W., Douglas, J. J., Cole, K. P. & Stephenson, C. R. J. A scalable and operationally simple radical trifluoromethylation. *Nat. Commun.* **6**, 7919, doi:10.1038/ncomms8919 (2015).
18 Ekroos, M. & Sjogren, T. Structural basis for ligand promiscuity in cytochrome P450 3A4. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 13682-13687, doi:10.1073/pnas.0603236103 (2006).
19 Gibbs, M. A. & Hosea, N. A. Factors affecting the clinical development of cytochrome p450 3A substrates. *Clin. Pharmacokinet.* **42**, 969-984, doi:10.2165/00003088-200342110-00003 (2003).
20 O'Hara, F., Blackmond, D. G. & Baran, P. S. Radical-based regioselective C–H functionalization of electron-deficient heteroarenes: scope, tunability, and predictability. *J. Am. Chem. Soc.* **135**, 12122-12134, doi:10.1021/ja406223k (2013).
21 Nagase, M., Kuninobu, Y. & Kanai, M. 4-Position-selective C-H perfluoroalkylation and perfluoroarylation of six-membered heteroaromatic compounds. *J. Am. Chem. Soc.* **138**, 6103-6106, doi:10.1021/jacs.6b01753 (2016).

22 Finet, J.-P. *Ligand coupling reactions with heteroatomic compounds*. 1st edn, (Pergamon, 1998).
23 Uchida, Y., Onoue, K., Tada, N. & Nagao, F. Ligand coupling reaction on the phosphorus atom. *Tetrahedron Lett.* **30**, 567-570, doi:10.1016/S0040-4039(00)95256-0 (1989).
24 Hilton, M. C., Zhang, X., Boyle, B. T., Alegre-Requena, J. V., Paton, R. S. & McNally, A. Heterobiaryl synthesis by contractive C-C coupling via P(V) intermediates. *Science* **362**, 799-804, doi:10.1126/science.aas8961 (2018).
25 Boyle, B. T., Hilton, M. C. & McNally, A. Nonsymmetrical bis-azine biaryls from chloroazines: a strategy using phosphorus ligand-coupling. *J. Am. Chem. Soc.* **141**, 15441-15449, doi:10.1021/jacs.9b08504 (2019).
26 Krishnamurti, V., Barrett, C. & Prakash, G. K. S. Siladifluoromethylation and deoxo-trifluoromethylation of P(V)-H compounds with TMSCF3: route to P(V)-CF_2(-) transfer reagents and P-CF_3 compounds. *Org. Lett.* **21**, 1526-1529, doi:10.1021/acs.orglett.9b00381 (2019).
27 Anders, E. & Markus, F. Neue methode zur regiospezifischen substitution einiger reaktionsträcer N-heteroaromatischer ringsysteme. *Tetrahedron Lett* **28**, 2675-2676, doi:Doi 10.1016/S0040-4039(00)96178-1 (1987).
28 Hilton, M. C., Dolewski, R. D. & McNally, A. Selective functionalization of pyridines via heterocyclic phosphonium Salts. *J. Am. Chem. Soc.* **138**, 13806-13809, doi:10.1021/jacs.6b08662 (2016).
29 Barbe, G. & Charette, A. B. Highly chemoselective metal-free reduction of tertiary amides. *J. Am. Chem. Soc.* **130**, 18-19, doi:10.1021/ja077463q (2008).
30 Fujimoto, H., Kodama, T., Yamanaka, M. & Tobisu, M. Phosphine-catalyzed intermolecular acylfluorination of alkynes via a P(V) intermediate. *J. Am. Chem. Soc.* **142**, 17323-17328, doi:10.1021/jacs.0c08928 (2020).
31 Levy, J. N., Alegre-Requena, J. V., Liu, R. R., Paton, R. S. & McNally, A. Selective halogenation of pyridines using designed phosphine reagents. *J. Am. Chem. Soc.* **142**, 11295-11305, doi:10.1021/jacs.0c04674 (2020).
32 Lim, S. & Radosevich, A. T. Round-trip oxidative addition, ligand metathesis, and reductive elimination in a P(III)/P(V) synthetic cycle. *J. Am. Chem. Soc.* **142**, 16188-16193, doi:10.1021/jacs.0c07580 (2020).
33 Dolewski, R. D., Fricke, P. J. & McNally, A. Site-selective switching strategies to functionalize polyazines. *J. Am. Chem. Soc.* **140**, 8020-8026, doi:10.1021/jacs.8b04530 (2018).
34 Ji, Y., Brueckl, T., Baxter, R. D., Fujiwara, Y., Seiple, I. B., Su, S., Blackmond, D. G. & Baran, P. S. Innate C-H trifluoromethylation of heterocycles. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 14411-14415, doi:10.1073/pnas.1109059108 (2011).
35 Fujiwara, Y., Dixon, J. A., Rodriguez, R. A., Baxter, R. D., Dixon, D. D., Collins, M. R., Blackmond, D. G. & Baran, P. S. A new reagent for direct difluoromethylation. *J. Am. Chem. Soc.* **134**, 1494-1497, doi:10.1021/ja211422g (2012).

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A patent application based on the subject matter of this manuscript has been filed with the United States Patent and Trademark Office

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