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A Unified Strategy for the Synthesis of Difluoromethyl- and Vinylfluoride-Containing Scaffolds

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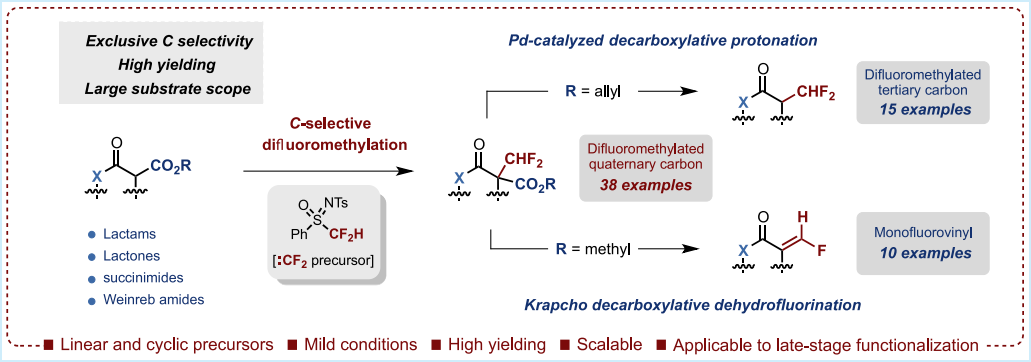
Supporting Information



ABSTRACT: Here, we report a general method for the synthesis of quaternary and tertiary difluoromethylated compounds and their vinylfluoride analogues. The strategy, which relies on a two-step sequence featuring a *C*-selective electrophilic difluoromethylation and either a palladium-catalyzed decarboxylative protonation or a Krapcho decarboxylation, is practical, scalable, and high yielding. Considering the generality of the method and the attractive properties offered by the difluoromethyl group, this approach provides a valuable tool for late-stage functionalization and drug development.

For several decades now, the introduction of fluorine atoms and fluorinated groups has drawn the attention of the synthetic organic chemistry community[1] because these functional groups have a tendency to exhibit enhanced properties, compared to their nonfluorinated counterparts; these include greater metabolic stability, lipophilicity, membrane permeability, and bioavailability.[2,3] The difluoromethyl group in particular was shown to exhibit a weak hydrogen bond donating ability and thus act as a bioisostere to carbinols, thiols, amides, and hydroxamic acids.[4] Interestingly, although fluorination and perfluoroalkylation reactions have now reached a certain maturity, the development of an efficient and reliable difluoromethylation reaction to access tertiary difluoromethylated compounds still remains a challenge.[5] Indeed, several limitations such as the choice of the difluoromethylating agent, its regioselectivity, its rather limited substrate scope and the stability of the difluoromethylated products themselves still preclude the use of this reaction as a reliable synthetic tool.[6] While significant progress has recently been made to access quaternary difluoromethylated compounds through electrophilic *C*-selective difluoromethylation processes by Mikami,[7a] Kappe,[7b] Shen,[7c] Liu,[7d] Shibata,[7e] and Hu[7f] (see Figure 1), examples of methods affording tertiary difluoromethylated derivatives are still rather scarce. In this context, several effective difluoromethylating agents have been recently developed. Hu and co-workers, for instance, were the first to introduce a tosylsulfoximine-based reagent to promote the difluoromethylation of *C*-nucleophiles (**I**; see Figure 1),[8] while Shibata and co-workers reported the sulfonium and sulfoxinium salts **II** and **III** (Figure 1), which both displayed high reactivity albeit moderate C/O selectivity.[6,9] More recently, Shen,[7c] Liu,[7d] and Shibata[7e] unveiled three new reagents (**IV**, **V**, and **VI**; see Figure 1), which induced excellent C-selectivities in the difluoromethylation of β-keto esters. These fundamental advances were completed by a recent study by Hu and co-workers, who generalized the use of $TMSCF_2Br$ (**VI**; see Figure 1) to a larger range of C-centered nucleophiles.[7f] Surprisingly, while all of these reagents have been used to prepare quaternary difluoromethylated compounds, they all failed to provide the related tertiary derivatives. In this context, we were interested in developing a general method that would not only allow a straightforward access to a wide range of synthetically and biologically relevant quaternary (Q-CHF_2) and tertiary (T-CHF_2) C-difluoromethylated scaffolds, but also their vinylfluoride (V-CHF) analogues. As we will see, the combination of a highly C-selective difluoromethylation with either a palladium-catalyzed

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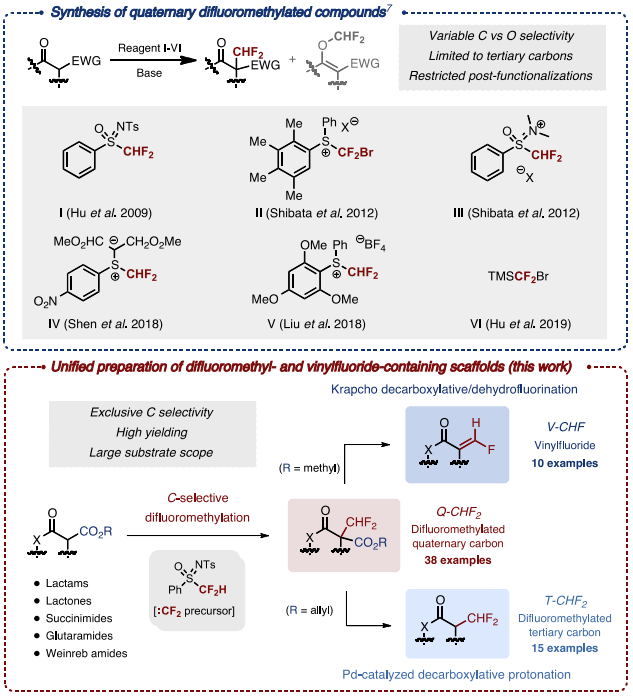


Figure 1. Unified preparation of difluoromethyl- and vinylfluoride-containing scaffolds.

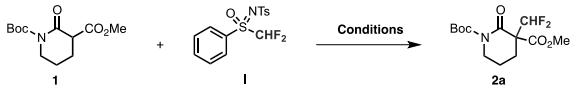
decarboxylative protonation or a Krapcho decarboxylation/dehydrofluorination enables a practical and scalable route to a variety of fluorinated building blocks (Figure 1).[10,11] These methods were eventually applied to the late-stage functionalization of various natural products and APIs.

The choice of the difluoromethylating agent was the starting point of our study. Indeed, several criteria needed to be met; ideally, the difluoromethylating agent needed to exhibit high regioselectivity while the transient difluoromethylating species needed to be generated in an unbiased and controlled fashion to minimize any undesirable side reaction that could occur during the process. Hu's reagent, *S*-(difluoromethyl)-*S*-phenyl-*N*-tosylsulfoximine **I**, appeared to be the perfect candidate as the generation of the difluorocarbene was proven to be solely induced by the enolate, independent of the base used.[8,12] In addition, this solid and bench-stable reagent is easy to use and can be prepared on a multigram scale in only three steps, starting from thiophenol.[13]

To conduct the optimization of the difluoromethylation step, we chose *N*-Boc-protected *β*-methylester valerolactam **1** as a model substrate. Interestingly, a complete *C*-selectivity of the reaction was observed; the desired *C*-difluoromethylated lactam **2a**, being the only product detected by ^{19}F and ^{1}H nuclear magnetic resonance (NMR) of the crude reaction mixture. A thorough screening of the conditions showed the ineffectiveness of organic bases such as Et_3N and DBU (see Table 1, entries 1 and 2) and mild inorganic bases such as K_2CO_3 (see the Supporting Information for a complete base screen). The use of stronger bases such as NaH, LiHMDS, or KHMDS led to higher yields (see Table 1, entries 3−5); however, the best results were obtained with non-nucleophilic alkoxides, such as potassium *tert*-butoxide, which afforded the desired lactam in 66% yield (see Table 1, entry 6).

Both the concentration and the stoichiometry proved to be crucial for the reaction to proceed efficiently with a concentration of 0.15 M, 2.1 equiv of base, and 2 equiv of **I**

Table 1. Systematic Study[a]



entry	base (equiv)	**I** (equiv)	solvent	temperature	yield[b] (%)
1	Et_3N (2.1)	1.5	DCM	−78 °C to rt	trace
2	DBU (2.6)	1.5	DCM	−78 °C to rt	trace
3	NaH (2.1)	1.5	THF	−78 °C to rt	34
4	LiHMDS (2.1)	1.5	THF	−78 °C to rt	56
5	KHMDS (2.1)	1.5	THF	−78 °C to rt	52
6	*t*-BuOK (2.1)	1.5	THF	−78 °C to rt	66
7	*t*-BuOK (1.1)	2.0	THF	0 °C	36
8	*t*-BuOK (2.1)	2.0	THF	0 °C	66
9	*t*-BuOK (2.1)[c]	2.0	THF	0 °C	10
10	*t*-BuOK (2.1)	2.0	THF	0 °C	69
11	***t*-BuOK (2.1)**[d]	**2.0**	**DCM**	**−40 °C**	**81**

[a]All reactions were performed on a 0.1 mmol scale during 24 h. **I** is added after stirring **1** with the base for 30 min. [b]Yield determined by ^{1}H NMR, using dibromomethane as an internal standard. [c]Reaction performed using 2.1 equiv of 18-crown-6. [d]Reaction completed after 12 h.

being the best conditions (see Table 1, entry 8). A drastic loss in reactivity was observed when the "naked" enolate was engaged. Indeed, in the presence of 18-crown-6, the yield decreased from 66% to 10%, although 1 equiv of **I** was consumed (Table 1, entry 9), thus clearly stressing the dual role of the enolate, which acts as both a base and a nucleophile.

A thorough screening of the nature of the solvent showed the superiority of DCM over all the other solvents as the corresponding *C*-difluoromethylated product was obtained in 69% yield after 6 h (see the Supporting Information for a complete solvent screen). This yield could be further improved by simply conducting the reaction at −40 °C (81%; see Table 1, entry 11).

With these optimal conditions in hand, we naturally turned our attention toward the scope of the reaction. As a general trend, no discrepancies were observed when varying either the protecting group on the nitrogen atom, the nature of the ester, or the scale of the reaction (**2**−**5**). This prompted us to use the less bulky Bn-protecting group for the rest of the study. Other six-membered ring heterocyclic scaffolds were evaluated such as glutaramides (**6**), quinolinones (**7**), and tetrahydropyrimidine-2,4-diones (**8**); all afforded high yields ranging from 58% to 96%. Good to excellent reactivities were also observed with the smaller five-membered ring *γ*-lactams (**9**),[10c] succinimides (**11**) and oxindoles (**12**), as the corresponding *C*-difluoromethylated products were obtained in good to excellent yields, ranging from 74% to 93%. Replacing the ester by a ketone was not detrimental to either the reactivity or the selectivity as the corresponding *C*-difluoromethylated product **10** was obtained in 74% yield. The method could also be successfully applied to the seven-membered ring caprolactam **14** and to the four-membered ring *β*-lactam **13**; however, the latter was isolated in only 17% yield. This was associated with the relative instability of the corresponding enolate intermediate. Finally, butyrolactones also proved to be good candidates, as showcased by the moderate to good yields obtained for **15** and **16**. Several attempts to conduct a direct *α*-difluoromethylation on substrates lacking the ester moiety were made, first on the Boc-protected *δ*-valerolactam itself and then on the Boc-protected *δ*-valerolactam bearing a phenyl

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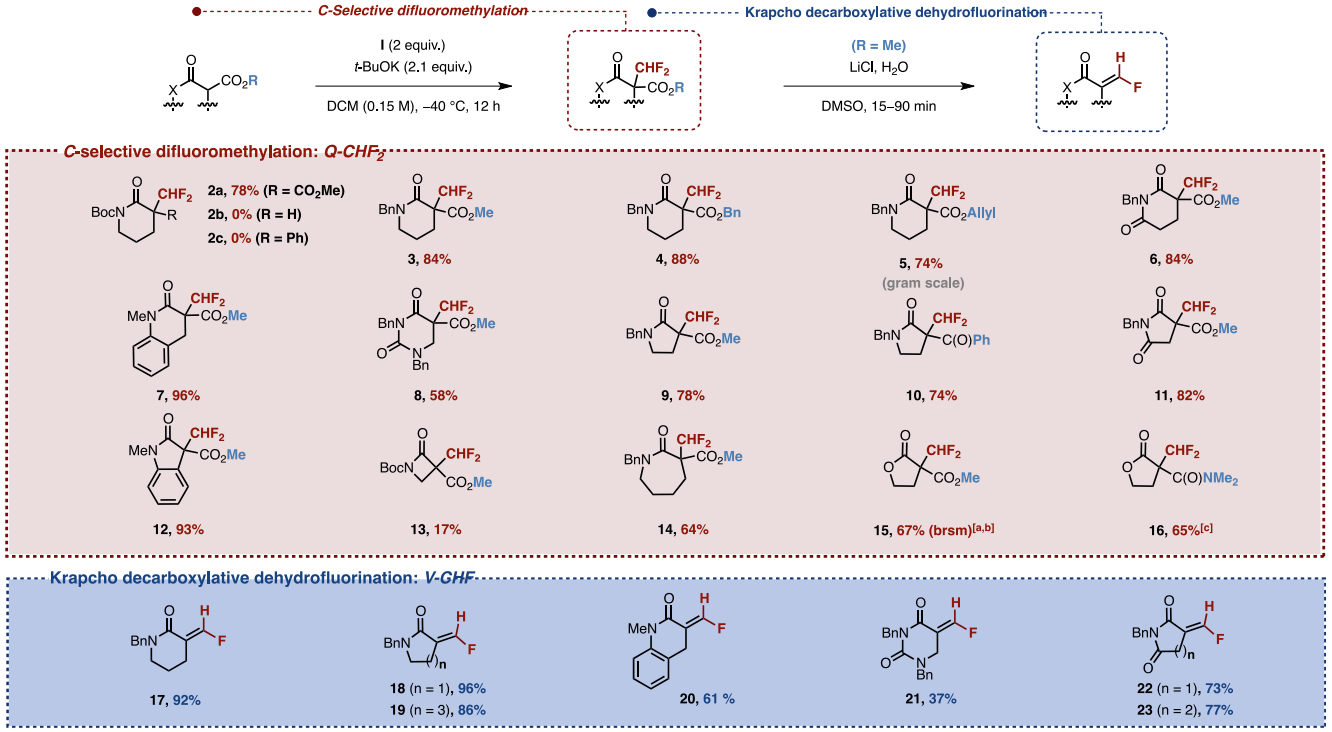

Figure 2. C-selective difluoromethylation with Q-CHF_2 and Krapcho decarboxylative dehydrofluorination with V-CHF. The superscripted "[*a*]" indicates that the reaction was performed in THF (0.1 M) at rt for 3 d. The superscripted "[*b*]" indicates that the yield was based on recovered starting material (26% isolated yield). The superscripted "[*c*]" indicates that the reaction was allowed to warm up to rt after 12 h of stirring at −40 °C, and stirring was continued at the same temperature for an additional 36 h.

substituent at the α-position; however, no conversion was observed, confirming the importance of the β-keto ester motif for the difluoromethylation step (see the Supporting Information for more details).

Keeping in mind our objective to provide a tool for the synthesis of tertiary difluoromethylated scaffolds, we decided to subject our quaternary difluoromethylated methyl ester derivative **3** to the traditional Krapcho decarboxylation conditions (DMSO, LiCl, H_2O, heating). Unfortunately, instead of the desired decarboxylation product, we isolated the corresponding *E*-vinylfluoride analogue **17** in 92% yield (see Figure 2). This outcome, which is most likely due to the increased acidity of the tertiary difluoromethylated intermediate, which favors the loss of HF through an E_1cB process, was actually also observed by Tunemoto and co-workers.[16] Nevertheless, we decided to take advantage of this reactivity pattern to synthesize various key vinylfluoride derivatives. We rapidly realized that only 15 min were necessary to achieve full conversion, high yields, and exclusive *E* stereoselectivity.

We believe this selectivity is due to the increased stability of the pro-*E* enolate intermediate obtained upon decarboxylation and the $E1_{CB}$ type mechanism, which forces an *anti* elimination (see the Supporting Information for full discussion). Generally, the 5-, 6-, and 7-membered ring lactams and quinolinones were readily converted to the corresponding vinylfluorides in good to excellent yields, ranging from 61% to 96% (**17**−**20**; see Figure 2). Slightly milder conditions were used in the case of the tetrahydropyrimidine-2,4-dione, glutaramide, and succinimide derivatives, because of stability issues; however the yields remained relatively high (**21**−**23**; see Figure 2). Hence, although the oxindole derivative could not be isolated, this metal-free, fast, trivial to set up, and entirely diastereoselective sequence showed relatively wide applicability, as showcased by the various exocyclic (*E*)-monofluoroalkene derivatives obtained.

In our effort to develop a viable route to tertiary difluoromethylated compounds[17,18] and considering our expertise in the field of Pd-AAA,[19] we next decided to investigate yet another route involving a palladium-catalyzed decarboxylative protonation of substrates bearing an activated allyl ester.[20] Indeed, if successful, this would not only provide the straightforward access to the tertiary difluoromethylated scaffolds that we were aiming for, it would also be the first example of a palladium-catalyzed decarboxylative protonation applied to a difluoromethylated precursor. Therefore, a second and wider difluoromethylation scope was conducted; the results are depicted in Figure 3.

As expected, the differences between the allyl and the methyl esters in the difluoromethylation step were negligible; all the substrates engaged led to the *C*-difluoromethylated products in high yields ranging from 69% to 92% (**24**−**31**) with the exception of glutaramide **25** and butyrolactone **31**, which were obtained in only 26% and 37% yield, respectively.

Considering the importance of Weinreb amides in routine organic synthesis,[11] we decided to apply the method to such compounds. We were pleased to observe that these acyclic scaffolds could also be successfully difluoromethylated in good to excellent yields, ranging from 54% to 97% (see Figure 3, **32**−**39**). The reaction proved to tolerate various substitution patterns at the α-position, from simple alkyls to more-complex side chains without showing any side reactivity.

Following these results, we next evaluated the palladium-catalyzed decarboxylative protonation. Luckily, we rapidly managed to obtain the desired decarboxylated products by

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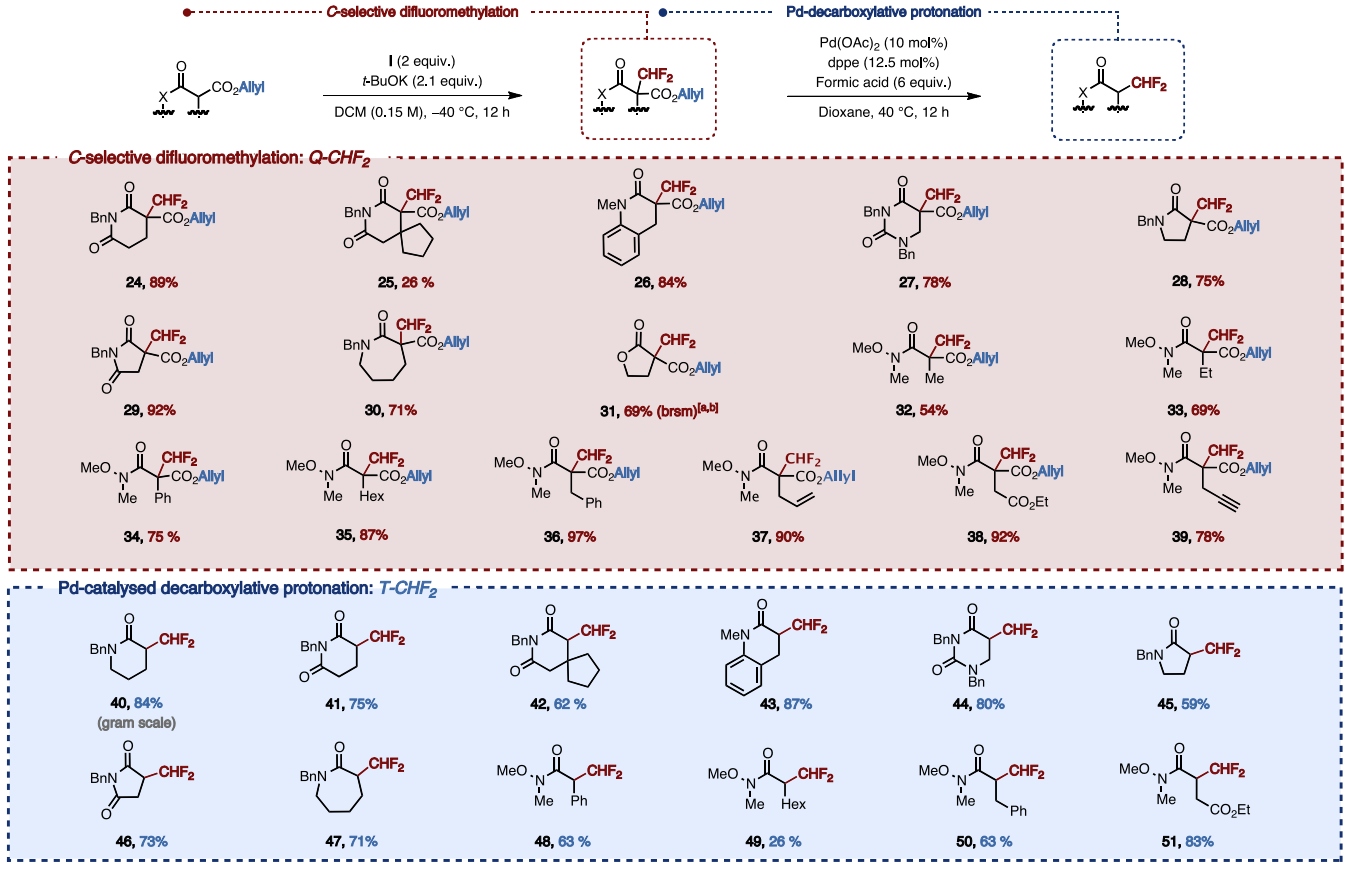

Figure 3. C-selective difluoromethylation with Q-CHF_2 and Pd-carboxylative pronation with T-CHF_2. The superscripted "[*a*]" indicates that reactions were performed in THF (0.1 M) at room temperature for 3 d. The superscripted "[*b*]" indicates that the yield is based on recovered starting material (37% isolated yield).

simply heating the allyl esters in the presence of $Pd(OAc)_2$, dppe, and formic acid.[21] Lactams, glutaramides, succinimides, and quinolinones all proved to be good candidates as the corresponding tertiary difluoromethylated compounds were obtained in good to high yields, ranging from 59% to 87%, including the azapirone derivative **42**.[22] Most importantly, the reaction could be run on a gram scale without any noticeable loss in efficiency (**40**; see Figure 3). The reaction also proved to be applicable to Weinreb amides, as showcased by the formation of the corresponding tertiary difluoromethylated products **48**–**51** in yields ranging from 26% to 83%.

The scope culminated with the application of this C-selective difluoromethylation to the late-stage functionalization of biologically relevant targets including natural products [matrine (**53**, 33%), sclareolide (**54**, 65%), pyroglutaminol (**57**, 44%)] and APIs [aniracetam (**52**, 45%), phensuximide (**55**, 60%)] (see Figure 4). In the case of sclareolide, the difluoromethylation also proved to be remarkably stereoselective as the corresponding difluoromethylated product **54** was obtained as a single diastereomer. The difluoromethylated analogues of aniracetam, matrine, and sclareolide were eventually subjected to the Pd-catalyzed decarboxylative protonation conditions and the desired tertiary difluoromethylated products **58**, **59**, and **60** were all obtained in good yields and an excellent diastereoselectivity in the case of the sesquiterpene lactone. Surprisingly, in the case of compounds **55**, **56**, and **57**, the decarboxylation predominantly led to the vinylfluorides **61**, **62**, and **63**, along with the desired tertiary difluoromethylated products due to the increased acidity of these compounds, which favors the E1cB elimination process. To push the reaction toward the complete formation of the vinylfluoride derivatives, the crude reaction mixtures were adsorbed onto silica in the presence of Et_3N, which allowed isolation of the phensuximide (**61**, 75%), costinone B[23] (**62**, 79%), and pyroglutaminol (**63**, 79%) derivatives in overall good yields and with an exclusive (*E*)-configuration. Interestingly, these last three compounds could not be obtained under the Krapcho decarboxylation conditions, which showcases the complementarity between the two methods. Finally, the Yamazaki conditions [LDA, THF, − 78 °C], initially developed for the dehydrofluorination of trifluoromethyl moieties, could also be applied (Ⓐ in the bottom panel of Figure 4),[24] while alternative post-functionalization reactions, including the conversion of valerolactam **3** to the corresponding amide **64** [NH_3, MeOH, reflux, 78% yield (Ⓑ in the bottom panel of Figure 4)] and piperidine **65** [$LiAlH_4$, THF, reflux, 52% yield (© in the bottom panel of Figure 4)] were relatively trivial (see the Supporting Information for details). This latter result is all the more appealing, since piperidines are arguably the most prevalent heterocycle in approved drugs.[10a]

In summary, we have developed a highly straightforward, synthesis of both quaternary and tertiary difluoromethylated scaffolds and their (*E*)-vinylfluoride analogues. This strategy, which combines a C-selective difluoromethylation with either a palladium-catalyzed decarboxylative protonation or a Krapcho decarboxylation, is practical, usually high-yielding and scalable. Moreover, it can be applied to the late-stage functionalization

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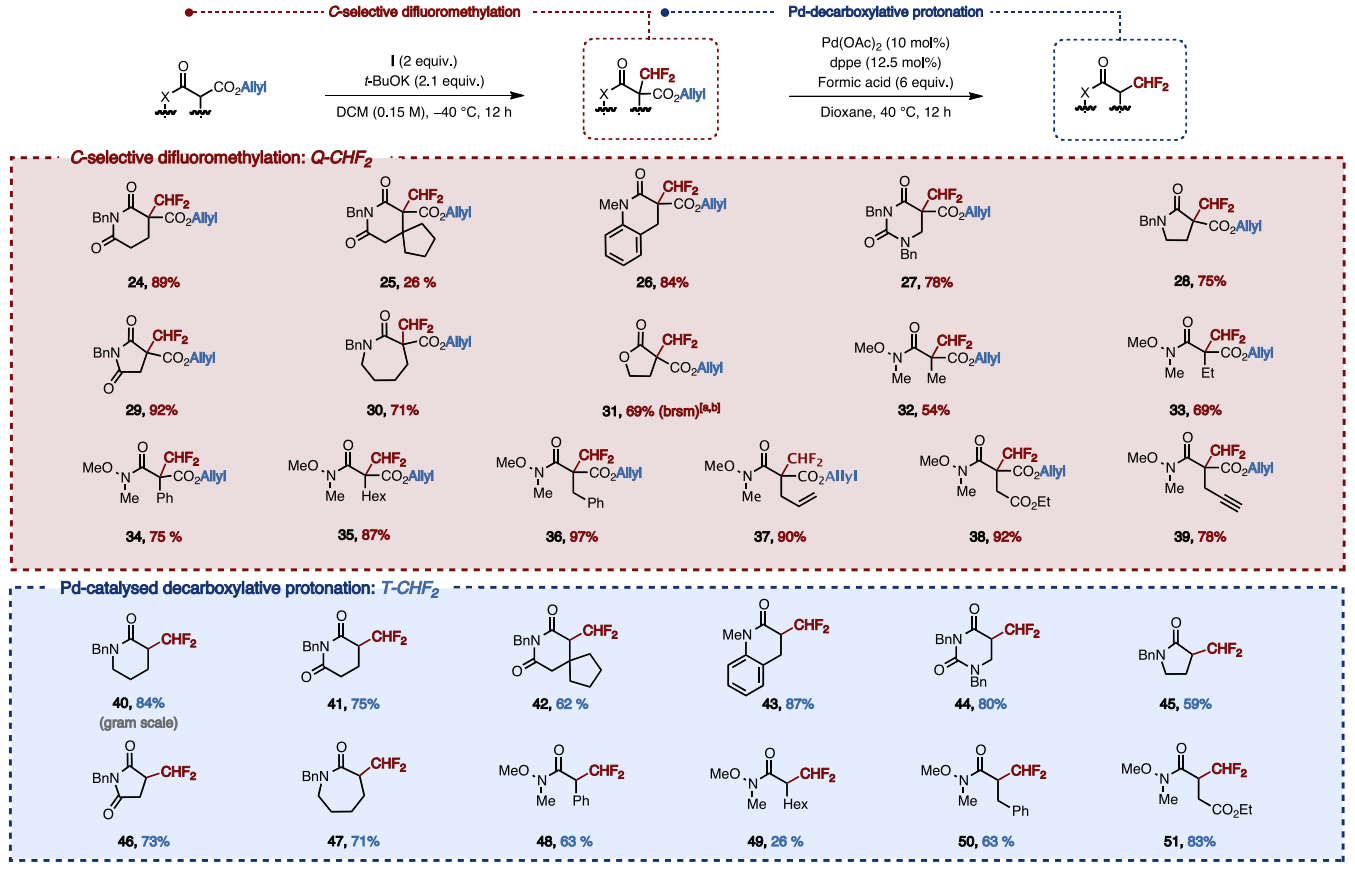

Figure 4. Late-stage functionalization of various natural products and APIs such as aniracetam, matrine, sclareolide, phensuximide, Costinone B, and pyroglutaminol. The superscripted [*a*] indicates that the reaction was run using 3 equiv of **I** and 3.1 equiv of *t*-BuOK stirring for 12 h at −40 °C and 72 h at 40 °C. The superscripted [*b*] indicates that the yield determined by NMR on the crude reaction mixture, using an internal standard (26% isolated yield).

of natural products and APIs, which is particularly useful in the context of drug development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02887.

Details of experimental procedures; ^{1}H and ^{13}C NMR spectra; HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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