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Copper-Catalyzed Four Component Reaction for the Synthesis of *N*-Difluoroethyl Imides

Yu Gao, Shan-Qing Peng, De-Yong Liu, Pei-Xin Rui, Xiang-Guo Hu *[a]

Abstract: A general and efficient method for the synthesis *N*-difluoroethyl imides has been developed. This copper-catalyzed four component reaction proceeds *via* in-*situ* generated difluorodiazomethane, which does not require the prior formation and transferring. The reaction is scalable, tolerant a range of functional groups, and also suitable for the late-stage functionalization of drugs and drug-like molecules.

Introduction

An imide is a basic functional group that is structurally related to an acid anhydride but more resistant towards hydrolysis. For this reason, imides have been frequently used as key intermediates in organic synthesis. They are also important structural motifs found in a great number of bioactive molecules and pharmaceuticals. Notable examples such as Thalidomide,[1] Ethosuximide,[2] Penimide,[3] Captan,[4] Aniracetam[5] and Palau'imide[6] are shown in Figure 1. At the same time, a difluoromethyl group (CF_2H) is an attractive entity from drug development perspective.[7-8] The slightly acidic C–H bond of the difluoromethyl group (CF_2H)[9] can act both as a lipophilic hydrogen-bond donor and a bioisostere for hydroxyl and thiol groups.[10] Furthermore, as a fluoroalkyl group, it can possibly improve the metabolic stability, oral bioavailability and solubility of molecules if incorporated.[7]

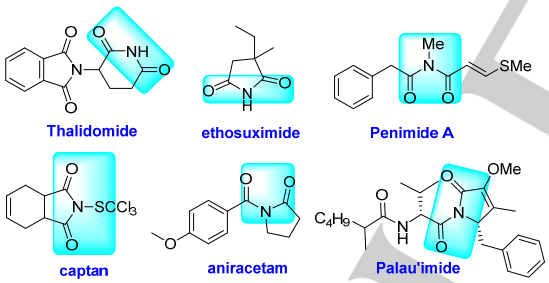
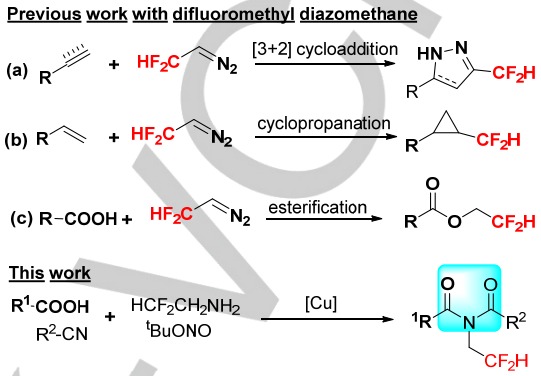


Figure 1 Selected examples of imide containing drugs and bioactive compounds

Considering the aforementioned two aspects, the combination of an imide and a CF_2H moiety would offer much possibility in the searching of novel bioactive compounds. However, the literature surveying shows that the research on CF_2H-containing imides is scarce, and the access to this kind of compounds is mainly relied on multi-step syntheses.[11]



Scheme 1. Reactions that involve difluoromethyl diazomethane (CF_2HCHN_2).

Difluoromethyl diazomethane (HCF_2CHN_2), first reported by Mykhailiuk, has emerged as a versatile building block for the synthesis of difluoromethylated compounds.[12] Compared to its well-known trifluorinated counterparts,[13] the reaction of HCF_2CHN_2 is still underdeveloped and largely limited to [2+3]-cycloaddition with alkynes and alkenes,[14] cyclopropanation with alkenes[15] and esterification of carboxylic acids[16] (Scheme 1).

Herein, we report a copper-catalyzed four component reaction for the facile synthesis imides bearing a CF_2H group, employing all commercially available reagents (Scheme 1). The reaction proceeds from the in-*situ* generated difluoromethyl diazomethane (HCF_2CHN_2) that does not need prior formation and transferring. The optimization, the generality with respect to both the carboxylic acid and nitrile, and the application of this reaction for late-stage functionalization are discussed.

Results and Discussion

Based on our recent work on the formation of trifluoroethyl imides from carboxylic acids with trifluoromethyl diazomethane,[16b] we envisioned that an efficient synthesis of difluoromethyl imides could be developed if proper conditions could be identified. Challenges, however, exist: (1) as the activation barrier for the esterification of carboxylic acids with HCF_2CHN_2 is quite low (22.6 kJ/mol),[16b] how to suppress this uncatalyzed esterification is a big problem; (2) reactions with CF_2HCHN_2 (possibly due to its instable nature)[12] disclosed are generally less efficient than those with CF_3CHN_2,[12-15] so the efficacy and generality would be another issue to address.

To address the second issue raised above, we determined to use HCF_2CHN_2 generated in-*situ* from 2, 2-difluoromethylamine ($HCF_2CH_2NH_2$) and *tert*-butyl nitrite (TBN) without discrete operation. Thus, the optimization was carried out by mixing all

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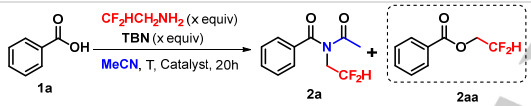
the reagents together at once (Table 1). [14h, 16b] The ester formation was indeed a problem as anticipated, and the previously established thermal conditions for CF_3CHN_2 yielded completely ester **2aa** from **2a**, while copper-catalyzed conditions afforded the imide product **2a** as the minor product (33% yield).[16b] The selectivity in Entries 1-2 indicates that the formation of imide **2a** may have a larger activation barrier than that of the esterification. To overcome this kinetic preference, we performed the reaction at 80 °C and **2a** was obtained in 46% yield. Increasing the amount of the $HCF_2CH_2NH_2$ and TBN slightly enhanced the yield, giving **2a** in 52% yield (Entry 4). Diluting the concentration was very beneficial to the reaction and a higher yield was obtained in 86% at the concentration of 0.05 mmol/mL (Entries 4-6); presumably, this positive result was ascribed to the increased amount of acetonitrile that only participates in the imide formation, relative to other reagents. Comparison experiments proved that high temperature was indeed advantageous for the formation of imide products (Entries 7-9). Catalyst screening showed that copper salts were generally effective for the reaction, with $Cu(OTf)_2$ giving the best result (Entries 10–20). Under this optimized conditions, **2a** was obtained in 90% yield**,** and ester product **2aa** was decreased to 4% yield (Table 1, entry 12). Lowering or increasing the amount of $Cu(OTf)_2$ resulted in a slightly lower yield (Entries 21–22). Overall, the first issue raised previously, that is, the ester formation, was also addressed through the reaction optimization.

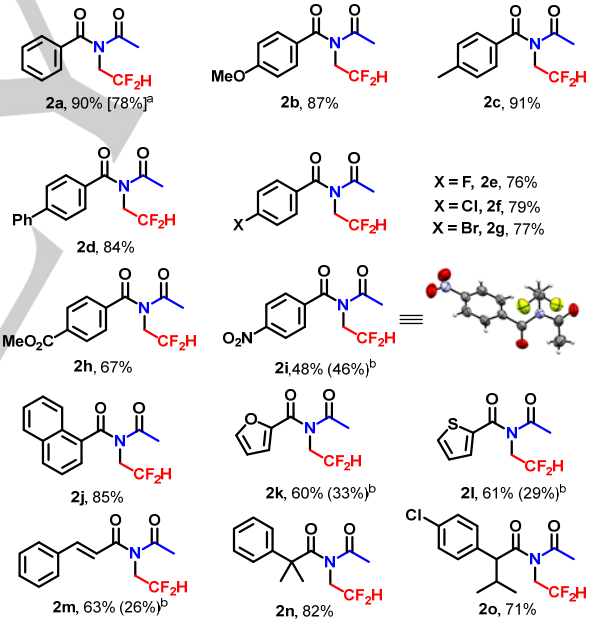
Table 1. Optimization of the reaction conditions.



Entry	Catalyst (x mol%)	Concentration of 1a (mmol/mL) / T (°C)	Yield (%)[a,b]
1[c]	/	0.2/80	Trace (69)
2[c]	CuI (5)	0.2/ 25	33 (42)
3[c]	CuI (5)	0.2/80	46 (23)
4	CuI (5)	0.2/80	52 (13)
5	CuI (5)	0.1/80	81 (9)
6	CuI (5)	0.05/80	86 (7)
7	CuI (5)	0.05/0	7 (3)
8	CuI (5)	0.05/40	38 (21)
9	CuI (5)	0.05/60	59 (9)
10	$CuCl_2$ (5)	0.05/80	67 (13)
11	$CuBr_2$ (5)	0.05/80	71 (12)
12	$Cu(acac)_2$ (5)	0.05/80	87 (8)
13	**$Cu(OTf)_2$ (5)**	**0.05/80**	**90 (4)**
14	$Cu(NO_3)\cdot 3H_2O$ (5)	0.05/80	83 (9)
15	$Cu(OAc)_2\cdot H_2O$ (5)	0.05/80	86 (8)
16	CuCl (5)	0.05/80	77 (4)
17	CuBr (5)	0.05/80	82 (3)
18	$Cu(MeCN)_4PF_6$ (5)	0.05/80	79 (5)
19	Cu(OTf)·toluene (5)	0.05/80	76 (7)
20	CuTc (5)	0.05/80	87 (4)
21	$Cu(OTf)_2$ (1)	0.05/80	82 (7)
22	$Cu(OTf)_2$ (10)	0.05/80	87 (4)

Conditions: **1a** (0.2 mmol, 1.0 equiv), $CF_2HCH_2NH_2$ (0.5 mmol, 2.5 equiv), TBN (0.5 mmol, 2.5 equiv), catalyst (x mol%), acetonitrile (4 mL), 20 h. [a]Yields determined by ^{19}F-NMR spectroscopy using $PhCF_3$ as an internal standard; [b] values in the parentheses are the yields of ester **2aa**; [c] $CF_2HCH_2NH_2$ (0.4 mmol, 2.0 equiv), TBN (0.4 mmol, 2.0 equiv).

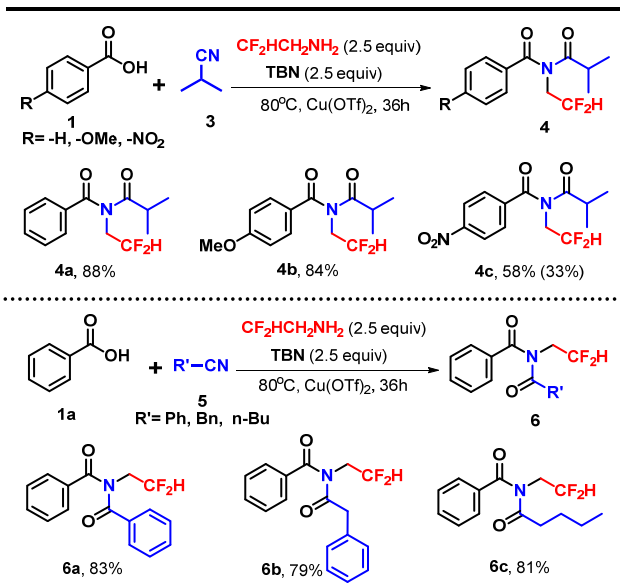
With the optimized reaction conditions in hand (Entry 13, Table 1), we next examined the substrate scope of this copper-catalyzed 4-component reaction with respect to the carboxylic acid (Scheme 2). For aromatic acids, different substituents including alkyl, alkyloxyl, ester, and phenyl were all tolerated (**2a-2h**). It is noteworthy that halide substituents, especially bromo group, were intact under the reaction conditions (**2e-2g**), which allows further functionalization via transitional-metal catalyzed coupling reactions. However, the efficacy of this reaction decreased sharply with the substrate bearing an electron-withdrawing nitro group. In particular, the corresponding ester **2ia** (structure not shown) was isolated in 46% yield along with **2i**. Nevertheless, the ester side products are much less polar than the corresponding imide products, thus causing no difficulties for the purification. The structure of **2i** was confirmed unambiguously by means of X-ray crystallographic analysis (CCDC 1862470).[14] Compounds with bicycloaryl and heteroaryl ring systems were also viable substrates, affording the desired products (**2j**−**2l**) in 60-85% yields. The double bond of cinnamic acid **1m** was unaffected under the reaction conditions, thus delivering the desired products (**2m**) in 63% yield. Aliphatic acids **1n-1o** also underwent the reaction successfully, and **2n-2o** were obtained in 82% and 71% yield, respectively. These two results also highlighted that the reaction is not sensitive to the steric hindrance of carboxylic acid, given the congested nature of the starting carboxylic acids **1n-1o**. Finally, the practicality of this reaction was demonstrated by running the reaction of **1a** on gram scale and the corresponding imide **2a** was obtained in 78%.



Scheme 2. Substrate scope of Cu-catalyzed four component reaction with carboxylic acids; Conditions: carboxylic acids (0.2 mmol, 1 equiv), 2,2-difluoroethylamine (0.5 mmol, 2.5 equiv), *tert*-butyl nitrite (0.5 mmol, 2.5 equiv), $Cu(OTf)_2$ (5 mol%), acetonitrile (4 mL), 80°C, 20 h; [a] 78% is Gram scale yield; [b] yields in the parentheses are the yields for the corresponding esters.

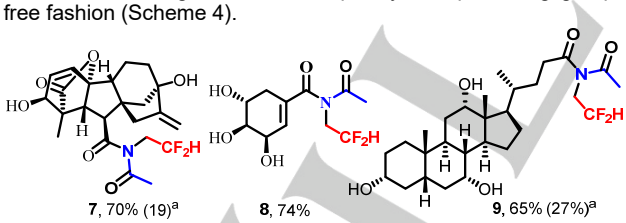
Next, we investigated reaction further with other kinds of nitriles under the established conditions (Scheme 3). To our delight, the reaction of three representative aromatic acids **1a-c** underwent reaction successfully using isobutyl nitrile **3** as the reaction component and similar yields were obtained with those when acetonitrile was used at a longer reaction time (Scheme 3). These experiments suggest that the reaction can tolerate the steric hindrance of the nitrile component to some extent. Other

three nitriles with a phenyl, benzyl and long alkyl chain were also found as good substrates and the reaction occurred successfully in 79- 83% yields (Scheme 3).



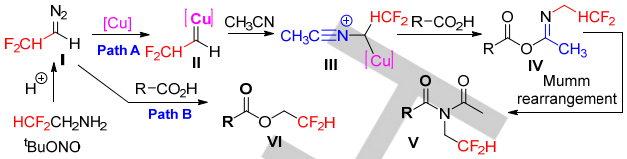
Scheme 3. Substrate scope of Cu-catalyzed four component reaction with various nitriles; **Conditions:** carboxylic acids (0.2 mmol, 1 equiv), 2,2-difluoroethylamine (0.5 mmol, 2.5 equiv), TBN (0.5 mmol, 2.5 equiv), $Cu(OTf)_2$ (5 mol%), nitrile (4 mL), 80 °C.

To examine the synthetic utility of this reaction in medicinal chemistry, we have applied this method for late-stage functionalization[17] of drugs and drug-like molecules (Scheme 4).. The imide **7** derived from gibberellic acid (**1p**) was obtained in 70% yield, again showcasing the reaction works well with stereochemically hindered acids and tolerates sensitive functionalities such as ester, alkene and hydroxyl groups. Reaction with shikimic acid (**1q**), and cholic acid (**1r**), bearing multiple hydroxyl groups, further demonstrated the utility of this reaction in building molecular complexity in a protecting group free fashion (Scheme 4).



Scheme 4. late stage-functionalization of complex molecules; [a] yields in the parentheses are for the corresponding ester.

Based on our work with CF_3CHN_2,[16b] a plausible reaction mechanism for this copper-catalyzed four component reaction is depicted as the following (Scheme 5). The in-*situ* generated HCF_2CHN_2 **I**[12] reacts with the copper catalyst to form the carbenoid **II**[18] which yields the nitrilium salt **III** after attacking by the acetonitrile. Addition of the carboxylic acid onto the nitrilium **III**, followed by the Mumm rearrangement,[19] affords the imide product **IV**. The unproductive but kinetically favored esterification to yield **IV** was suppressed successfully by reaction at a relatively high temperature and dilute concentration in the presence of a copper catalyst.



Scheme 5. Plausible reaction mechanism for this copper-catalyzed four component reaction.

Conclusions

A copper-catalyzed four component reaction for the efficient synthesis difluoroethyl imides (imides containing a HCF_2 moiety) has been developed. The reaction proceeds via the in-*situ* generated difluoromethyl diazomethane (HCF_2CHN_2), without the requirement for the prior formation and transferring of this potentially dangerous reagent. The kinetically favored, uncatalyzed background reaction, the esterification of acids with HCF_2CHN_2, was successfully suppressed. This imide formation tolerates a range of functional groups and is insensitive to the steric effect of the carboxylic acids and nitriles. Furthermore, the reaction is scalable and suitable for the late-stage functionalization of drugs and drug-like molecules in a protecting group free fashion, which should make it valuable in the searching of novel imide-based bioactive compounds in future.

Experimental Section

General Information: All purchased reagents were used without further purification unless otherwise noted. All solvents were dried over 4Å molecular sieves before used unless stated. Reactions were stirred using Teflon-coated magnetic stirrers. Analytical TLC was performed with 0.20 mm silica gel 60F plates with 254 nm fluorescent indicator. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O} or a solution 0.5% ninhydrin in n-butanol. Chromatographic purification of products was carried out by flash column chromatography on silica gel (230-400 mesh). Melting points were determined using a WRX-4 visual melting point apparatus. Both melting points and boiling points are uncorrected. Infrared spectra were recorded on an IR Affinity-1. NMR spectra were measured in $CDCl_3$ (with TMS as internal standard) or DMSO-d_6 or CD_3OD on a Bruker AV400 (^1H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz) magnetic resonance spectrometer. High-resolution mass spectra (HRMS) were recorded on a SYNAPT G2Si High Definition MS System. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The HRMS were measured under ESI model (specified in the section of characterization data).

General procedure for the synthesis of TBN:

It is important to use freshly prepared TBN to get reproducible yields, which was synthesized according to a reported procedure.[20] ^{t}-BuOH was added (38 mL, 0.4 mol) dropwise to an ice-cold solution of con.H_2SO_4 (22 mL, 0.4 mol) in H_2O (25.0 mL), followed by the addition of a solution of sodium nitrite (42.0 g in 100 mL of H_2O). The reaction mixture was kept at approximately 0 °C during the addition. After the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. After the separation of the aqueous layer, the

organic portion was washed with saturated aq. $NaHCO_3$ solution and saturated aq. NaCl solution successively. The organic layer was then dried over anhydrous Na_2SO_4 and purified by distillation. The TBN is a light yellow liquid that was collected at about 80°C (ca. 25 mL). It was stored in a refrigerator and used for the four-component reaction directly.

Copper-Catalyzed Four Component reaction:

The carboxylic acid (0.2 mmol, 1 equiv) was dissolved in acetonitrile (4 mL), and stirred at room temperature. *Tert*-butyl nitrite (60 μL, 0.5 mmol, 2.5 equiv.) and 2, 2-difluoroethylamine (36 μL, 0.5 mmol, 2.5 equiv.) were added dropwise, then the reaction temperature was warmed to 80 °C. When the reaction was completed (Monitored by TLC), the crude product was evaporated and purified by column chromatography on silica gel using petroleum–AcOEt as eluent to afford the desired adduct **2**.

***N*-acetyl-*N*-(2, 2-difluoroethyl) benzamide (2a)[16b]**

Colorless oil (40 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 2H, Ar-H), 7.61 – 7.56 (m, 1H, Ar-H), 7.48 (dd, J = 8.2, 6.8 Hz, 2H, Ar-H), 6.07 (tt, J = 56.8, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.14 (td, J = 13.6, 4.5 Hz, 2H, $C\underline{H}_2CF_2H$), 2.13 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 173.2, 134.7, 133.0, 129.0, 128.6, 113.3 (t, J = 242.5 Hz, $\underline{C}F_2H$), 47.6 (t, J = 28.4 Hz, $\underline{C}CF_2H$), 25.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.30 (dt, J = 56.7, 13.7 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -122.30 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{11}H_{11}F_2NO_2Na^+$ $[M+Na]^+$ 250.0650, found 250.0654.

***N*-acetyl-*N*-(2, 2-difluoroethyl)-4-methoxybenzamide (2b)[16b]**

Pale yellow oil (45 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.57 (m, 2H, Ar-H), 7.06 – 6.92 (m, 2H, Ar-H), 6.08 (tt, J = 56.7, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.15 (td, J = 13.7, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 3.89 (s, 3H, $OC\underline{H}_3$), 2.11 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.13, 173.06, 163.8, 131.4, 126.6, 114.4, 113.4 (t, J = 242.5 Hz, $\underline{C}F_2H$), 55.6, 47.8 (t, J = 28.4 Hz, $\underline{C}CF_2H$), 25.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.19 (dt, J = 57.1, 13.8 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.19 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{12}H_{14}F_2NO_3^+$ $[M+H]^+$ 258.0936, found 258.0938.

***N*-acetyl-4-methyl-*N*-(2, 2-difluoroethyl) benzamide (2c)**

Pale yellow oil (44 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.51 (m, 2H, Ar-H), 7.35 – 7.22 (m, 2H, Ar-H), 6.07 (tt, J = 56.8, 4.5 Hz, 1H, $CF_2\underline{H}$), 4.15 (td, J = 13.6, 4.5 Hz, 2H, $C\underline{H}_2CF_2H$), 2.44 (s, 3H, Ar-$C\underline{H}_3$), 2.12 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 173.2, 144.2, 131.8, 129.7, 129.0, 113.3 (t, J = 242.6 Hz, $\underline{C}F_2H$), 47.8 (t, J = 28.5 Hz, $\underline{C}CF_2H$), 25.8, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.27 (dt, J = 57.0, 13.8 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.27 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{12}H_{14}F_2NO_2^+$ $[M+H]^+$ 242.0993, found 242.0987.

***N*-acetyl-*N*-(2, 2-difluoroethyl)-[1, 1'-biphenyl]-4-carboxamide (2d)**

White solid (51 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 4H, Ar-H), 7.66 – 7.59 (m, 2H, Ar-H), 7.54 – 7.46 (m, 2H, Ar-H), 7.45 – 7.37 (m, 1H, Ar-H), 6.10 (tt, J = 56.8, 4.5 Hz, 1H, $CF_2\underline{H}$), 4.18 (td, J = 13.6, 4.5 Hz, 2H, $C\underline{H}_2CF_2H$), 2.20 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 173.2, 146.0, 139.4, 133.2, 129.4, 129.1, 128.5, 127.7, 127.3, 113.3 (t, J = 242.6 Hz, $\underline{C}F_2H$), 47.9 (t, J = 28.5 Hz, $\underline{C}CF_2H$), 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.19 (dt, J = 57.0, 13.6 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.19 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{17}H_{16}F_2NO_2^+$ $[M+H]^+$ 304.1149, found 304.1144.

***N*-acetyl-*N*-(2, 2-difluoroethyl)-4-fluorobenzamide (2e)**

Pale yellow oil (37 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.61 (m, 2H, Ar-H), 7.26 – 7.08 (m, 2H, Ar-H), 6.07 (tt, J = 56.7, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.13 (td, J = 13.6, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 2.17 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 172.6, 166.8, 164.2, 131.4 (d, J = 9.3 Hz), 130.8 (d, J = 3.3 Hz), 116.5, 116.3, 113.2 (t, J = 242.6 Hz, $\underline{C}F_2H$), 47.8 (t, J = 28.3 Hz, $\underline{C}CF_2H$), 25.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.1~ -104.26 (m, 1F, Ar-F), -122.24 (dt, J = 57.1, 13.7 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -104.22 (s, Ar-F), -122.24 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{11}H_{11}F_3NO_2^+$ $[M+H]^+$ 246.0742, found 246.0736.

***N*-acetyl-4-chloro-*N*-(2, 2-difluoroethyl) benzamide (2f)**

Pale yellow oil (43 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.48 (m, 2H, Ar-H), 7.44 – 7.36 (m, 2H, Ar-H), 5.99 (tt, J = 56.7, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.05 (td, J = 13.5, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 2.11 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.7, 138.5, 132.0, 129.0, 128.4, 112.1 (t, J = 242.7 Hz, $\underline{C}F_2H$), 46.8 (t, J = 28.3 Hz, $\underline{C}CF_2H$), 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.24 (dt, J = 56.4, 13.2 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.24 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{11}H_{11}ClF_2NO_2^+$ $[M+H]^+$ 262.0446, found 262.0441.

***N*-acetyl-4-bromo-*N*-(2, 2-difluoroethyl) benzamide (2g)**

Pale yellow oil (48 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.59 (m, 2H, Ar-H), 7.56 – 7.47 (m, 2H, Ar-H), 6.06 (tt, J = 56.7, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.12 (td, J = 13.5, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 2.19 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 172.8, 133.5, 132.4, 130.1, 128.0, 113.1 (t, J = 242.7 Hz, $\underline{C}F_2H$), 47.8 (t, J = 28.3 Hz, $\underline{C}CF_2H$), 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.22 (dt, J = 56.4, 13.1 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.22 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{11}H_{11}BrF_2NO_2^+$ $[M+H]^+$ 305.9941, found 305.9936.

methyl 4-(acetyl (2, 2-difluoroethyl)carbamoyl) benzoate (2h)

White solid (38 mg, 67% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.11 (m, 2H, Ar-H), 7.71 – 7.65 (m, 2H, Ar-H), 6.07 (tt, J = 56.7, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.12 (td, J = 13.4, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 3.96 (s, 3H, $CO_2C\underline{H}_3$), 2.21 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 172.9, 138.6, 133.7, 130.1, 128.3, 113.1 (t, J = 242.7 Hz, $\underline{C}F_2H$), 52.5, 47.7 (t, J = 28.4 Hz, $\underline{C}CF_2H$), 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.28 (dt, J = 56.6, 13.5 Hz, $C\underline{F}_2H$).; ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.28 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{13}H_{14}F_2NO_4^+$ $[M+H]^+$ 286.0885, found 286.0888.

N-acetyl-N-(2, 2-difluoroethyl)-4-nitrobenzamide (2i)[16b]

Pale yellow oil (29 mg, 48% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 2H, Ar-H), 7.50 – 7.43 (m, 2H, Ar-H), 6.06 (tt, J = 56.7, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.12 (td, J = 13.5, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 2.19 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 171.8, 149.8, 140.4, 129.1, 124.1, 113.0 (t, J = 242.9 Hz, $\underline{C}F_2H$), 47.7 (t, J = 28.0 Hz, $\underline{C}CF_2H$), 25.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.23 (dt, J = 56.6, 13.6 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -122.23 (s, $C\underline{F}_2H$); HRMS (ESI) m/z calcd for $C_{11}H_{11}F_2N_2O_4^+$ $[M+H]^+$ 273.0681, found 273.0680.

***N*-acetyl-*N*-(2, 2-difluoroethyl)-1-naphthamide (2j)**

Pale yellow oil (47 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.98 (m, 2H, Ar-H), 7.92 (dd, J = 8.0, 1.5 Hz, 1H, Ar-H), 7.67 – 7.55 (m, 3H, Ar-H), 7.51 (dd, J = 8.2, 7.1 Hz, 1H, Ar-H), 6.10 (tt, J = 56.9, 4.5 Hz, 1H, $CF_2\underline{H}$), 4.12 (td, J = 13.4, 4.5 Hz, 2H, $C\underline{H}_2CF_2H$), 2.20 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 172.9, 133.7, 132.6, 132.3, 129.9, 128.8, 128.2, 127.1, 126.7, 124.8, 124.3, 113.1 (t, J = 242.6 Hz, $\underline{C}F_2H$), 47.3 (t, J = 28.9 Hz, $\underline{C}CF_2H$), 26.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.38 (d, J = 57.0 Hz, $C\underline{F}_2H$); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.39

(s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{17}H_{16}F_2NO_2^+$ [M+H]$^+$ 278.0993, found 278.0987.

***N*-acetyl-*N*-(2, 2-difluoroethyl) furan-2-carboxamide (2k)**

Pale yellow oil (26 mg, 60 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 1.7, 0.8 Hz, 1H, Ar-H), 7.33 (dd, J = 3.6, 0.8 Hz, 1H, Ar-H), 6.63 (dd, J = 3.6, 1.7 Hz, 1H, Ar-H), 6.07 (tt, J = 56.8, 4.5 Hz, 1H, $CF_2\underline{H}$), 4.21 (td, J = 13.4, 4.6 Hz, 2H, $C\underline{H}_2CF_2H$), 2.23 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 162.1, 146.9, 146.6, 120.7, 113.3 (t, J = 242.7 Hz, C$\underline{F}_2$H), 113.1, 47.2 (t, J = 29.0 Hz, $\underline{C}CF_2H$), 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.25 (dt, J = 56.5, 13.1 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.25 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_9H_{10}F_2NO_3^+$ [M+H]$^+$ 218.0629, found 218.0616.

***N*-acetyl-*N*-(2, 2-difluoroethyl) thiophene-2-carboxamide (2l)**

Pale yellow oil (26 mg, 57 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 5.0, 1.2 Hz, 1H, Ar-H), 7.59 (dd, J = 3.8, 1.2 Hz, 1H, Ar-H), 7.17 (dd, J = 5.0, 3.8 Hz, 1H, Ar-H), 6.09 (tt, J = 56.8, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.19 (td, J = 13.5, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 2.22 (s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 167.0, 137.6, 134.6, 133.6, 128.1, 113.2 (t, J = 242.7 Hz, C$\underline{F}_2$H), 48.3 (t, J = 28.6 Hz, $\underline{C}CF_2H$), 25.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.03 (dt, J = 57.1, 13.8 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.03 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_9H_{10}F_2NO_2S^+$ [M+H]$^+$ 234.0400, found 234.0395.

***N*-acetyl-*N*-(2, 2-difluoroethyl) cinnamamide (2m)**

White soild (32 mg, 63 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 15.5 Hz, 1H, Ar-H), 7.52 – 7.46 (m, 2H, Ar-H), 7.37 – 7.30 (m, 3H, Ar-H), 7.01 (d, J = 15.5 Hz, 1H, Ar-H)), 5.97 (tt, J = 56.7, 4.6 Hz, 1H, $CF_2\underline{H}$), 4.03 (td, J = 13.0, 4.6 Hz, 2H, $C\underline{H}_2CF_2H$), 2.41(s, 3H, $COC\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 168. 1, 145.1, 133.3, 129.8, 128.0, 127.4, 118.4, 112.4 (t, J = 242.6 Hz, C$\underline{F}_2$H), 46.0 (t, J = 28.6 Hz, $\underline{C}CF_2H$), 24.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.92 (dt, J = 56.5, 12.8 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -121.92 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{17}H_{16}F_2NO_2^+$ [M+H]$^+$ 254.0993, found 254.0987.

***N*-acetyl-*N*-(2, 2-difluoroethyl)-2-methyl-2-phenylpropanamide (2n)**

Pale yellow oil (44 mg, 82 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H, Ar-H), 7.30 – 7.26 (m, 1H, Ar-H), 7.24 – 7.20 (m, 2H, Ar-H), 5.85 (tt, J = 57.4, 4.7 Hz, 1H, $CF_2\underline{H}$), 3.45 (td, J = 12.7, 4.6 Hz, 2H, $C\underline{H}_2CF_2H$), 2.35 (s, 3H, $COC\underline{H}_3$), 1.65 (s, 6H, $2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.3, 173.9, 143.6, 129.1, 127.2, 125.2, 112.8 (t, J = 242.8 Hz, $\underline{C}F_2H$), 49.9, 46.9 (t, J = 29.6 Hz, $\underline{C}CF_2H$), 28.8, 25.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.89 (dt, J = 57.4, 12.7 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -121.89 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{14}H_{18}F_2NO_2^+$ [M+H]$^+$ 270.1306, found 270.1300.

***N*-acetyl-2-(4-chlorophenyl)-*N*-(2, 2-difluoroethyl)-3-methylbutanamide (2o)**

Pale yellow oil (44 mg, 71 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H, Ar-H), 7.28 – 7.23 (m, 2H, Ar-H), 5.92 (dddd, J = 57.3, 56.0, 5.6, 3.6 Hz, 1H, $CF_2\underline{H}$), 4.10 – 3.97 (m, 1H, $C\underline{H}CF_2H$), 3.96 (d, J = 10.0 Hz, 1H, $C\underline{H}CH_3$), 3.92 – 3.79 (m, 1H, $C\underline{H}CF_2H$), 2.48 – 2.31 (m, 4H, $COCH_3$ and $C\underline{H}$-^{i}Pr), 1.02 (d, J = 6.5 Hz, 3H, CH_3), 0.67 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 173.4, 136.0, 133.5, 130.0, 129.0, 113.2 (t, J = 242.7 Hz, $\underline{C}F_2H$), 59.0, 46.6 (dd, J = 30.7, 26.4 Hz, $\underline{C}CF_2H$), 33.1, 26.2, 21.5, 20.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -120.26 – -123.19 (m, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -120.37 – -123.27 (m, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{15}H_{19}ClF_2NO_2^+$ [M+H]$^+$ 318.1072, found 318.1067.

***N*-(2, 2-difluoroethyl)-*N*-isobutyrylbenzamide (4a)**

Colorless oil (43 mg, 84 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 2H, Ar-H), 7.62 – 7.57 (m, 1H, Ar-H), 7.53 – 7.46 (m, 2H, Ar-H), 6.11 (tt, J = 56.9, 4.5 Hz, 1H, $CF_2\underline{H}$), 4.12 (td, J = 13.4, 4.5 Hz, 2H, $C\underline{H}_2CF_2H$), 2.74 (hept, J = 6.7 Hz, 1H, $C\underline{H}$), 1.06 (d, J = 6.7 Hz, 6H, $2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 173.8, 135.0, 133.0, 129.1, 128.7, 113.4 (t, J = 242.7 Hz, $\underline{C}F_2H$), 48.3 (t, J = 28.6 Hz, $\underline{C}CF_2H$), 36.2, 19.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.19 (dt, J = 56.7, 13.5 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.19 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{13}H_{16}F_2NO_2^+$ [M+H]$^+$ 256.1144, found 256.1150.

***N*-(2, 2-difluoroethyl)-*N*-isobutyryl-4-methoxybenzamide (4b)**

Colorless oil (47 mg, 80 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.59 (m, 2H, Ar-H), 7.03 – 6.87 (m, 2H, Ar-H), 6.11 (tt, J = 56.9, 4.5 Hz, 1H, $CF_2\underline{H}$), 4.11 (td, J = 13.6, 4.6 Hz, 2H, $C\underline{H}_2CF_2H$), 3.89 (s, 3H, $OC\underline{H}_3$), 2.73 (hept, J = 6.7 Hz, 1H, $C\underline{H}$), 1.06 (d, J = 6.7 Hz, 6H, $2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 173.2, 163.7, 131.3, 126.9, 114.4, 113.5 (t, J = 242.7 Hz, $\underline{C}F_2H$), 55.6, 48.4 (t, J = 28.5 Hz, $\underline{C}CF_2H$), 35.9, 19.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.08 (dt, J = 57.1, 13.6 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H} NMR (376 MHz, $CDCl_3$) δ -122.08 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{14}H_{18}F_2NO_3^+$ [M+H]$^+$ 286.1249, found 286.1248.

***N*-(2, 2-difluoroethyl)-*N*-isobutyryl-4-nitrobenzamide (4c)**

Colorless oil (35 mg, 58 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.28 (m, 2H, Ar-H), 7.87 – 7.65 (m, 2H, Ar-H), 6.10 (tt, J = 56.6, 4.4 Hz, 1H, $CF_2\underline{H}$), 4.11 (td, J = 13.3, 4.4 Hz, 2H, $C\underline{H}_2CF_2H$), 2.90 (hept, J = 6.8 Hz, 1H, $C\underline{H}$), 1.15 (d, J = 6.7 Hz, 6H, $2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 171.9, 149.8, 140.7, 129.0, 124.2, 113.1 (t, J = 243.0 Hz, $\underline{C}F_2H$), 47.9 (t, J = 28.2 Hz, $\underline{C}CF_2H$), 35.5, 19.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.13 (dt, J = 56.6, 13.3 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.13 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{13}H_{14}F_2N_2O_4Na^+$ [M+Na]$^+$ 323.0814, found 323.0811.

***N*-benzoyl-*N*-(2, 2-difluoroethyl) benzamide (6a)**

Colorless oil (48 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 4H, Ar-H), 7.23 – 7.16 (m, 2H, Ar-H), 7.14 – 7.04 (m, 4H, Ar-H), 6.28 (tt, J = 56.8, 4.6 Hz, 1H, $CF_2\underline{H}$), 4.33 (td, J = 13.5, 4.6 Hz, 2H, $C\underline{H}_2CF_2H$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 134.7, 131.2, 127.9, 127.3, 112.6 (t, J = 243.0 Hz, $\underline{C}F_2H$), 47.3 (t, J = 28.5 Hz, $\underline{C}CF_2H$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.24 (dt, J = 57.0, 13.5 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.24 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{16}H_{14}F_2NO_2^+$ [M+H]$^+$ 290.0987, found 290.0989.

***N*-(2, 2-difluoroethyl)-*N*-(2-phenylacetyl)benzamide (6b)**

Colorless oil (48 mg, 79 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (td, J = 7.2, 1.4 Hz, 1H, Ar-H), 7.47 – 7.43 (m, 2H, Ar-H), 7.40 – 7.34 (m, 2H, Ar-H), 7.21 – 7.15 (m, 3H, Ar-H), 7.04 (dd, J = 7.7, 1.7 Hz, 2H, Ar-H), 5.98 (tt, J = 56.8, 4.5 Hz, 1H, $CF_2\underline{H}$), 3.99 (td, J = 13.4, 4.5 Hz, 2H, $C\underline{H}_2CF_2H$), 3.77 (s, 2H, $PhC\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 173.7, 134.3, 133.7, 133.1, 129.3, 129.1, 128.7, 128.6, 127.3, 113.2 (t, J = 242.7 Hz, $\underline{C}F_2H$), 48.5 (t, J = 28.7 Hz, $\underline{C}CF_2H$), 44.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.03 (dt, J = 57.0, 13.7 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.03 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{17}H_{16}F_2NO_2^+$ [M+H]$^+$ 304.1144, found 304.1147.

***N*-(2, 2-difluoroethyl)-*N*-pentanoylbenzamide (6c)**

Colorless oil (43 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 2H, Ar-H), 7.62 – 7.57 (m, 1H, Ar-H), 7.49 (dd, J = 8.2, 6.8 Hz, 2H, Ar-H), 6.09 (tt, J = 56.9, 4.5 Hz, 1H, $CF_2\underline{H}$), 4.13 (td, J = 13.5, 4.5 Hz, 2H $C\underline{H}_2CF_2H$), 2.52 – 2.21 (m, 2H, $COC\underline{H}_2$), 1.56 (p, J = 7.5 Hz, 2H, $COCH_2C\underline{H}_2$), 1.21 (h, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 0.81 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 173.8, 134.9, 133.0, 129.1, 128.6, 113.3 (t, J = 242.6 Hz, $\underline{C}F_2H$), 47.9 (t, J = 28.5 Hz, $\underline{C}CF_2H$), 37.8,

27.5, 22.5, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.23 (dt, J = 56.8, 13.6 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.23 (s, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{14}H_{18}F_2NO_2^+$ $[M+H]^+$ 270.1300, found 270.1303.

(1S,2S,4aR,4bR,7S,9aS,10S,10aR)-*N*-acetyl-*N*-(2,2-difluoroethyl)-2,7-dihydroxy-1-methyl-8-methylene-13-oxo-1,2,4b,5,6,7,8,9,10,10a-decahydro-4a,1-(epoxymethano)-7,9a-methanobenzo[a]azulene-10-carboxamide (7)

Colorless oil (71 mg, 70 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, J = 9.2 Hz, 1H), 5.99 (tt, J = 56.6, 4.3 Hz, 1H, $CF_2\underline{H}$), 5.88 (dd, J = 9.2, 3.6 Hz, 1H), 5.22 (t, J = 2.3 Hz, 1H), 4.97 (t, J = 2.1 Hz, 1H), 4.16 – 4.05 (m, 2H), 4.05 – 3.91 (m, 2H), 3.33 (d, J = 9.1 Hz, 1H), 2.52 (s, 2H), 2.41 (s, 3H), 2.26 – 2.06 (m, 3H), 2.04 – 1.88 (m, 3H), 1.83 (d, J = 10.9 Hz, 1H), 1.79 – 1.68 (m, 2H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0 (d, J = 1.7 Hz), 176.8, 173.4, 155.4, 132.7, 132.5, 113.0 (t, J = 242.9 Hz, $\underline{C}F_2$H), 107.7, 91.0, 78.3, 70.0, 55.8, 53.3, 52.29, 50.28, 50.22, 47.5 (t, J = 27.9 Hz, $\underline{C}CF_2$H), 45.9, 43.3, 38.2, 25.5, 17.3, 14.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.66 (ddt, J = 56.0, 27.8, 13.0 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -121.66 (d, J = 28.0 Hz, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{23}H_{28}F_2NO_6^+$ $[M+H]^+$ 452.1879, found 452.1882.

(3R,4S,5R)-*N*-acetyl-*N*-(2,2-difluoroethyl)-3,4,5-trihydroxycyclohex-1-ene-1-carboxamide (8)

Colorless oil (41 mg, 74 % yield); ^{1}H NMR (400 MHz, Methanol-d_4) δ 6.11 (dd, J = 3.5, 1.8 Hz, 1H), 5.94 (tt, J = 56.6, 4.3 Hz, 1H, $CF_2\underline{H}$), 4.29 (dt, J = 3.9, 1.9 Hz, 1H, C$\underline{H}$CF$_2$H), 4.07 – 3.93 (m, 3H), 3.65 (dd, J = 7.0, 4.1 Hz, 1H), 2.63 (ddt, J = 18.0, 4.4, 2.0 Hz, 1H), 2.22 (dt, J = 5.2, 1.6 Hz, 1H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, Methanol-d_4) δ 177.9, 177.6, 139.5, 138.0, 117.7 (t, J = 241.2 Hz, $\underline{C}F_2$H), 74.9, 70.8, 69.7, 50.5 (t, J = 27.9 Hz, $\underline{C}CF_2$H), 34.3, 28.5; ^{19}F NMR (376 MHz, Methanol-d_4) δ -123.70 (dq, J = 56.5, 14.7 Hz, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, Methanol-d_4) δ -123.70 (d, J = 15.8 Hz, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{11}H_{16}F_2NO_5^+$ $[M+H]^+$ 280.0991, found 280.0993.

(R)-*N*-acetyl-*N*-(2,2-difluoroethyl)-4-((3R,5S,7R,8R,9S,10S,12S,13R,14S,17R)-3,7,12-trihydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl) pentanamide (9)

Colorless oil (78 mg, 65 % yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (tt, J = 56.8, 4.6 Hz, 1H, $CF_2\underline{H}$), 4.03 (td, J = 13.0, 4.6 Hz, 2H, C$\underline{H}$CF$_2$H), 3.97 (d, J = 2.9 Hz, 1H), 3.84 (d, J = 2.9 Hz, 1H), 3.64 (s, 3H), 3.42 (dt, J = 11.1, 6.4 Hz, 1H), 2.79 (ddd, J = 14.7, 10.1, 4.3 Hz, 1H), 2.66 (ddd, J = 15.8, 9.2, 5.7 Hz, 1H), 2.44 (s, 3H), 2.20 (dtd, J = 12.8, 9.0, 5.0 Hz, 2H), 1.96 – 1.71 (m, 8H), 1.65 (d, J = 13.5 Hz, 2H), 1.62 – 1.48 (m, 4H), 1.48 – 1.35 (m, 4H), 1.32 – 1.21 (m, 1H), 1.10 (td, J = 12.3, 11.5, 4.8 Hz, 1H), 1.00 (d, J = 5.9 Hz, 3H), 0.88 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 173.4, 113.4 (t, J = 242.5 Hz, $\underline{C}F_2$H), 73.1, 71.8, 68.4, 47.0, 46.8 (t, J = 28.5 Hz, $\underline{C}CF_2$H), 46.4, 41.6, 41.5, 39.5, 35.4, 35.2, 34.8, 34.6, 30.7, 30.2, 28.1, 27.5, 26.30, 26.27, 23.2, 22.4, 17.5, 12.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -121.85 – -122.17 (m, C$\underline{F}_2$H); ^{19}F {^{1}H}NMR (376 MHz, $CDCl_3$) δ -122.00 (d, J = 2.6 Hz, C$\underline{F}_2$H); HRMS (ESI) m/z calcd for $C_{28}H_{46}F_2NO_5^+$ $[M+H]^+$ 514.3339, found 514.3337.

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Keywords: imide • diazomethane • multicomponent • Copper • difluoromethyl

[1] Thalidomide: (a) T. Hideshima, D. Chauhan, Y. Shima, N. Raje, F. E. Davies, Y. T. Tai, S. P. Treon, B. Lin, R. L. Schlossman, P. Richardson, G. Muller, D. I. Stirling, K. C. Anderson, *Blood*, **2000**, 96, 2943-2950; (b) J. B. Bartlett, K. Dredge, A. G. Dalgleish, *Nat. Rev. Cancer*, **2004**, 4, 314-322.

[2] Ethosuximide: (a) T. R. Browne, F. E. Dreifuss, P. R. Dyken, D. J. Goode, J. K. Penry, R. J. Porter, B. G. White, P. T. White, *Neurology*, **1975**, 25, 515-524; (b) N. Leresche, H. R. Parri, G. Erdemli, A. Guyon, J. P. Turner, S. R. Williams, E. Asprodini, V. Crunelli, *J. Neurosci.*, 1998, **18**, 4842-4853; (c) M. Z. Goren, F. Onat, *Cns Drug Rev.*, **2007**, 13, 224-239.

[3] Penimide: T. Pacher, A. Raninger, E. Lorbeer, L. Brecker, P. P.-H., H. Greger, *J. Nat. Prod.* **2010**, 73, 1389-1393.

[4] Captan: D. F. Rawn, S. C. Quade, W. F. Sun, A. Fouguet, A. Belanger, M. Smith, *Food chem.*, **2008**, 109, 790-796.

[5] Aniracetam: K. Nakamura, M. Kurasawa, *Eur. J. Pharmacol.*, **2001**, **420**, 33-43.

[6] Palau'imide: H. Luesch, W. Y. Toshida, R. E. Moore, V. J. Paul, *Tetrahedron*, **2002**, 58, 7959-7966.

[7] For the application in pharmaceutical area: (a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, 37, 320–330; (b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.*, **2014**, 114, 2432-2506; (c) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.*, **2015**, 58, 8315-8359.

[8] For review of the syntheses: (a) C. F. Ni, M. Y. Hu, J. B. Hu, *Chem. Rev.*, **2015**, 115, 765-825; (b) J. Hu, W. Zhang, F. Wang, *Chem. Commun.*, **2009**, 7465-7478; (c) Z. Feng, Y.-L. Xiao, X. Zhang, *Acc. Chem. Res.*, **2018**, DOI: 10.1021/acs.accounts.8b00230; For selected examples: (d) Z. Feng, Q. Q. Min, X. P. Fu, L. An, X. G. Zhang, *Nat. Chem.* **2017**, *9*, 918-923; (e) C. Xu, W.-H. Guo, X. He, Y.-L. Guo, X.-Y. Zhang, X. Zhang, *Nat. Commun.* **2018**, *9*, 1170; (f) X. Yang, Z. Chen, Y. Cai, Y.-Y. Huang, N. Shibata, *Green Chem.* **2014**, *16*, 4530-4534; (f) X. Yang, F. Cheng, Y.-D. Kou, S. Pang, Y.-C. Shen, Y.-Y. Huang, N. Shibata, *Angew. Chem. Int. Ed.* **2017**, *56*, 1510-1514; (g) S. M. Banik, J. W. Medley, E. N. Jacobsen, *Science* **2016**, *353*, 51-54.

[9] J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.*, **1995**, 60, 1626-1631.

[10] N. A. Meanwell, *J. Med. Chem.*, **2011**, 54, 2529-2591.

[11] (a) D. Schirlin, F. Gerhart, J. M. Hornsperger, M. Hamon, J. Wagner, M. J. Jung, *J. Med. Chem.*, **1988**, 31, 30-36; (b) S. N. Osipov, P. Tsouker, L. Hennig, K. Burger, *Tetrahedron*, **2004**, 60, 271-274; (c) L. Kuznetsova, I. M. Ungureanu, A. Pepe, I. Zanardi, X. Wu, I. Ojima, *J. Fluorine Chem.*, **2004**, 125, 487-500.

[12] P. K. Mykhailiuk, *Angew. Chem. Int. Ed.*, **2015**, 54, 6558–656.

[13] For a review: (a) L. Mertens, R. M. Koenigs, *Org. Biomol. Chem.*, **2016**, 14, 10547-10556; For selected examples: (b) B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 4294; (c) B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 1101; (d) Morandi, B.; Carreira, E. M., *Angew. Chem. Int. Ed.* **2011,** *50*, 9085; (e) F. Li, J. Nie, L. Sun, Y. Zheng, J.-A. Ma, *Angew. Chem. Int. Ed.* **2013**, *52*, 6255; (f) C.-L. Zhu, L.-J. Yang, S. Li, Y. Zheng, J.-A. Ma, *Org. Lett.* **2015**, *17*, 3442; (g) Z. Chen, S.-Q. Fan, Y. Zheng, J.-A. Ma, *Chem. Commun.* **2015**, *51*, 16545; (h) Z. Chen, Y. Zheng, J.-A. Ma, *Angew. Chem. Int. Ed.* **2017**, *56*, 4569; (i) O. A. Argintaru, D. Ryu, I. Aron, G. A. Molander, *Angew. Chem. Int. Ed.* **2013**, *52*, 13656; (i) G. A. Molander, D. Ryu, *Angew. Chem. Int. Ed.* **2014**, *53*, 14181; (j) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2017**, *15*, 7296; (k) A. V. Arkhipov, V. V. Arkhipov, J. Cossy, V. O. Kovtunenko, P. K. Mykhailiuk, *Org. Lett.* **2016**, *18*, 3406; (l) P. K. Mykhailiuk, S. Afonin, G. V. Palamarchuk, O. V. Shishkin, A. S. Ulrich and I. V. Komarov, *Angew. Chem. Int. Ed.*, 2008, **47**, 5765-5767; (m) H. Q. Luo, G. J. Wu, Y. Zhang, J. B. Wang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14503; (n) S. Hyde, J. Veliks, B. Liegault, D. Grassi, M. Taillefer, V. Gouverneur, *Angew. Chem. Int. Ed.* **2016**, *55*, 3785; (o) J. Britton, T. F. Jamison, *Angew. Chem. Int. Ed.* **2017**, *56*, 8823.

[14] (a) L. Mertens, K. J. Hock, R. M. Koenigs, *Chem. Eur. J.* **2016**, *22*, 9542-9545; (b) W. Y. Han, J. Zhao, J. S. Wang, G. Y. Xiang, D. L. Zhang, M. Bai, B. D. Cui, N. W. Wan, Y. Z. Chen, *Org. Biomol. Chem.*, **2017**, 15, 5571-5578; (c) P. S. Lebed, J. Fenneteau, Y. Wu, J. Cossy, P. K. Mykhailiuk, *Eur. J. Org. Chem.,* **2017**, 6114-6120; (d) K. J. Hock, L. Mertens, F. K. Metze, C. Schmittmann, R. M. Koenigs, *Green Chem.* **2017**, *19*, 905-909; (e) J. Britton, T. F. Jamison, *Angew. Chem. Int. Ed.* **2017***, 56,* 8823-8827; (f) W. Y. Han, J. S. Wang, J. Zhao, L. Long, B. D. Cui, N. W. Wan, Y. Z. Chen, *J. Org. Chem.,* **2018**, 83, 6556-6565; (g) X.-W. Zhang, W.-L. Hu, S. Chen and X.-G. Hu, *Org. Lett.*, **2018**, 20, 860-863. For a paper describing masked difluoromethyl diazomethane: (h) J.-L. Zeng, Z. Chen, F.-G. Zhang, J.-A. Ma, *Org. Lett.* **2018**, *20*, 4562-4565.

[15] (a) K. J. Hock, L. Mertens, R. M. Koenigs, *Chem. Commun.,* **2016**, 52, 13783-13786; (b) W.-Y. Han, J. Zhao, J.-S. Wang, B.-D. Cui, N.-W. Wan, Y.-Z. Chen, *Tetrahedron,* **2017**, 73, 5806-581.

[16] (a) P. K. Mykhailiuk, I. Kishko, V. Kubyshkin, N. Budisa, J. Cossy, *Chem-Eur. J.,* **2017,** *23,* 13279-13283*;* (b) S.-Q. Peng, X.-W. Zhang, L. Zhang, X.-G. Hu, *Org. Lett.,* **2017**, 19, 5689-5692.

[17] for a review of late-stage functionalization (a) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.*, **2016**, 45, 546-576; For late-stage functionalization in fluorine chemistry: (b) C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.*, **2015**, 54, 3216-3221.

[18] X. Zhao, Y. Zhang and J. B. Wang, *Chem. Commun.*, **2012**, 48, 10162-10173.

[19] (a) J. J. Chen, Y. Shao, L. Ma, M. H. Ma and X. B. Wan, *Org. Biomol. Chem.*, **2016**, 14, 10723-10732; (b) (a) O. Mumm, *Ber. Dtsch. Chem. Ges.* 1910, 43, 886−893.

[20] G. Meng, T. Yang and Y. Liu, *Org. Prep. Proced. Int.*, **2011**, 43, 354-359.

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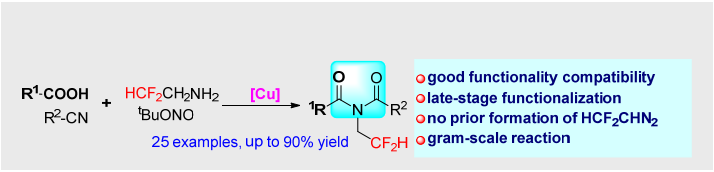

A general and efficient method for the synthesis *N*-difluoroethyl imides has been developed. This copper-catalyzed four component reaction proceeds *via* in-*situ* generated difluorodiazomethane, which does not require the prior formation and transferring. The reaction is scalable, tolerant a range of functional groups, and also suitable for the late-stage functionalization of drugs and drug-like molecules.

difluoromethyl, copper-catalyzed*

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Page No. – Page No.

Copper-Catalyzed Four Component Reaction for the Synthesis of *N*-Difluoroethyl Imides