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Article

Defluorinative Multicomponent Cascade Reaction of Trifluoromethylarenes via Photoexcited Palladium Catalysis

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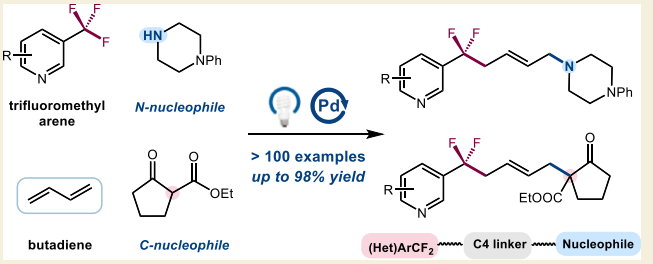
ABSTRACT: The incorporation of aromatic difluoromethyl motifs has proven to be a fruitful strategy for enhancing the therapeutic profiles of modern pharmaceutical candidates. While the defluorofunctionalization of trifluoromethylarenes offers a promising pathway toward diverse aromatic difluoromethyl compounds, current methods are predominantly limited to two-component reactions. Multicomponent cascade reactions (MCRs) involving a transient aromatic difluoromethyl radical are still uncommon and highly sought after, owing to their capacity to rapidly generate challenging molecular structures. In this study, we present a photocatalytic manifold that combines commercially available trifluoromethylarenes, feedstock dienes, and various nucleophiles to achieve a modular defluorinative MCR. This method features mild reaction conditions and a broad substrate scope with excellent functional group compatibility. Furthermore, this protocol enables a previously unreported process of defluorinative editing for the resulting MCR aromatic difluoromethyl adducts. Preliminary mechanistic studies support the proposed photoexcited palladium catalytic cycle.



KEYWORDS: *defluorination, photocatalysis, multicomponent reaction, palladium-catalyzed, difluoromethyl motifs*

INTRODUCTION

Organofluorine compounds are an important class of molecules found extensively across natural products, pharmaceuticals, agrochemicals, and advanced materials.[1−8] In particular, aromatic difluoromethyls ($ArCF_2$), which are prevalent in drug molecules and serve as privileged bioisosteres of benzoyl groups,[9−17] have garnered increasing attention due to their high lipophilicity, metabolic stability and desirable electronic properties (Figure 1a).[18] Consequently, there is a growing demand for the development of direct methodologies for the efficient and selective integration of $ArCF_2$ moieties into various organic frameworks. Over the past few decades, considerable efforts have been devoted to construct this valuable motif through deoxyfluorination,[19,20] site-selective C−H fluorination[21-23] and fluoroalkylation.[24−28] In contrast, the selective functionalization of a single C−F bond in commercially available trifluoromethylated arenes ($ArCF_3$) would generate significant opportunities to readily access the $ArCF_2$ functionality in modern drug discovery.

Conventional methods for activating C−F bond for this class of substrate typically involve electrochemical reduction,[29,30] low-valent metals,[31-33] or frustrated Lewis pairs.[34,35] However, the reactivity and selectivity of these processes usually suffer from the high energy of C(sp^3)−F cleavage (~481 kJ/mol for $PhCF_3$)[36] and the tendency toward exhaustive defluorination.[37] Recently, photoredox catalysis has emerged as a potent platform for the C(sp^3)−F cleavage of $ArCF_3$. Notable works from research groups led by König,[38] Jui,[39,40] Gouverneur,[41] Molander,[42,43] Glorius,[44] Zhang,[45] and others[46−50] have demonstrated the feasibility of single-electron reduction of the C(sp^3)−F bond. Nevertheless, these pioneering advancements have primarily focused on two-component coupling, highlighting the inherent limitation of direct addition between $ArCF_2$ radicals and acceptors (H, CO_2, alkene, *etc.*) (Figure 1b, left). Multicomponent cascade reactions, known for their sustainable nature in rapidly synthesizing complex structures, drugs, natural products, and materials in a single step, play an essential role in the synthetic toolkit of organic chemists.[51,52] Hence, it is extremely desirable to develop innovative MCRs involving the challenging selective/cascade defluorination of $ArCF_3$, thereby inspiring rational reaction design (Figure 1b, right).[53,54] 1,3-Butadienes, easily accessible feedstocks and valuable building blocks, present an attractive platform for efficient difunctionalization to access complex and high-value molecules.[55−57] Despite the demonstrated utility, a three-component coupling of *N*-/*C*-based nucleophiles, butadiene, and $ArCF_3$ for the 1,4-difunctioalization of butadiene, which

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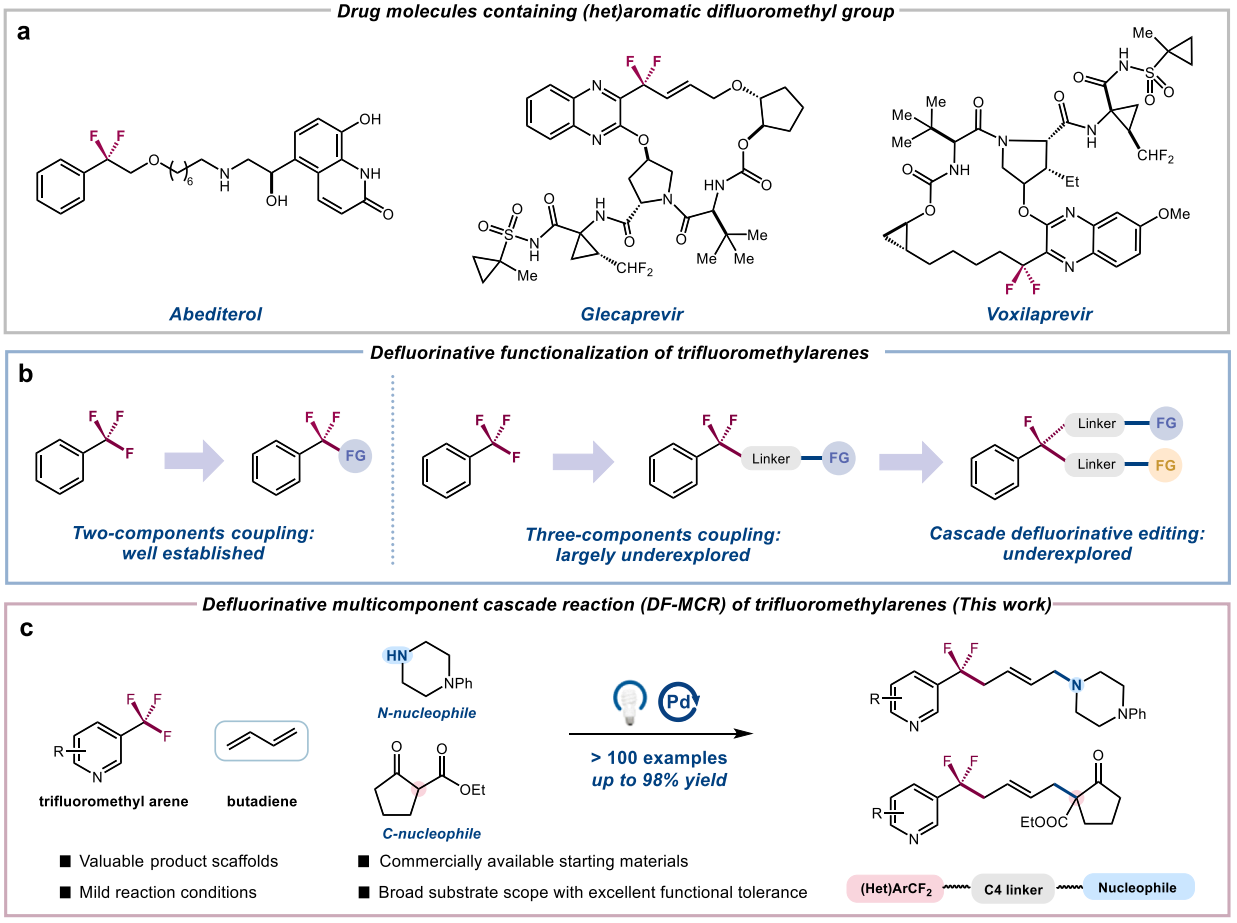
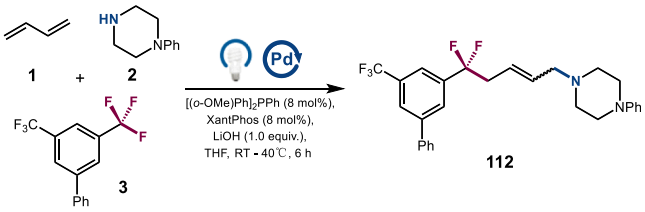


Figure 1. Development and construction of (het)aromatic difluoromethyl-contained motifs. **a**, Representative drug molecule containing (het)aromatic difluoromethyl group. **b**, Defluorinative functionalization of trifluoromethylarenes. **c**, Defluorinative multicomponent cascade reaction (DF-MCR) of trifluoromethylarenes.

Table 1. Optimization of Reaction Conditions[a]



Entry	Variation of standard condition	Yield[b]
1	None	85%(E/Z = 1:2)
2	K_2CO_3 instead of LiOH	29%
3	TMG instead of LiOH	72%
4	$Pd(PPh_3)_2Cl_2$ instead of $Pd(PPh_3)_4$	79%
5	$Pd_2(dba)_3$ instead of $Pd(PPh_3)_4$	19%
6	MeCN instead of THF	43%
7	no XantPhos	28%
8	no (o−OMe)Ph_2PPh	72%
9	no $Pd(PPh_3)_4$	N.D.
10	in the dark	N.D.
11	no LiOH	trace
12	0.3 mmol scale	91%[c](E/Z = 1:2)

[a]Reaction conditions: **1** (0.30 mmol), **2** (0.15 mmol), **3** (0.45 mmol), $Pd(PPh_3)_4$ (1.5 mol%), XantPhos (8 mol%), $[(o\text{-OMe})Ph]_2PPh$ (8 mol%), LiOH (0.15 mmol), THF (0.1 M), λ_{max} = 440 nm Kessil (40 W), N_2, RT − 40 °C, 6 h. [b]GC yield with 1,3,5-trimethylbenzene as internal standard. [c]12 h, isolated yield. N.D., not detected.

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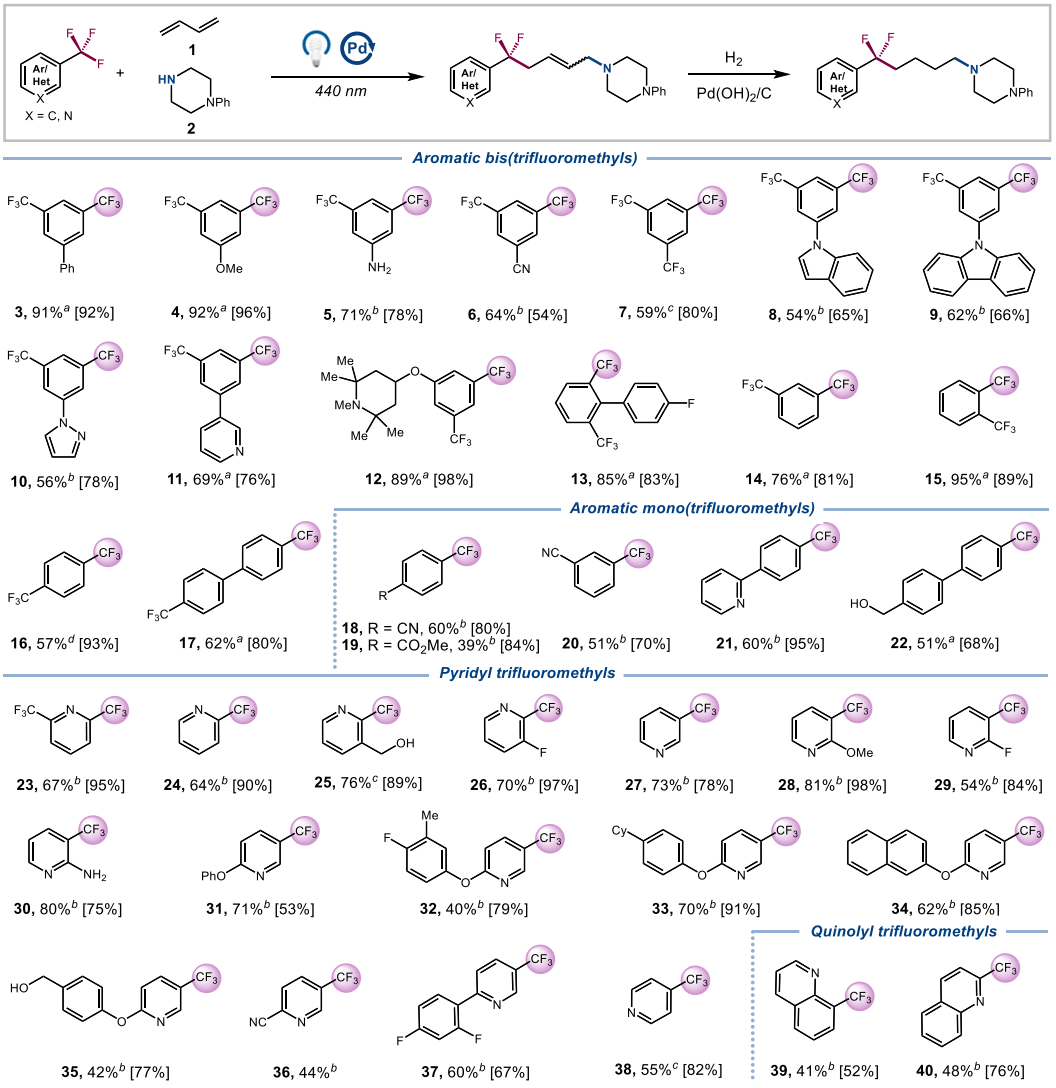
Scheme 1. Scope of Trifluoromethylarenes[abcd]



[a]Reaction conditions:(Het)ArCF_3 (0.9 mmol), **1** (0.6 mmol), **2** (0.3 mmol), $Pd(PPh_3)_4$ (1.5 mol%), XantPhos (8 mol%), $[(o\text{-OMe})Ph]_2PPh$ (8 mol%), LiOH (0.3 mmol), THF (0.1 M), λ_{max} = 440 nm Kessil (40 W), N_2, RT − 40°C, 12 h. Hydrogenation yield is shown in square brackets. See Supporting Information for hydrogenation procedures. [b]w/o $[(o\text{-OMe})Ph]_2PPh$, with $Mg(OTf)_2$ (20 mol%), 12−24 h. [c]TMG (0.3 mmol) instead of LiOH as base. [d]K_3PO_4 (0.3 mmol) instead of LiOH as base.

could provide a straightforward and practical strategy for the rapid synthesis of intriguing ArCF_2-C4 linker-nucleophile molecules, has remained elusive thus far.[58−61]

Drawing inspiration from the recent achievements in visible light-induced palladium catalysis,[62−69] we envisioned that the aforementioned transformation could be realized through this paradigm with commercially available materials, eliminating the need for an exogeneous photosensitizer. Herein, we report a modular, practical, and general photoexcited palladium-catalyzed 1,4-difunctionalization of butadiene with ArCF_3 and *N*-/C-based nucleophiles (Figure 1c, > 100 examples, up to 98% yield). The mild reaction conditions tolerate a wide range of functional groups and bioactive molecules that are typically incompatible with traditional palladium catalysis, thereby creating new opportunities to expedite drug discovery and the exploration of advanced materials. Furthermore, the adaptability and versatility of this approach are highlighted through a subsequent defluorinative coupling of the resultant products, which would be challenging to achieve using the currently established methods.

RESULTS AND DISCUSSION

We began our investigations by selecting 1,3-butadiene **1**, 1-phenylpiperazine **2** and 3,5-bis(trifluoromethyl)-1,1'-biphenyl **3** as the model substrates, and we were delighted to find that the desired product **112** was obtained in 85% yield under the standard condition, albeit as a mixture of *E*/*Z* isomers (Table 1, entry 1). It is intriguing that only trace amounts of over-defluorinated side products were detected by LC-MS analysis, likely attributed to the overwhelming loading of trifluoromethylarenes, which surpasses the generation of difluoromethylarene products. Other bases, such as K_2CO_3, and TMG, proved to be less effective, resulting in lower yields (entries 2 and 3). Furthermore, other palladium species (1.5 mol%) led to inferior results (entries 4 and 5, see Supporting Information for details). Switching the solvent to MeCN resulted in a significant decrease in the yield of the DF-MCR product **112**, likely due to the poor

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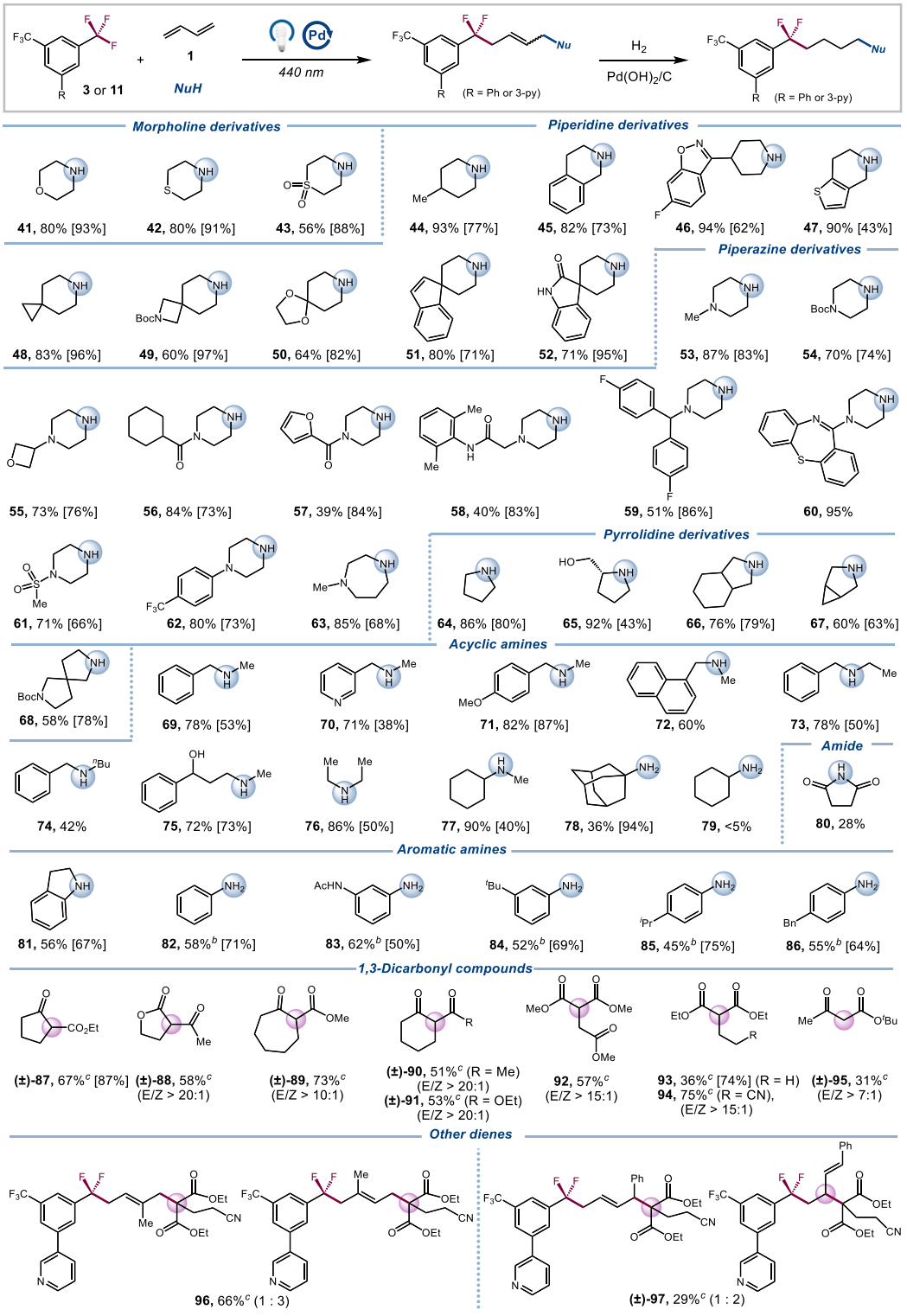
Scheme 2. Scope of Nucleophiles[abc]



[a]Reaction conditions: **3** (0.9 mmol), **1** (0.6 mmol), amine (0.3 mmol), $Pd(PPh_3)_4$ (1.5 mol%), XantPhos (8 mol%), $[(o\text{-OMe})Ph]_2PPh$ (8 mol%), LiOH (0.3−0.9 mmol, when amine hydrochloride was used, 1.0 equiv. of hydrochloride consumed additional 1.0 equiv. of LiOH), THF (0.1 M), λ_{max} = 440 nm Kessil (40 W), N_2, RT−40 °C, 12 h. Hydrogenation yield is shown in square brackets. See Supporting Information for hydrogenation procedures. [b]w/o $[(o\text{-OMe})Ph]_2PPh$, with $Mg(OTf)_2$ (20 mol%). [c]**11** (0.9 mmol), **1** (0.6 mmol), 1,3-dicarbonyl compound (0.3 mmol), $Pd(PPh_3)_4$ (1.5 mol%), XantPhos (8 mol%), $[(o\text{-OMe})Ph]_2PPh$ (8 mol%), LiOH (0.3 mmol), THF (0.1 M), λ_{max} = 440 nm Kessil (40 W), N_2, RT− 40 °C, 12 h. Hydrogenation yield is shown in square brackets. See Supporting Information for hydrogenation procedures.

solubility for the catalyst and base (43% yield) (entry 6, see Supporting Information for details). The inclusion of two types of phosphine ligands proved to be crucial for enhancing the reaction efficiency. A yield of only 28% was observed in the

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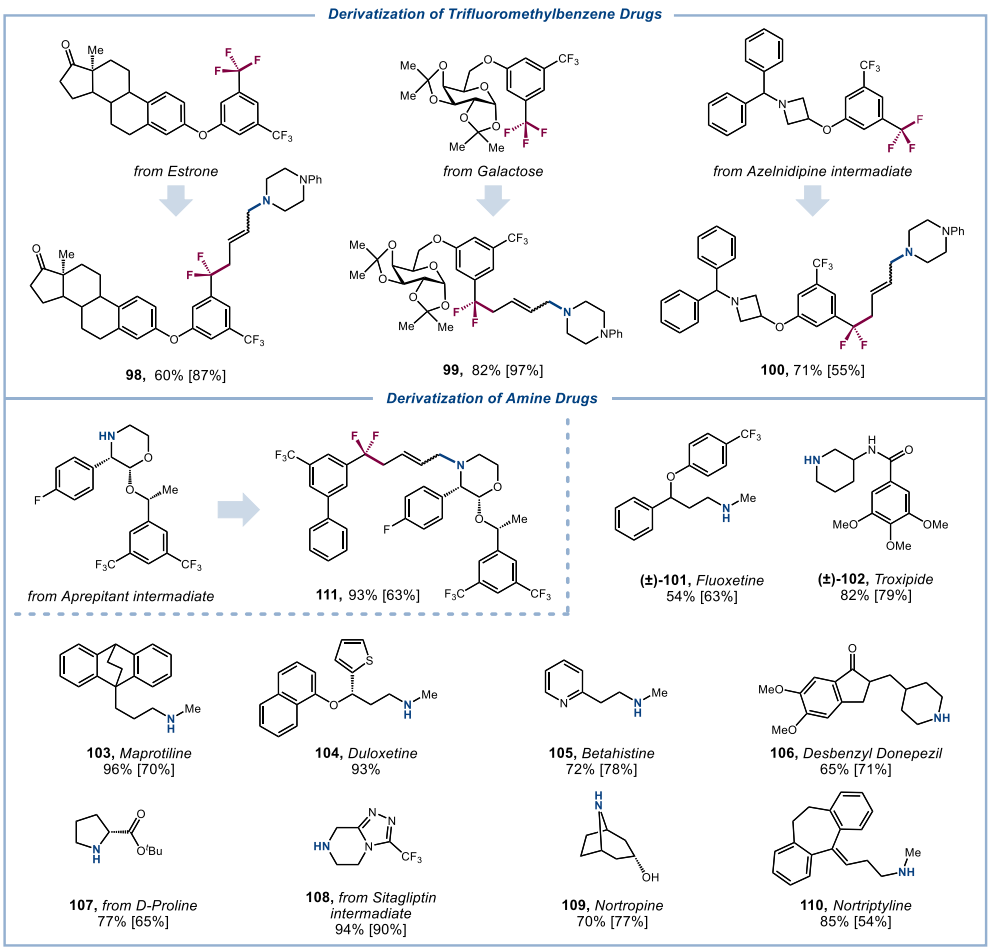
Scheme 3. Late-stage Modification of Natural Products and Drug Derivatives[a]



[a]Reaction conditions: $ArCF_3$ (0.9 mmol), 1,3-butadiene (0.6 mmol), amine (0.3 mmol), $Pd(PPh_3)_4$ (1.5 mol%), XantPhos (8 mol%), $[(o\text{-}OMe)Ph]_2PPh$ (8 mol%), LiOH (0.3−0.9 mmol, when amine hydrochloride was used, 1.0 equiv. of hydrochloride consumed additional 1.0 equiv. LiOH), THF (0.1 M), λ_{max} = 440 nm Kessil (40 W), N_2, RT − 40°C, 12 h. Hydrogenation yield is shown in square brackets. See Supporting Information for hydrogenation procedures.

absence of XantPhos, while a slightly reduced yield of 72% was obtained without the assistance of $(o\text{-}OMe)Ph_2PPh$ (entries 7 and 8). Finally, control experiments showed that the presence of the palladium catalyst, light, and LiOH was essential for achieving useful efficiencies of this transformation (entries 9−11). Notably, a 91% isolated yield was achieved when the reaction was carried out on a 0.3 mmol scale (entry 12).

With the optimized conditions in hand, we first evaluated the generality of the protocol with respect to trifluoromethylarenes. To simplify purification, the products were isolated as the corresponding hydrogenated DF-MCR adducts after reduction with $Pd(OH)_2/C$. As shown in Scheme 1, a wide array of aromatic bis(trifluoromethyl) compounds bearing electron-donating and electron-withdrawing substituents were found to be competent substrates (**3**-**17**, 54−95% yield). Notably, various functional groups such as (het)arenes, ethers, unprotected amines, and nitriles were all compatible, providing practical handles for further derivatization. Additionally, aromatic mono(trifluoromethyl) compounds (**18**−**21**) underwent smooth reactions to yield the desired products in 39−60% yield. It is worth mentioning that the benzylic alcohol **22** was cleanly preserved, providing MCR product in 51% yield.

Considering the significance of nitrogen-containing heterocycles in bioactive molecules synthesis, we were pleased to find that a broad range of pyridine substrates with trifluoromethyl groups at 2-, 3-, and 4- positions readily engage in this DF-MCR (**23**−**38**, 40−81% yield). Interestingly, the addition of 20% $Mg(OTf)_2$ significantly enhance the conversion of the $ArCF_3$ and improved the MCR yields. We assumed that Mg^{2+} could facilitate C-F bond cleavage or promote single electron transfer (SET) from Pd(0) to (het)aromatic trifluoromethyls by anchoring to the nitrogen atom.[70,71] Furthermore, this reactivity could be extended to the quinoline substrates, albeit with slightly lower yields (**39** and **40**, 41% and 48% yield, respectively).

Next, we explored the range of nucleophiles in this new protocol (Scheme 2). It was gratifying to discover that a diverse array of medicinally relevant nitrogen-based nucleophiles could engage in this transformation. Commercially available morpholine derivatives (**41**−**43**), piperidine derivatives (**44**−**52**), piperazine derivatives (**53**−**63**) and pyrrolidine derivatives (**64**−**68**) were all tolerated in this DF-MCRs with moderate to excellent yields (39−95% yield). Pleasingly, the presence of other polar functional groups such as amides and alcohols did not impede the reaction efficiency (**52**, **56**−**58**, and **65**). Moreover, the protocol could employ acyclic amine such as

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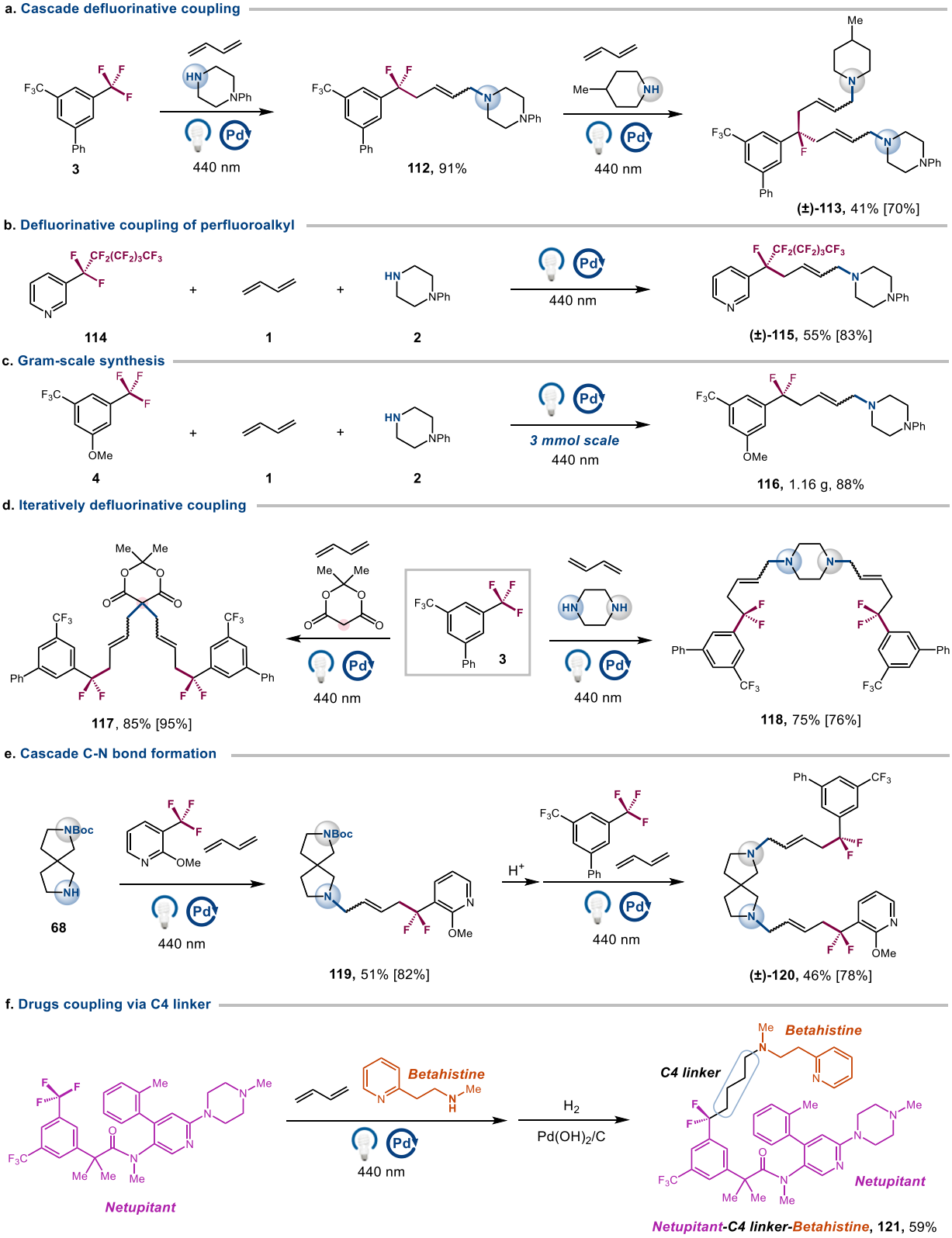
Scheme 4. Synthetic Applications[a]



[a]Reaction conditions: $ArCF_2R$ (0.9 mmol), **1** (0.6 mmol), amine (0.3 mmol), $Pd(PPh_3)_4$ (1.5 mol%), XantPhos (8 mol%), $[(o\text{-OMe})Ph]_2PPh$ (8 mol%), LiOH (0.3 mmol), THF (0.1 M), λ_{max} = 440 nm Kessil (40 W), N_2, RT − 40 °C, 12 h. Hydrogenation yield is shown in square brackets. See SI for hydrogenation procedures.

benzylamines (**69**−**74**), alkyl amines (**75**−**77**) as nucleophiles, affording the desired products in good yields (42−90% yield). Additionally, primary amines (**78**) were reactive under the optimized conditions, albeit with slightly lower yield (36% yield). Amides were also applicable substrates; however, only 28% yield of the desired product was obtained, likely due to the

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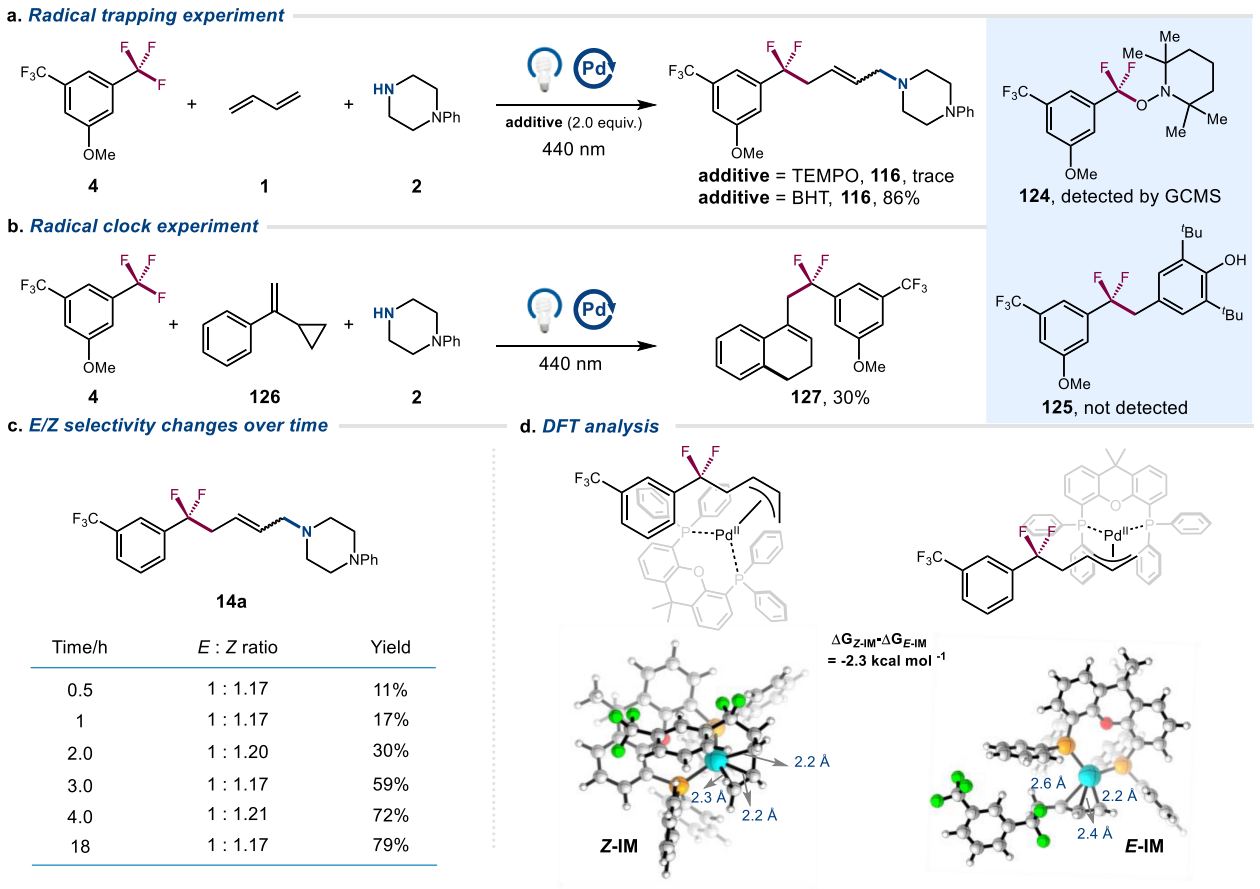

Time/h	*E* : *Z* ratio	Yield
0.5	1 : 1.17	11%
1	1 : 1.17	17%
2.0	1 : 1.20	30%
3.0	1 : 1.17	59%
4.0	1 : 1.21	72%
18	1 : 1.17	79%

Figure 2. Preliminary mechanistic experiments. **a**, Radical trapping experiment. **b**, Radical clock experiment. **c**, *E*/*Z* Selectivity changes over time. **d**, DFT analysis.

less nucleophilic nature of succinimide (**80**). Remarkably, this transformation could also accommodate aromatic amines (**81**−**86**) delivering the target products with useful levels of efficiency (45−62% yield). Encouraged by these promising results, we next sought to extend the protocol to carbon-based nucleophiles. Gratifyingly, various 1,3-dicarbonyl cyclic ester or ketones (**87**−**91**, 51−73% yield) could serve as coupling partners. Additionally, a range of acyclic 1,3-dicarbonyl compounds (**92**−**95**) was examined in the DF-MCRs, yielding the desired products at useful levels (31−75% yield). Notably, this protocol demonstrates good to excellent *E*/*Z* selectivity with the *C*-nucleophiles, in stark contrast to previous instances with *N*-nucleophiles that usually resulted in low *E*/*Z* selectivity. Finally, other 1,3-conjugated dienes were examined. Under standard conditions, 2-methyl-1,3-butadiene exhibited good reactivity with a regioselectivity of 1:3 (**96**, 66% yield). However, when 1-phenyl-1,3-butadiene was used in the reaction, 1,2-addition was superior to 1,4-addition with 2:1 regioselectivity in 29% yield (**97**).

Having demonstrated the success of these DF-MCRs, we were further motivated to explore late-stage modification of natural products and pharmaceuticals (scheme 3). Trifluoromethylarenes derived from estrone, galactose, and azelnidipine were proved to be effective substrates for late-stage defluorinative coupling with 1,3-butadiene **1** and 1-phenylpiperazine **2** under standard conditions, resulting in the corresponding products **98**−**100** in 60−82% yields. Furthermore, a series of amine-containing drug molecules could also be employed to furnish the target $ArCF_2$-C4 linker-amines in synthetically useful yields. Methyl amines such as fluoxetine (**101**), maprotiline (**103**), doluxetine (**104**), betahistine (**105**) and nortriptyline (**110**) were reacted smoothly to give the desired products in moderate to excellent yields (54−96% yield). Cyclic amines such as troxipide (**102**), desbenzyl donepezil (**106**), *D*-proline (**107**), sitagliptin (**108**), nortropine (**109**), and aprepitant (**111**) were also competent to deliver satisfying results (65−94% yield), showcasing the broad compatibility of our protocol with complex structural scaffolds.

To highlight the potential utility of the DF-MCRs in organic synthesis, several applications were showcased. First, a cascade defluorinative coupling of **3** was demonstrated, providing benzylic monofluoromethyl compound **113** under standard condition (scheme 4a). To our knowledge, this represents the first instance of DF-MCRs adducts engaging in a metal-laphotoredox-catalyzed cascade defluorinative editing process. It is noteworthy that perfluoroalkylarene **114** could also be utilized for selectively defluorinative coupling, producing the corresponding product **115** in 55% yield (Scheme 4b). Additionally, a gram-scale reaction was performed under the standard conditions, giving the target products **116** in 88% yield (Scheme 4c). Moreover, when piperazine was employed as the nucleophile for iteratively defluorinative coupling, two C−N bonds were formed in a single step to afford **118** in 75% yield (Scheme 4d, right). Similar result was also observed with malonic acid cyclic isopropylidene ester as a carbon-based nucleophile (**117**, 85% yield) (Scheme 4d, left). Furthermore, a cascade C−N bond formation was carried out to provide **119** and **120** in moderate yield by using *t*-butyloxycarboryl protected

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amine **68** as a nucleophile (Scheme 4e). Finally, two medicinally significant drugs (netupitant and betahistine) could be employed in this newly developed three-component cascade coupling to generate the C4-linked drug derivative **121** in 59% yield, a synthesis that would be challenging if using existing synthetic methodologies (Scheme 4f).

To gain insight into this transformation, several mechanistic studies were conducted. First, when the reaction was carried out in the presence of TEMPO, only a trace amount of product **116** was detected, along with the identification of the difluoromethyl-TEMPO adduct **124** (detected by GCMS). This observation suggests the involvement of difluoromethyl radical intermediates in the process (Figure 2a). In contrast, when BHT was used as an inhibitor, we found that the yield of **116** remained largely unaffected, and no BHT adduct **125** was found in the reaction system, likely due to the rapid recombination of the difluoromethyl radical with Pd (I) species to form the difluoromethyl Pd(II) complex (Figure 2a). Furthermore, an α-cyclopropylstyrene **126** was employed in a radical clock experiment, where ring-opening followed by intramolecular cyclization resulted in the formation of the corresponding product **127** in 30% yield, supporting the radical mechanism in this process (Figure 2b). A tracking experiment revealed that the E/Z ratio of **14a** did not change over time, indicating that irradiation did not alter the configuration of the double bond during the photocatalysis process (Figure 2c). The slightly favorable Z-configuration suggested by the E/Z ratio led to speculation that the Z-configuration in the metal complex intermediates is more stable than the E-configuration. Thus, density functional theory (DFT) calculations were performed to investigate some details of these two configurations in the Pd (II) complex before product releases. The geometries were optimized in a vacuum at the B3LYP-D3 level. The mixed basis set was adopted (LanL2DZ for Pd and 6−31G* for nonmetallic atoms) and it was improved for single-point calculations (LanL2DZ for Pd and 6−311G** for nonmetallic atoms) with the inclusion of solvent effects of THF (SMD model). As shown in Figure 2d, the π-center of the substrate faces inward to XantPhos in Z- **IM**, while it faces outward to the ligand in E- **IM**. This suggests that the substrate may be stabilized by XantPhos in the former, a viewpoint supported by the Gibbs free energy calculations. Specifically, the ΔG of Z-**IM** is 2.3 kcal mol^{-1} lower than that of E-**IM**. This observation may explain the higher proportion of Z-products compared to E-products in the experimental results compared with those reported in the literature. We also conducted UV−vis experiments and found that $Pd(PPh_3)_4$ can be excited at approximately 340 nm with moderate absorbance. A similar result was observed upon the addition of XantPhos, resulting in a red shift to around 360 nm and decreased absorbance. It was unexpected that the addition of $[(2\text{-OMe})Ph]_2PPh$ led to a significant increase in absorbance (Figure S6). Furthermore, ^{31}P NMR experiments revealed that either XantPhos or $[(2\text{-OMe})Ph]_2PPh$ can facilitate the ligand exchange process of $Pd(PPh_3)_4$ (Figures S12 and S13). These results suggest the generation of a Pd(0)-XantPhos-$[(2\text{-OMe})Ph]_2PPh$ complex in the reaction system, which likely serves as the active catalyst for this reaction.

On the basis of mechanistic experiments and earlier precedents,[58−69] a putative mechanistic pathway was proposed (Figure 3). Initially, under visible light conditions (blue LED), a direct single electron transfer from excited Pd(0) complex **A** to trifluoromethylarenes generates intermediate **B** (Tables S6-S11, Figures S12 and S13), which then produces a hybrid

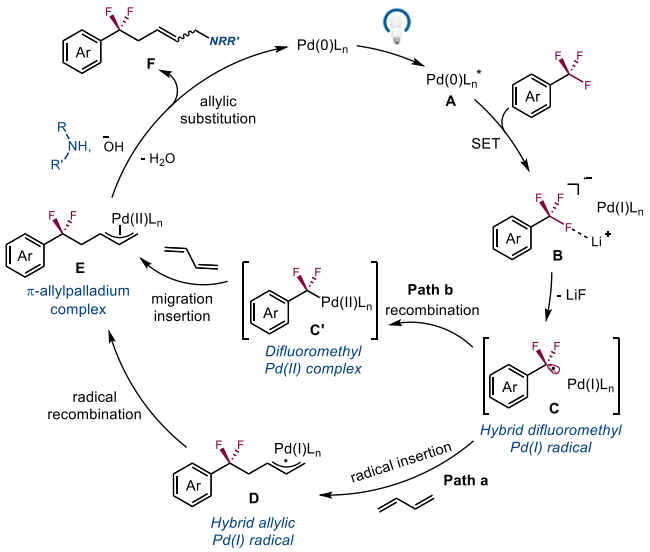

Figure 3. Proposed mechanism.

difluoromethyl Pd(I) radical intermediate **C** via Li^+ assisted C-F bond cleavage (Table S2).[70,71] Subsequently, **C** may undergo a radical addition into 1,3-dienes to form hybrid allylic Pd(I) radical species **D** (path a), or it may proceed through the recombination of the resulting difluoromethyl radical with Pd(I) leading to the formation of the difluoromethyl Pd(II) complex **C'**[45] (path b). This is followed by radical recombination of **D** or the migration insertion of **C'**, resulting in the generation of π-allylpalladium complexes **E**. Meanwhile, OH^- can serve as a suitable base in THF conditions to enhance the nucleophilicity of the amine, which then attacks the π-allylpalladium complexes **E** to yield the desired DF-MCR product **F** and regenerate the palladium catalyst in a redox-neutral process.

CONCLUSIONS

In summary, we have demonstrated a general catalytic protocol for the defluorinative multicomponent coupling of trifluoromethylarenes, dienes, and *N*-/*C*-based nucleophiles enabled by the photoexcited palladium catalytic system. These transformations were characterized by their wide applicability, mild redox-neutral conditions, and capacity for the late-stage modification of natural products or drugs. Furthermore, the successful cascade editing of difluoromethyl groups within this protocol underscores its potential for efficiently accessing complex molecular diversity. Mechanistic investigations are presented and discussed.

METHODS

General Procedure for Three Components Coupling

To an 8 mL vial equipped with a stir bar was added $Pd(PPh_3)_4$ (5.2 mg, 4.6 μmol, 0.015 equiv.), XantPhos (14.0 mg, 0.024 mmol, 0.08 equiv.), bis(2-methoxyphenyl)phenylphosphine (7.8 mg, 0.024 mmol, 0.08 equiv.), substituted trifluoromethylbenzene (0.90 mmol, 3.0 equiv.), amine or 1,3-dicarbonyl compound (if solid or high boiling point liquid, 0.30 mmol, 1.0 equiv.), LiOH (7.2 mg, 0.30 mmol, 1.0 equiv.) and THF (3.0 mL). The solution was degassed by bubbling with nitrogen for 8 min, and 1,3-butadiene (2.0 mol/L in THF, 300 μL, 0.60 mmol, 2.0 equiv) was syringed into the reaction vessel before sealing with parafilm. The reaction was carried out in a steel chamber under the irradiation at room temperature via blue LEDs (40 W,

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λ_{max} = 440 nm) for 12 h. The reaction mixture was removed from the light, cooled to ambient temperature, and quenched by exposure to air. After the removal of the solvent, the residue was purified by flash chromatography on silica gel to afford the desired product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00899.

General information, synthesis of starting materials, details of reaction optimization, synthetic applications and preliminary mechanistic experiments, computation data, characterization of all compounds, references, and NMR Spectra (PDF)

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Author Contributions

X.Z. conceptualized the project. Z.L., K.W., B.Z., P.L., and X.Z. designed, performed, and analyzed experiments. L.B. conducted the DFT calculations. Z.L., B.Z., and X.Z. prepared the manuscript, which was revised by all authors. All authors have given approval to the final version of the manuscript. CRediT: **Zhibin Li** data curation, methodology, writing - original draft; **Lei Bao** formal analysis, investigation; **Kaihang Wei** investigation, methodology; **Bei-Bei Zhan** investigation, writing - original draft; **Ping Lu** validation; **Xiaheng Zhang** conceptualization, funding acquisition, project administration, writing - original draft, writing - review & editing.

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Notes

The authors declare the following competing financial interest(s): X. Zhang, Z. Li and K. Wei are inventors on a Chinese patent application (Application No. CN202410093803X).

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