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2-Amino-5,6-Difluorophenyl-1*H*-Pyrazole-Directed Pd^{II} Catalysis: Arylation of Unactivated *β*-C(sp^3)−H Bonds

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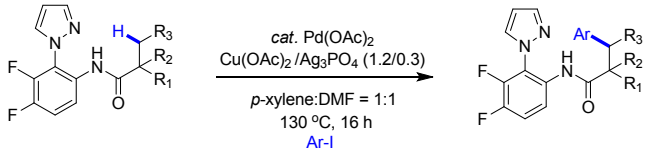


Compatible with substrates containing *α*-hydrogen atoms
Readily removable directing group
41 examples, up to 78% yield

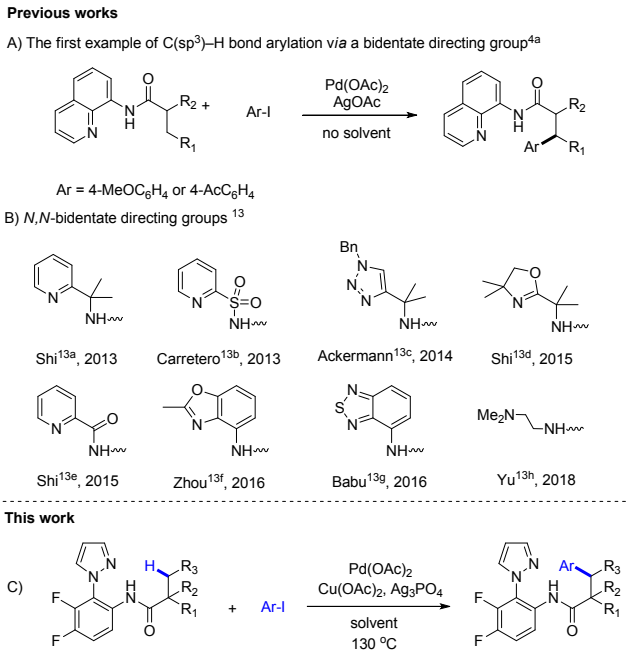
ABSTRACT: Palladium-catalyzed arylation of unactivated *β*-C(sp^3)−H bonds in carboxylic acid derivatives with aryl iodides is described for the first time using 2-amino-5,6-difluorophenyl-1*H*-pyrazole as an efficient and readily removable directing group. Two fluoro groups are installed at the 5- and 6-position of the anilino moiety in 2-aminophenyl-1*H*-pyrazole, clearly enhance the directing ability of the auxiliary. In addition, the protocol employs $Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3) as additives, evidently reducing the stoichiometric amount of expensive silver salts. Furthermore, this process exhibits high *β*-site selectivity, compatibility with diverse substrates containing *α*-hydrogen atoms, and excellent functional group tolerance.

INTRODUCTION

The immense potential of organic synthesis based on transition-metal-catalyzed functionalization of C(sp^2)−H bonds has been extensively explored over the decades.[1] In comparison, direct functionalization of unactivated C(sp^3)−H bonds remains underdeveloped and continues to be highly challenging because of the high bond dissociation enery and the absence of stabilizing π-orbital interactions with the metal center.[2] However, directing-group-assisted strategy has become a powerful and promising method for achieving diverse transformations of inert C(sp^3)−H bonds,[3] such as arylation,[4] alkoxylation,[5] alkenylation,[6] alkynylation,[7] carbonylation,[8] amination,[9] and others.[10]

β-substituted carboxylic acid derivatives are frequently found in a wide array of bioactive compounds.[11] Therefore, direct functionalization of their *β*-C(sp^3)−H bonds is highly appealing. According to previous reports, the bidentate directing groups showed much better performance than the monodentate ones.[12] In 2005, Daugulis and co-workers first demonstrated that 8-aminoquinoline could be employed as bidentate directing group to promote *β*-arylation of aliphatic amide derivatives (Scheme 1A).[4a] Following this pioneering work, numerous *N,N*-bidentate directing groups have been reasonably developed for the unactivated C(sp^3)−H bond arylation in aliphatic amide derivatives (Scheme 1B).[13]

Scheme 1. Directing Group Strategies for Unactivated C(sp^3)−H Bond Arylation of Aliphatic Amides.



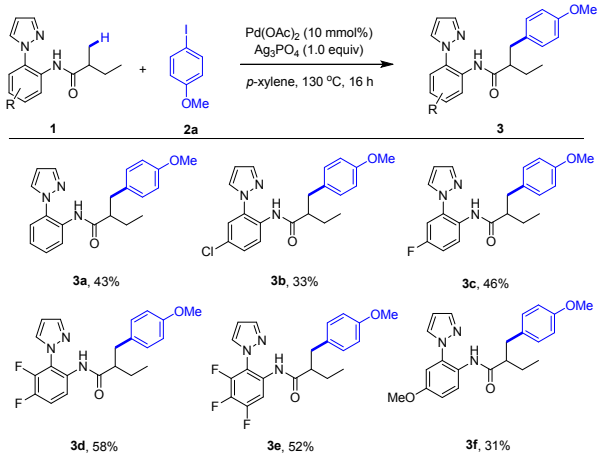
Despite all these great advances, some inherent limitations

also remain. For instance, arylation of secondary C(sp^3)−H bond or various substrates containing α-hydrogen atoms can not be tolerated,[4d, e, 14] possibly because that the palladacycle can undergo β-hydride elimination with the α-hydrogen atom, which inhibited the desired step.[3a, 4b] Additionally, strong auxiliaries give thermodynamically stable palladacycles, as a result, the subsequent functionalization steps are less reactive. In contrast, the palladacycles are less stable with weakly coordinating directing groups, which is unfavorable to C−H cleavage step.[1a, 15] To break through these limitations, efforts are still in high demand to develop new types of directing groups.

Recently, Li's and Baidya's groups presented 2-aminophenyl-1*H*-pyrazole as an effective *N,N*-bidentate auxiliaries to realize various C(sp^2)−H functionalizations.[16] Most recently, our groups reported *ortho*-arylation of aromatic amides directed by 2-amino-5-chlorophenyl-1*H*-pyrazole with general work conditions, broader substrate scope and wider functional group tolerance.[17] Compared to C(sp^2)−H bond activation, C(sp^3)−H functionalizations directed by amino-pyrazole auxiliaries deserve to be paid more attention. Meanwhile, considering adjusting the coordination ability of this auxiliary, we undertake to introduce halide substituents which exert inductive and conjugation effects with the benzene ring at the anilino moiety. Herein, we describe the first palldium-catalyzed arylation of unactivated β-C(sp^3)−H in carboxylic acid derivatives using 2-amino-5,6-difluorophenyl-1*H*-pyrazole as a bidentate auxiliary (Scheme 1C). Particularly, the protocol can afford arylated product of carboxylic acid derivatives that contain α-hydrogen atoms in moderate to good yields, *ortho*-substituted aryl iodides are also tolerated.

RESULTS AND DISCUSSION

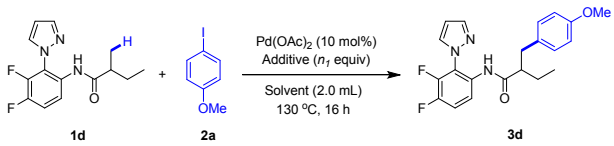
Table 1. Influence of Substituent Electronegativity on the Directing Groups.[a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (10 mol%), Ag_3PO_4 (1.0 equiv), *p*-xylene (3.0 mL), 130 °C, 16 h. [b] Isolated yields of **3**.

Initially, our efforts focused on substituent electronegativity on the 2-aminophenyl-1*H*-pyrazole directing group. The reaction was conducted in the presence of substrate **1** (0.3 mmol), $Pd(OAc)_2$ (10 mol%), 4-iodoanisole **2a** (3.0 equiv), Ag_3PO_4 (1.0 equiv) in *p*-xylene (3.0 mL) at 130 °C for 16 hours (Table 1). And the target product **3a** was obtained in 43% yield by the unmodified directing group. In fact, a chloro group at the 5-position offered a lower yield than the unmodified directing group (**3a**, **3b**). To our delight, the addition of a fluoro substituent group at the anilino moiety improved the yield of the arylated product **3c**. When two fluoro groups were separately installed at the 5- and 6-position, the yield of **3d** evidently increased to 58%. However, with more fluoro groups, the yield of **3e** was slightly diminished. Additionally, we also introduced a methoxy substituent group at the 5-position, which offered a lower yield (**3f**). 2-Amino-5,6-difluorophenyl-1*H*-pyrazole was ultimately opted as the most effective directing group for further surveys.

Table 2. Optimization of the Reaction Conditions. [a]



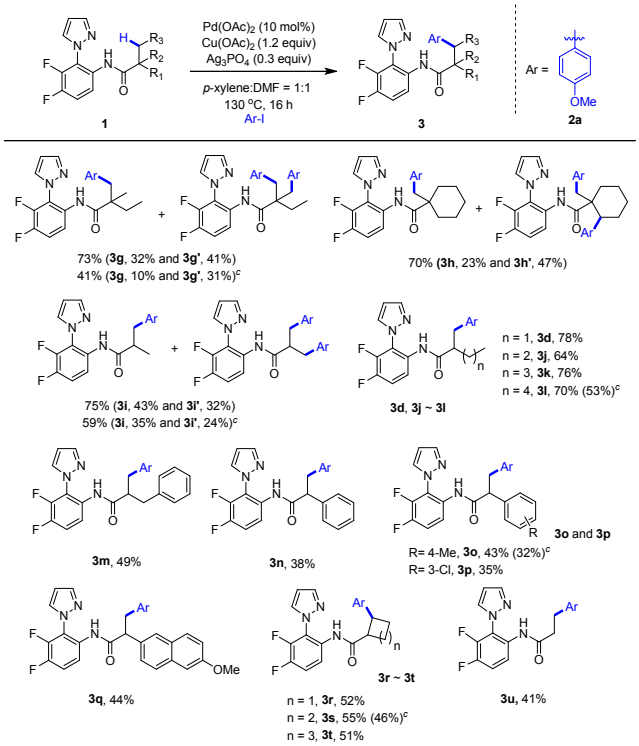
Entry	Additive (n_1 equiv)	Solvent	Yield (%)[b]
1	Ag_3PO_4 (1.0)	*p*-xylene	58
2	AgOAc (2.0)	*p*-xylene	47
3	AgTFA (2.0)	*p*-xylene	32
4	Ag_2CO_3 (2.0)	*p*-xylene	20
5	$Cu(OAc)_2$ (2.0)	*p*-xylene	56
6	$Cu(acac)_2$ (2.0)	*p*-xylene	51
7	$CuCl_2$ (2.0)	*p*-xylene	<5
8	$Cu(OAc)_2/Ag_3PO_4$ (1.6/0.4)	*p*-xylene	71
9	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	*p*-xylene	72
10	$Cu(OAc)_2/Ag_3PO_4$ (0.8/0.2)	*p*-xylene	64
11	$Cu(OAc)_2/Ag_3PO_4$ (1.0/0.5)	*p*-xylene	55
12	$Cu(OAc)_2/Ag_3PO_4$ (1.3/0.2)	*p*-xylene	64
13	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	DMF	58
14	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	DCE	55
15	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	DMSO	45
16	**$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)**	***p*-xylene/DMF (1:1)**	**78**
17	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	*p*-xylene/DMF (3:1)	70
18	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	*p*-xylene/DMF (1:3)	63
19	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	*p*-xylene/DMF (1:1)	67[c] (76[d])
20	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	*p*-xylene/DMF (1:1)	0[e] (0[f], 0[g])
21	$Cu(OAc)_2/Ag_3PO_4$ (1.2/0.3)	*p*-xylene/DMF (1:1)	0[h] (51[i])
22	Ag_3PO_4 (0.3)	*p*-xylene/DMF (1:1)	36 (27[i])

[a] Reaction conditions: **1d** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (10 mol%), additive (n_1 equiv), solvent (3.0 mL), 130 °C, 16 h. [b] Isolated yields of **3d**. [c] 120 °C. [d] 140 °C. [e] 4-Bromoanisole instead of 4-iodoanisole. [f] 4-Chloroanisole instead of 4-iodoanisole. [g] 4-Methoxyphenylboronic acid instead of 4-iodoanisole. [h] No $Pd(OAc)_2$. [i] No Ag_3PO_4.

With the optimized directing group in hand, We attempted to improve the yield of the arylated product by changing the reaction conditions (Table 2). We first screened various Ag salts, and Ag_3PO_4 was considered as the best one (entries 1−4). Inspired by previous literature,[4d, 18] we attempted to employ $Cu(OAc)_2$ as the single additive instead of expensive silver salts, successfully obtaining **3d** in 56% yield (entry 5). And this is significant, since iodide scavenging is completed without the need for silver salts. Notably, direct arylation of C(sp^3)−H aided by Cu salts is rather rare in bidentate directing groups.[4c, d, 14a, 19] Subsequently, we screened other copper (II)

salts, and $Cu(acac)_2$ resulted in inferior efficiency (entry 6) while $CuCl_2$ was almost inefficient (entres 7). Considering the economy and reaction efficiency, we attempt to use $Cu(OAc)_2$ (1.6 equiv) as the primary additive in concert with small stoichiometric amount of Ag_3PO_4 (0.4 equiv) (entry 8), and the yield of **3d** was distinctly improved to 71%. Reducing the mixed additives to 1.5 equiv had no adverse effect on the yield (entry 9). But, further reducing additives lead to relative lower yield (entry 10). Additionly, increasing or decreasing the amount of Ag_3PO_4 in the common additives was detrimental (entries 11 and 12). In contrast to our initial solvent choice of *p*-xylene, DCE, DMF and DMSO were all diminished the yield of **3d** (entries 13−15). However, when *p*-xylene and DMF was used as mixed solvent (*p*-xylene:DMF, 1:1, v/v), the yield of the product **3d** was improved to 78% (entry 16). Changing the ratio of *p*-xylene and DMF, no better reaction yields were observed. (entries 17 and 18). Inferior reaction performance was observed in the reaction temperature of 120 °C or 140 °C (entry 19). Then several other arylation reagents instead of **2a** were not reactive (entry 20). Finally, control experiments were conducted. No desired product was detected without $Pd(OAc)_2$, which demonstrated the essential role of $Pd(OAc)_2$ as catalyst (entry 21). Movever, 51% and 36% isolated yield of **3d** was separately obtained in the absence of Ag_3PO_4 and without $Cu(OAc)_2$, while $Pd(OAc)_2$ alone was only able to furnish **3d** in 27% yield under similar conditions (entries 21 and 22). It was proved that $Cu(OAc)_2$ and Ag_3PO_4 played crucial roles and had a cooperative effect on promoting the transformation. From the series of above examinations, entry 16 was determined to be the optimal reaction conditions.

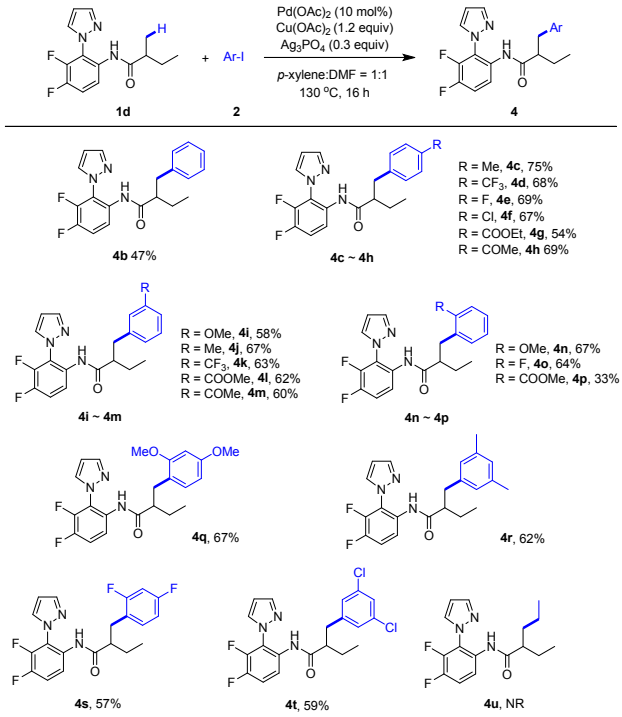
Table 3. Substrate Scope of the Aliphatic Amides.[a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (0.36 mmol), Ag_3PO_4 (0.09 mmol), *p*-xylene (1.5 mL), DMF (1.5 mL), 130 °C, 16 h. [b] Isolated yields of **3**. [c] $Cu(OAc)_2$ (0.6 mmol) in the absence of Ag_3PO_4.

With the established reaction conditions, a series of aliphatic amides derived from carboxylic acids with α-quaternary centers or α-tertiary centers were examined. The results are summarized in Table 3. The substrate **1g** reacted with **2a** to afford the target β-monoarylated product **3g** in 32% yield and β,β-diarylated product **3g'** in 41% yield due to the existence of two equivalent reactive β-C(sp^3)−H sites. As for substrate **1h**, the corresponding product **3h** of β-methyl C(sp^3)−H bond arylation was observed in 23% yield along with 47% yield of β-methyl and β-methylene C(sp^3)−H bonds diarylated product **3h'**. We then examined the site selectivity of substrates containing β-methyl, linear β-methylene C(sp^3)−H bonds and γ-C(sp^2)−H bonds. Arylation of the β-methyl C(sp^3)−H bonds was exclusively observed in moderate to good yields, indicating the high selectivity of the directing group (**3d**, **3i**−**3q**). Additionally, we found that alkyl side chains at the α-position had little effect on the yields of the target products and substrates bearing aryl groups were less reactive than those with aliphatic chains. Noteworthy, aliphatic amides with α-hydrogen atoms all reacted smoothly. Moreover, the arylation of β-methylene C(sp^3)−H bond with four-, five-, and six-membered cycloalkyl substituted aliphatic amides was also tolerated, exclusively affording the corresponding monoarylated products (**3r**−**3t**) in moderate overall yields (51−55%), and no diarylated products were obtained. For α-secondary substrate **1u**, arylated product **3u** was successfully obtained in 41% yield. It should be noted that the target products were obtained severally when employing $Cu(OAc)_2$ as the sole additive (**3g**, **3i**, **3l**, **3o**, **3s**), which has economic advantage and potential application value in organic synthetic chemistry.

Table 4. Substrate Scope of Aryl Iodides.[a,b]

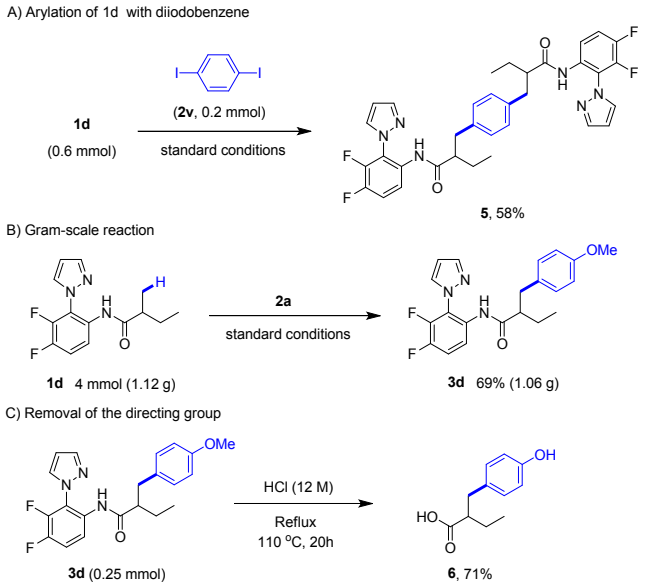


[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (0.36 mmol), Ag_3PO_4 (0.09 mmol), *p*-xylene (1.5 mL), DMF (1.5 mL), 130 °C, 16 h. [b] Isolated yields of **4**.

Next, the scope of substrates bearing various substituents on the iodoarene rings was examined (Table 4). *para*-Substituents

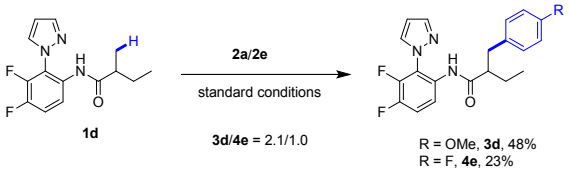
including Me, CF_3, F, Cl, Br, COOEt and COMe were tolerated to afford the target products **4c**−**4h** in moderate to good yields (54−75%), whereas the reaction of **1d** with unsubstituted phenyl iodide (**2b**) formed **4b** in a lower yield (47%). *meta*-OMe, Me, CF_3, COOMe and COMe-subsitituded aryl iodides also reacted well with **1d** to yield the products **4i**−**4m** in moderate yields (58−67%). The reactions of **1d** with *ortho*-methoxy and *ortho*-fluoro-substituted aryl iodides generated the target products **4n** and **4o** in 64−67% yields. Notably, an obvious diminution aroused from *ortho*-COOMe substituent, and as a result **4p** was only obtained in 33% yield. In addition, disubstituted iodobenzene derivatives reacted cleanly to give the arylated products (**4q**−**4t**) with the moderate yields from **1d**. However, when iodoethane was used to reacted with **1d**, arylated product **4u** was not detected. Electron-rich aryl iodides were found to give slightly higher yields than electron-poor aryl iodides. The molecular structure of the desired product **4k** was further confirmed by the X-ray single crystal structure (See Supporting Information). [20]

Scheme 2. Further Study on Pd-Catalyzed C(sp^3)−H Arylation Reaction



In addition, we also tested the structural generality of the reaction by using 1,4-diiodobenzene (**2v**) as an aryl iodide under the optimized conditions (Scheme 2A). The result displayed that the reaction of **1d** (0.6 mmol) with **2v** (0.2 mmol) proceeded smoothly to obtain the difunctionalized product (**5**) in 58% yield. Reproducibility and scalability of this protocol were successfully tested by proforming a gram-scale reaction (Scheme 2B). Further, the directing group could be effectively removed through treatment of arylated product with HCl (12 M) at 110 °C to give the free arylated acid **6** in 71% yield (Scheme 2C). And aryl methyl ether is also demethylated with the reaction.

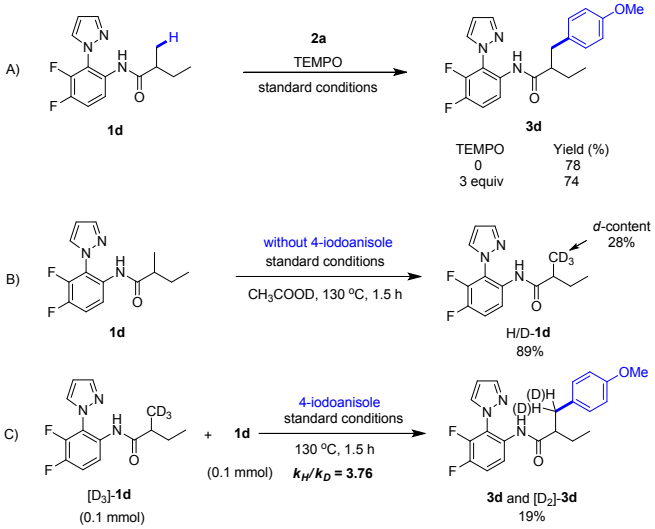
Scheme 3. Competition Experiment.



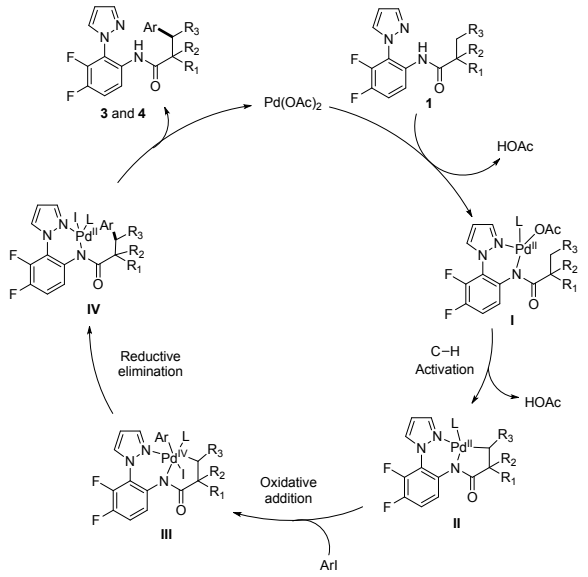
A competition experiment with electronically biased aryl iodides was carried out to futher probe the electronic effect, in order to collect some mechanistic information regarding the arylation reaction.[21] The mixture of **2a** and **2e** (1:1) was treated with aliphatic amide derivative **1d** under standard reaction conditions. It was observed that **3d** gave higher yield than **4e** (Scheme 3), which indicated that electron-donating aryl groups would facilitate the reaction.

To gain insights into the reaction mechanism, a radical quencher 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was added under standard conditions (Scheme 4A). It was found that TEMPO have negligible effect on the yield, thus it was unlikely to render a radical pathway. Additionally, we carried out deuterium labelling experiments to investigate further mechanism.[13c, 14a, 22] When substrate **1d** was exposed to the standard consitions without 4-iodoanisole in AcOD, deuterium was observed at *beta* position of aliphatic amide (Scheme 4B), which indicated that the possibility of arylation of *β*-C(sp^3)−H bonds. Finally, deuterium labeling kinetic isotope effect (KIE, k_H/k_D = 3.76) implied that the rate-determining step involved breaking a C(sp^3)−H bond (Scheme 4C).

Scheme 4. The Effect of TEMPO and Deuterium Labelling Experiments.



Scheme 5. Plausible Reaction Mechanism.



From the above experimental results and relevant literature reports,[4b, f, g, 13d, f, h] a proposed mechanism for the reaction is depicted in Scheme 5. The substrate **1d** is probably coordinated with Pd (II), to form *N,N*-chelated complex **I**, which further undergoes *β*-C(sp^3)–H bond activation *via* a concerted metalation deprotonation passway to give intermediate **II**. The next step involves oxidative addition of aryl iodides generating Pd (IV) complex **III**. Subsequently, accompanied by reductive elimination, the arylated product **3d** is furnished by exchanging ligand. Meanwhile, the active Pd (II) catalyst is regenerated to accomplish the catalytic cycle. We speculates that Cu and Ag salts play dual roles in this transformation.[19a, 23] First, Cu^{II} and Ag^{I} salts may be facilitate oxidative addition of aryl iodides to Pd^{II} centers. Second, they acts as iodide scavengers for success of the transformation.

CONCLUSION

In summary, we have developed a Pd-catalyzed arylation of unactivated *β*-C(sp^3)–H bonds in carboxylic acid derivatives *via* 2-amino-5,6-difluorophenyl-1*H*-pyrazole as an easily removable auxiliary in the presence of $Cu(OAc)_2$ and Ag_3PO_4 (1.2/0.3) as additives. These findings prove that the transformation is significantly facilitated by introducing two fluoro groups at initial directing group. This protocol exhibits excellent *β*-site selectivity, which is compatible with diverse substrates containing *α*-hydrogen atoms and arylation of methylene C(sp^3)−H bonds. Futher explorations of new reactions with the novel modified *N,N*-bidentate directing group are underway in our lab.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all reagents were obtained from commercial sources and used as received without further purification. All solvents were only dried over 4 Å molecular sieves. Reaction products were purified *via* column chromatography on silica gel (100–200 mesh). Melting points were determined using an open capillaries and uncorrected. NMR spectra were determined on Bruker AV400 in $CDCl_3$ with TMS as internal standard for ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz), respectively. HRMS were measured on a QSTAR Pulsar I LC/TOF MS mass spectrometer or Micromass GCTTM gas chromatograph-mass spectrometer.

General Procedure for the Preparation of Substrates. [16a, 24] To a solution of fluorinated nitrobenzene (5 mmol) and DMSO (20.0 mL) was slowly added NaOH (200.0 mg, 5 mmol), and pyrazole (408.5 mg, 6 mmol) in sequence. After the addition, the mixture was stirred at room temperture for 4 h. Water (20 mL × 3) was added to the mixture, then the product extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product. A mixture of iron powder (1.07 g, 19.1 mmol) and NH_4Cl (0.14 g, 2.6 mmol), in water (5.0 mL) was heated to 100 °C (oil bath) for 15 min. Then the crude product of the previous step was quickly added, and and stirred for corresponding time (TLC monitored). Upon completion of the reaction, the mixture was cooled to room temperature and neutralized with 5% $NaHCO_3$ solution(V/V) and extracted with ethyl acetate (20 mL × 3) and dryed with $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product of 2-aminophenyl-1*H*-pyrazole derivatives.

To a solution of the carboxylic acid (6 mmol) and DCM (15.0 mL) at 0 °C (ice-water bath) was added 1–3 drops of DMF. After effervescing subsided, oxalyl chloride (2.0 mL) was added drop wise. After stirring and refluxing at 40 °C (oil bath) for 10 h, the reaction was concentrated *in vacuo* to give the acid chloride as an oil. It was taken back with DCM (5 mL), cooled back 0°C. A solution of 2-aminophenyl-1*H*-pyrazole derivatives in DCM (15.0 mL) was added, followed by Et_3N (607.1 mg, 6 mmol). The corresponding acid chloride was added drop wise. Then the reaction was stirred at 0 °C for 10 min, and then room temperture for 2 h. The mixture was washed with saturated Na_2CO_3 and brine. Then the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 80:1 to 30:1) to supply the substrate **1**.

*N-(2-(1H-Pyrazol-1-yl)phenyl)-2-methylbutanamide (**1a**)*. White solid; 1.08 g, 89% yield; m.p. 44.9–46.1 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): *δ* 10.22 (s, 1H), 8.48 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.81 (d, *J* = 1.6 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.38−7.30 (m, 2H), 7.15 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 6.50 (t, *J* = 2.4 Hz, 1H), 2.32−2.23 (m, 1H), 1.75−1.64 (m, 1H), 1.54−1.43 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): *δ* 175.1, 141.0, 131.8, 130.3, 129.1, 128.1, 123.8, 123.1, 122.5, 107.1, 44.5, 27.3, 17.2, 11.7; HRMS (EI): *m/z* [M^+] calcd. for $C_{14}H_{17}N_3O$: 243.1372; found: 243.1371.

*N-(4-Chloro-2-(1H-pyrazol-1-yl)phenyl)-2-methylbutanamide (**1b**)*. Yellow solid; 1.21 g, 87% yield; m.p. 33.2–35.0 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): *δ* 10.33 (s, 1H), 8.48 (d, *J* = 8.8 Hz, 1H), 7.81−7.80 (m, 2H), 7.29−7.26 (m, 2H), 6.51 (t, *J* = 2.4 Hz, 1H), 2.32−2.23 (m, 1H), 1.75−1.64 (m, 1H), 1.54−1.43 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): *δ* 175.2, 141.4, 130.4, 130.2, 129.6, 128.5, 127.8, 124.1, 122.2, 107.6, 44.5, 27.2, 17.1, 11.7; HRMS (EI): *m/z* [M^+] calcd. for $C_{14}H_{16}N_3OCl$: 277.0982; found: 277.0980.

*N-(4-Fluoro-2-(1H-pyrazol-1-yl)phenyl)-2-methylbutanamide (**1c**)*. White solid; 0.82 g, 63% yield; m.p. 38.3–40.0 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): *δ* 10.23 (s, 1H), 8.44 (dd, J_1 = 10.0 Hz, J_2 = 5.6 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 2.8 Hz, 1H), 7.08−7.04 (m, 2H), 6.51 (dd, J_1 = 2.4 Hz, J_2 = 2.0 Hz, 1H), 2.31−2.22 (m, 1H), 1.74−1.63 (m, 1H), 1.53−1.43 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): *δ* 175.1, 158.3 (d, J_{CF} = 242.9 Hz), 141.4, 130.2, 129.81 (d, J_{CF} = 9.3 Hz), 127.9 (d, J_{CF} = 3.1 Hz), 124.8 (d, J_{CF} = 8.3 Hz), 114.4 (d, J_{CF} = 21.3 Hz), 109.5 (d, J_{CF} = 25.9 Hz), 107.6, 44.4, 27.3, 17.2, 11.7. HRMS (EI): *m/z* [M^+] calcd. for $C_{14}H_{16}N_3OF$: 261.1277; found: 261.1278.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-methylbutanamide (**1d**)*. White solid; 0.58 g, 42% yield; m.p. 45.4–47.1 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): *δ* 9.59 (s, 1H), 8.18−8.14 (m, 1H), 7.86 (d, *J* = 1.6 Hz, 1H), 7.81 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.19 (q, *J* = 9.2 Hz, 1H), 6.56 (t, *J* = 2.0 Hz, 1H), 2.26−2.17 (m, 1H), 1.70−1.59 (m, 1H), 1.50−1.40 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): *δ* 175.1, 146.9 (dd, J_{CF} = 244.8, 11.9 Hz), 143.8 (dd, J_{CF} = 248.9, 15.5 Hz), 141.6, 133.1 (d, J_{CF} = 6.4 Hz), 129.8 (d, J_{CF} = 3.2 Hz), 120.0 (d, J_{CF} = 9.8 Hz), 118.0 (dd, J_{CF} = 6.6, 4.6 Hz), 115.9 (d, J_{CF} = 17.3 Hz), 107.5, 44.3, 27.2, 17.0, 11.6; HRMS (EI): *m/z* [M^+] calcd. for $C_{14}H_{15}N_3OF_2$: 279.1183; found: 279.1182.

*2-Methyl-N-(3,4,5-trifluoro-2-(1H-pyrazol-1-yl)phenyl)butanamide (**1e**)*. Yellow oil; 0.42 g, 28% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): *δ* 9.57 (s, 1H), 8.30−8.25 (m, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.77 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 6.57 (t, *J* = 2.4 Hz, 1H), 2.25−2.17 (m, 1H), 1.70−1.59 (m, 1H), 1.51−1.40 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): *δ* 174.1, 148.7 (ddd, J_{CF} = 247.5, 9.8, 4.5 Hz), 143.9 (ddd, J_{CF} = 248.9, 12.2, 5.3 Hz), 140.9, 135.2 (ddd, J_{CF} = 248.2, 16.3, 14.4 Hz), 132.0 (d, J_{CF} = 6.0 Hz), 128.5 (dd, J_{CF} = 11.4, 3.6 Hz), 114.5 (dd, J_{CF} = 10.9, 4.4 Hz), 106.6, 104.9 (dd, J_{CF} = 23.6, 3.5 Hz), 43.3, 26.1, 15.9, 10.5; HRMS (EI): *m/z* [M^+] calcd. for $C_{14}H_{14}N_3OF_3$: 297.1089; found: 297.1092.

*N-(4-methoxy-2-(1H-pyrazol-1-yl)phenyl)-2-methylbutanamide (**1f**)*. Yellow solid; 1.13 g, 83% yield; m.p. 60.4–62.0 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): *δ* 9.88 (s, 1H), 8.30 (d, *J* = 9.2 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.77 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 6.48 (t, *J* = 2.0 Hz, 1H), 3.82 (s, 3H), 2.28−2.19 (m, 1H), 1.71−1.64 (m, 1H), 1.50−1.43 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): *δ* 174.9, 155.9, 141.1, 130.4, 130.2, 125.0, 124.7, 112.6, 108.9, 107.2, 55.8, 44.3, 27.3, 17.2, 11.7; HRMS (EI): *m/z* [M^+] calcd. for $C_{15}H_{19}N_3O_2$: 273.1477; found: 273.1476.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2,2-dimethylbutanami-

*de **(1g)***. White solid; 0.59 g, 40% yield; m.p. 55.6–57.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.71 (s, 1H), 8.17−8.13 (m, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.80 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 7.19 (q, J = 9.2 Hz, 1H), 6.56 (dd, J_1 = 2.4 Hz, J_2 = 2.0 Hz, 1H), 1.53 (q, J = 7.6 Hz, 2H), 1.14 (s, 6H), 0.76 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 176.7, 146.8 (dd, J_{CF} = 244.7, 11.9 Hz), 143.8 (dd, J_{CF} = 248.9, 15.6 Hz), 141.6, 133.1 (d, J_{CF} = 6.2 Hz), 130.1 (d, J_{CF} = 3.3 Hz), 120.1 (d, J_{CF} = 10.1 Hz), 118.0 (dd, J_{CF} = 6.6, 4.5 Hz), 115.9 (d, J_{CF} = 17.4 Hz), 107.5, 43.6, 33.8, 24.7 (2C), 9.0; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{15}H_{17}N_3OF_2$: 293.1340; found: 293.1339.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-1-methylcyclohexanecarboxamide **(1h)***. White solid; 0.59 g, 37% yield; m.p. 53.6–54.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.73 (s, 1H), 8.18−8.14 (m, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.79 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H), 7.19 (q, J = 9.2 Hz, 1H), 6.55 (6, J = 2.0 Hz, 1H), 1.96−1.93 (m, 2H), 1.50−1.44 (m, 3H), 1.32−1.27 (m, 5H), 1.12 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 176.6, 146.8 (dd, J_{CF} = 244.6, 11.9 Hz), 143.9 (dd, J_{CF} = 248.8, 15.5 Hz), 141.7, 133.1 (d, J_{CF} = 6.1 Hz), 130.2 (d, J_{CF} = 3.2 Hz), 120.1 (d, J_{CF} = 10.1 Hz), 118.0 (d, J_{CF} = 6.5, 4.6 Hz), 115.9 (d, J_{CF} = 17.3 Hz), 107.5, 44.0, 35.5 (2C), 26.7, 25.6, 22.9 (2C); HRMS (EI): *m/z* [M$^+$] calcd. for $C_{17}H_{19}N_3OF_2$: 319.1496; found: 319.1497.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)isobutyramide **(1i)***. White solid; 0.57 g, 43% yield; m.p. 76.5–78.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.64 (s, 1H), 8.20−8.15 (m, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.8 (dd, J_1 = 4.4 Hz, J_2 = 2.8 Hz, 1H), 7.19 (q, J = 9.6 Hz, 1H), 6.56 (t, J = 2.4 Hz, 1H), 2.49−2.42 (m, 1H), 1.17 (s, 3H), 1.15 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 175.5, 146.8 (dd, J_{CF} = 244.8, 12.0 Hz), 143.8 (dd, J_{CF} = 248.8, 15.4 Hz), 141.6, 133.2 (d, J_{CF} = 6.5 Hz), 129.9 (d, J_{CF} = 3.2 Hz), 119.9 (d, J_{CF} = 10.2 Hz), 117.8 (dd, J_{CF} = 6.6, 4.6 Hz), 115.9 (d, J_{CF} = 17.1 Hz), 107.5, 36.9, 19.2 (2C); HRMS (EI): *m/z* [M$^+$] calcd. for $C_{13}H_{13}N_3OF_2$: 265.1027; found: 265.1028.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-methylpentanamide **(1j)***. White solid; 0.61 g, 42% yield; m.p. 62.1–63.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.57 (s, 1H), 8.17−8.13 (m, 1H), 7.86 (d, J = 1.6 Hz, 1H), 7.80 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.18 (q, J = 9.2 Hz, 1H), 6.55 (t, J = 2.0 Hz, 1H), 2.34−2.25 (m, 1H), 1.64−1.55 (m, 1H), 1.41−1.32 (m, 1H), 1.28−1.19 (m, 2H), 1.13 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 175.2, 146.9 (dd, J_{CF} = 244.9, 12.0 Hz), 143.8 (dd, J_{CF} = 248.9, 15.5 Hz), 141.6, 133.1 (d, J_{CF} = 6.4 Hz), 129.8 (d, J_{CF} = 3.2 Hz), 120.0 (d, J_{CF} = 10.2 Hz), 118.0 (dd, J_{CF} = 6.6, 4.6 Hz), 115.9 (d, J_{CF} = 17.2 Hz), 107.4, 42.5, 36.4, 20.3, 17.5, 13.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{15}H_{17}N_3OF_2$: 293.1340; found: 293.1341.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-methylhexanamide **(1k)***. White solid; 0.55 g, 36% yield; m.p. 60.5–62.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.56 (s, 1H), 8.16−8.12 (m, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.81 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H), 7.19 (q, J = 9.2 Hz, 1H), 6.56 (t, J = 2.4 Hz, 1H), 2.32−2.23 (m, 1H), 1.65−1.56 (m, 1H), 1.43−1.34 (m, 1H), 1.32−1.88 (m, 4H), 1.13 (d, J = 6.8 Hz, 3H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 175.3, 146.9 (dd, J_{CF} = 244.9, 11.9 Hz), 143.8 (dd, J_{CF} = 248.9, 15.5 Hz), 141.7, 133.1 (d, J_{CF} = 6.3 Hz), 129.8 (d, J_{CF} = 3.3 Hz), 120.0 (d, J_{CF} = 9.3 Hz), 118.1 (dd, J_{CF} = 6.7, 4.7 Hz), 115.9 (d, J_{CF} = 17.4 Hz), 107.5, 42.7, 33.9, 29.3, 22.6, 17.5, 13.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{16}H_{19}N_3OF_2$: 307.1496; found: 307.1494.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-methylheptanamide **(1l)***. White solid; 0.59 g, 37% yield; m.p. 39.3–41.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.58 (s, 1H), 8.17−8.13 (m, 1H), 7.85 (d, J = 1.6 Hz, 1H), 7.80 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.18 (q, J = 9.6 Hz, 1H), 6.55 (t, J = 2.0 Hz, 1H), 2.32−2.23 (m, 1H), 1.64−1.55 (m, 1H), 1.42−1.33 (m, 1H), 1.97−1.25 (m, 6H), 1.13 (d, J = 6.8 Hz, 3H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 175.3, 146.9 (dd, J_{CF} = 244.8, 12.1 Hz), 143.8 (dd, J_{CF} = 248.9, 15.5 Hz), 141.6, 133.1 (d, J_{CF} = 6.4 Hz), 129.8 (d, J_{CF} = 3.2 Hz), 120.0 (d, J_{CF} = 9.8 Hz), 118.0 (dd, J_{CF} = 6.6, 4.7 Hz), 115.9 (d, J_{CF} = 17.3 Hz), 107.5, 42.8, 34.2, 31.7, 26.8, 22.5, 17.5, 14.0.; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{17}H_{21}N_3OF_2$: 321.1653; found: 321.1650.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-methyl-3-phenylpropanamide **(1m)***. Yellow oil; 0.68 g, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.56 (s, 1H), 8.16−8.12 (m, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.74 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.23−7.18 (m, 3H), 7.17−7.15 (m, 1H), 7.12−7.09 (m, 2H), 6.52 (t, J = 2.4 Hz, 1H), 2.99 (dd, J_1 = 13.6 Hz, J_2 = 7.2 Hz, 1H), 2.67 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz, 1H), 2.61−2.52 (m, 1H), 1.17 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 174.3, 146.9 (dd, J_{CF} = 245.1, 12.1 Hz), 143.7 (dd, J_{CF} = 248.8, 15.4 Hz), 141.6, 139.2, 133.1 (d, J_{CF} = 6.7 Hz), 129.5 (d, J_{CF} = 3.3 Hz), 128.8 (2C), 128.4 (2C), 126.4, 119.9 (d, J_{CF} = 9.3 Hz), 117.9 (dd, J_{CF} = 6.7, 4.8 Hz), 115.9 (d, J_{CF} = 17.5 Hz), 107.5, 44.8, 40.2, 17.1; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{19}H_{17}N_3OF_2$: 341.1340; found: 341.1342.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-phenylpropanamide **(1n)***. Yellow oil; 0.52 g, 32% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.40 (s, 1H), 8.19−8.14 (m, 1H), 7.65 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H), 7.52 (d, J = 1.6 Hz, 1H), 7.33−7.27 (m, 3H), 7.23−7.21 (m, 2H), 7.16 (q, J = 9.6 Hz, 1H), 6.41 (t, J = 2.4 Hz, 1H), 3.65 (q, J = 7.2 Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.0, 146.8 (dd, J_{CF} = 244.9, 11.9 Hz), 143.8 (dd, J_{CF} = 248.8, 15.4 Hz), 141.6, 140.3, 132.7 (d, J_{CF} = 6.2 Hz), 129.9 (d, J_{CF} = 3.2 Hz), 129.0 (2C), 127.8 (2C), 127.5, 119.9 (d, J_{CF} = 10.2 Hz), 117.6 (dd, J_{CF} = 6.6, 4.6 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 107.1, 48.4, 18.0; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{18}H_{15}N_3OF_2$: 327.1183; found: 327.1185.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(p-tolyl)propanamide **(1o)***. Yellow solid; 0.58 g, 34% yield; m.p. 57.6–59.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.32 (s, 1H), 8.19−8.15 (m, 1H), 7.65 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.16 (q, J = 9.2 Hz, 1H), 7.13−7.08 (m, 4H), 6.42 (t, J = 2.4 Hz, 1H), 3.61 (q, J = 7.2 Hz, 1H), 2.36 (s, 3H), 1.52 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.2, 146.8 (dd, J_{CF} = 244.8, 11.9 Hz), 143.8 (dd, J_{CF} = 248.8, 15.4 Hz), 141.5, 137.2, 137.0, 132.7 (d, J_{CF} = 6.1 Hz), 130.0 (d, J_{CF} = 3.2 Hz), 129.7 (2C), 127.7 (2C), 119.9 (d, J_{CF} = 10.6 Hz), 117.5 (dd, J_{CF} = 6.5, 4.6 Hz), 115.9 (d, J_{CF} = 17.4 Hz), 107.0, 47.9, 21.1, 18.0; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{19}H_{17}N_3OF_2$: 341.1340; found: 341.1339.

*2-(3-Chlorophenyl)-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)propanamide **(1p)***. White solid; 0.56 g, 31% yield; m.p. 72.5–73.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.50 (s, 1H), 8.18−8.14 (m, 1H), 7.70 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.28−7.26 (m, 1H), 7.25−7.23 (m, 2H), 7.21−7.17 (m, 1H), 7.14−7.12 (m, 1H), 6.46 (t, J = 2.0 Hz, 1H), 3.64 (q, J = 7.2Hz, 1H), 1.54 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 172.1, 147.0 (dd, J_{CF} = 245.2, 12.0 Hz), 143.7 (dd, J_{CF} = 249.1, 15.5 Hz), 142.3, 141.6, 134.7, 132.8 (d, J_{CF} = 6.5 Hz), 130.2, 129.6 (d, J_{CF} = 3.2 Hz), 128.0, 127.7, 126.0, 119.9 (d, J_{CF} = 9.9 Hz), 117.7 (dd, J_{CF} = 6.5, 4.7 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 107.3, 48.0, 17.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{18}H_{14}N_3OF_2Cl$: 361.0793; found: 361.0789.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)propanamide **(1q)***. Yellow solid; 0.61 g, 30% yield; m.p. 106.2–107.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.29 (s, 1H), 8.21−8.17 (m, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 7.53 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H), 7.26−7.24 (m, 1H), 7.20 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.17−7.12 (m, 2H), 6.79 (d, J = 1.6 Hz, 1H), 6.14 (t, J = 2.0 Hz, 1H), 3.95 (s, 3H), 3.89 (q, J = 7.2 Hz, 1H), 1.83 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.3, 157.9, 146.8 (dd, J_{CF} = 244.6, 11.6 Hz), 143.8 (dd, J_{CF} = 248.8, 15.4 Hz), 141.3, 135.2, 134.0, 132.5 (d, J_{CF} = 5.5 Hz), 130.0 (d, J_{CF} = 3.1 Hz), 129.3, 129.1, 127.7, 126.7, 126.2, 119.8 (d, J_{CF} = 9.1 Hz), 119.2, 117.4 (dd, J_{CF} = 6.5, 4.7 Hz), 115.8 (d, J_{CF} = 17.2 Hz), 106.9, 105.6, 55.4, 48.3, 17.8; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{23}H_{19}N_3O_2F_2$: 407.1445; found: 407.1447.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)cyclobutanecarboxamide **(1r)***. Yellow solid; 0.54 g, 39% yield; m.p. 88.7–90.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.55 (s, 1H), 8.22−8.18 (m, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.80 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.18 (q, J = 9.6 Hz, 1H), 6.54 (t, J = 2.4 Hz, 1H), 3.13−3.05 (m, 1H), 2.29−2.16 (m, 4H), 2.01−1.90 (m, 1H), 1.87−1.80 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.6, 146.8 (dd, J_{CF} = 244.8, 12.0 Hz), 143.8 (dd, J_{CF} = 248.7, 15.4 Hz), 141.6, 133.2 (d, J_{CF} = 6.6 Hz), 129.8 (d, J_{CF} = 3.2 Hz), 119.7 (d, J_{CF} = 10.1 Hz), 117.6 (dd, J_{CF} = 6.0, 4.6 Hz), 115.9 (d, J_{CF} = 17.3 Hz), 107.4, 41.1, 25.2 (2C), 17.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{14}H_{13}N_3OF_2$: 277.1027; found: 277.1026.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)cyclopentanecarboxa-

*mide (**1s**)*. White solid; 0.62 g, 43% yield; m.p. 83.1–84.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.58 (s, 1H), 8.19−8.15 (m, 1H), 7.88 (d, J = 1.2 Hz, 1H), 7.81 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.19 (q, J = 9.2 Hz, 1H), 6.57 (t, J = 2.0 Hz, 1H), 2.67−2.59 (m, 1H), 1.92−1.85 (m, 2H), 1.78−1.69 (m, 4H), 1.63−1.57 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 174.9, 146.8 (dd, J_{CF} = 244.7, 11.9 Hz), 143.8 (dd, J_{CF} = 248.8, 15.5 Hz), 141.6, 133.2 (d, J_{CF} = 6.5 Hz), 133.0 (d, J_{CF} = 3.2 Hz), 119.8 (d, J_{CF} = 10.0 Hz), 117.8 (dd, J_{CF} = 6.5, 4.6 Hz), 115.9 (d, J_{CF} = 17.3 Hz), 107.4, 47.1, 30.1 (2C), 25.8 (2C); HRMS (EI): *m/z* [M$^+$] calcd. for $C_{15}H_{15}N_3OF_2$: 291.1183; found: 291.1182.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)cyclohexanecarboxamide (**1t**)*. White solid; 0.64 g, 42% yield; m.p. 92.1–93.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.59 (s, 1H), 8.19−8.14 (m, 1H), 7.88 (d, J = 1.6 Hz, 1H), 7.81 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.18 (q, J = 9.2 Hz, 1H), 6.56 (t, J = 2.0 Hz, 1H), 2.20−2.13 (m, 1H), 1.86 (dd, J_1 = 12.8 Hz, J_2 = 2.0 Hz, 2H), 1.80−1.76 (m, 2H), 1.68−1.65 (m, 1H), 1.44−1.35 (m, 2H), 1.29−1.21 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 174.6, 146.8 (dd, J_{CF} = 244.8, 12.0 Hz), 143.8 (dd, J_{CF} = 248.8, 15.5 Hz), 141.6, 133.2 (d, J_{CF} = 6.5 Hz), 129.9 (d, J_{CF} = 3.2 Hz), 119.9 (d, J_{CF} = 9.2 Hz), 117.9 (dd, J_{CF} = 6.5, 4.7 Hz), 115.9 (d, J_{CF} = 17.2 Hz), 107.5, 46.4, 29.3 (2C), 25.7, 25.6 (2C); HRMS (EI): *m/z* [M$^+$] calcd. for $C_{16}H_{17}N_3OF_2$: 305.1340; found: 305.1339.

N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)propionamide (***1u***). Yellow soild; 0.47 g, 37% yield; m.p. 59.3–61.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.61 (s, 1H), 8.20−8.16 (m, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.81 (dd, J_1 = 4.4 Hz, J_2 = 2.8 Hz, 1H), 7.17 (q, J = 9.6 Hz, 1H), 6.54 (t, J = 2.0 Hz, 1H), 2.32 (q, J = 7.6 Hz, 2H), 1.15 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 172.3, 146.8 (dd, J_{CF} = 244.8, 11.9 Hz), 143.8 (dd, J_{CF} = 248.8, 15.6 Hz), 141.7, 133.2 (d, J_{CF} = 6.7 Hz), 129.7 (d, J_{CF} = 3.2 Hz), 119.7 (d, J_{CF} = 10.2 Hz), 117.7 (dd, J_{CF} = 6.5, 4.8 Hz), 115.9 (d, J_{CF} = 17.4 Hz), 107.4, 31.0, 9.3; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{12}H_{11}N_3OF_2$: 251.0870; found: 251.0869.

General Procedure for Pd(II)-Catalyzed C(sp^3)–H Bond Arylation. A mixture of substrate **1** (0.3 mmol), aryl iodide **2** (0.9 mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%), $Cu(OAc)_2$ (65.4 mg, 0.36 mmol), Ag_3PO_4 (37.7 mg, 0.09 mmol), in *p*-xylene (1.5 mL) and DMF (1.5 mL) was charged in a glass sealed-tube and stirred at 130 °C (oil bath) for 16 h. Upon completion of the reaction, saturated brine (15 mL) and dichloromethane (15 mL) were added to the mixture, then the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 70:1 to 20:1) to supply the desired products **3** and **4**.

*N-(2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)butanamide (**3a**)*.Yellow oil; 45.1 mg, 43% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 10.34 (s, 1H), 8.38 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.36–7.31 (m, 1H), 7.28 (d, J = 1.2 Hz, 1H), 7.16–7.12 (m, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.46 (t, J = 2.0 Hz, 1H), 3.74 (s, 3H), 2.90 (dd, J_1 = 13.6 Hz, J_2 = 8.4 Hz, 1H), 2.70 (dd, J_1 = 14.0 Hz, J_2 = 6.4 Hz, 1H), 2.39–2.32 (m, 1H), 1.75–1.68 (m, 1H), 1.60–1.53 (m, 1H), 0.88 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.7, 157.9, 141.0, 131.6, 131.4, 130.1, 129.7 (2C), 129.2, 128.0, 124.0, 123.4, 122.5, 113.7 (2C), 107.1, 55.1, 53.3, 38.0, 25.6, 11.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{23}N_3O_2$: 349.1790; found: 349.1792.

*N-(4-Chloro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)butanamide (**3b**)*. Yellow oil; 37.9 mg, 33% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 10.11 (s, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.30–7.26 (m, 2H), 7.01 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.47 (t, J = 2.4 Hz, 1H), 3.73 (s, 3H), 2.88 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H), 2.70 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.37–2.33 (m, 1H), 1.76–1.68 (m, 1H), 1.60–1.54 (m, 1H), 0.89 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.8, 157.9, 141.3, 131.4, 130.1, 130.0, 129.8, 129.7 (2C), 128.7, 127.7, 124.4, 122.2, 113.7 (2C), 107.5, 55.1, 53.4, 38.0, 25.6, 11.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{22}N_3O_2Cl$: 383.1401; found: 383.1400.

*N-(4-Fluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)butanamide (**3c**)*. Yellow oil; 50.7 mg, 46% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.99 (s, 1H), 8.33 (dd, J_1 = 9.2 Hz, J_2 = 5.6 Hz, 1H), 7.73 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.054 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 7.03–7.00 (m, 3H), 6.70 (d, J = 8.4 Hz, 2H), 6.47 (s, 1H), 3.74 (s, 3H), 2.88 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H), 2.70 (dd, J_1 = 14.0 Hz, J_2 = 6.0 Hz, 1H), 2.36–2.32 (m, 1H), 1.75–1.68 (m, 1H), 1.60–1.53 (m, 1H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.8, 158.5 (d, J_{CF} = 243.0 Hz), 157.9, 141.3, 131.5, 130.0, 129.9, 129.7 (2C), 127.5 (d, J_{CF} = 3.2 Hz), 125.1 (d, J_{CF} = 8.4 Hz), 114.4 (d, J_{CF} = 21.4 Hz), 113.7 (2C), 109.6 (d, J_{CF} = 25.8 Hz), 107.5, 55.1, 53.3, 38.0, 25.6, 11.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{22}N_3O_2F$: 367.1696; found: 367.1695.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)butanamide (**3d**)*. Yellow oil; 66.9 mg, 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.41 (s, 1H), 8.07–8.02 (m, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.70 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.16 (q, J = 9.6 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 6.51 (t, J = 2.4 Hz, 1H), 3.75 (s, 3H), 2.83 (dd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, 1H), 2.67 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.32–2.24 (m, 1H), 1.71–1.63 (m, 1H), 1.57–1.51 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.8, 158.0, 147.0 (dd, J_{CF} = 245.0, 12.0 Hz), 143.8 (dd, J_{CF} = 248.9, 15.5 Hz), 141.5, 133.0 (d, J_{CF} = 6.4 Hz), 131.3, 129.6 (2C), 129.4 (d, J_{CF} = 3.3 Hz), 120.1 (d, J_{CF} = 10.9 Hz), 118.3 (dd, J_{CF} = 6.7, 4.6 Hz), 115.8 (d, J_{CF} = 17.5 Hz), 113.8 (2C), 107.4, 55.1, 53.2, 38.0, 25.6, 11.8; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{21}N_3O_2F_2$: 385.1602; found: 385.1601.

*2-(4-Methoxybenzyl)-N-(3,4,5-trifluoro-2-(1H-pyrazol-1-yl)phenyl-)butanamide (**3e**)*. Yellow oil; 62.7 mg, 52% yield; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.37 (s, 1H), 8.20–8.14 (m, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.65 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.52 (t, J = 2.0 Hz, 1H), 3.75 (s, 3H), 2.82 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H), 2.68 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.29–2.25 (m, 1H), 1.71–1.64 (m, 1H), 1.58–1.52 (m, 1H), 0.86 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.9, 158.0, 149.6 (ddd, J_{CF} = 247.5, 9.6, 4.5 Hz), 144.9 (ddd, J_{CF} = 249.1, 12.0, 5.3 Hz), 141.8, 136.4 (ddd, $^1J_{CF}$ = 249.4, $^2J_{CF}$ = 31.0, J_{CF} = 14.9 Hz), 132.9 (d, J_{CF} = 6.0 Hz), 131.1, 129.6 (2C), 129.0 (ddd, J_{CF} = 11.8, 3.5, 1.9 Hz), 115.5 (dd, J_{CF} = 10.7, 4.0 Hz), 113.8 (2C), 107.5, 106.1 (dd, J_{CF} = 23.4, 3.4 Hz), 55.1, 53.4, 37.9, 25.5, 11.8; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{20}N_3O_2F_3$: 403.1508; found: 403.1509.

*N-(4-methoxy-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)butanamide (**3f**)*. White solid; 35.3 mg, 44% yield; m.p. 134.2–135.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.65 (s, 1H), 8.18 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.88 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 6.81 (d, J = 2.8 Hz, 1H), 6.70 (d, J = 8.4 Hz, 2H), 6.43 (t, J = 2.0 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 2.88 (dd, J_1 = 13.6 Hz, J_2 = 8.4 Hz, 1H), 2.67 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.35–2.27 (m, 1H), 1.73–1.64 (m, 1H), 1.57–1.51 (m, 1H), 0.85 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 173.5, 157.9, 156.1, 141.0, 131.7, 130.6, 130.0, 129.7 (2C), 125.1, 124.5, 113.7 (2C), 112.6, 108.9, 107.1, 55.7, 55.1, 53.1, 38.0, 25.6, 11.8; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{22}H_{25}N_3O_3$: 379.1896; found: 379.1895.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)-2-methylbutanamide (**3g**)*. Yellow oil; 38.6 mg, 32% yield (11.5mg, 10% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.57 (s, 1H), 8.14−8.10 (m, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.70 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.20 (q, J = 9.6 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 6.48 (t, J = 2.0 Hz, 1H), 3.75 (s, 3H), 2.95 (d, J = 13.6 Hz, 1H), 2.54 (d, J = 13.6 Hz, 1H), 1.87−1.78 (m, 1H), 1.43−1.34 (m, 1H), 1.06 (s, 3H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm): δ 175.4, 158.1, 146.6 (dd, J_{CF} = 244.9, 11.9 Hz), 143.8 (dd, J_{CF} = 248.9, 15.5 Hz), 141.5, 132.9 (d, J_{CF} = 6.3 Hz), 131.0 (2C), 129.7 (d, J_{CF} = 3.2 Hz), 129.4, 120.2 (d, J_{CF} = 9.9 Hz), 118.2 (dd, J_{CF} = 6.7, 4.6 Hz), 115.9 (d, J_{CF} = 17.4 Hz), 113.3 (2C), 107.4, 55.10, 48.7, 45.3, 32.6, 19.5, 8.9; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{22}H_{23}N_3O_2F_2$: 399.1758; found: 399.1759.

*N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2,2-bis(4-methoxybenzyl)butanamide (**3g'**)*. Yellow oil; 62.3 mg, 41% yield (46.5 mg, 31% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.42 (s, 1H), 8.12−8.08 (m, 1H), 7.59−7.57 (m, 2H), 7.20 (q, J = 9.2 Hz, 1H), 6.98 (d, J = 8.4

Hz, 4H), 6.68 (d, J = 8.8 Hz, 4H), 6.37 (t, J = 2.0 Hz, 1H), 3.75 (s, 6H), 3.04 (d, J = 14.0 Hz, 2H), 2.74 (d, J = 14.0 Hz, 2H), 1.41 (q, J = 7.2 Hz, 2H), 1.04 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 174.8, 158.0 (2C), 146.9 (dd, J_{CF} = 244.9, 11.9 Hz), 143.7 (dd, J_{CF} = 248.7, 15.3 Hz), 141.3, 132.6 (d, J_{CF} = 6.3 Hz), 130.8 (4C), 129.4 (d, J_{CF} = 3.2 Hz), 129.3 (2C), 120.2 (d, J_{CF} = 9.4 Hz), 118.4 (dd, J_{CF} = 6.6, 4.7 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 113.4 (4C), 107.3, 55.1 (2C), 53.1, 40.5 (2C), 22.6, 8.6; HRMS (EI): *m/z* [M^+] calcd. for $C_{29}H_{29}N_3O_3F_2$: 505.2177; found: 505.2175.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-1-(4-methoxybenzyl)cyclohexanecarboxamide ***(3h)***. Yellow oil; 29.0 mg, 23% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.53 (s, 1H), 8.18−8.16 (m, 1H), 7.71 (s, 2H), 7.19 (q, J = 9.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 6.48 (s, 1H), 3.74 (s, 3H), 2.68 (s, 2H), 1.99 (d, J = 11.2 Hz, 2H), 1.59−1.52 (m, 4H), 1.35−1.30 (m, 2H), 1.25−1.22 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 174.7, 158.1, 146.8 (dd, J_{CF} = 244.7, 11.9 Hz), 143.8 (dd, J_{CF} = 248.7, 15.5 Hz), 141.5, 132.8 (d, J_{CF} = 6.3 Hz), 130.8 (2C), 129.8 (d, J_{CF} = 3.1 Hz), 128.7, 120.0 (d, J_{CF} = 9.8 Hz), 117.9 (d, J_{CF} = 6.8, 4.6 Hz), 115.8 (d, J_{CF} = 17.3 Hz), 113.2 (2C), 107.3, 55.1, 49.3, 35.3, 33.9, 25.8, 25.7, 23.1, 23.0; HRMS (EI): *m/z* [M^+] calcd. for $C_{24}H_{25}N_3O_2F_2$: 425.1915; found: 425.1916.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-1-(4-methoxybenzyl)-2-(4-methoxyphenyl)cyclohexanecarboxamide ***(3h')***. Yellow oil; 74.3 mg, 47% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.18 (s, 1H), 7.99−7.95 (m, 1H), 7.61 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.10 (q, J = 8.8 Hz, 1H), 6.82 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 8.4 Hz, 2H), 6.40 (t, J = 2.4 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.03 (d, J = 13.6Hz, 1H), 2.88−2.84 (m, 2H), 2.02−1.91 (m, 2H), 1.86−1.81 (m, 2H), 1.73−1.71 (m, 2H), 1.50−1.45 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.5, 158.1, 157.9, 146.7 (dd, J_{CF} = 244.6, 12.0 Hz), 143.7 (dd, J_{CF} = 248.5, 15.5 Hz), 141.4, 135.2, 132.6 (d, J_{CF} = 6.4 Hz), 130.8 (2C), 130.6 (2C), 129.3 (d, J_{CF} = 3.1 Hz), 128.8, 119.9 (d, J_{CF} = 9.4 Hz), 118.1 (dd, J_{CF} = 6.5, 4.5 Hz), 115.7 (d, J_{CF} = 17.3 Hz), 113.3 (2C), 113.1 (2C), 107.2, 55.1, 52.0 (2C), 51.0, 44.0, 30.8, 30.0, 24.1, 22.4; HRMS (EI): *m/z* [M^+] calcd. for $C_{31}H_{31}N_3O_3F_2$: 531.2333; found: 531.2329.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-3-(4-methoxyphenyl)-2-methylpropanamide ***(3i)***. Brown oil; 47.6 mg, 43% yield (38.8 mg, 35% yield); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.53 (s, 1H), 8.14−8.10 (m, 1H), 7.80 (d, J = 1.6 Hz, 1H), 7.74 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.17 (q, J = 9.6 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 6.52 (t, J = 2.0 Hz, 1H), 3.76 (s, 3H), 2.90 (dd, J_1 = 13.6 Hz, J_2 = 7.2 Hz, 1H), 2.61 (dd, J_1 = 13.6 Hz, J_2 = 7.2 Hz, 1H), 2.56−2.47 (m, 1H), 1.16 (d, J = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 174.4, 158.0, 146.9 (dd, J_{CF} = 245.1, 12.2 Hz), 143.7 (dd, J_{CF} = 248.9, 15.6 Hz), 141.6, 133.0 (d, J_{CF} = 6.6 Hz), 131.2, 129.8 (2C), 129.5 (d, J_{CF} = 3.2 Hz), 119.9 (d, J_{CF} = 10.1 Hz), 117.9 (dd, J_{CF} = 6.6, 4.8 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 113.8 (2C), 107.4, 55.2, 45.1, 39.4, 17.1; HRMS (EI): *m/z* [M^+] calcd. for $C_{20}H_{19}N_3O_2F_2$: 371.1445; found: 371.1444.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)-3-(4-methoxyphenyl)propanamide ***(3i')***. Brown oil; 45.6 mg, 32% yield (34.5 mg, 24%); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.22 (s, 1H), 7.96−7.92 (m, 1H), 7.68 (d, J = 1.6 Hz, 1H), 7.59 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 7.12 (q, J = 9.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 4H), 6.70 (d, J = 8.8 Hz, 4H), 6.45 (t, J = 2.0 Hz, 1H), 3.75 (s, 6H), 2.90 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 2H), 2.73 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 2H), 2.60−2.54 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 172.1, 157.0 (2C), 145.9 (dd, J_{CF} = 245.0, 12.0 Hz), 142.6 (dd, J_{CF} = 249.0, 15.3 Hz), 140.4, 131.7 (d, J_{CF} = 6.7 Hz), 130.0 (2C), 128.6 (4C), 128.0 (d, J_{CF} = 3.1 Hz), 118.9 (d, J_{CF} = 9.7 Hz), 117.2 (dd, J_{CF} = 6.7, 4.2Hz), 114.6 (d, J_{CF} = 17.3 Hz), 112.8 (4C), 106.2, 54.1 (2C), 53.0, 36.9 (2C); HRMS (EI): *m/z* [M^+] calcd. for $C_{27}H_{25}N_3O_3F_2$: 477.1864; found: 477.1866.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)pentanamide ***(3j)***. Yellow oil; 77.1 mg, 64% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.39 (s, 1H), 8.05−8.01 (m, 1H), 7.79 (d, J = 1.6 Hz, 1H), 7.71 (t, J = 2.8 Hz, 1H), 7.16 (q, J = 9.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.0 Hz, 2H), 6.51 (s, 1H), 3.75 (s, 3H), 2.84 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H), 2.66 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.40−2.33 (m, 1H), 1.67−1.59 (m, 1H), 1.49−1.40 (m, 1H), 1.29−1.16 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.9, 158.0, 147.0 (dd, J_{CF} = 245.0, 11.9 Hz), 143.8 (dd, J_{CF} = 248.9, 15.4 Hz), 141.6, 133.0 (d, J_{CF} = 6.3 Hz), 131.3, 129.6 (2C), 129.3 (d, J_{CF} = 3.2 Hz), 120.1 (d, J_{CF} = 10.2 Hz), 118.3 (dd, J_{CF} = 6.5, 4.6 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 113.8 (2C), 107.4, 55.1, 51.4, 38.3, 34.7, 20.6, 14.0; HRMS (EI): *m/z* [M^+] calcd. for $C_{22}H_{23}N_3O_2F_2$: 399.1758; found: 399.1759.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)hexanamide ***(3k)***. Yellow oil; 93.8 mg, 76% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.40 (s, 1H), 8.05−8.01 (m, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.70 (dd, J_1 = 3.2 Hz, J_2 = 2.8 Hz, 1H), 7.16 (q, J = 9.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 6.51 (t, J = 2.0 Hz, 1H), 3.75 (s, 3H), 2.84 (dd, J_1 = 14.0 Hz, J_2 = 9.2 Hz, 1H), 2.67 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.38−2.31 (m, 1H), 1.69−1.60 (m, 1H), 1.52−1.43 (m, 1H), 1.26−1.21 (m, 2H), 1.19−1.13 (m, 2H), 0.81 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.9, 157.9, 147.0 (dd, J_{CF} = 244.9, 11.8 Hz), 143.8 (dd, J_{CF} = 249.1, 15.5 Hz), 141.6, 132.9 (d, J_{CF} = 6.4 Hz), 131.3, 129.6 (2C), 129.3 (d, J_{CF} = 3.2 Hz), 120.1 (d, J_{CF} = 10.4 Hz), 118.3 (dd, J_{CF} = 6.6, 4.6 Hz), 115.8 (d, J_{CF} = 17.3 Hz), 113.8 (2C), 107.4, 55.2, 51.7, 38.3, 32.4, 29.5, 22.6, 14.0; HRMS (EI): *m/z* [M^+] calcd. for $C_{23}H_{25}N_3O_2F_2$: 413.1915; found: 413.1913.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxybenzyl)heptanamide ***(3l)***. Yellow oil; 89.1 mg, 70% yield (67.9 mg, 53%); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.39 (s, 1H), 8.04−8.00 (m, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.70 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 7.16 (q, J = 9.2 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.51 (t, J = 2.4 Hz, 1H), 3.75 (s, 3H), 2.84 (dd, J_1 = 14.0 Hz, J_2 = 9.2 Hz, 1H), 2.66 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 1H), 2.38−2.31 (m, 1H), 1.69−1.60 (m, 1H), 1.47−1.43 (m, 1H), 1.19−1.17 (m, 6H), 0.88−0.81 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 174.0, 157.9, 147.0 (dd, J_{CF} = 245.0, 11.8 Hz), 143.7 (dd, J_{CF} = 249.0, 15.5 Hz), 141.6, 132.9 (d, J_{CF} = 6.4 Hz), 131.3, 129.6 (2C), 129.3 (d, J_{CF} = 3.2 Hz), 120.1 (d, J_{CF} = 9.6 Hz), 118.4 (dd, J_{CF} = 6.6, 4.6 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 113.7 (2C), 107.4, 55.1, 51.7, 38.3, 32.6, 31.8, 27.1, 22.5, 14.0; HRMS (EI): *m/z* [M^+] calcd. for $C_{24}H_{27}N_3O_2F_2$: 427.2071; found: 427.2072.

2-Benzyl-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)-3-(4-methoxyphenyl)propanamide ***(3m)***. Brown oil; 69.6 mg, 49% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.24 (s, 1H), 7.98−7.95 (m, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.58 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 7.18 (q, J = 6.8 Hz, 2H), 7.14−7.12 (m, 1H), 7.12−7.09 (m, 3H), 6.99 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.45 (t, J = 2.0 Hz, 1H), 3.75 (s, 3H), 2.98 (dd, J_1 = 13.2 Hz, J_2 = 8.8 Hz, 1H), 2.92 (dd, J_1 = 14.0 Hz, J_2 = 9.6 Hz, 1H), 2.80 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 1H), 2.75 (dd, J_1 = 14.0 Hz, J_2 = 6.0 Hz, 1H), 2.65−2.59 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.0, 158.0, 147.0 (dd, J_{CF} = 245.0, 12.2 Hz), 143.6 (dd, J_{CF} = 249.0, 15.6 Hz), 141.4, 139.0, 132.8 (d, J_{CF} = 6.4 Hz), 130.9, 129.7 (2C), 129.0 (d, J_{CF} = 3.3 Hz), 128.7 (2C), 128.5 (2C), 126.4, 119.9 (d, J_{CF} = 10.2 Hz), 118.2 (dd, J_{CF} = 6.5, 4.7 Hz), 115.7 (d, J_{CF} = 17.3 Hz), 113.8 (2C), 107.3, 55.1, 53.8, 38.7, 38.0; HRMS (EI): *m/z* [M^+] calcd. for $C_{26}H_{23}N_3O_2F_2$: 447.1758; found: 447.1759.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-3-(4-methoxyphenyl)-2-phenylpropanamide ***(3n)***. Yellow oil; 49.2 mg, 38% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.49 (s, 1H), 8.11−8.07 (m, 1H), 7.63 (t, J = 3.2 Hz, 1H), 7.60 (d, J = 1.6 Hz, 1H), 7.29−7.27 (m, 1H), 7.25−7.23 (m, 2H), 7.19 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 2H), 7.15 (q, J = 10.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 6.42 (t, J = 2.0 Hz, 1H), 3.74 (s, 3H), 3.63 (t, J = 7.2 Hz, 1H), 3.48 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1H), 2.97 (dd, J_1 = 13.6 Hz, J_2 = 7.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 171.6, 158.0, 146.9 (dd, J_{CF} = 245.3, 12.0 Hz), 143.7 (dd, J_{CF} = 249.0, 15.4 Hz), 141.6, 138.7, 132.8 (d, J_{CF} = 6.5 Hz), 131.2, 129.9 (2C), 129.6 (d, J_{CF} = 3.3 Hz), 128.8 (2C), 128.2 (2C), 127.5, 119.9 (d, J_{CF} = 9.7 Hz), 117.9 (dd, J_{CF} = 6.6, 4.4 Hz), 115.8 (d, J_{CF} = 17.3 Hz), 113.7 (2C), 107.2, 56.9, 55.2, 38.1; HRMS (EI): *m/z* [M^+] calcd. for $C_{25}H_{21}N_3O_2F_2$: 433.1602; found: 433.1604.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-3-(4-methoxyphenyl)-2-(p-tolyl)propanamide ***(3o)***. Brown oil, 61.3 mg, 43% yield (45.8 mg, 32% yield); ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.43 (s, 1H), 8.12−8.07 (m, 1H), 7.63 (t, J = 2.8 Hz, 1H), 7.59 (d, J = 1.6 Hz, 1H),

7.15 (t, J = 9.2 Hz, 1H), 7.13−7.10 (m, 1H), 7.08 (s, 3H), 6.96 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.43 (t, J = 2.0 Hz, 1H), 3.74 (s, 3H), 3.60 (t, J = 7.6 Hz, 1H), 3.47 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1H), 2.95 (dd, J_1 = 14.0 Hz, J_2 = 7.6 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 171.9, 158.0, 146.9 (dd, J_{CF} = 244.8, 11.6 Hz), 143.8 (dd, J_{CF} = 248.8, 15.3 Hz), 141.5, 137.1, 135.6, 132.8 (d, J_{CF} = 6.3 Hz), 131.4, 129.9 (2C), 129.7 (d, J_{CF} = 3.2 Hz), 129.5 (2C), 128.0 (2C), 119.9 (d, J_{CF} = 9.8 Hz), 117.8 (dd, J_{CF} = 5.9, 5.3 Hz), 115.8 (d, J_{CF} = 17.3 Hz), 113.7 (2C), 107.1, 56.4, 55.2, 38.0, 21.1; HRMS (EI): m/z [M^+] calcd. for $C_{26}H_{23}N_3O_2F_2$: 447.1758; found: 447.1759.

2-(3-Chlorophenyl)-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)-3-(4-methoxyphenyl)propanamide ***(3p)***. Yellow oil; 48.7 mg, 35% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.57 (s, 1H), 8.07−8.04 (m, 1H), 7.67−7.65 (m, 2H), 7.21 (s, 1H), 7.21−7.17 (m, 2H), 7.14 (t, J = 8.4 Hz, 1H), 7.11−7.08 (m, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.45 (t, J = 2.4 Hz, 1H), 3.74 (s, 3H), 3.61 (t, J = 7.6 Hz, 1H), 3.46 (dd, J_1 = 13.6 Hz, J_2 = 7.6 Hz, 1H), 2.95 (dd, J_1 = 13.6 Hz, J_2 = 7.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 170.9, 158.1, 147.1 (dd, J_{CF} = 245.5, 12.0 Hz), 143.7 (dd, J_{CF} = 249.2, 15.5 Hz), 141.5, 140.7, 134.6, 132.8 (d, J_{CF} = 6.6 Hz), 130.7, 130.0, 129.8 (2C), 129.3 (d, J_{CF} = 3.3 Hz), 128.3, 127.7, 126.3, 120.0 (d, J_{CF} = 10.3 Hz), 118.0 (dd, J_{CF} = 6.3, 4.8 Hz), 115.8 (d, J_{CF} = 17.5 Hz), 113.8 (2C), 107.4, 56.5, 55.2, 38.0; HRMS (EI): m/z [M^+] calcd. for $C_{25}H_{20}N_3O_2F_2Cl$: 467.1212; found: 467.1214.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(6-methoxynaphthalen-2-yl)-3-(4-methoxyphenyl)propanamide ***(3q)***. Yellow solid; 68.1 mg, 44% yield; m.p. 82.8–84.2 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.41 (s, 1H), 8.15−8.11 (m, 1H), 7.66 (d, J = 3.6 Hz, 1H), 7.64 (d, J = 2.8 Hz, 1H), 7.54−7.52 (m, 2H), 7.28 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.18−7.14 (m, 2H), 7.11 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 1.6 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.20 (t, J = 2.4 Hz, 1H), 3.93 (s, 3H), 3.79 (t, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.60 (dd, J_1 = 14.0 Hz, J_2 = 6.8 Hz, 1H), 3.08 (dd, J_1 = 14.0 Hz, J_2 = 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 171.9, 157.9, 157.8, 146.9 (dd, J_{CF} = 245.5, 12.3 Hz), 143.7 (dd, J_{CF} = 248.8, 15.2 Hz), 141.3, 134.0, 133.5, 132.6 (d, J_{CF} = 6.2 Hz), 131.3, 129.9 (2C), 129.7 (d, J_{CF} = 3.2 Hz), 129.4, 129.0, 127.6, 127.5, 126.4, 119.9 (d, J_{CF} = 9.4 Hz), 119.1, 117.7 (dd, J_{CF} = 6.5, 4.5 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 113.7 (2C), 107.0, 105.6, 56.7, 55.4, 55.1, 37.7; HRMS (EI): m/z [M^+] calcd. for $C_{30}H_{25}N_3O_3F_2$: 513.1864; found: 513.1859.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxyphenyl)cyclobutanecarboxamide ***(3r)***. Brown oil; 59.2 mg, 52% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.20 (s, 1H), 7.84 (d, J = 1.6 Hz, 1H), 7.80−7.75 (m, 1H), 7.66 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.05 (q, J = 9.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 6.54 (t, J = 2.0 Hz, 1H), 3.91−3.85 (m, 1H), 3.70 (s, 3H), 3.44−3.38 (m, 1H), 2.54−2.48 (m, 1H), 2.47−2.40 (m, 1H), 2.33−2.28 (m, 1H), 2.20−2.15 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 171.1, 158.0, 146.6 (dd, J_{CF} = 244.6, 12.4 Hz), 143.6 (dd, J_{CF} = 248.4, 15.5 Hz), 141.5, 133.1 (d, J_{CF} = 6.6 Hz), 132.4, 129.3 (d, J_{CF} = 3.2 Hz), 128.2 (2C), 119.6 (d, J_{CF} = 10.8 Hz), 117.7 (dd, J_{CF} = 6.9, 4.7 Hz), 115.7 (d, J_{CF} = 17.2 Hz), 113.5 (2C), 107.3, 55.2, 47.6, 42.6, 24.9, 20.0; HRMS (EI): m/z [M^+] calcd. for $C_{21}H_{19}N_3O_2F_2$: 383.1445; found: 383.1443.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxyphenyl)cyclopentanecarboxamide ***(3s)***. Yellow solid; 65.2 mg, 55% yield (54.9, 46% yield); m.p. 86.5–87.9 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.21 (s, 1H), 7.85−7.83 (m, 1H), 7.81 (d, J = 1.2 Hz, 1H), 7.64 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.05 (q, J = 9.6 Hz, 1H), 6.95 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 8.4 Hz, 2H), 6.53 (t, J = 2.0 Hz, 1H), 3.69 (s, 3H), 3.32 (dd, J_1 = 15.6 Hz, J_2 = 8.4 Hz, 1H), 2.92 (dd, J_1 = 14.4 Hz, J_2 = 8.0 Hz, 1H), 2.19−2.13 (m, 1H), 2.10−2.05 (m, 2H), 2.01−1.91 (m, 2H), 1.75−1.67 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 172.8, 157.8, 146.6 (dd, J_{CF} = 244.5, 12.1 Hz), 143.5 (dd, J_{CF} = 248.4, 15.5 Hz), 141.4, 133.0 (d, J_{CF} = 6.4 Hz), 133.0, 129.4 (d, J_{CF} = 3.2 Hz), 128.6 (2C), 119.5 (d, J_{CF} = 9.8 Hz), 117.5 (dd, J_{CF} = 6.6, 4.6 Hz), 115.6 (d, J_{CF} = 17.3 Hz), 113.4 (2C), 107.2, 55.1, 52.9, 49.0, 31.5, 28.3, 24.7; HRMS (EI): m/z [M^+] calcd. for $C_{22}H_{21}N_3O_2F_2$: 397.1602; found: 397.1599.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methoxyphenyl)cyclohexanecarboxamide ***(3t)***. White solid, 62.8 mg, 51% yield; m.p. 137.1–138.6 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 8.98 (s, 1H), 8.00−7.97 (m, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.58 (dd, J_1 = 3.6 Hz, J_2 = 2.8 Hz, 1H), 7.10 (q, J = 9.2 Hz, 1H), 7.04 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 6.46 (s, 1H), 3.72 (s, 3H), 2.87−2.82 (m, 1H), 2.61 (d, J = 3.2 Hz, 1H), 2.40−2.30 (m, 1H), 1.99−1.89 (m, 3H), 1.73−1.66 (m, 2H), 1.53 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 1H), 1.39 (dd, J_1 = 24.0 Hz, J_2 = 11.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.0, 157.7, 146.7 (dd, J_{CF} = 248.4, 15.5 Hz), 143.7 (dd, J_{CF} = 248.7, 15.3 Hz), 141.5, 136.1, 132.8 (d, J_{CF} = 6.3 Hz), 129.5 (d, J_{CF} = 3.2 Hz), 128.3 (2C), 119.8 (d, J_{CF} = 10.1 Hz), 117.8 (dd, J_{CF} = 6.6, 4.7 Hz), 115.7 (d, J_{CF} = 17.4 Hz), 113.5 (2C), 107.2, 55.1, 49.0, 44.4, 28.9, 27.2, 25.7, 21.7; HRMS (EI): m/z [M^+] calcd. for $C_{23}H_{23}N_3O_2F_2$: 411.1758; found: 411.1756.

N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)-3-(4-methoxyphenyl)propanamide ***(3u)***. Yellow oil, 43.6 mg, 41% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.62 (s, 1H), 8.19−8.14 (m, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.80 (dd, J_1 = 4.4 Hz, J_2 = 2.8 Hz, 1H), 7.18 (q, J = 9.6 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 6.54 (t, J = 2.4 Hz 1H), 3.77 (s, 3H), 2.91 (t, J = 7.6 Hz, 2H), 2.57 (t, J = 8.0 Hz 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 170.7, 158.1, 146.9 (dd, J_{CF} = 245.1, 12.0 Hz), 143.7 (dd, J_{CF} = 248.8, 15.5 Hz), 141.7, 133.2 (d, J_{CF} = 6.6 Hz), 132.3, 129.5 (d, J_{CF} = 3.2 Hz), 129.2 (2C), 119.8 (d, J_{CF} = 9.6 Hz), 117.8 (dd, J_{CF} = 6.1, 4.8 Hz), 115.9 (d, J_{CF} = 17.5 Hz), 114.0 (2C), 107.4, 55.3, 39.9, 30.4; HRMS (EI): m/z [M^+] calcd. for $C_{19}H_{17}N_3O_2F_2$: 357.1289; found: 357.1287.

2-Benzyl-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)butanamide ***(4b)***. Yellow solid; 50.1 mg, 47% yield, m.p. 63.2–64.8 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.42 (s, 1H), 8.07−8.03 (m, 1H), 7.80 (d, J = 1.6 Hz, 1H), 7.70 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.20−7.17 (m,, 2H), 7.15−7.12 (m, 2H), 7.09 (d, J = 6.8 Hz, 2H), 6.51 (t, J = 2.4 Hz, 1H), 2.92 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H), 2.74 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.37−2.30 (m, 1H), 1.72−1.64 (m, 1H), 1.59−1.52 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.7, 147.0 (dd, J_{CF} = 244.9, 12.0 Hz), 143.8 (dd, J_{CF} = 249.0, 15.0 Hz), 141.6, 139.3, 133.0 (d, J_{CF} = 6.4 Hz), 129.3 (d, J_{CF} = 3.2 Hz), 128.7 (2C), 128.4 (2C), 126.3, 120.1 (d, J_{CF} = 3.7 Hz), 118.3 (d, J_{CF} = 3.6 Hz), 115.9 (d, J_{CF} = 17.3 Hz), 107.5, 52.9, 38.8, 25.6, 11.7; HRMS (EI): m/z [M^+] calcd. for $C_{20}H_{19}N_3OF_2$: 355.1496; found: 355.1497.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-methylbenzyl)butanamide ***(4c)***. Yellow oil; 82.8 mg, 75% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.42 (s, 1H), 8.08−8.03 (m, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.70 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.18 (q, J = 9.6 Hz, 1H), 6.70 (d, J = 1.2 Hz, 4H), 6.51 (t, J = 2.4 Hz, 1H), 2.87 (dd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, 1H), 2.69 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 2.35−2.31 (m, 1H), 2.27 (s, 3H), 1.71−1.63 (m, 1H), 1.58−1.51 (m, 1H), 0.84 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.8, 147.0 (dd, J_{CF} = 245.2, 11.8 Hz), 143.8 (dd, J_{CF} = 247.4, 16.4 Hz), 141.6, 136.2, 135.6, 132.9 (d, J_{CF} = 7.0 Hz), 129.4, 129.1 (2C), 128.6 (2C), 120.1 (d, J_{CF} = 10.2 Hz), 118.3, 115.8 (d, J_{CF} = 17.0 Hz), 107.3, 53.0, 38.4, 25.6, 21.1, 11.7; HRMS (EI): m/z [M^+] calcd. for $C_{21}H_{21}N_3OF_2$: 369.1653; found: 369.1652.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-(trifluoromethyl)benzyl)butanamide ***(4d)***. White solid; 86.5 mg, 68% yield; m.p. 80.4–81.8 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.50 (s, 1H), 8.03−8.00 (m, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.67 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.20−7.13 (m, 3H), 6.49 (t, J = 2.0 Hz, 1H), 2.95 (dd, J_1 = 14.0 Hz, J_2 = 9.2 Hz, 1H), 2.78 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 1H), 2.37−2.29 (m, 1H), 1.78−1.68 (m, 1H), 1.61−1.55 (m, 1H), 0.89 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 172.0, 146.1 (dd, J_{CF} = 245.4, 11.9 Hz), 142.4, 142.6 (dd, J_{CF} = 249.3, 15.6 Hz), 140.4, 132.0 (d, J_{CF} = 6.5 Hz), 127.9 (2C), 127.9, 127.4 (d, J_{CF} = 32.2 Hz), 124.2 (q, J_{CF} = 3.7 Hz, 2C), 123.2 (q, J_{CF} = 270.2 Hz), 119.0 (d, J_{CF} = 9.6 Hz), 117.2 (dd, J_{CF} = 6.8, 4.7 Hz), 114.8 (d, J_{CF} = 17.2 Hz), 106.5, 51.8, 37.5, 25.0, 10.7; HRMS (EI): m/z [M^+] calcd. for $C_{21}H_{18}N_3OF_5$: 423.1370; found: 423.1367.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(4-fluorobenzyl)butanamide ***(4e)***. Yellow oil; 77.0 mg, 69% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.43 (s, 1H), 8.04−8.00 (m, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.71 (dd, J_1 = 4.4 Hz, J_2 = 2.8 Hz, 1H), 7.16 (q, J = 9.6 Hz, 1H), 7.01 (dd, J_1 = 8.4 Hz, J_2 = 5.2 Hz, 2H), 6.82 (t, J = 8.8 Hz, 2H), 6.52 (t, J = 2.4 Hz, 1H), 2.85 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H), 2.70 (dd,

J_1 = 13.6 Hz, J_2 = 5.6 Hz, 1H), 2.31−2.23 (m, 1H), 1.74−1.66 (m, 1H), 1.59−1.52 (m, 1H), 0.86 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.5, 161.4 (d, J_{CF} = 242.6 Hz), 147.0 (dd, J_{CF} = 245.1, 11.8 Hz), 143.7 (dd, J_{CF} = 249.1, 15.5 Hz), 141.6, 134.9 (d, J_{CF} = 3.1 Hz), 133.0 (d, J_{CF} = 6.5 Hz), 130.0 (d, J_{CF} = 7.8 Hz, 2C), 129.1 (d, J_{CF} = 3.3 Hz), 120.1 (d, J_{CF} = 10.5 Hz), 118.3 (dd, J_{CF} = 6.8, 4.8 Hz), 115.8 (d, J_{CF} = 17.5 Hz), 115.2 (d, J_{CF} = 21.0 Hz, 2C), 107.4, 53.3, 38.0, 25.9, 11.8; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{20}H_{18}N_3OF_3$: 373.1402; found: 373.1401.

2-(4-Chlorobenzyl)-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)butanamide ***(4f)***. Yellow solid, 78.2 mg, 67% yield; m.p. 95.8–97.6 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.41 (s, 1H), 8.04−8.00 (m, 1H), 7.75 (d, J = 1.6 Hz, 1H), 7.70 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.16 (q, J = 9.2 Hz, 1H), 7.09 (d, J = 8.4 Hz 2H), 6.97 (d, J = 8.4 Hz 2H), 6.54 (t, J = 2.4 Hz, 1H), 2.84 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H), 2.70 (dd, J_1 = 13.6 Hz, J_2 = 5.2 Hz, 1H), 2.31−2.23 (m, 1H), 1.75−1.68 (m, 1H), 1.59−1.52 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.3, 147.1 (dd, J_{CF} = 245.2, 12.1 Hz), 143.7 (dd, J_{CF} = 249.0, 15.5 Hz), 141.5, 137.7, 133.0 (d, J_{CF} = 6.5 Hz), 132.0, 130.0 (2C), 129.1 (d, J_{CF} = 3.3 Hz), 128.5 (2C), 120.1 (d, J_{CF} = 9.9 Hz), 118.3 (dd, J_{CF} = 6.5, 4.5 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 107.5, 53.1, 38.2, 25.8, 11.8; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{20}H_{18}N_3OF_2Cl$: 389.1106; found: 389.1108.

Ethyl 4-(2-((3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)carbamoyl)butyl)benzoate ***(4g)***. Yellow oil; 68.9 mg, 54% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.46 (s, 1H), 8.02−7.98 (m, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 1.6 Hz 1H), 7.67 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.16 (q, J = 9.6 Hz, 1H), 7.12 (d, J = 8.0 Hz 2H), 6.48 (t, J = 2.0 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 2.94 (dd, J_1 = 13.6 Hz, J_2 = 9.6 Hz, 1H), 2.78 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 1H), 2.37−2.29 (m, 1H), 1.76−1.69 (m, 1H), 1.60−1.53 (m, 1H), 1.39 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 172.2, 165.5, 146.0 (dd, J_{CF} = 245.3, 11.9 Hz), 143.6, 142.6 (dd, J_{CF} = 249.1, 15.7 Hz), 140.5, 131.9 (d, J_{CF} = 6.6 Hz), 128.6 (2C), 127.9 (d, J_{CF} = 3.3 Hz), 127.6 (2C), 127.5, 119.0 (d, J_{CF} = 10.5 Hz), 117.3 (dd, J_{CF} = 6.6, 4.5 Hz), 114.7 (d, J_{CF} = 17.5 Hz), 106.4, 59.8, 51.8, 37.8, 24.9, 13.4, 10.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{23}H_{23}N_3O_3F_2$: 427.1707; found: 427.1708.

2-(4-Acetylbenzyl)-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)butanamide ***(4h)***. Yellow oil; 82.3 mg, 69% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.53 (s, 1H), 8.03−7.99 (m, 1H), 7.76 (d, J = 2.0 Hz, 2H), 7.74 (s, 1H), 7.68 (dd, J_1 = 4.4 Hz, J_2 = 2.8 Hz, 1H), 7.19−7.12 (m, 3H), 6.48 (t, J = 2.4 Hz, 1H), 2.96 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H), 2.79 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1H), 2.54 (s, 3H), 2.38−2.31 (m, 1H), 1.76−1.68 (m, 1H), 1.60−1.53 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 197.7, 173.1, 148.3 (dd, J_{CF} = 245.3, 12.0 Hz), 145.1, 143.6 (dd, J_{CF} = 249.3, 15.7 Hz), 141.5, 135.3, 132.9 (d, J_{CF} = 6.7 Hz), 129.0 (d, J_{CF} = 3.4 Hz), 128.9 (2C), 128.5 (2C), 120.0 (d, J_{CF} = 10.4 Hz), 118.3 (dd, J_{CF} = 6.6, 4.6 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 107.4, 52.7, 38.7, 26.6, 25.9, 11.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{22}H_{21}N_3O_2F_2$: 397.1602; found: 397.1601.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(3-methoxybenzyl)butanamide ***(4i)***. Yellow solid, 67.3 mg, 58% yield; m.p. 78.8–80.5 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.42 (s, 1H), 8.09−8.05 (m, 1H), 7.79 (d, J = 1.6 Hz, 1H), 7.71 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 7.16 (q, J = 9.2 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.69−6.65 (m, 3H), 6.50 (t, J = 2.4 Hz, 1H), 3.73 (s, 3H), 2.89 (dd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, 1H), 2.70 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.35−2.30 (m, 1H), 1.71−1.62 (m, 1H), 1.60−1.51 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.7, 159.5, 147.0 (dd, J_{CF} = 245.0, 12.0 Hz), 143.8 (dd, J_{CF} = 249.1, 15.5 Hz), 141.6, 140.9, 133.0 (d, J_{CF} = 6.4 Hz), 129.4, 129.3, 121.1, 120.1 (d, J_{CF} = 9.2 Hz), 118.2 (dd, J_{CF} = 6.6, 4.6 Hz), 115.8 (d, J_{CF} = 17.5 Hz), 114.4, 111.7, 107.4, 55.1, 52.8, 38.9, 25.6, 11.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{21}N_3O_2F_2$: 385.1602; found: 385.1601.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(3-methylbenzyl)butanamide ***(4j)***. Yellow oil; 74.1 mg, 67% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.41 (s, 1H), 8.08−8.04 (m, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.71 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.17 (q, J = 9.2 Hz, 1H), 6.08 (t, J = 7.2 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 6.89 (d, J = 7.6 Hz, 1H), 6.51 (t, J = 2.4 Hz, 1H), 2.88 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H), 2.69 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 2.33−2.30 (m, 1H), 2.27 (s, 3H), 1.71−1.63 (m, 1H), 1.58−1.51 (m, 1H), 0.83 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.8, 147.0 (dd, J_{CF} = 245.0, 11.8 Hz), 143.8 (dd, J_{CF} = 249.0, 15.5 Hz), 141.5, 139.2, 137.9, 133.0 (d, J_{CF} = 6.4 Hz), 129.6, 129.4 (d, J_{CF} = 3.2 Hz), 128.3, 127.1, 125.7, 120.1 (d, J_{CF} = 10.2 Hz), 118.2 (dd, J_{CF} = 6.5, 4.4 Hz), 115.9 (d, J_{CF} = 17.5 Hz), 107.4, 52.9, 38.7, 25.6, 21.4, 11.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{21}N_3OF_2$: 369.1653; found: 369.1652.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(3-(trifluoromethyl)-benzyl)butanamide ***(4k)***. White solid; 79.8 mg, 63% yield; m.p. 83.6–84.9 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.50 (s, 1H), 8.04−8.00 (m, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.70 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.39−7.37 (m, 1H), 7.35 (s, 1H), 7.30−7.27 (m, 2H), 7.17 (q, J = 9.6 Hz, 1H), 6.49 (t, J = 2.4 Hz, 1H), 2.97 (dd, J_1 = 13.6 Hz, J_2 = 9.6 Hz, 1H), 2.78 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 1H), 2.35−2.27 (m, 1H), 1.76−1.68 (m, 1H), 1.60−1.53 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.1, 147.1 (dd, J_{CF} = 245.5, 12.2 Hz), 143.6 (dd, J_{CF} = 249.2, 15.7 Hz), 141.5, 140.3, 133.0 (d, J_{CF} = 6.7 Hz), 132.2, 130.6 (d, J_{CF} = 31.7 Hz), 129.0 (d, J_{CF} = 3.3 Hz), 128.8, 125.4 (q, J_{CF} = 3.8 Hz), 124.1 (q, J_{CF} = 266.8 Hz), 123.3 (q, J_{CF} = 3.7 Hz), 120.1 (d, J_{CF} = 10.1 Hz), 118.3 (dd, J_{CF} = 6.7, 4.5 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 107.5, 53.0, 38.6, 25.9, 11.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{18}N_3OF_5$: 423.1370; found: 423.1372.

Methyl 3-(2-((3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)carbamoyl)-butyl)benzoate ***(4l)***. Yellow solid; 76.5 mg, 62% yield; m.p. 89.6–91.2 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.47 (s, 1H), 8.05−8.00 (m, 1H), 7.80−7.78 (m, 2H), 7.75 (d, J = 2.0 Hz 1H), 7.68 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.27 (d, J = 8.4 Hz 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.15 (q, J = 9.2 Hz, 1H), 6.47 (t, J = 2.4 Hz, 1H), 3.90 (s, 3H), 2.94 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H), 2.78 (dd, J_1 = 13.6 Hz, J_2 = 5.6 Hz, 1H), 2.37−2.29 (m, 1H), 1.74−1.66 (m, 1H), 1.58−1.51 (m, 1H), 0.84 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.3, 167.0, 147.0 (dd, J_{CF} = 245.1, 11.9 Hz), 144.1 (dd, J_{CF} = 249.0, 15.5 Hz), 141.5, 139.7, 133.5, 133.0 (d, J_{CF} = 6.6 Hz), 130.2, 129.8, 129.1 (d, J_{CF} = 3.2 Hz), 128.4, 127.7, 120.1 (d, J_{CF} = 9.3 Hz), 118.3 (dd, J_{CF} = 6.6, 4.8 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 107.4, 52.9, 52.1, 38.6, 25.7, 11.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{22}H_{21}N_3O_3F_2$: 413.1551; found: 413.1549.

2-(3-Acetylbenzyl)-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)butanamide ***(4m)***. White solid; 71.6 mg, 60% yield; m.p. 92.3–94.0 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.51 (s, 1H), 8.06−8.02 (m, 1H), 7.76 (d, J = 2.0 Hz, 1H), 7.72−7.69 (m, 3H), 7.37−7.26 (m, 2H), 7.15 (q, J = 9.2 Hz, 1H), 6.48 (t, J = 2.0 Hz, 1H), 2.97 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H), 2.79 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 1H), 2.54 (s, 3H), 2.38−2.30 (m, 1H), 1.74−1.66 (m, 1H), 1.59−1.52 (m, 1H), 0.85 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 198.1, 173.3, 147.0 (dd, J_{CF} = 245.3, 12.0 Hz), 143.6 (dd, J_{CF} = 249.0, 15.4 Hz), 141.6, 139.9, 137.2, 133.6, 133.0 (d, J_{CF} = 6.7 Hz), 129.1 (d, J_{CF} = 3.3 Hz), 128.6, 128.4, 126.6, 120.0 (d, J_{CF} = 9.0 Hz), 118.2 (dd, J_{CF} = 6.6, 4.6 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 107.4, 52.9, 38.6, 26.7, 25.8, 11.7; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{22}H_{21}N_3O_2F_2$: 397.1602; found: 397.1600.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(2-methoxybenzyl)butanamide ***(4n)***. White solid; 77.7 mg, 67% yield; m.p. 114.9–115.5 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.28 (s, 1H), 8.08−8.04 (m, 1H), 7.79 (d, J = 1.6 Hz, 1H), 7.70 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.19−7.11 (m, 2H), 7.01 (dd, J_1 = 7.6 Hz, J_2 = 2.0 Hz, 1H), 6.79−6.75 (m, 2H), 6.51 (t, J = 2.4 Hz, 1H), 3.80 (s, 3H), 2.81 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 2H), 2.46−2.39 (m, 1H), 1.71−1.63 (m, 1H), 1.54−1.48 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 174.3, 157.3, 146.8 (dd, J_{CF} = 244.8, 11.9 Hz), 143.9 (dd, J_{CF} = 248.8, 15.2 Hz), 141.5, 133.0 (d, J_{CF} = 6.1 Hz), 130.7, 129.7 (d, J_{CF} = 3.2 Hz), 127.7, 127.5, 120.3, 120.0 (d, J_{CF} = 9.2 Hz), 118.1 (dd, J_{CF} = 6.3, 4.8 Hz), 115.9 (d, J_{CF} = 17.1 Hz), 110.2, 107.4, 55.2, 50.5, 33.9, 25.5, 11.8; HRMS (EI): *m/z* [M$^+$] calcd. for $C_{21}H_{21}N_3O_2F_2$: 385.1602; found: 385.1600.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(2-fluorobenzyl)butanamide ***(4o)***. Yellow solid; 71.7 mg, 64% yield; m.p. 59.6–61.4 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.52 (s, 1H), 8.06−8.02 (m, 1H), 7.81 (d, J = 1.6 Hz, 1H), 7.71 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.17 (t, J = 9.6 Hz, 1H), 7.09 (q, J = 7.6 Hz, 2H), 6.96−6.90 (m, 2H), 6.51

(t, J = 2.4 Hz, 1H), 2.86 (d, J = 7.6 Hz, 2H), 2.44−2.36 (m, 1H), 1.74−1.66 (m, 1H), 1.58−1.51 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.5, 161 (d, J_{CF} = 243.5 Hz), 147.0 (dd, J_{CF} = 244.8, 12.0 Hz), 143.7 (dd, J_{CF} = 248.9, 15.5 Hz), 141.6, 132.9 (d, J_{CF} = 6.6 Hz), 131.3 (d, J_{CF} = 4.8 Hz), 129.3 (d, J_{CF} = 3.2 Hz), 128.2 (d, J_{CF} = 8.1 Hz), 126.1 (d, J_{CF} = 15.6 Hz), 123.9 (d, J_{CF} = 3.5 Hz), 120.1 (d, J_{CF} = 9.1 Hz), 118.2 (dd, J_{CF} = 6.6, 4.6 Hz), 115.8 (d, J_{CF} = 17.4 Hz), 115.2 (d, J_{CF} = 21.8 Hz), 107.4, 51.1, 32.4, 25.6, 11.7; HRMS (EI): m/z [M^+] calcd. for $C_{20}H_{18}N_3OF_3$: 373.1402; found: 373.1401.

Methyl 2-(2-((3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl)carbamoyl)-butyl)benzoate ***(4p)***. Yellow solid; 40.9 mg, 33% yield; m.p. 82.0–84.2 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.28 (s, 1H), 8.07−8.03 (m, 1H), 7.85 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H), 7.66 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.31−7.27 (m, 1H), 7.20 (d, J = 6.0 Hz, 1H), 7.16 (d, J = 5.6 Hz, 1H), 7.13 (t, J = 4.4 Hz, 1H), 6.47 (t, J = 2.0 Hz, 1H), 3.89 (s, 3H), 3.21 (dd, J_1 = 12.8 Hz, J_2 = 6.0 Hz, 1H), 3.09 (dd, J_1 = 12.8 Hz, J_2 = 8.8 Hz, 1H), 2.50−2.53 (m, 1H), 1.77−1.69 (m, 1H), 1.59−1.53 (m, 1H), 0.83 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 174.0, 167.6, 146.9 (dd, J_{CF} = 244.8, 11.6 Hz), 143.9 (dd, J_{CF} = 250.3, 16.4 Hz), 141.6, 141.4, 132.8 (d, J_{CF} = 6.2 Hz), 132.0, 131.9, 131.1, 129.5 (d, J_{CF} = 3.2 Hz), 128.9, 126.5, 120.1 (d, J_{CF} = 10.6 Hz), 118.2 (dd, J_{CF} = 6.2, 4.8 Hz), 115.8 (d, J_{CF} = 17.3 Hz), 107.3, 52.2, 52.0, 37.9, 25.7, 11.8; HRMS (EI): m/z [M^+] calcd. for $C_{22}H_{21}N_3O_3F_2$: 413.1551; found: 413.1548.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(2,4-dimethoxybenz-yl)butanamide ***(4q)***. Yellow solid; 83.3 mg, 67% yield; m.p. 95.0–97.1 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.26 (s, 1H), 8.10−8.06 (m, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.69 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.16 (q, J = 9.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.51 (t, J = 2.4 Hz, 1H), 6.34(d, J = 2.4 Hz, 1H), 6.28 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.73 (d, J = 7.6 Hz, 2H), 2.41−2.33 (m, 1H), 1.69−1.62 (m, 1H), 1.53−1.47 (m, 1H), 0.82 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 174.4, 159.5, 158.2, 146.8 (dd, J_{CF} = 244.7, 11.8 Hz), 143.8 (dd, J_{CF} = 248.7, 15.3 Hz), 141.5, 132.9 (d, J_{CF} = 6.1 Hz), 130.9, 129.7 (d, J_{CF} = 3.2 Hz), 120.0 (d, J_{CF} = 10.9 Hz), 119.9, 118.1 (dd, J_{CF} = 6.3, 4.6 Hz), 115.9 (d, J_{CF} = 17.6 Hz), 107.3, 103.6, 98.5, 55.3, 55.2, 50.8, 33.3, 25.5, 11.8; HRMS (EI): m/z [M^+] calcd. for $C_{22}H_{23}N_3O_3F_2$: 415.1707; found: 415.1708.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(3,5-dimethylbenzyl-)butanamide ***(4r)***. Brown oil; 70.7 mg, 62% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.39 (s, 1H), 8.09−8.05 (m, 1H), 7.80 (d, J = 1.6 Hz, 1H), 7.72 (dd, J_1 = 4.0 Hz, J_2 = 2.8 Hz, 1H), 7.17 (q, J = 9.6 Hz, 1H), 6.76 (s, 1H), 6.71 (s, 2H), 6.51 (t, J = 2.4 Hz, 1H), 2.84 (dd, J_1 = 13.2 Hz, J_2 = 8.4 Hz, 1H), 2.64 (dd, J_1 = 13.6 Hz, J_2 = 6.4 Hz, 1H), 2.32−2.28 (m, 1H), 2.22 (s, 6H), 1.70−1.62 (m, 1H), 1.57−1.51 (m, 1H), 0.82 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.9, 147.0 (dd, J_{CF} = 245.0, 11.9 Hz), 143.8 (dd, J_{CF} = 249.0, 15.4 Hz), 141.5, 139.2, 137.7 (2C), 132.9 (d, J_{CF} = 6.4 Hz), 129.4 (d, J_{CF} = 3.2 Hz), 128.0, 126.6 (2C), 120.1 (d, J_{CF} = 9.2 Hz), 118.2 (dd, J_{CF} = 6.5, 4.6 Hz), 115.8 (d, J_{CF} = 17.3 Hz), 107.4, 53.0, 38.7, 25.6, 21.3 (2C), 11.7; HRMS (EI): m/z [M^+] calcd. for $C_{22}H_{23}N_3OF_2$: 383.1809; found: 383.1810.

N-(3,4-Difluoro-2-(1H-pyrazol-1-yl)phenyl)-2-(2,4-difluorobenzyl)-butanamide ***(4s)***. Yellow solid; 67.0 mg, 57% yield; m.p. 105.5–107.7 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.54 (s, 1H), 8.04−8.00 (m, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.72 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.16 (q, J = 9.6 Hz, 1H), 7.04−6,99 (m, 1H), 6.68−6.61 (m, 2H), 6.52 (t, J = 2.4 Hz, 1H), 2.80 (d, J = 8.0 Hz, 2H), 2.38−2.30 (m, 1H), 1.75−1.68 (m, 1H), 1.58−1.51 (m, 1H), 0.86 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.3, 161.6 (dd, J_{CF} = 245.3, 11.7 Hz), 160.9 (dd, J_{CF} = 246.1, 11.7 Hz), 147.1 (dd, J_{CF} = 245.3, 11.9 Hz), 143.7 (dd, J_{CF} = 249.0, 15.6 Hz), 141.6, 132.9 (d, J_{CF} = 6.8 Hz), 131.8 (dd, J_{CF} = 9.3, 6.4 Hz), 129.1 (d, J_{CF} = 3.2 Hz), 122.0 (dd, J_{CF} = 15.7, 3.7 Hz), 120.0 (d, J_{CF} = 9.4 Hz), 118.3 (dd, J_{CF} = 6.7, 4.6 Hz), 115.8 (d, J_{CF} = 17.2 Hz), 110.9 (dd, J_{CF} = 20.6, 3.5 Hz), 107.4, 103.7 (t, J_{CF} = 25.5 Hz), 51.3, 31.8, 25.7, 11.7; HRMS (EI): m/z [M^+] calcd. for $C_{20}H_{17}N_3OF_4$: 391.1308; found: 391.1307.

2-(3,5-Dichlorobenzyl)-N-(3,4-difluoro-2-(1H-pyrazol-1-yl)phenyl-)butanamide ***(4t)***. Yellow solid; 75.0 mg, 59% yield; m.p. 91.0–92.4 °C; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.54 (s, 1H), 8.04−8.00 (m, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.75 (dd, J_1 = 4.4 Hz, J_2 = 2.8 Hz, 1H), 7.18 (q, J = 9.6 Hz, 1H), 7.09 (t, J = 1.6 Hz, 1H), 6.96 (s, 1H), 6.95 (s, 1H), 6.51 (t, J = 2.4 Hz, 1H), 2.84 (dd, J_1 = 13.6 Hz, J_2 = 9.6 Hz, 1H), 2.66 (dd, J_1 = 13.6 Hz, J_2 = 5.2 Hz, 1H), 2.30−2.22 (m, 1H), 1.75−1.67 (m, 1H), 1.58−1.51 (m, 1H), 0.86 (t, J = 7.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 172.8, 147.1 (dd, J_{CF} = 245.3, 12.0 Hz), 143.6 (dd, J_{CF} = 249.1, 15.5 Hz), 142.7, 141.5, 134.7 (2C), 132.9 (d, J_{CF} = 6.9 Hz), 128.9 (d, J_{CF} = 3.3 Hz), 127.2 (2C), 126.8, 120.2 (d, J_{CF} = 10.2 Hz), 118.4 (dd, J_{CF} = 6.7, 4.8 Hz), 115.8 (d, J_{CF} = 17.5 Hz), 107.5, 52.8, 38.2, 25.9, 11.7; HRMS (EI): m/z [M^+] calcd. for $C_{20}H_{17}N_3OF_2Cl_2$: 423.0717; found: 423.0719.

General Procedure for Arylation of 1d with Diiodobenzene. A mixture of substrate **1d** (167.6 mg, 0.6 mmol), 1,4-diiodobenzene **2v** (66.0 mg, 0.2 mmol), $Pd(OAc)_2$ (13.5 mg, 10 mol%), $Cu(OAc)_2$ (130.8 mg, 0.72 mmol), Ag_3PO_4 (75.3 mg, 0.18 mmol) in *p*-xylene (1.5 mL) and DMF (1.5 ml) was charged in a glass sealed-tube and stirred at 130 °C (oil bath) for 16 h. Upon completion of the reaction, saturated brine (15 mL) and dichloromethane (15 mL) were added to the mixture, then the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 30:1 to 10:1) to supply the product **5**. *2,2'-(1,4-Phenylenebis(methyle-ne))bis(N-(3,4-difluoro-2-(1H-pyra-zol-1-yl)phenyl)butanamide)* ***(5)***. Yellow gum; 73.3 mg, 58% yield; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 9.42 (s, 2H), 8.03−7.97 (m, 2H), 7.78 (t, J = 2.4 Hz, 2H), 7.71−7.69 (m, 2H), 7.14 (q, J = 9.6 Hz, 2H), 6.91 (d, J = 1.6 Hz, 4H), 6.51 (t, J = 2.0 Hz, 2H), 2.83 (dd, J_1 = 13.6 Hz, J_2 = 8.4 Hz, 2H), 2.68−2.61 (m, 2H), 2.31−2.23 (m, 2H), 1.66−1.58 (m, 2H), 1.53−1.46 (m, 2H), 0.79 (td, J_1 = 7.6 Hz, J_2 = 2.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 173.7, 173.6, 147.0 (dd, J_{CF} = 245.1, 11.3 Hz, 2C), 143.8 (dd, J_{CF} = 241.5, 17.5 Hz, 2C), 141.5 (2C), 137.1 (2C), 133.0 (t, J_{CF} = 6.3 Hz, 2C), 129.3 (t, J_{CF} = 3.3 Hz, 2C), 128.8 (2C), 128.7 (2C), 120.0 (d, J_{CF} = 9.6 Hz, 2C), 118.2 (2C), 115.8 (d, J_{CF} = 17.7 Hz, 2C), 107.4 (2C), 52.8, 52.6, 38.3 (2C), 25.6, 25.5, 11.7 (2C); HRMS (EI): m/z [M^+] calcd. for $C_{34}H_{32}N_6O_2F_4$: 632.2523; found: 632.2521.

General Procedure for Gram-Scale Reaction. A mixture of substrate **1d** (1.12 g, 4 mmol), 4-iodoanisole **2a** (2.81 g, 12 mmol), $Pd(OAc)_2$ (111.7 mg, 10 mol%), $Cu(OAc)_2$ (871.8 mg, 4.8 mmol), Ag_3PO_4 (502.3 mg, 1.2 mmol), in *p*-xylene (20 mL) and DMF (20 mL) was charged in a round-bottomed flask (100 mL) and stirred at 130 °C (oil bath) for 16 h. Upon completion of the reaction, saturated brine (100 mL) and dichloromethane (100 mL) were added to the mixture, then the aqueous layer was extracted with dichloromethane (30 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 60:1 to 30:1) to supply the desired product **3d** (1.06 g, 69%).

General Procedure for the Removal of the Directing Group. The reaction was performed in an air atmosphere. A mixture of the arylated producted **3d** (96.4 mg, 0.25 mmol) and HCl (5 mL, 12 M) were added to a round-bottomed flask (25 mL) and stirred at 110 °C (oil bath) for 20 h. Upon completion of the reaction, water (20 mL) and was slowly added to the mixture, then the aqueous layer was extracted with ethyl acetate (20 mL × 5). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: dichloromethane/ methanol = 200:1 to 100:1) to supply the free acid **6**. *2-(4-hydroxybenz-yl)butanoic acid* ***(6)***. Yellow oil; 34.4 mg, 71%; ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 6.97 (d, J = 8.0 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 2.80 (dd, J_1 = 14.0 Hz, J_2 = 9.6 Hz, 1H), 2.71 (dd, J_1 = 14.0 Hz, J_2 = 6.0 Hz, 1H), 2.58−2.51 (m, 1H), 1.70−1.55 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm): δ 180.6, 152.9, 130.0, 128.9 (2C), 114.4 (2C), 48.6, 36.1, 24.1, 10.7; HRMS (EI): m/z [M^+] calcd. for: $C_{11}H_{14}O_3$: 194.0943; found: 194.0942.

General Procedure for Competition Experiment. A mixture of substrate **1d** (83.8 mg, 0.3 mmol), 1-iodo-4-methoxybenzene **2a** (105.3 mg, 0.45 mmol), 1-fluoro-4-iodobenzene **2e** (99.9 mg, 0.45

mmol), $Pd(OAc)_2$ (6.7 mg, 10 mol%), $Cu(OAc)_2$ (65.4 mg, 0.36 mmol), Ag_3PO_4 (37.7 mg, 0.09 mmol), in *p*-xylene (1.5 mL) and DMF (1.5 mL) was charged in a glass sealed-tube and stirred at 130 °C (oil bath) for 16 h. Upon completion of the reaction, saturated brine (15 mL) were added to the mixture, then the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 70:1 to 30:1) to supply the desired product **3d** (28.3 mg, 23%) and **4e** (52.7 mg, 48%).

General Procedure for Deuterium Labelling Experiments. A mixture of substrate **1d** (55.8 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol%), $Cu(OAc)_2$ (43.6 mg, 0.24 mmol), Ag_3PO_4 (25.1 mg, 0.06 mmol), in *p*-xylene (1.0 mL), DMF (1.0 mL) and AcOD (1.0 mL) was charged in a glass sealed-tube and stirred at 130 °C (oil bath) for 1.5 h. After the reaction, saturated brine (15 mL) was added to the mixture, then the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 50:1 to 30:1) to supply the product H/D-**1d** (49.7 mg, 89%). The ^{1}H NMR of H/D-**1d** was ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.58 (s, 1H), 8.18−8.14 (m, 1H), 7.86 (s, 1H), 7.81 (d J = 3.2 Hz, 1H), 7.18 (q, J = 9.6 Hz, 1H), 6.55 (t, J = 2.4 Hz, 0.82H), 2.24−2.17 (m, 1H), 1.67−1.60 (m, 1H), 1.48−1.41 (m, 1H), 1.13 (d, J = 6.8 Hz, 2.16H), 0.84 (t, J = 7.2 Hz, 3H).

The preparation of [D_3]-1d. Under the atmosphere of N_2, to a stirred solution of lithium diisopropylamide (LDA) (20 mL, 2.0 M/L in THF) cooled at -15 °C (ice salt bath) was added dropwise butyric acid (0.80 g, 9.0 mmol). After 30 min, 1,3-dimethylpropyleneurea (DMPU) (1.15 g, 9.0 mmol) was added drop by drop. Then, the mixture was stirred at room temperture for 1 h and cooled again at -15 °C, CD_3I (2.84 g, 20 mmol) in 10 mL of anhydrous THF was added dropwise. Then, the reaction mixture was raised to room temperature and stirred for 3 h. Finally, the reaction was neutralized by ice cold 20% H_2SO_4. The aqueous layer was extracted with ethyl acetate (15 mL × 3). The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford 2-[$^2H_3$]methylbutyric acid (0.71 g, 75%).[25] The following steps are same as those for the substrates. [D_3]-**1d** was obtained in 40% yield (0.56 g). The ^{1}H NMR of [D_3]-**1d** was ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.57 (s, 1H), 8.18−8.14 (m, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.81 (dd, J_1 = 4.0 Hz, J_2 = 2.4 Hz, 1H), 7.19 (q, J = 9.2 Hz, 1H), 6.56 (t, J = 2.4 Hz, 1H), 2.20 (t, J = 6.8 Hz, 1H), 1.67−1.59 (m, 1H), 1.48−1.41 (m, 1H), 0.84 (t, J = 7.6 Hz, 3H).

A mixture of substrate [D_3]-**1d** (28.2 mg, 0.1 mmol), 1d (27.9 mg, 0.1 mmol), 4-iodoanisole (140.4 mg, 0.6 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol%), $Cu(OAc)_2$ (43.6 mg, 0.24 mmol), Ag_3PO_4 (25.1 mg, 0.06 mmol), in *p*-xylene (1.0 mL) and DMF (1.0 mL) was charged in a glass sealed-tube and stirred at 130 °C (oil bath) for 1.5 h. Upon completion of the reaction, saturated brine (15 mL) was added to the mixture, then the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined organic layer was dried over anhydrous $MgSO_4$. Finally, the solution was concentrated *in vacuo* to provide a crude product, which was further purified *via* a column chromatography on silica gel (eluents: petroleum ether/ethyl acetate = 70:1 to 30:1) to supply the product **3d** and [D_2]-**3d** (14.9 mg, 19%). The ^{1}H NMR of **3d** and [D_2]-**3d** was ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.40 (s, 1H), 8.06−8.02 (m, 1H), 7.79 (d, J = 1.6 Hz, 1H), 7.70 (dd, J_1 = 3.6 Hz, J_2 = 2.4 Hz, 1H), 7.16 (q, J = 9.6 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.70 (d, J = 8.8 Hz, 2H), 6.51 (t, J = 2.0 Hz, 1H), 3.75 (s, 1H), 2.84 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 0.79H), 2.67 (dd, J_1 = 13.6 Hz, J_2 = 6.0 Hz, 0.79H), 2.30−2.26 (m, 1H), 1.65−1.57 (m, 1H), 1.56−1.51 (m, 1H), 0.84 (t, J = 7.2 Hz, 3H). The ^{1}H NMR analysis showed that the ratio of **3d** to [D_2]-**3d** is 3.76.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Spectral data for all new compounds (PDF)

Crystallographic data for **4k** (CIF)

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Notes

The authors declare no competing financial interest.

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