OL Organic Letters

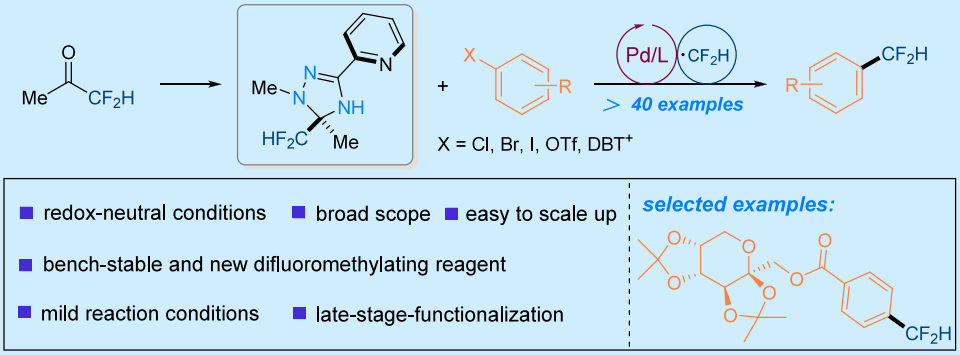
pubs.acs.org/OrgLett Letter

Difluoromethylation of Aryl Halides via Palladium-Catalyzed Redox-Neutral Deacylation

Shihao Li, Mingming Li, Yan Liu, Jingwen Hao, Shaojun Zheng, Zitong Rong, Yi-Si Feng,* Nai-Dong Chen,* and Pan Pan*

Cite This: https://doi.org/10.1021/acs.orglett.5c04966 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A novel difluoromethylating reagent was developed via the dehydration condensation between 1,1-difluoroacetone and N′-methylpicolinohydrazonamide (MPHA). This reagent is suitable for palladium-catalyzed coupling reactions, offering a broad substrate scope (43 examples) and excellent scalability (gram-scale synthesis), and can be efficiently employed for the modification of drug molecules to enable the facile synthesis of difluoromethylated (hetero)arenes. Mechanistic studies indicate that the successful release of the difluoromethyl radical results from aromatization-driven C−C bond cleavage.

The precise assembly of fluorine-containing compounds is a key driver fueling progress in pharmaceuticals, agrochemicals, and materials science.[1] Among them, difluoromethyl aromatics, featuring the unique difluoromethyl (CF_2H) group, possess distinct physicochemical properties and remarkable bioisosteric effects, granting them considerable application potential.[2] A prominent example is elenbecestat, an investigational drug for Alzheimer's disease (AD), which successfully incorporates this moiety (Figure 1a).[3] Consequently, replacing the original functional groups with the difluoromethyl group in specific molecules can maintain or even enhance biological activity, while simultaneously improving pharmacokinetic properties, offering a promising path toward the development of efficient and low-toxicity new-generation drug candidates.[4] Nevertheless, the efficient and precise introduction of difluoromethyl (CF_2H) groups remains a major challenge in organic synthesis.

Conventional strategies, such as the deoxydifluoromethylation of aldehydes or nucleophilic substitutions with halodifluoromethyl reagents, are often plagued by limitations including harsh reaction conditions, limited functional group tolerance, and challenges in controlling regio- and chemoselectivity.[5] In addition, Transition-metal-catalyzed cross-coupling reactions offer an alternative route for the difluoromethylation of aromatic rings, yet this strategy largely relies on highly reactive metal-based difluoromethyl reagents (such as $(SIPr)Ag(CF_2H)$,[6] $(HF_2C)_2Zn(DMPU)_2$,[7] $(HF_2C)_2Zn(TMEDA)$,[8] $nBu_3Sn(CF_2H)$),[9] which are generally prone to decomposition and challenging to store. Although chlorodifluoromethane ($ClCF_2H$)[10] and bro-modifluoromethane ($BrCF_2H$)[11] have been widely reported as precursors of difluoromethylation, their gaseous nature greatly reduces the convenience of operation. Moreover, the requirement for excess ozone to consume $ClCF_2H$ and $BrCF_2H$ presents an additional drawback.[12] Collectively, these limitations hinder the application of such reagents in the late-stage modification of complex bioactive molecules. It is worth noting that while recent reports have described the difluoromethylation of aryl halides utilizing CF_2H radicals,[13] developing new difluoromethylating reagents that feature novel structures, high reactivity and selectivity, and operational simplicity remains a critical objective with substantial research and practical value.

Received: November 28, 2025
Revised: December 27, 2025
Accepted: December 31, 2025
Published: January 5, 2026

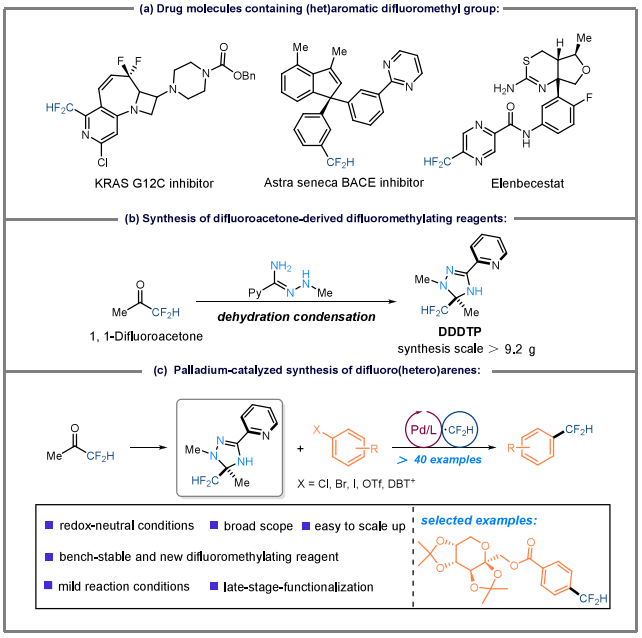
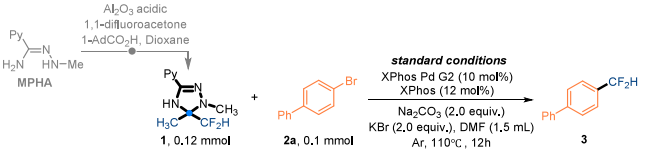


Figure 1. Magic difluoromethyl effect: development of the DDDTP reagent for a broad range of (hetero)aryl precursors.

Among various radical precursors, ketone derivatives have garnered significant interest in recent years. Because ketones are widely present in natural products, developing them into cost-effective synthetic building blocks for value-added transformations has become a prominent research hotspot.[14] Over the past decade, numerous strategies for the efficient activation of both cyclic and linear ketones have been reported.[15] Inspired by the work of Dong[16] and Xue[17] and their colleagues, we have developed a novel difluoromethylating reagent (Figure 1b). This reagent is prepared via dehydration condensation between commercially available 1,1-difluoroacetone and N′-methylpicolinohydrazonamide (MPHA). Notably, the reagent is solid, which facilitates handling, storage, and scale-up. In preliminary experiments, it efficiently mediated the palladium-catalyzed difluoromethylation of diverse substrates, including (hetero)aryl bromides, iodides, phenolic derivatives, and aryl sulfonium salts, thereby establishing a novel synthetic route to difluoromethylated aromatic hydrocarbons (Figure 1c).

We commenced this study by using 2-(5-(difluoromethyl)-1,5-dimethyl-4,5-dihydro-1H-1,2,4-triazol-3-yl)pyridine (DDDTP) **1** and 4-bromo-1,1′-biphenyl **2a** as model substrates for difluoromethylarene synthesis. After extensive investigation of the reaction conditions (see the SI for details), we found that a mixture of **1** and **2a** in the presence of XPhos Pd G2 as the palladium catalyst, XPhos as the ligand, sodium carbonate as the base, and potassium bromide as an additive in N,N-dimethylformamide (DMF) at 110 °C for 12 h, afforded the desired product difluoromethylarene **3** in 82% isolated yield (Table 1, entry 1). When other solvents are used, including dioxane, acetonitrile (MeCN), dimethyl sulfoxide (DMSO) and *N*-methylpyrrolidone (NMP), the reaction efficiency is greatly reduced (Table 1, entries 2−5). Other bases, such as potassium carbonate (K_2CO_3), 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG), and potassium hydroxide (KOH), can also promote this transformation, but all proved inferior to sodium carbonate (Table 1, entries 6−8). The evaluation of temperature effects revealed that the

Table 1. Optimization of the Reaction Conditions[a]



entry	change from optimal conditions	yield (%)[a]
1	**none**	**89 (82)**[b]
2	Dioxane instead of DMF	26
3	MeCN instead of DMF	13
4	DMSO instead of DMF	44
5	NMP instead of DMF	33
6	K_2CO_3 instead of Na_2CO_3	77
7	BTMG instead of Na_2CO_3	61
8	KOH instead of Na_2CO_3	49
9	130 °C instead of 110 °C	66
10	90 °C instead of 110 °C	78
11	70 °C instead of 110 °C	trace
12	no XPhos Pd G2 (10 mol %)	N.D.
13	no Na_2CO_3	N.D.
14	no KBr	72
15	no Xphos	53

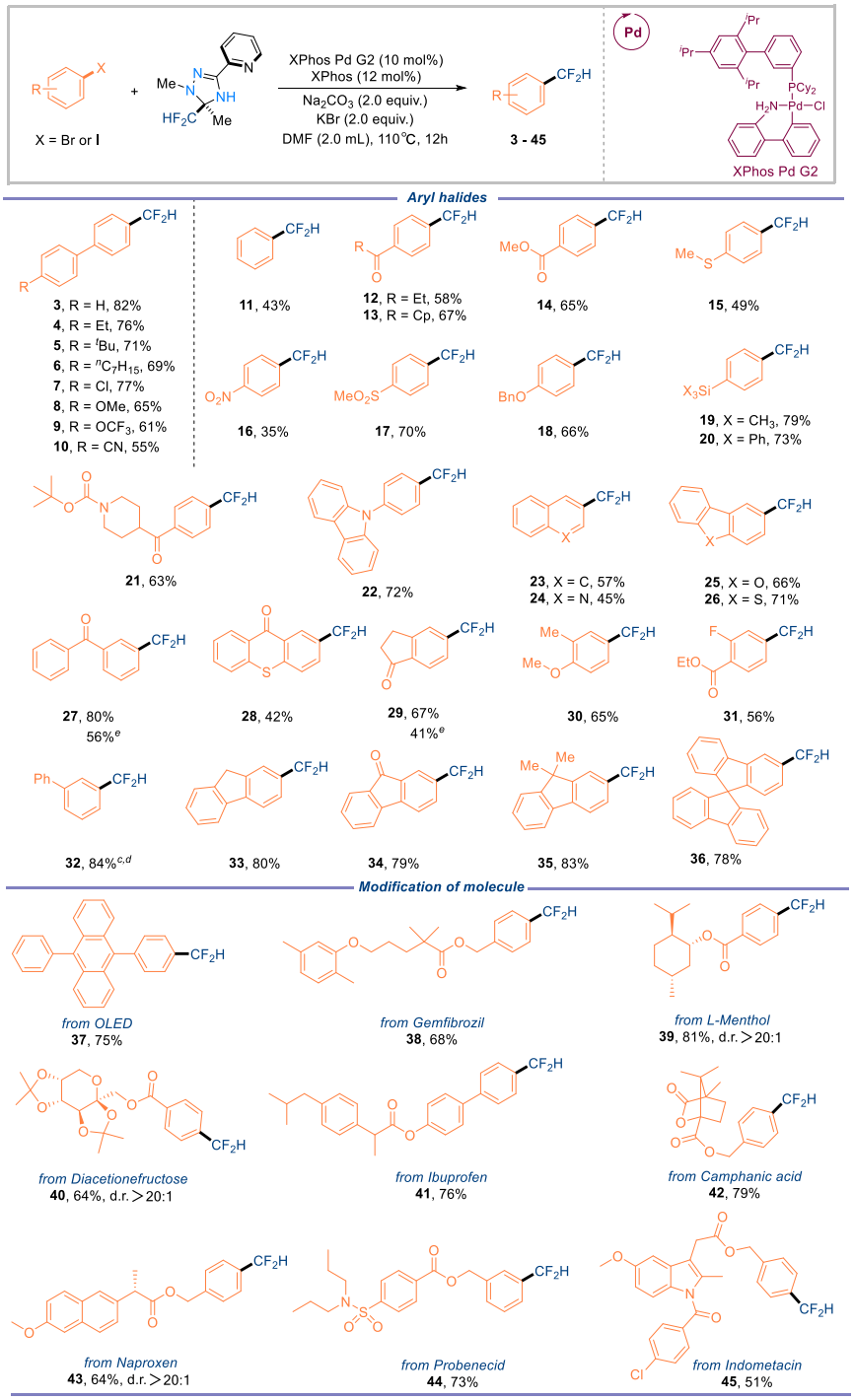
[a]Standard conditions: **1** (0.12 mmol), **2** (0.1 mmol), XPhos (12 mol %), XPhos Pd G2 (10 mol %), Na_2CO_3 (0.2 mmol), KBr (0.2 mmol), in DMF (1.5 mL) at 110 °C for 12h under Ar atmosphere. Yields were determined by 1H NMR spectroscopy with dibromomethane as the internal standard. [b]Isolated yield on 0.2 mmol scale. N.D. = not detected.

reaction was sensitive to temperature changes. When the temperature was increased to 130 °C, the yield of the target product decreased significantly, which was likely due to catalyst deactivation from the formation of palladium black at high temperature (Table 1, entry 9). In contrast, when the temperature was reduced to 90 °C, only a slight decrease in yield was observed (Table 1, entry 10). A further reduction to 70 °C almost completely suppressed the model reaction (Table 1, entry 11). Additional control experiments confirmed that both the palladium catalyst and sodium carbonate were essential for the reaction (Table 1, entries 12 and 13). In contrast, the absence of the additive or the ligand led to lower yields of the target product, 72% and 53% respectively (Table 1, entries 14 and 15).

With the optimal reaction conditions established (Table 1, entry 1), we proceeded to investigate the substrate scope and limitations of the difluoromethylation of aryl bromides. As shown in Scheme 1, the developed method proved effective for synthesizing a series of aryl difluoromethylated compounds. We began by systematically evaluating monosubstituted aryl bromides to probe both electronic and steric effects. The results demonstrate the robustness of this transformation toward both electron-rich and electron-deficient arenes. Regardless of whether the substrates bore strong electron-donating groups (such as methoxy (**8**)) or strong electron-withdrawing groups (such as chloro (**7**), cyano (**10**), and the medicinally important trifluoromethoxy (**9**)) the reactions afforded the target products efficiently. These results point to the insensitivity of the catalytic process to variations in the aromatic ring's electron density. Furthermore, the method demonstrated excellent adaptability against steric effects. Even with increasingly bulky substituents, from hydrogen (**3**) and ethyl (**4**) to the highly hindered *tert*-butyl (**5**) and long-chain

https://doi.org/10.1021/acs.orglett.5c04966
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Substrate Scope of (Hetero)aryl Halides and Iodides[a,b]



[a]All yields isolated on 0.2 mmol scale. Conditions: 2-(5-(difluoromethyl)-1,5-dimethyl-4,5-dihydro-1H-1,2,4-triazol-3-yl)pyridine (1.2 equiv), aryl bromides (1.0 equiv), XPhos Pd G2 (10 mol %), XPhos (12 mol %), Na_2CO_3 (2.0 equiv) and KBr (2.0 equiv) in DMF (2.0 mL) was stirred at 110 °C for 12 h under an Ar atmosphere. [b]Isolated yield. [c]At 90 °C. [d]Aryl iodides (1.0 equiv) was used. [e]Aryl chlorides (1.0 equiv) was used.

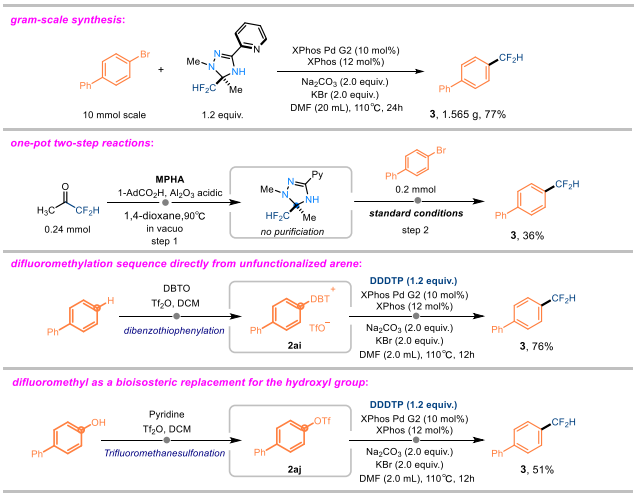
alkyl (**6**) groups, the reaction proved effective. This pronounced steric tolerance underscores the method's high potential for the late-stage modification of structurally complex molecules. Encouraged by the above findings, we expanded the substrate scope to investigate its compatibility toward a variety of common functional groups. The substrates examined included unsubstituted bromobenzene (**11**) as well as those bearing ester (**14**), methylthio (**15**), nitro (**16**), methylsulfonyl (**17**), benzyloxy (**18**), silyl (**19**, **20**), and carbazole (**22**) groups. Furthermore, the protocol was also compatible with ketone-containing substrates (**12**, **27**), even those incorporating challenging structural motifs such as a highly strained cyclopropane (**13**) or a Boc-protected amino group (**21**). The catalytic system was successfully applied to structurally demanding bromoarenes, including those with a bulky naphthalene core (**23**) and a spiro carbon center (**36**); the

https://doi.org/10.1021/acs.orglett.5c04966
Org. Lett. XXXX, XXX, XXX−XXX

corresponding products were isolated in yields of 57% and 78%, respectively. Heteroaromatic rings are prevalent in drugs and functional materials, but their unique coordination properties and electronic characteristics often pose challenges in metal-catalyzed reactions.[18] Encouragingly, this method was efficiently applied to quinoline substrates (**24**), overcoming common issues such as catalyst deactivation. Furthermore, the reaction was also successfully extended to other heterocyclic frameworks including benzofuran, benzothiophene, and thiochromanone (**25**, **26**, and **28**). Multisubstituted and fused-ring bromoarenes were also viable substrates, affording the target products in moderate to excellent yields (**29**−**31**, **33**−**35**). Driven by these results, we want to know whether this strategy is suitable for difluoromethylation of complex molecules. 9-(4-broMophenyl)-10-phenylanthracene, a molecule that is widely used in fluorescent dyes and electronic devices, achieved an excellent yield (**37**). Substrates derived from common natural extracts, such as L-menthol, diacetonefructose, and camphanic acid, afforded moderate yields in the difluoromethylation reaction (**39**, **40** and **42**). Furthermore, derivatives of nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, naproxen, and indomethacin, were efficiently converted (**41**, **43** and **45**). The lipid-lowering drug gemfibrozil was also effectively difluoromethylated (**38**). Notably, derivatives of probenecid—which is a sulfonamide uricosuric agent for chronic gout—underwent the reaction efficiently, affording the product in up to 73% yield (**44**). The successful difluoromethylation of these diverse substrates highlights the broad utility of the palladium catalytic system and its significant potential for applications across materials science, natural products, and pharmaceutical development.

Next, we applied the developed difluoromethylation protocol to several key scenarios. As shown in Scheme 2,

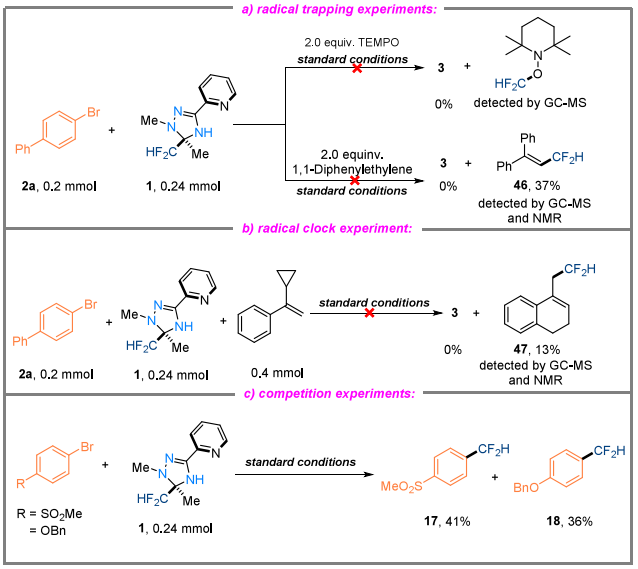
Scheme 2. Synthetic Applications



initially, a gram-scale reaction was conducted under the optimized conditions, affording the product in 77% yield and demonstrating the excellent scalability of the method. Subsequently, to validate its utility in late-stage functionalization, a one-pot, two-step procedure was successfully applied to bromoarenes, yielding the desired products in 36% yield. To further broaden the substrate scope, a direct C−H difluoromethylation strategy for arenes was developed. Using this approach, biphenyl was converted to the key arylsulfonium salt **2ai** via reaction with trifluoromethanesulfonic anhydride and dibenzothiophene oxide (DBTO). Furthermore, the difluoromethyl group, a modification known to maintain efficacy while significantly enhancing metabolic resistance and thereby extending in vivo half-life, serves as a critical bioisostere of the hydroxyl group.[19] Based on this principle, we designed a derivatization route for 4-Phenylphenol. Specifically, 4-phenylphenol reacted with trifluoromethanesulfonic anhydride to obtain intermediate **2aj**, which was difluoromethylated with DDDTP under standard conditions and successfully provided the target compound in good yield.

A series of control experiments were performed to probe the mechanism of the palladium-catalyzed deacetylation-difluoroarylation reaction, as shown in Scheme 3. First, radical

Scheme 3. Mechanistic Experiments

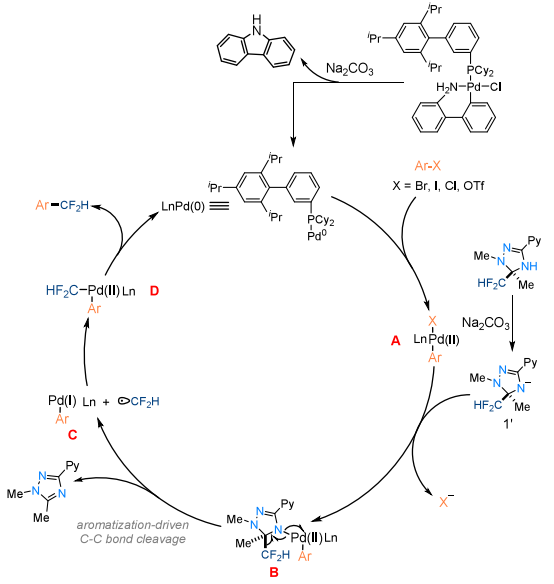


trapping experiments were conducted separately using TEMPO (2,2,6,6-tetramethylpiperidinooxy) and DPE (1,1-diphenylethylene) to assess the involvement of difluoromethyl radicals. Under the standard conditions, the formation of product **3** was suppressed in both cases, and GC-MS analysis identified the corresponding difluoromethyl radical adducts, confirming the presence of these radical species within the catalytic system. Furthermore, a radical clock experiment employing (1-cyclopropylvinyl)benzene under the standard conditions led to the detection of the ring-opened product, 4-(2,2-difluoroethyl)-1,2-dihydronaphthalene, by GC-MS. This result provides strong evidence for the generation of a free difluoromethyl radical intermediate during catalysis. We then turned to intermolecular competition experiments to evaluate the influence of substituent electronic effects on reaction efficiency. This investigation was prompted by our initial studies, which showed that products **17** and **18** were obtained in comparable yields. Consequently, a direct competition between the electron-deficient 1-bromo-4-(methylsulfonyl)-benzene and the electron-rich 1-(benzyloxy)-4-bromobenzene was carried out. The reaction afforded the two products in a nearly 1:1 ratio (**17**:**18** = 53:47). This equimolar distribution indicates the absence of a significant electronic bias and demonstrates that the reaction outcome is largely independent of the substituents' electronic properties.

https://doi.org/10.1021/acs.orglett.5c04966
Org. Lett. XXXX, XXX, XXX−XXX

Based on the above mechanism research and previous literature reports,[20] a possible palladium catalytic cycling pathway has been proposed, as shown in Scheme 4. This

Scheme 4. Proposed Mechanism



catalytic cycle is initiated by the formation of an LnPd(0) species via a C(sp^2)−N bond reductive elimination, a process promoted by the deprotonation of precatalyst XPhos Pd G2 with sodium carbonate. The **A** (LnPd(II)) is generated in situ via oxidative addition of LnPd(0) to the aryl halide. Concurrently, deprotonation of DDDTP with sodium carbonate affords the corresponding triazole anion,[17] which undergoes transmetalation with **A** (LnPd(II) to form **B** (LnPd(II)). The decomposition of **B** (LnPd(II)) yields **C** (LnPd(I)), a free difluoromethyl radical, and the aromatic byproduct 2-(1,5-dimethyl-1H-1,2,4-triazol-3-yl)pyridine, a selectivity driven by the higher thermodynamic stability of the difluoromethyl radical relative to methyl radical, which renders C−CF_2H bond cleavage thermodynamically more favorable. The resulting radical is captured by **C** (LnPd(I)) to give **D** (LnPd(II)). Finally, reductive elimination from **D** (LnPd(II)) yields the difluoromethylarene product and regenerates the LnPd(0) catalyst, thereby closing the catalytic cycle. DFT calculations provide robust support for the proposed reaction mechanism (section 8.1 − 8.4, Supporting Information). However, the reaction pathway involving direct oxidation of the triazolyl anion by Ln-Pd(I) or Ln-Pd(II) cannot be entirely excluded (section 8.5, Supporting Information).[15h]

In summary, we developed a bench-stable radical difluoromethylating reagent based on the dehydration condensation between commercially available difluoroacetone and MPHA. This reagent exhibited excellent substrate compatibility under a palladium-catalyzed system, including (hetero)aryl bromides, chlorides, iodides, phenolic derivatives, and aryl sulfonium salts. It is worth noting that this protocol could be scaled up to the gram scale and was successfully applied to the late-stage functionalization of complex natural products and drug molecules. DFT calculations revealed that the release of the difluoromethyl radical proceeds through a single-electron transfer subsequent to the deprotonation of DDDTP, which subsequently triggers C−C bond cleavage driven by aromatization. Our laboratory is currently exploring further applications of these reagents to broaden their scope in diverse cross-coupling reactions.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c04966.

Experimental details, characterization data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Yi-Si Feng − *School of Chemistry and Chemical Engineering, Hefei University of Technology, He'fei City 230000 Anhui Province, China*; orcid.org/0000-0002-1646-0955; Email: fengyisi@hfut.edu.cn

Nai-Dong Chen − *Anhui Province Key Laboratory of Conservation and Utilization for Dabie Mountain Special Bio-Resources, Experimental Training Teaching Management Department, and Anhui Provincial Key Laboratory for Quality Evaluation and Improvement of Traditional Chinese Medicine, West Anhui University, Lu'an City 237012 Anhui Province, China*; orcid.org/0000-0002-1289-561X; Email: 2004cnd@163.com

Pan Pan − *Anhui Province Key Laboratory of Conservation and Utilization for Dabie Mountain Special Bio-Resources, West Anhui University, Lu'an City 237012 Anhui Province, China*; Email: 22000049@wxc.edu.cn

Authors

Shihao Li − *Anhui Province Key Laboratory of Conservation and Utilization for Dabie Mountain Special Bio-Resources, Experimental Training Teaching Management Department, and Anhui Provincial Key Laboratory for Quality Evaluation and Improvement of Traditional Chinese Medicine, West Anhui University, Lu'an City 237012 Anhui Province, China*

Mingming Li − *School of Chemistry and Chemical Engineering, Hefei University of Technology, He'fei City 230000 Anhui Province, China*

Yan Liu − *School of Chemistry and Chemical Engineering, Hefei University of Technology, He'fei City 230000 Anhui Province, China*

Jingwen Hao − *Anhui Provincial Key Laboratory for Quality Evaluation and Improvement of Traditional Chinese Medicine, West Anhui University, Lu'an City 237012 Anhui Province, China*

Shaojun Zheng − *Anhui Provincial Key Laboratory for Quality Evaluation and Improvement of Traditional Chinese Medicine, West Anhui University, Lu'an City 237012 Anhui Province, China*

Zitong Rong − *Anhui Province Key Laboratory of Conservation and Utilization for Dabie Mountain Special Bio-Resources, West Anhui University, Lu'an City 237012 Anhui Province, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.5c04966

https://doi.org/10.1021/acs.orglett.5c04966
Org. Lett. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by High-level Talent Project of West Anhui University (WGKQ2022084), Open Project of Anhui Province Key Laboratory of Conservation and Utilization for Dabie Mountain Special Bio-Resources (Grant No. WXZR202321), Bengbu Tianyi Chemical Co., Ltd. (Grant No. 0045025111). Chenggong Zheng from Zhejiang University is acknowledged for useful discussions on the reaction mechanism.

■ REFERENCES

(1) For selected reviews, see: (a) Mori, T.; Ujihara, K.; Matsumoto, O.; Yanagi, K.; Matsuo, N. Synthetic studies of fluorine-containing compounds for household insecticides. *J. Fluor. Chem.* **2007**, *128*, 1174−1181. (b) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. Organic fluorine compounds: a great opportunity for enhanced materials properties. *Chem. Soc. Rev.* **2011**, *40*, 3496. (c) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (d) Müller, K.; Faeh, C.; Diederich, F. O. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Sci.* **2007**, *317*, 1881−1886. (e) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359−4369.

(2) For selected reviews, see: (a) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience.* **2020**, *23*, 101467. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (c) Erickson, J. A.; McLoughlin, J. I. Hydrogen Bond Donor Properties of the Difluoromethyl Group. *J. Org. Chem.* **1995**, *60*, 1626−1631.

(3) Kumar, D.; Ganeshpurkar, A.; Kumar, D.; Modi, G.; Gupta, S. K.; Singh, S. K. Secretase inhibitors for the treatment of Alzheimer's disease: Long road ahead. *Eur. J. Med. Chem.* **2018**, *148*, 436−452.

(4) For selected reviews, see: (a) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359. (b) 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.* **2017**, *60*, 797−804.

(5) For selected reviews, see: (a) Belhomme, M. C.; Besset, T.; Poisson, T.; Pannecoucke, X. Recent Progress toward the Introduction of Functionalized Difluoromethylated Building Blocks onto $C(sp^2)$ and C(sp) Centers. *Chem.—Eur. J.* **2015**, *21*, 12836−12865. (b) Rong, J.; Ni, C.; Hu, J. Metal-Catalyzed Direct Difluoromethylation Reactions. *Asian J. Org. Chem.* **2017**, *6*, 139−152. (c) Yerien, D. E.; Barata-Vallejo, S.; Postigo, A. Difluoromethylation Reactions of Organic Compounds. *Chem.—Eur. J.* **2017**, *23*, 14676−14701. (d) Middleton, W. J. New fluorinating reagents. *Dialkylaminosulfur fluorides. J. Org. Chem.* **1975**, *40*, 574−578. (e) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. Bis(2-methoxyethyl)aminosulfur Trifluoride: A New Broad-Spectrum Deoxofluorinating Agent with Enhanced Thermal Stability. *J. Org. Chem.* **1999**, *64*, 7048−7054.

(6) For selected reviews, see: (a) Gu, Y.; Chang, D.; Leng, X.; Gu, Y.; Shen, Q. Well-Defined, Shelf-Stable (NHC)Ag(CF_2H) Complexes for Difluoromethylation. *Organometallics.* **2015**, *34*, 3065−3071. (b) Lu, C.; Lu, H.; Wu, J.; Shen, H. C.; Hu, T.; Gu, Y.; Shen, Q. Palladium-Catalyzed Difluoromethylation of Aryl Chlorides and Triflates and Its Applications in the Preparation of Difluoromethylated Derivatives of Drug/Agrochemical Molecules. *J. Org. Chem.* **2018**, *83*, 1077−1083.

(7) For selected reviews, see: (a) Xu, L.; Vicic, D. A. Direct Difluoromethylation of Aryl Halides via Base Metal Catalysis at Room Temperature. *J. Am. Chem. Soc.* **2016**, *138*, 2536−2539. (b) Jiang, X.; Gong, W.; Li, X.; Wang, S.; Gu, Z.; Yang, Y.; Zeng, X. Pd-Catalyzed Divergent Site-Selective Difluoromethylation and Difluoromethylcarbonylation of Aryl Sulfonium Salts. *ACS Catal.* **2024**, *14*, 13557−13566. (c) Pan, F.; Boursalian, G. B.; Ritter, T. Palladium-Catalyzed Decarbonylative Difluoromethylation of Acid Chlorides at Room Temperature. *Angew. Chem., Int. Ed.* **2018**, *57*, 16871−16876.

(8) Aikawa, K.; Serizawa, H.; Ishii, K.; Mikami, K. Palladium-Catalyzed Negishi Cross-Coupling Reaction of Aryl Halides with (Difluoromethyl)zinc Reagent. *Org. Lett.* **2016**, *18*, 3690−3693.

(9) Prakash, G. K. S.; Ganesh, S. K.; Jones, J. P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. Copper-Mediated Difluoromethylation of (Hetero)aryl Iodides and β-Styryl Halides with Tributyl(difluoromethyl)stannane. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090−12094.

(10) Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X. Chlorodifluoromethane-triggered formation of difluoromethylated arenes catalysed by palladium. *Nat. Chem.* **2017**, *9*, 918−923.

(11) For selected reviews, see: (a) Fu, X. P.; Xiao, Y. L.; Zhang, X. Nickel-Catalyzed Difluoromethylation of Arylboronic Acids with Bromodifluoromethane. *Chin. J. Chem.* **2018**, *36*, 143−146. (b) Bacauanu, V.; Cardinal, S.; Yamauchi, M.; Kondo, M.; Fernández, D. F.; Remy, R.; MacMillan, D. W. C. Metallaphotoredox Difluoromethylation of Aryl Bromides. *Angew. Chem., Int. Ed.* **2018**, *57*, 12543−12548.

(12) Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.; Iwumene, N.; am Ende, C. W.; Trabanco, A. A.; Gouverneur, V. Late-stage difluoromethylation: concepts, developments and perspective. *Chem. Soc. Rev.* **2021**, *50*, 8214−8247.

(13) For selected reviews, see: (a) Zou, Z.; Li, H.; Huang, M.; Zhang, W.; Zhi, S.; Wang, Y.; Pan, Y. Electrochemical-Promoted Nickel-Catalyzed Oxidative Fluoroalkylation of Aryl Iodides. *Org. Lett.* **2021**, *23*, 8252−8256. (b) Zhou, N.; Chai, M.; Fu, N. Dual transition metal electrocatalysis for difluoromethylation of Aryl halides using potassium difluoroacetate. *Nat. Commun.* **2025**, *16*, 10734.

(14) For selected reviews, see: (a) Lang, S.; Murphy, J. A. Azide rearrangements in electron-deficient systems. *Chem. Soc. Rev.* **2006**, *35*, 146−156. (b) Deng, L.; Dong, G. Carbon−Carbon Bond Activation of Ketones. *Trends Chem.* **2020**, *2*, 183−198.

(15) For selected reviews, see: (a) Miao, H.-J.; Zhang, J.-H.; Li, W.; Yang, W.; Xin, H.; Gao, P.; Duan, X.-H.; Guo, L.-N. Aromatization-driven deconstructive functionalization of spiro dihydroquinazolinones via dual photoredox/nickel catalysis. *Chem. Sci.* **2024**, *15*, 8993−8999. (b) Zhou, X.; Xu, Y.; Dong, G. Deacylation-aided C−H alkylative annulation through C−C cleavage of unstrained ketones. *Nat. Catal.* **2021**, *4*, 703−710. (c) Zhang, B.; Bai, H.; Zhan, B.; Wei, K.; Nie, S.; Zhang, X. Deacylative arylation and alkynylation of unstrained ketones. *Sci. Adv.* **2024**, *10*, eado0225. (d) Li, Q.-Z.; He, M.-H.; Zeng, R.; Lei, Y.-Y.; Yu, Z.-Y.; Jiang, M.; Zhang, X.; Li, J.-L. Molecular Editing of Ketones through N-Heterocyclic Carbene and Photo Dual Catalysis. *J. Am. Chem. Soc.* **2024**, *146*, 22829−22839. (e) Wu, H.; Chen, S.; Liu, C.; Zhao, Q.; Wang, Z.; Jin, Q.; Sun, S.; Guo, J.; He, X.; Walsh, P. J.; Shang, Y. Construction of C−S and C−Se Bonds from Unstrained Ketone Precursors under Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202314790. (f) Kim, S.; Chen, C.-N.; Snyder, S. A.; Dong, G. Deacylative Polyfluoroarylation via C−C Cleavage of Alkyl Ketones. *Org. Lett.* **2025**, *27*, 11052−11057. (g) Liu, R.; Zeng, H. Aerobic alcoholization via aromatization driven C−C bond cleavage of unstrained ketones. *Green. Chem.* **2025**, *27*, 7329−7335. (h) Wan, Y.; Kang, T.; Xu, Z.; Xiong, W.; Li, G.; Dong, J.; Xue, D. Enabling Efficient Synthesis of Dihydrostilbenoid via Palladium-Catalyzed Redox-Neutral Deacylative Arylation. *ACS Catal.* **2025**, *15*, 9776−9784. (i) Wei, K.; Tang, Y.; Chen, X.; Zhan, B.; Zhang, X. Stereodivergent Deacylative

https://doi.org/10.1021/acs.orglett.5c04966
Org. Lett. XXXX, XXX, XXX−XXX

Mizoroki−Heck Reaction of Unstrained Ketones. *Angew. Chem., Int. Ed.* **2025**, e18599 DOI: 10.1002/anie.202518599.
(16) For selected reviews, see: (a) Zhou, X.; Xu, Y.; Dong, G. Olefination via Cu-Mediated Dehydroacylation of Unstrained Ketones. *J. Am. Chem. Soc.* **2021**, *143*, 20042−20048. (b) Zhang, Z.; Dong, G. Carbonyl-to-sulfur swap enabled by sequential double carbon-carbon bond activation. *Sci.* **2025**, *388*, 1436−1440. (c) Zhou, X.; Yu, T.; Dong, G. Site-Specific and Degree-Controlled Alkyl Deuteration via Cu-Catalyzed Redox-Neutral Deacylation. *J. Am. Chem. Soc.* **2022**, *144*, 9570−9575.
(17) Li, J.; Xiao, Y.; Li, Z.; Yan, Y.; Song, G.; Li, G.; Dong, J.; Wang, C.; Kang, T.; Xue, D. Acetone Derivatives for Nickel-Catalyzed Methylation, Trideuteromethylation, and ^{13}C-Methylation of (Hetero)Aryl Chlorides. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202511648.
(18) For selected reviews, see: (a) Nakao, Y.; Kanyiva, K. S.; Hiyama, T. A Strategy for C−H Activation of Pyridines: Direct C-2 Selective Alkenylation of Pyridines by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2008**, *130*, 2448−2449. (b) Wen, P.; Li, Y.; Zhou, K.; Ma, C.; Lan, X.; Ma, C.; Huang, G. Palladium-Catalyzed C-2 Selective C-H Olefination of Pyridines. *Adv. Syn. Catal.* **2012**, *354*, 2135−2140. (c) Goriya, Y.; Ramana, C. V. Ruthenium-Catalyzed C6-Propenylation Reactions of Substituted Pyridine Derivatives: Directed and Direct C-H Activation. *Chem.—Eur. J.* **2012**, *18*, 13288−13292.
(19) For selected reviews, see: (a) Mao, E.; Prieto Kullmer, C. N.; Sakai, H. A.; MacMillan, D. W. C. Direct Bioisostere Replacement Enabled by Metallaphotoredox Deoxydifluoromethylation. *J. Am. Chem. Soc.* **2024**, *146*, 5067−5073. (b) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822−5880. (c) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. CF_2H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017**, *139*, 9325−9332.
(20) Wolesensky, R. M.; Morales-Colón, M. T.; Sanford, M. S. Initiation of Palladium Precatalysts: Efficiency and Product Selectivity as a Function of Ligand, Substrate, and Reaction Conditions. *ACS Catal.* **2025**, *15*, 18758−18768.

https://doi.org/10.1021/acs.orglett.5c04966
Org. Lett. XXXX, XXX, XXX−XXX