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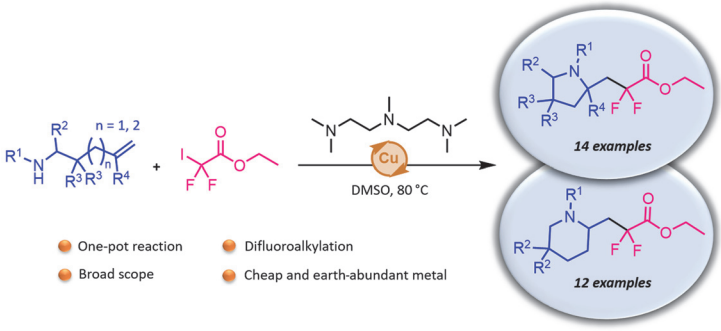
Copper-Catalyzed Radical Cascade Annulation for the Preparation of Difluorinated Pyrrolidines and Piperidines

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This article is dedicated to Professor Alain Krief on the occasion of his 80th birthday

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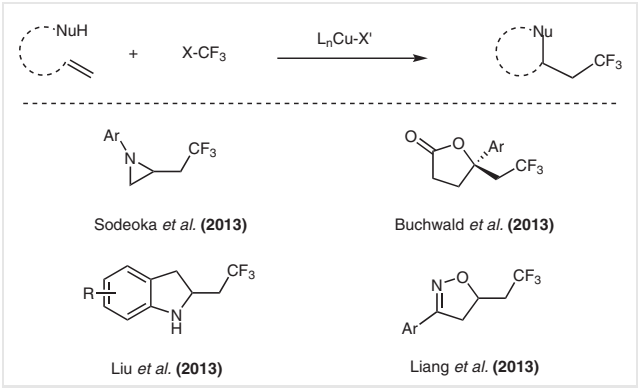
Abstract In this work, we developed a one-pot, copper-catalyzed aminodifluoroalkylation of enylaniline derivatives. This approach allows the catalytic construction of a broad range of pyrrolidines and piperidines substituted with a *gem*-difluoro moiety.

Key words pyrrolidine, piperidine, heterocycles, copper, fluorine, catalysis

The development of new methodologies for the introduction of fluorine atoms into organic molecules is widely recognized as an important tool in synthetic chemistry.[1] Indeed, this atom can have a strong impact on the overall biological activity and bioavailability of a target molecule, and is widely applied in the fields of pharmacochemistry and agrochemistry. For instance, lipophilicity, pK_a, and metabolic stability, are some of the parameters that fluorine can tune; thus, there is an ever-growing demand for efficient methodologies that allow the construction of complex structures incorporating this atom.[2]

Among the wide array of methods available, radical-based methodologies have now emerged as highly efficient for the incorporation of important fluorine-containing fragments such as perfluoroalkyl and difluoroalkyl groups.[3] Indeed, fluoroalkyl radicals such as $^{\bullet}CF_2$-Y can easily be generated from a X-CF_2-Y precursor via SET/reduction process, and then undergo various cascade reactions, leading to the formation of complex structures incorporating these fragments. One elegant way to generate $^{\bullet}CF_2CO_2Et$ radicals uses photoredox catalysis,[4] although such interesting methodologies often require expensive catalysts based on metals such as ruthenium or iridium and often suffer from limited applications. However, other favored pathways can be used for the generation of these radicals such as reversible one-electron reduction processes by transition-metal complexes. Copper has proven to be one of the most efficient metals for such transformations, and has been widely used in important processes such as atom-transfer radical cyclization[5] (ATRC) and atom-transfer radical polymerization[6] (ATRP).

Among the possible cascades available with $^{\bullet}CF_2$-Y radicals, the use of substrates bearing both a terminal double bond and a heteroatom-based nucleophile (e.g., alcohols, arylamines, carboxylic acids) can lead to the formation of new fluoroalkyl-substituted heterocycles. Through variation of the size of the scaffold, the nature of the nucleophile, and the structure of the radical precursor, this method can lead to the efficient construction of a wide range of original heterocycles, as exemplified by the early work of Sodeoka[7] (aziridines), Buchwald[8] (lactones), Liu[9] (indolines) and Liang[10] (isoxazolines) (Scheme 1).



Scheme 1 Reported copper-catalyzed reactions to synthesize CF_3-containing heterocycles

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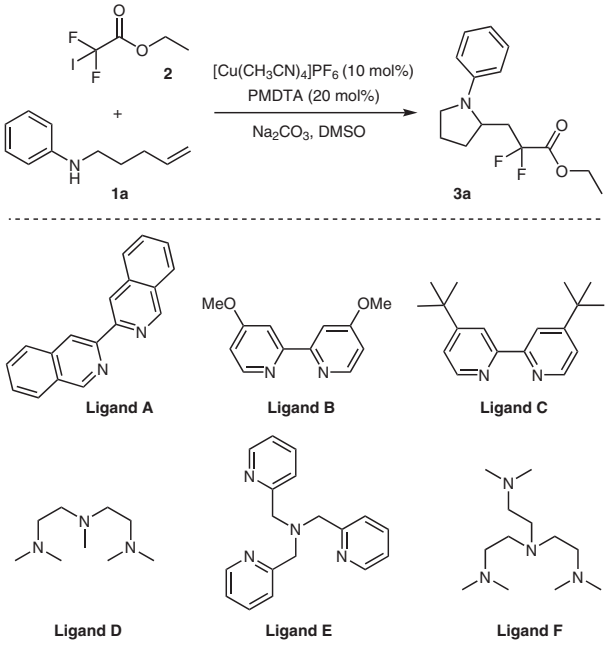
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Regarding the nucleophile, there is still a limited number of reported examples that use nitrogen-based nucleophiles for the preparation of fluorinated heterocycles such as pyrrolidines and piperidines using this methodology.[9,11,12] It is important to mention the copper-catalyzed strategy developed by Wang's group to obtain difluoroalkylated pyrrolizidines and indolizidines.[13] However, this strategy is limited to the use of primary amines to enable the formation of the second cycle of the bicyclic product. Another relevant example is the asymmetric synthesis of pyrrolidines published by Liu *et al.* using copper and a chiral phosphoric acid as ligand.[14] In this elegant work, the enantioselectivity is achieved thanks to the interaction between the chiral copper-complex and the urea substrates. Very recently, a nickel-catalyzed strategy was also developed by Wu *et al.* to access a broad range of difluorinated aziridines.[3] This method was extended to a small number of pyrrolidines and piperidines, which could be obtained in very good yields. Nevertheless, no substituents could be introduced on the newly formed cycles using this methodology. Based on our experience in copper catalysis, we were thus interested in developing a copper-catalyzed strategy that would allow more freedom of substitution for the preparation of difluoroalkylated pyrrolidines and piperidines.[15]

We decided to start our investigation with a model substrate and selected *N*-(pent-4-enyl)aniline (**1a**), along with ethyl 2,2-difluoro-2-iodoacetate (**2**) as the radical precursor, to optimize the formation of the model pyrrolidine **3a**. In order to allow a fast optimization of the reaction parameters, all experiments were quantified with respect to the desired heterocycle by ^{1}H NMR analysis of the crude reaction mixture, using dimethylsulfone as an internal standard. After a few preliminary trials, we found that using 20 mol% of a commercially available copper(I) salt along with 1 equivalent of *N*,*N*,*N*′,*N*″,*N*‴-pentamethyldiethylenetriamine (PMDTA; Ligand D), which is thought to play a role as stabilizing ligand and as a base for the capture of the formed hydroiodic acid (HI), allowed us to observe the formation of the desired heterocycle **3a** in 82% NMR yield (Table 1, entry 1). Following this result, we were interested to try other conditions with the aim of further improving the yield and to have a better understanding of the reaction. The most relevant experiments are reported in Table 1.

As a first deviation, it was observed that the use of solvents that were less polar than DMSO, such as CH_3CN, reduced the yield significantly (Table 1, entry 2). This evidence might suggest that the polarity/coordinating abilities of the solvent is an important parameter for the potential stabilization of radial/ionic intermediates. Next, the amount of ligand was reduced to 40 mol% by using 1 equivalent of Na_2CO_3 as an inorganic base to prevent acidification of the reaction medium due to the formation of HI (entry 3). However, a slightly lower yield was observed, and other nitrogen-based ligands were tested using the same conditions (entries 4–8). Since none of these deviations improved the yield, it was decided to pursue our study using 1 equivalent of PMDTA as optimal conditions, mainly considering the practical set up of the reaction. The fact that PMDTA appears to be the most suitable ligand for this reaction is consistent with previous studies,[3,16,17] which have shown that tridentate ligands on copper are more effective for promoting reversible SET, as the efficiency of the catalytic system mainly relies on the reducing potential of the copper-complex and because the flexibility of such ligands also allows

Table 1 Optimization of the Reaction Conditions[a]



Entry	Deviation	Yield (%)[b]
1	–	82
2	CH_3CN	38
3	Na_2CO_3 (1 equiv), Ligand D (40 mol%)	78
4	Na_2CO_3 (1 equiv), Ligand A (40 mol%)	0
5	Na_2CO_3 (1 equiv), Ligand B (40 mol%)	16
6	Na_2CO_3 (1 equiv), Ligand C (40 mol%)	18
7	Na_2CO_3 (1 equiv), Ligand E (40 mol%)	56
8	Na_2CO_3 (1 equiv), Ligand F (40 mol%)	62
9	1% H_2O	32
10	5 h instead of 18 h	79
11	Schlenk instead of sealed tube	50
12	degassed DMSO	81

[a] Reaction conditions: **1a** (0.25 mmol, 1.0 equiv), **2** (0.30 mmol, 1.2 equiv), tetrakis(acetonitrile)copper(I) hexafluorophosphate (10 mol%) in DMSO (3 mL) at 80 °C under inert atmosphere for 18 hours.
[b] NMR yield measured from the crude mixture using 10 mol% dimethylsulfone as internal standard.

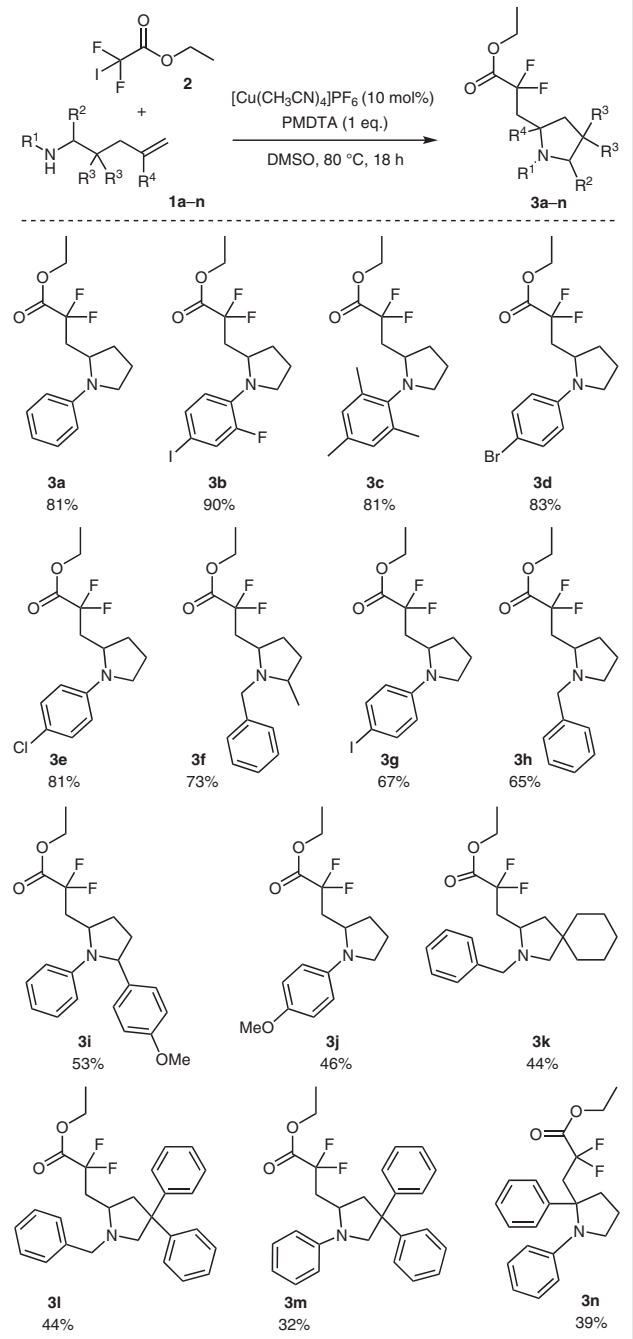
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adaptation of the geometry of the Cu(I)/Cu(II) complexes. As it is well known that the presence of impurities often affects radical-based mechanisms, we also checked the purity of the solvent, usually taken from a sealed bottle from commercial suppliers. Indeed, the introduction of a small amount of water did have a strong negative effect on the reaction outcome (entry 9), and care was then always taken to use rigorously anhydrous solvents. Still, the use of commercially available solvents was sufficient for our purpose, as careful degassing did not significantly improve the yield (entry 12).

With the optimal conditions in hand (Table 1, entry 1), we then set out to investigate the scope of our method on a range of secondary amines (Scheme 2). First, modifications of the aromatic ring attached to the nitrogen atom were tested and the corresponding pyrrolidines **3b–e**, and **3g** were isolated in good yields, even in the case of more sterically demanding aromatic rings. The introduction of a substituent R^2 at the α-position of the nitrogen allowed the disubstituted pyrrolidines **3f** to be isolated in good yield, but without control of the *cis*/*trans* diastereoselectivity, as both isomers were obtained in a 1:1 ratio. It was also observed that the introduction of a *gem*-disubstituent R^3 at the β-position had a negative impact on the yield of the corresponding heterocycles **3k**, **3l**, and **3m**. As it is well known that the introduction of a phenyl group on the double bond of the substrate (R^4 = Ph) can potentially stabilize radical/cationic intermediates for similar reactions,[1] we were also interested to try this variation (**3n**). However, a moderate yield of 39% was observed, likely due to the high steric demand of the newly formed quaternary carbon, and because the reaction proceeded via a metallacycle intermediate rather than a stabilized carbocation. Moreover, the influence of the nucleophilicity of the nitrogen atom was investigated with the replacement of the aryl with a benzyl group (**3f**, **3h**, **3k**, and **3l**). Although we were able to isolate the desired *N*-benzyl substituted heterocycles, some decrease in the yields were noted compared to the *N*-aryl substituted products. This was mainly attributed to the formation of various side products, such as the *N*-alkylation of substrate **1** by the iododifluoroacetate reagent **2**, due to the increased nucleophilic character of the nitrogen. Lastly, when the R^1 substituent attached to the nitrogen was replaced with alkyl groups other than benzyl (R^1 = Me, *n*Bu), or sulfonyl groups (R^1 = Ts), very little to almost no product was observed.

Having this methodology in hand, we were thus naturally interested in investigating the possibility of extending it to the preparation of piperidine derivatives. Using *N*-(hex-5-en-1-yl)aniline (**4a**) as a model substrate, a second phase of optimization was carried out and we were able to isolate the desired heterocycle **5a** in 75% isolated yield, thanks to a slight change of the reaction parameters (40 mol% PMDTA instead of 1 equivalent for pyrrolidine)



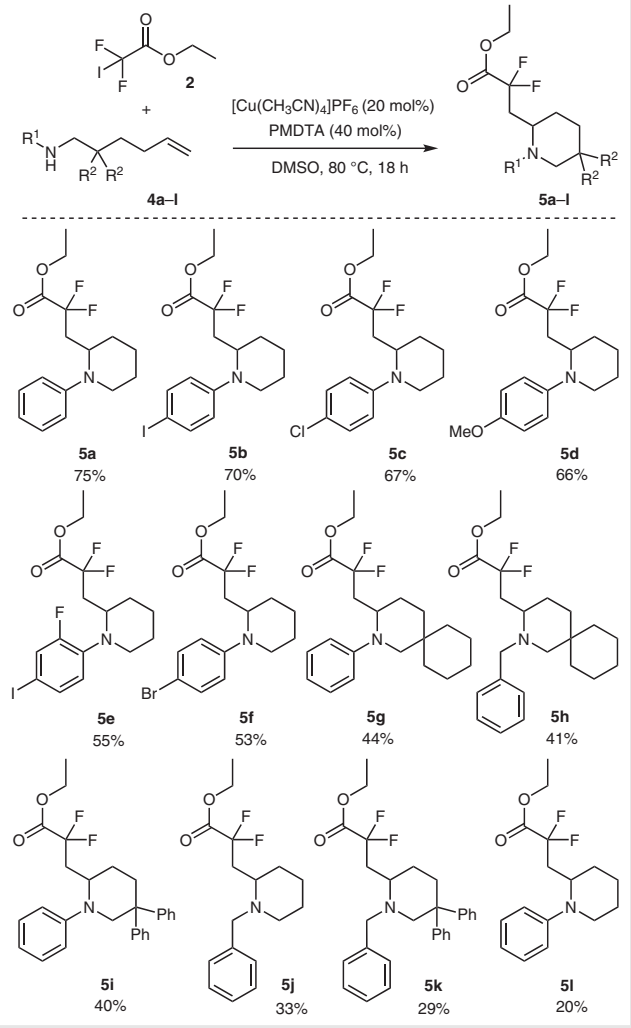
Scheme 2 Scope of difluorinated pyrrolidines. *Reaction conditions*: **1a–n** (0.25 mmol, 1.0 equiv), **2** (0.30 mmol, 1.2 equiv), tetrakis(acetonitrile)copper(I) hexafluorophosphate (10 mol%), PMDTA (1 equiv.) in DMSO (3 mL) at 80 °C under inert atmosphere for 18 hours. Isolated yields after purification.

(Scheme 3). Based on this result, we thus set out to investigate the scope of our methodology for piperidine derivatives. Interestingly, the reaction performed well for piperidine scaffolds bearing an electron-withdrawing (**5b**, **5c**, **5e**, **5f**) or electron-donating (**5d**) *para*-substituent. Additional-

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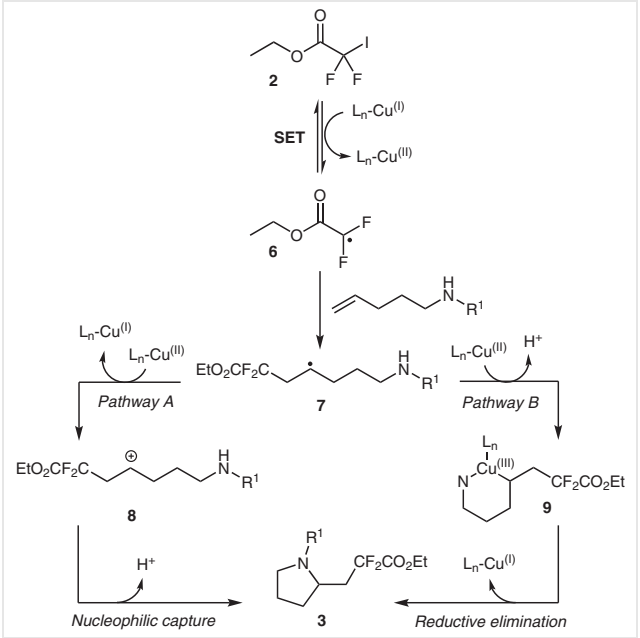
ly, we observed that arylamine derivatives (**5g**, **5i**) bearing a bulky group in the β-position of the aliphatic chain tend to give higher yields than their corresponding benzylamine products (**5h**, **5k**), whereas the opposite trend was observed in the case of five-membered rings (Scheme 2; **3l**, **3m**).



Scheme 3 Scope of difluorinated piperidines. *Reaction conditions*: **4a–l** (0.25 mmol, 1.0 equiv), **2** (0.30 mmol, 1.2 equiv), tetrakis(acetonitrile)copper(I) hexafluorophosphate (20 mol%), PMDTA (40 mol%) in DMSO (3 mL) at 80 °C under inert atmosphere for 18 hours. Isolated yields after purification.

A mechanistic pathway could be proposed (Scheme 4), based on similar reactions found in the literature.[1,16,18] Despite, the large array of reported inter- and intramolecular reactions involving copper-mediated radical formation and addition on double bonds coupled with redox processes and nucleophilic captures, there is still a debate on the exact pathway and the nature of the intermediates involved in such reactions. However, the first step of the mechanism is well established as a single-electron transfer from the Cu(I) catalyst to the iodo-reagent **2** that will reversibly generate the radical $^{\bullet}CF_2CO_2Et$ and a Cu(II) complex. The radical **6** can then add onto the double bond of the enylaniline substrate to generate the secondary carbon radical intermediate **7**. From this, two pathways can be envisaged to rationalize the formation of the heterocycles. First, oxidation of the radical **7** by the Cu(II) complex will generate a carbocation, which will then be trapped by the nucleophilic attack of nitrogen atom (Scheme 4, Pathway A). Alternatively, it can be envisaged that a Cu(III) intermediate **9** is generated by trapping of the radical by the Cu(II) complex, along with ligand exchange with the nucleophile, to generate the metallacycle **9** (Scheme 4, Pathway B). Final generation of the heterocycle would then occur via reductive elimination and regeneration of the Cu(I) active catalyst. This mechanism could be intuitively found to be favored for pyrrolidines, as a six-membered ring metallacycle **9** is generated during the transformation. On the other hand, in the case of piperidines, a less thermodynamically and kinetically favored seven-membered-ring intermediate would be formed.

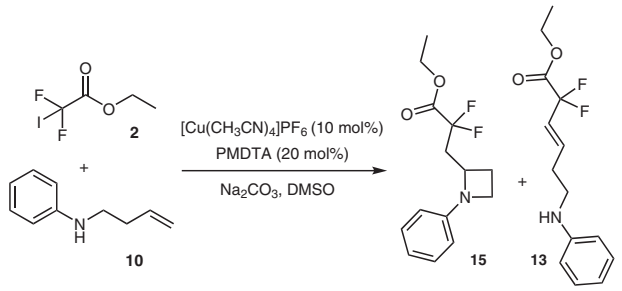
Based on the results obtained for five- and six-membered rings, we were intrigued by the possibility of extending our methodology to the synthesis of more strained rings, such as azetidines, which are of great interest in the field of agricultural and pharmaceutical chemistry.[19] We thus carried out a new screening of the reaction conditions to optimize the formation of azetidine **15** (Table 2).



Scheme 4 Proposed mechanism for the generation of difluoroalkylated pyrrolidines

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Table 2 Optimization of the Reaction Conditions for Azetidines[a]



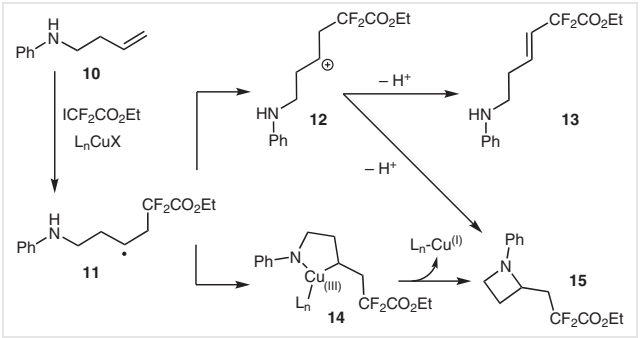
Entry	Deviation	Yield (%)[b]	
		15	**13**
1	–	28	58
2	Ligand D (1 equiv), Cu (20 mol%), no base	0	51
3	Ligand E	35	32

[a] Reaction conditions: **10** (0.25 mmol, 1.0 equiv), **2** (0.30 mmol, 1.2 equiv), tetrakis(acetonitrile)copper(I) hexafluorophosphate (10 mol%), in DMSO (3 mL) at 80 °C under inert atmosphere for 18 hours.
[b] NMR yield measured from the crude mixture using 10 mol% dimethylsulfone as internal standard.

Although the expected product was formed in a modest yield, the reaction produced a higher amount of an alkene by-product, which may suggest that the carbocationic pathway is favored in this case. However, the metallacycle route cannot be fully ruled out. Different solvents, ligands, and copper sources were thus screened, but the undesired alkene was always obtained as the major product, along with minor amounts of the azetidine **15** and starting material **10**. Eventually, the best conditions yielded 35% of the azetidine and 32% of the alkene by-product with tris(2-pyridylmethyl)amine (TPMA) as ligand (Table 2, entry 3) and the pure azetidine **15** was isolated in a modest 20% yield.

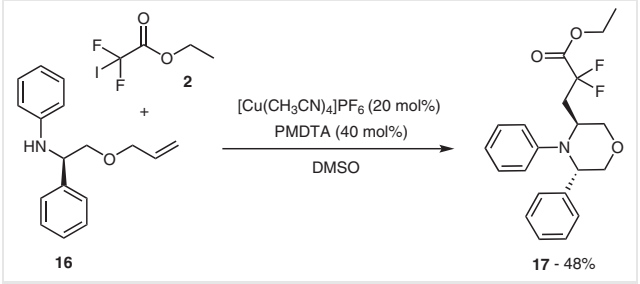
Applying the same ideas as previously, a possible mechanism could be proposed for the formation of the observed azetidine **15** and alkene by-product **13** (Scheme 5). Starting from substrate **10**, the first formed radical **11** can evolve according to two possible pathways. If the recombination of the radical can occur with the copper(II) intermediate, then a kinetically and thermodynamically favored five-membered ring metallacycle **14** is expected to be formed, favoring the formation of an azetidine **15** after reductive elimination. On the other hand, the oxidative pathway, leading to the formation of carbocation **12**, would most probably favor fast proton elimination to alkene **13** over intramolecular nucleophilic capture to **15**.

Finally, we decided to extend our methodology to the formation of other families of heterocycles and selected one example of a chiral morpholine, easily available from a cheap chiral amino-acid source. Substrate **16** was easily prepared in a four-step procedure from (*R*)-phenylglycinol and subjected to our optimized conditions (Scheme 6). The



Scheme 5 Proposed mechanism for the generation of difluoroalkylated azetidines

desired morpholine was isolated as a mixture of *cis*- and *trans*-isomers and the *trans*-diastereomer could be fully separated in 48% yield; its structure was confirmed by 2D NMR experiments.



Scheme 6 Extension of the methodology to the synthesis of a difluorinated morpholine scaffold

In conclusion, we developed a one-pot strategy for the preparation of difluorinated pyrrolidines and piperidines bearing different substituents. The advantage of this methodology is the simultaneous formation of the *N*-heterocycle ring with the incorporation of a *gem*-difluoro-moiety. Indeed, according to the FDA database, almost 60% of bioactive molecules present a *N*-heterocycle, and the incorporation of fluorine fragments is often desirable for medicinal chemistry applications. Numerous procedures are described in the literature to introduce a fluorine atom into a linear molecule,[13] but its incorporation into heterocycles is still a challenge.[2,14] Therefore, this work offers a new, versatile procedure to access relevant difluorinated pyrrolidines and piperidines in one step.

Synthesis of Pyrrolidines 3a–n; General Procedure

Tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.05 mmol) was added to a flame-dried sealed tube under argon atmosphere. After addition of anhydrous DMSO (3 mL), the generic reagent **1a–n** (0.25 mmol), ethyl iododifluoroacetate (**2**, 0.30 mmol), and PMDTA (0.25 mmol) were added to the sealed tube and stirred at 80 °C for 18

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hours. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (PE/EtOAc).

Ethyl 2,2-Difluoro-3-(1-phenylpyrrolidin-2-yl)propanoate (3a)

Yield: 81%; brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 2 H), 6.73 (tt, *J* = 7.3, 1.0 Hz, 1 H), 6.65–6.58 (m, 2 H), 4.43–4.19 (m, 2 H), 4.15–4.03 (m, 1 H), 3.50–3.36 (m, 1 H), 3.24–3.10 (m, 1 H), 2.49 (dtd, *J* = 22.8, 15.0, 1.8 Hz, 1 H), 2.25–1.98 (m, 5 H), 1.34 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2 (t, *J* = 32.6 Hz), 146.6, 129.5, 116.4, 115.9 (t, *J* = 250.5 Hz), 112.1, 63.2, 52.6 (t, *J* = 3.7 Hz), 48.1, 37.3 (t, *J* = 21.7 Hz), 31.5, 23.2, 14.1.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –104.07 (d, *J* = 261.5 Hz, 1 F), –105.69 (d, *J* = 262.9 Hz, 1 F).

IR (FTIR): 2975, 2838, 1764, 1363–1092 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}F_2NO_2$: 284.14566; found: 284.14599.

Synthesis of Piperidine Derivatives 5a–n; General Procedure

Tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.05 mmol) was added to a flame-dried sealed tube under argon atmosphere. After addition of anhydrous DMSO (3 mL), the generic reagent **4a–n** (0.25 mmol), ethyl iododifluoroacetate (**2**, 0.30 mmol), and PMDTA (0.10 mmol) were added to the sealed tube and stirred at 80 °C for 18 hours. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (PE/EtOAc).

Ethyl 2,2-Difluoro-3-(1-phenylpiperidin-2-yl)propanoate (5a)

Yield: 75%; yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (t, *J* = 7.8 Hz, 2 H), 6.90 (d, *J* = 7.5 Hz, 2 H), 6.81 (t, *J* = 7.5 Hz, 1 H), 4.23–4.16 (m, 1 H), 4.15–4.07 (m, 2 H), 3.36 (d, *J* = 12.8 Hz, 1 H), 3.01–2.93 (m, 1 H), 2.60–2.41 (m, 1 H), 2.37–2.20 (m, 1 H), 1.87–1.81 (m, 1 H), 1.69–1.61 (m, 5 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1 (t, *J* = 30.0 Hz), 149.9, 129.3, 119.4, 117.0, 116.3 (t, *J* = 247.5 Hz), 63.0, 51.3, 43.3, 33.4 (t, *J* = 22.5 Hz), 28.5, 24.5, 19.5, 13.8.

^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$): δ = –101.13 (d, *J* = 258.0 Hz, 1F), –107.87 (d, *J* = 258.0 Hz, 1F).

IR (neat): 2938, 2861, 1764, 1600, 1497, 1252, 1199, 1134, 1015, 752, 690 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}O_2NF_2^+$: 298.16131; found: 298.16136.

Synthesis of Azetidine 15

Tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.025 mmol) was added to a flame-dried sealed tube under argon atmosphere. After addition of anhydrous DMSO (3 mL), N-(3-butenyl)aniline (**10**, 0.25 mmol), ethyl iododifluoroacetate (**2**, 0.30 mmol), and TPMA (0.05 mmol) were added to the sealed tube and stirred at 80 °C for 18 hours. The reaction was quenched with saturated $NaHCO_3$ (10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and then purified by column chromatography (PE/EtOAc).

Ethyl 2,2-Difluoro-3-(1-phenylazetidin-2-yl)propanoate (15)

Yield: 20%; yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.16 (m, 2 H), 6.78 (tt, *J* = 7.2, 1.1 Hz, 1 H), 6.56–6.44 (m, 2 H), 4.34–4.20 (m, 2 H), 4.15 (dt, *J* = 10.8, 7.1 Hz, 1 H), 3.98 (ddd, *J* = 8.6, 7.0, 4.1 Hz, 1 H), 3.62 (ddd, *J* = 9.1, 8.4, 7.4 Hz, 1 H), 2.77–2.53 (m, 2 H), 2.53–2.31 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.85 (t, J= 126 Hz), 151.5, 129.0, 118.4, 111.9, 63.0, 58.3, 40.5, 24.0, 15.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –103.73, –103.88.

IR (FTIR): 2975, 2868, 1768, 1328 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}F_2NO_2$: 256.11436; found: 256.11704.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2004-6031.

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