Chemoselective catalytic hydrodefluorination of trifluoromethylalkenes towards mono-/gem-di-fluoroalkenes under metal-free conditions

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Fluorine-containing moieties show significant effects in improving the properties of functional molecules. Consequently, efficient methods for installing them into target compounds are in great demand, especially those enabled by metal-free catalysis. Here we show a diazaphospholene-catalyzed hydrodefluorination of trifluoromethylalkenes to chemoselectively construct gem-difluoroalkenes and terminal monofluoroalkenes by simple adjustment of the reactant stoichiometry. This metal-free hydrodefluorination features mild reaction conditions, good group compatibility, and almost quantitative yields for both product types. Stoichiometric experiments indicated a stepwise mechanism: hydridic addition to fluoroalkenes and subsequent β-F elimination from hydrophosphination intermediates. Density functional theory calculations disclosed the origin of chemoselectivity, regioselectivity and stereoselectivity, suggesting an electron-donating effect of the alkene-terminal fluorine atom.
The introduction of fluorine-containing motifs is a commonly used strategy for improving the properties of target molecules in medicines, agrochemicals, and materials, because of the specific characteristics of the fluorine atom, e.g., high lipophilicity, good absorbability, and strong electron-withdrawing ability. Among these important fluorine-containing motifs, gem-difluoroalkenes and terminal monofluoroalkenes, deemed, respectively, as mimics of carbonyl and amide groups, have attracted much attention in the modification of bioactive molecules (Fig. 1). For example, replacement of the carbonyl group in artemisinin by a gem-difluoroalkene can improve its antimalarial activity (Fig. 1a). In some cases, the introduced gem-difluoroalkene moiety reverses the regioselectivity of enzyme-catalyzed hydric reduction, overriding conventional reduction. Mono-fluoroalkenes with high stereoselectivities are also important fragments in bioactive compounds (Fig. 1b). These fluoralkenes can also serve as versatile building blocks in the construction of other fluorine-containing molecules. Consequently, the important functions of fluoralkenes provoked a great demand for relevant synthetic strategies.

As known, gem-difluoroalkenes could be conventionally constructed by functional-group interconversion, as represented by carbonyl olefination via Julia–Kocienski, Homer–Wadsworth–Emmons, and Wittig reactions (Fig. 2a). However, these reactions usually involve the preparation of complicated fluorinated precursors and are usually conducted under harsh conditions, e.g., in strongly basic solutions, thus leading to a limited substrate scope. One other good alternative could be defluorination of polyfluoroalkenes via transition-metal catalysis, photocatalysis, or the classical S_N2 reaction, delivering functionalized fluoralkenes via alkenylation, arylation, or hydrodefluorination (HDF) (Fig. 2b). Recently, Joubault, Poisson, and coworkers diastereoselectively synthesized monofluoroalkanes from the corresponding trifluoromethyl alkenes via successive dual-HDF with stoichiometric LiAlH_4 (Fig. 2b). However, the use of the strong hydric LiAlH_4 made the reaction incompatible with some electron-deficient groups, and this leads to undesirable over-reduction. Until now, most of the reported methods have only furnished either gem-difluoroalkenes or terminal monofluoroalkenes. Very recently, Wang and coworkers developed an aluminum-catalyzed tunable halodefluorination of trifluoralkyl-substituted alkenes via fluoride ion abstraction (Fig. 2c). In their system, an arbitrary number of fluorine atoms can be selectively replaced with chlorine or bromine atoms by modification of reaction conditions. However, the reaction suffered from drawbacks concerning excess use of one of the reactants (about 4 equiv.), moderate yields, unsatisfactory stereoselectivities, long reaction time (24–48 h) and high reaction temperatures (up to 120 °C).

In this work, we described a method for metal-free catalytic activation of C–F bonds in trifluoromethylalkenes under mild conditions. gem-Difluoroalkenes and terminal monofluoroalkenes can be chemoselectively produced in almost quantitative yields by simple adjustment of the amount of the terminal reductant PhSiH_3 (Fig. 2c).

Results and discussion

Investigation of the reaction conditions. Building on our previous work, we envisioned that diazaphospholenes of super hydricity may provide a good chance to realize HDF of trifluoromethylalkenes via an S_N2 path. A preliminary attempt indicated that the reaction of α-trifluoromethyl-styrene with diazaphospholene primarily gave the hydrophosphination intermediate. Only handful HDF products were obtained. However, the intermediate A was completely converted to 3a and 1-F at an elevated temperature (70 °C). This is the rare example of β-F elimination enabled by a non-metal neutral reductant, rather than by the well-established metal systems. When a second equivalent of diazaphospholene 1 was used, the in situ-generated gem-difluoroalkene 3a was further hydrodefluorinated at 70 °C to afford the dual-HDF product 4a in an almost quantitative yield after 1 h (Fig. 3b and Supplementary Figs. 3 and 4). The excellent

**Fig. 1 Bioactive molecules with gem-difluoroalkene and monofluoroalkene moieties.** a Examples of bioactive molecules with gem-difluoroalkene motifs. b Examples of bioactive molecules with terminal difluoroalkene motifs.
**Fig. 2** State of the art strategies for synthesis of gem-difluoroalkenes and monofluoroalkenes and this work. 

| Strategy | Description |
|----------|-------------|
| a | Synthesis of gem-difluoroalkenes and monofluoroalkenes via carbonyl olefination |
| b | Synthesis of gem-difluoroalkenes and monofluoroalkenes via CF₃-substituted alkenes |
| c | Tunable defluorination reactions |

**Wang's work:**

$$
\begin{align*}
R\text{CF}_3 + \text{TMS-X} &\xrightarrow{\text{Al(CF}_6\text{H}_3(\text{tol})_2\text{Cl}}} 3\text{equiv. CF}_3 + 4\text{equiv. TMSX} \\
&\text{60 °C (48 h) or 120 °C (24 h)}
\end{align*}
$$

**This work:**

$$
\begin{align*}
\text{ArH} + \text{MeCF}_2 + \text{PhSiH}_3 + \text{CH}_3\text{CN} &\xrightarrow{\text{cat. 1 (5 mol%) PhSiH}_3, \text{CH}_3\text{CN}} \text{ArF} + \text{MeH} + 0.7\text{equiv. PhSiH}_3 \\
&\text{50-80 °C, 1 or 12 h}
\end{align*}
$$

**Fig. 3** Investigation of reaction conditions. 

| Reaction | Description |
|----------|-------------|
| a | Stoichiometric reactions of trifluoromethyl alkene 2a with diazaphospholene 1 |
| b | Stoichiometric reactions of gem-difluoroalkene 3a with diazaphospholene 1 |
| c | Regeneration of diazaphospholene 1 with PhSiH₃ |
performance of diazaphospholene 1 in multiple-HDF prompted us to develop its chemoselective HDF of trifluoromethylalkenes for the synthesis of gem-difluoroalkenes and monofluoroalkenes. The successful regeneration of diazaphospholene 1 with fluorophilic PhSiH$_3$ via σ-bond metathesis suggested the possibility of a catalytic version of our design (Fig. 3c and Supplementary Fig. 5)66.

Scope of mono-HDF reactions. As expected, mono-HDF of trifluoromethylalkens 2 in CH$_2$CN with a 5 mol% catalyst loading and 0.33 equiv. of PhSiH$_3$ (i.e., 1 equiv. of Si–H bonds) proceeded smoothly to give gem-difluoroalkenes 3. The high-polarity solvent CH$_2$CN favors polar hydride transfer. Other solvents, like toluene and THF, gave the mono-HDF products in <10% yields. The reaction showed a wide substrate scope, as shown in Fig. 4. Generally, reductions performed with either electron-rich or -deficient substrates all occurred facilely to give almost quantitative yields. Substrate 2a furnished gem-difluoroalkene 3a in 99% yield after 12 h at 70 °C. Phenyl-substituted 2b and non-substituted 2c were efficiently reduced at lower temperatures. The reactions of substrates with electron-donating groups such as methoxy (2d), methylthio (2e), and dimethylamino (2f) also worked well, but needed slightly higher reaction temperatures and longer reaction times. Substrates bearing electron-withdrawing groups (2g–2l) showed high reactivities and gave the corresponding gem-difluoroalkenes 3g–3l in 91–99% yields. Notably, several functional groups (2j–2l) that are incompatible with the strong bases used in Wittig, Julia–Kocienski, and Homer–Wadsworth–Emmons reactions, or with strong nucelophiles in S$_2$C-type reactions, are well tolerated in our system. The known reduction67 of aryl ketones by diazaphospholene was completely depressed by the higher electrophilicity of the trifluoromethyl group in 2j. Substrate 2m with a susceptible acetal moiety furnished the product 3m quantitatively (99%) in a prolonged reaction time. The reaction was also applicable to the naphthalene analog 2n. The excellent performance in heterocyclic systems (3o–3r) shows that this reaction can chemoselectively reduce the trifluoromethyl moiety while leaving other unsaturated structures intact68,69. For tri-substituted alkens, only the Z isomer of 2s is applicable (the E isomer of 2s did not work, see SI for details), and 3s is produced in 91% yield. This is probably because of a steric effect in the initial hydride transfer. The low efficiency of the reaction of the endocyclic alkene 2t is probably also ascribable to a steric effect. Aliphatic trifluoromethylalkenes did not work in our conditions due to the low electrophilicity.

Scope of dual-HDF reactions. Because of the super-hydricity of the catalyst 1, the produced gem-difluoroalkenes 2 continued to react with the hydride 1. This explains why addition of a further 0.33 equiv. of PhSiH$_3$ gave dual-HDF products. Such a result indicates that chemoselective HDF can be achieved by simply adjusting the stoichiometry of the reactants. Accordingly, the preparation of monofluoroalkenes 4 by dual-HDF with 0.7 equiv. of PhSiH$_3$ (i.e., approximately 2 equiv. of Si–H bonds) was investigated. The results are summarized in Fig. 5. Overall, the reduction showed prominent chemoselectivity for most CF$_3$-containing substrates 2, and monofluoroalkenes 4 were generated quantitatively with good to excellent stereoselectivities, although the slightly elevated temperature (80 °C) was necessary for several electron-rich substrates. For examples, substrates 2a–2c gave monofluoroalkenes 4a–4c quantitatively with good E/Z stereoselectivities. Electron-donating groups (2d–2f) did not significantly depress successive C–F activations, and 4d–4f were obtained in good to excellent yields (75%–99%). Various electron-withdrawing groups (2g–2l) were also well tolerated (4g–4l, 92–99% yields). Notably, the acetal moiety of 2m was not sensitive to the dual-HDF conditions. Naphthalene 2n gave 4n in an excellent yield and with good diastereoselectivity. The heterocyclic trifluoromethylalkenes 2o–2r were also compatible and gave products 4o–4r in 64–99% yields with moderate to good E/Z stereoselectivities. Similarly to mono-HDF, only the Z isomer of 2s showed reactivity in dual-HDF. The exocyclic trifluoromethylalkene 2t did not react at all. Note that further increase of the amount of PhSiH$_3$ could remove the third fluoride from some substrates with electron-withdrawing groups.

Synthetic applications. To show the versatility of the present system, we used its potential for modifying drug molecules. Indometacin is a commonly used drug, which has significant antipyretic, anti-inflammatory, and antirheumatic activities70. As shown in Fig. 6, under our reaction conditions the indometacin derivative 5 is effectively transformed into either the mono-HDF product 6 in 85% yield or the dual-HDF product 7 in 30% yield, depending on the amount of the reductant PhSiH$_3$.

Mechanistic investigations. Density functional theory (DFT) calculations were used to gain mechanistic insights into the outstanding catalytic performance of diazaphospholene 1 in HDF. The calculations were performed at the (SMD)-M06-2X/6-311 + +G(2df,2p)//(SMD)-M06-2X/6-31 + +G(d) level of theory71,72 with trifluoromethylalkene 2c as the template substrate. The results are shown in Fig. 7. During the first HDF, hydride transfer from diazaphospholene 1 to 2c proceeds via TS1, with a Gibbs activation barrier of 18.9 kcal mol$^{-1}$, to generate the hydrophosphination intermediate A, in line with our room-temperature reaction conditions for initial hydrophosphination (Fig. 3a). Exothermic cis-β-F elimination from intermediate A furnishes the mono-HDF product 3c via TS2, with a 20.7 kcal mol$^{-1}$ barrier. This suggests a need for elevated temperatures.

The possible paths for the second HDF are more complicated because the hydride can be transferred to either the C1 or C2 site of 3c, to produce intermediates B or B’, respectively (Fig. 8a). Intuitively, the C2 site is preferred, because of the strong electron-withdrawing ability of the fluorine atom. However, our experimental and DFT results uniformly led to good regioselectivity for the hydride transfer to the C1 site, which proceeds via TS3 with an energy barrier about 15 kcal mol$^{-1}$ lower than the transfer to the C2 site via TS3’. This result is primarily attributed to the following two factors: (1) the stabilizing effect of the aromatic ring on the incipient benzylic carbamion during hydride addition at the C1 site, and (2) the repulsive interaction between the fluorine lone pairs of electrons and π-electrons, which makes the C1 site relatively electron deficient (Fig. 8b). Our results suggest that the alkene terminal fluorine atom has an electron-donating effect rather than the conventional electron-withdrawing effect. The NPA (natural population analysis) analysis also supported the regioselectivity in the second hydride transfer process.

The energy profile for the second HDF is given in Fig. 9. As shown, hydride transfer from 1 to 3c via TS3 has a higher Gibbs activation barrier (24.0 kcal mol$^{-1}$) than that of TS1 in the first HDF (18.9 kcal mol$^{-1}$). This 5.1 kcal mol$^{-1}$ difference guarantees excellent chemoselectivity for mono- and dual-HDF. A second cis-β-F elimination from B can give two isomers of the monofluoroalkene 4c. Based on the difference between TS4 and TS5 (0.9 kcal mol$^{-1}$), the E-isomer of the monofluoroalkene, E-4c, is preferentially formed. This stereoselectivity can be explained by using Newman projections of the conformers involved in cis-β-F elimination (Fig. 10a). The preferred conformer, which results in the E isomer being the major product, clearly diminishes electronic repulsion between the fluorine atom and the aromatic ring. Indeed, the stereoselectivity (E/Z = 82/18) calculated from
the Gibbs activation energies for both $\beta$-F elimination steps is in good agreement with the experimental result ($E/Z = 85/15$).

A plausible mechanism for this HDF process is outlined in Fig. 10b. First, hydride transfer from the catalyst 1 to trifluoromethylalkenes 2 furnishes the hydrophosphination intermediate A. Subsequent $\beta$-F elimination gives the mono-HDF products 3 and 1-F. After complete consumption of 2, the excess PhSiH$_3$ regenerates catalyst 1, which renders a second HDF to yield monofluoroalkenes 4.

In summary, we have developed a method for diazaphospholene-catalyzed chemoselective C-F bond activation of trifluoromethylalkenes, which enables the convenient construction...
Fig. 5 Synthesis of terminal monofluoroalkenes by diazaphospholene-catalyzed HDF of trifluoromethylalkenes. General reaction conditions: 2 (0.3 mmol), 1 (5 mol%), PhSiH₃ (0.7 equiv.), and CH₃CN (1 mL) were mixed in a tube under Ar. Isolated yields were given. The E/Z ratios were determined by ¹⁹F NMR spectroscopy. [a] Determined by ¹⁹F NMR spectroscopy. [b] Isolated yield for gram-scale synthesis: 2l (5.0 mmol), 1 (5 mol%), PhSiH₃ (0.7 equiv.), CH₃CN (5 mL), 50 °C, 3 h.
of gem-difluoroalkenes and terminal monofluoroalkenes under metal-free conditions with PhSiH₃ as the terminal reductant. NMR spectroscopic studies showed a hydrophosphination intermediate, which subsequently underwent β-F elimination at elevated temperatures. This metal-free strategy is applicable to a broad range of trifluoromethylalkenes. It shows good functional group tolerance and gives almost quantitative yields of both mono- and di-hydrodefluorinated products. DFT calculations suggested that the good chemoselectivity between mono- and dual-HDF stems from differences in the substrate electrophilicities, and the regioselectivity for hydride transfer to gem-difluoroalkenes is partly attributed to the electron-donating ability of the alkene terminal fluorine atoms. Other diazaphospholene-catalyzed HDF reactions are currently being investigated in our laboratory.

**Methods**

**General information.** Catalyst 1 has been synthesized and characterized in our previous work. Trifluoromethyalkenes 2 were synthesized according to references (see Supplementary Information for details). Other reagents and solvent were purchased from J&K or TCI Chemicals and used without further purification unless specified otherwise. Acetonitrile was purchased from J&K Chemical (99.9%, Extra dry, water <10 ppm, J&K seal) and degassed and distilled by standard methods. Reaction temperature refers to the temperature of an aluminum heating block or a silicon oil bath, which was controlled by an electronic temperature modulator from IKA.
Fig. 9 Mechanistic investigations for the second HDF process by DFT calculations. Energy profiles for HDF of 3c by 1 in acetonitrile calculated at the (SMD)-M06-2X/6-311+ +G(2df,2p)//(SMD)-M06-2X/6-31 + G(d) level of theory. All energies are in kcal mol\(^{-1}\).

Fig. 10 The origin of the Z/E selectivity and proposed mechanism. a Newman projections of the intermediate B involved in cis-\(\beta\)-F elimination. b Proposed reaction mechanism.
Reactions. All hydrofluorination reactions were carried out in dry glass wares under an argon atmosphere using Schlenk technique throughout the reaction procedures.

Analytics. 1H and 13C NMR, 19F NMR spectra were recorded in CDCl3 (δ = 7.26 ppm for 1H NMR, δ = 77.16 ppm for 13C NMR) on 400 MHz NMR instrument at Center of Basic Molecular Science (CBMS) of Tsinghua University.

DFT calculations. Geometry optimizations and frequency computations were performed using Gaussian 0975 at the M06-2X/6-31+G(d) level of theory, in conjunction with the SMD72 model to account for the solvation effect of acetone. To obtain more accurate electronic energies, single point energy calculations were performed at the SMD-M06-2X/6-311+G(2df, 2p) level with the SMD-M06-2X/6-31+G(d) structures.

Data availability
The authors declare that all the data supporting the findings of this work are available within the article and its Supplementary Information files.

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References
1. Yoder, N. C. & Kumar, K. Fluorinated amino acids in protein design and engineering. Chem. Soc. Rev. 31, 335–341 (2002).
2. Purser, S., Moore, P. R., Swallow, S. & Gouverneur, V. Fluorine in medicinal chemistry. Chem. Soc. Rev. 37, 320–330 (2008).
3. Hagmann, W. K. The many roles for fluorine in medicinal chemistry. J. Med. Chem. 51, 4539–4539 (2008).
4. Kirk, K. L. Fluorination in medicinal chemistry: methods, strategies, and recent developments. Org. Process Res. Dev. 12, 305–321 (2008).
5. Nie, J., Guo, H.-C., Cahard, D. & Ma, J.-A. Asymmetric construction of stereogenic carbon centers featuring a trifluoromethyl group from prochiral trifluoromethylated substrates. Chem. Rev. 111, 455–529 (2011).
6. Alonso, C., Martinez de Marigorta, E., Rubiales, G. & Palacios, F. Carbon trifluoromethylation reactions of hydrocarbon derivatives and heteroarenes. Chem. Rev. 115, 1847–1935 (2015).
7. Liu, Q., Ni, C. & Hu, J. China’s flourishing synthetic organic fluorine chemistry: innovations in the new millennium. Natl. Sci. Rev. 4, 303–325 (2017).
8. Tsui, G. C. & Hu, J. Organofluorine chemistry. Asian J. Org. Chem. 8, 566–567 (2019).
9. Marsh, E. N. G. Fluorinated proteins from design to synthesis and structure and stability. Acc. Chem. Res. 47, 2878–2886 (2014).
10. Leriche, C., He, X., Chang, C.-W. T. & Liu, H.-W. Reversal of the apparent procedures. SMD-M06-2X/[6-31]
11. Lu, Q., Shen, X., Ni, C. & Hu, J. Stereoselective carbonyl olefination with fluorosulfoximines: facile access to Z or E terminal monofluoroalkanes. Angew. Chem. Int. Ed. 56, 619–623 (2017).
12. Ma, X. & Song, Q. Recent progress on selective deconstructive modes of halofluoromethyl and trifluoromethyl-containing reagents. Chem. Soc. Rev. 49, 9197–9219 (2020).
13. Andrella, N. O., Xu, N., Gabdullin, B. M., Ehm, C. & Baker, R. T. Selective copper complex-catalyzed hydrodefluorination of fluoroketones and allylic fluorides: a tale of two mechanisms. J. Am. Chem. Soc. 141, 11508–11521 (2019).
14. Makakwa, Y., Nambo, M., Yokogawa, D. & Creedon, C. M. Alkyltrifluorines in the Ramberg–Bäcklund reaction: an efficient and modular synthesis of gem-difluoroalkanes. J. Am. Chem. Soc. 142, 15667–15672 (2020).
15. Burton, D. J., Yang, Z.-Y. & Qiu, W. Fluorinated Ylides and related compounds. Chem. Rev. 96, 1641–1716 (1996).
16. Zhu, L., Ni, C., Zhao, Y. & Hu, J. 1-Tert-Butyl-1-hexafluorocyclopentene. J. Fluor. Chem. 127, 637–642 (2006).
17. Meanwell, N. A. Synopsis of some recent tactical application of bioisosteres in drug design. J. Med. Chem. 54, 2529–2591 (2011).
18. Yanai, H. & Taguchi, T. Synthetic methods for fluoroolefins. Eur. J. Org. Chem. 2011, 5939–5954 (2011).
19. Couve-Bonnaire, S., Cahard, D. & Pannecooke, X. Chiral dipeptide mimics possessing a fluorooxirane moiety: a relevant tool for conformational and medicinal studies. Org. Biomol. Chem. 5, 1151–1157 (2007).
20. Meanwell, N. A. Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design. J. Med. Chem. 61, 5822–5880 (2018).
21. Drouin, M., Laxio Arenas, J. & Paquin, J.-F. Incorporating a monofluoroalkene into the backbones of short peptides: evaluating the impact on local hydrophobicity. ChemBioChem 20, 1817–1826 (2019).
22. Drouin, M. et al. Monofluoroalkene-isostere as a 19F-NMR label for the peptide backbone: synthesis and evaluation in membrane-bound PGLa and (KIGAKI), Chem. Eur. J. 16, 1511–1520 (2010).
23. McCarthy, J. R. et al. Stereoscopic method to (E) and (Z) terminal fluoroolefins and its application to the synthesis of 2-deoxy-2'-fluorouracil. J. Am. Chem. Soc. 113, 7439–7440 (1991).
24. Shimizu, M., Ohno, A. & Yamada, S. (10Z)- and (10E)-19-fluoro-L-25-dihydroxyvitamin D3: an improved synthesis via 19-Nor-10-exo-vitamin D. Chem. Pharm. Bull. 49, 312–317 (2001).
46. Lang, S. B., Wiles, R. J., Kelly, C. B. & Molander, G. A. Photoredox generation of carbon-centered radicals enables the construction of 1,1-difluoroalkene carbonyl mimics. Angew. Chem. Int. Ed. 56, 15073–15077 (2017).

47. Phelan, J. P. et al. Open-air alklylation reactions in photoredox-catalyzed DNA-encoded library synthesis. J. Am. Chem. Soc. 141, 3723–3732 (2019).

48. Du, H.-W. et al. Synthesis of monofluoroalkanes through visible-light-promoted difluorative alklylation of gem-difluoroalkanes with 4-alkyl-1,4-dihydroxypropionaldehydes. Chem. Commun. 51, 8326–8332 (2015).

49. Yao, J., Li, L. & Zhou, L. Synthesis of functionalized gem-difluoroalkanes via a photocatalytic decarboxylative/difluorative reaction. J. Org. Chem. 81, 7908–7916 (2016).

50. Kobayashi, O., Uraguchi, D. & Yamakawa, T. Synthesis of spirocyclic-1,3-diazaphospholes catalyzed by 1,3,2-diazaphosphenium triflates. J. Am. Chem. Soc. 140, 652–656 (2018).

51. Lucas, S. The pharmacology of indomethacin. Headache 56, 436–446 (2016).

52. Zhao, Y. & Truhlar, D. G. Density functionals with broad applicability in chemistry. Acc. Chem. Res. 41, 157–167 (2008).

53. Marenich, A. V., Cramer, C. J. & Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. J. Phys. Chem. B 113, 6378–6396 (2009).

54. Ichitsuka, T., Fujita, T. & Ichikawa, J. Nickel-catalyzed allylic C(sp3) bond activation of trifluoromethyl groups via β-fluorine elimination: synthesis of difluoro-1,4-dienes. ACS Catal. 5, 5947–5950 (2015).

55. Liu, Y., Zhou, Y., Zhao, Y. & Qu, J. Synthesis of gem-difluoroallylboronates via FeCl3-catalyzed boronation of trifluoromethyl alkenes. Org. Lett. 19, 946–949 (2017).

56. Xu, X., Li, H., Deng, L., Ong, H.-W. & Wu, J. Visible light-induced selective defluorovinylation of polyfluoroarenes, gem-difluoroalkanes, and trifluoromethylalkanes. Angew. Chem. Int. Ed. 59, 4009–4016 (2020).

57. Poutrel, P., Pannecoucke, X., Joubault, P. & Poisson, T. Stereoselective synthesis of terminal monofluoroalkanes from trifluoromethylated alkenes. Org. Lett. 22, 4858–4863 (2020).

58. Liu, Z., Tu, X.-S., Guo, L.-T. & Wang, X.-C. Aluminum-catalyzed tunable halodefluorination of trifluoromethyl- and difluoroalkyl-substituted olefins. Chem. Sci. 11, 11548–11553 (2020).

59. Zhang, J., Yang, J.-D. & Chen, J.-P. A nucleophilicity scale for the reactivity of diazaphospholanium hydrides: structural insights and synthetic applications. Angew. Chem. Int. Ed. 58, 5983–5987 (2019).

60. Reed, J. H. & Cramer, N. 1,3,2-diazaphospholanes catalyze the conjugate reduction of substituted acrylic acids. ChemCatChem 12, 4262–4266 (2020).

61. Speed, A. W. H. Applications of diazaphospholane hydrides in chemical catalysis. Chem. Soc. Rev. 49, 8335–8353 (2020).

62. Reed, J. H., Kletz, J., Steven, C. & Cramer, N. Stay positive: catalysis with 1,3,2-diazaphospholanes. Organometallics 39, 3521–3529 (2020).

63. Huchenski, B. S. N., Robertson, K. N. & Speed, A. W. H. Functionalization of bis-diazaphospholane-P-P bonds with diverse electrophiles. Eur. J. Org. Chem. 2020, 5140–5144 (2020).

64. Gudat, D., Haghverdi, A., Hupfer, H. & Nier, M. Stability and electrophilicity of phosphorus analogues of Arduengo carbenes—an experimental and computational study. Chem. Eur. J. 6, 3144–3425 (2000).

65. Fujita, T., Fuchibe, K. & Ichikawa, J. Transition-metal-mediated and -catalyzed C–F bond activation by fluoride elimination. Angew. Chem. Int. Ed. 58, 390–402 (2019).

66. Chong, C. C. & Kinjo, R. Hydrophosphination of CO2 and subsequent formate transfer in the 1,3,2-diazaphospholane–catalyzed N-formylation of amines. Angew. Chem. Int. Ed. 54, 12116–12120 (2015).

67. Chong, C. C., Hirao, H. & Kinjo, R. Metal-free σ-bond metathesis in 1,3,2-diazaphospholane-catalyzed hydroboration of carbonyl compounds. Angew. Chem. Int. Ed. 54, 190–194 (2015).

68. Hynes, T., Welsh, E. N., McDonald, R., Ferguson, M. J. & Speed, A. W. H. Pyridine hydroboration with a diazaphospholene precatalyst. Organometallics 37, 841–844 (2018).

69. Yao, J., Li, L. & Zhou, L. Synthesis of functionalized gem-difluoroalkanes via a photocatalytic decarboxylative/difluorative reaction. J. Org. Chem. 81, 7908–7916 (2016).

70. Kobayashi, O., Uraguchi, D. & Yamakawa, T. Synthesis of spirocyclic-1,3-diazaphospholes catalyzed by 1,3,2-diazaphosphenium triflates. J. Am. Chem. Soc. 140, 652–656 (2018).

71. Lucas, S. The pharmacology of indomethacin. Headache 56, 436–446 (2016).

72. Zhao, Y. & Truhlar, D. G. Density functionals with broad applicability in chemistry. Acc. Chem. Res. 41, 157–167 (2008).

73. Marenich, A. V., Cramer, C. J. & Truhlar, D. G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. J. Phys. Chem. B 113, 6378–6396 (2009).

74. Gudat, D., Haghverdi, A. & Nier, M. Umpolung of P–H bonds. Angew. Chem. Int. Ed. 39, 3084–3086 (2000).

75. Burck, S., Gudat, D., Nier, M. & Du Mont, W.-W. P-hydrogen-substituted 1,3,2-diazaphospholes: molecular hydrides. J. Am. Chem. Soc. 128, 3946–3955 (2006).

76. Frisch, M. J. T. et al. Gaussian 09, Revision D.01, Gaussian, Inc., Wallingford, CT (2013).

77. Zhao, Y. & Truhlar, D. G. Applications and validations of the Minnesota density functionals. Chem. Phys. Lett. 502, 1–13 (2011).

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Author contributions

J.-P.C. and J.-D.Y. conceived and supervised the project. The synthetic experiments and characterizations were carried out by J.Z. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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