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Very Important Publication

Ligand-Assisted Palladium(II)/(IV) Oxidation for sp^3 C–H Fluorination

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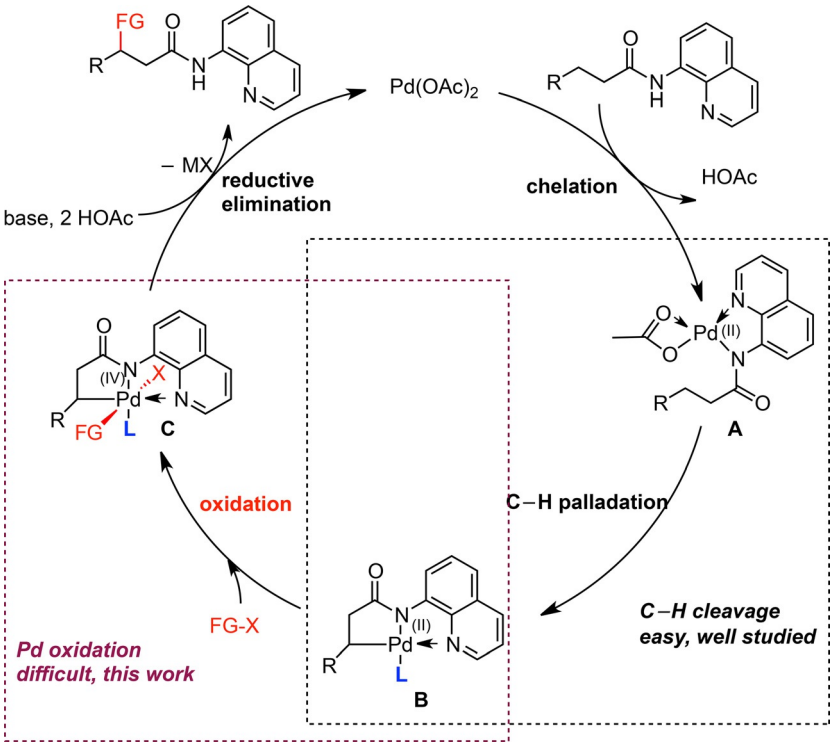
Abstract: The direct functionalization of inert sp^3 C–H bonds is limited to a few bond types. Although the activation of sp^3 C–H bonds can be accomplished under mild conditions using palladium catalysts, the subsequent functionalization is not trivial due to the high energy required to convert palladium(II) to palladium(IV). We have systematically studied the palladium oxidation using computation-guided experiments for reactions involving strong chelation control. We find that a mild external ligand could significantly accelerate the oxidation of palladium(II) to palladium(IV) for strong bidentate directing groups. The acceleration is believed to be a result of ligand stabilization of both the palladium(II) and palladium(IV) intermediates.

Keywords: C–H activation; directing group; fluorination; oxidation; palladium

Introduction

Direct inert sp^3 C–H bond functionalization is arguably one of the most effective methods to chemically modify hydrocarbon feedstocks.[1] Besides reactivity-dictated radical reactions, the use of a directing group (DG) is essential for selective C–H bond cleavage and subsequent functionalization. So far, there are two types of general DGs specifically designed to target inert sp^3 C–H bonds: weak coordinating DGs developed by Yu[2] and strong chelating DGs pioneered by Daugulis.[3] The common perception is that single point, weakly coordinating DGs require an external ligand to assist the key C–H metallation step,[4] while strong chelating DGs do not.[5] Yu and co-workers have shown that amino acid and pyridine ligands can drastically lower the activation barrier of the C–H cleavage step for weak DGs.[6] In sharp contrast, the Daugulis-type strong DGs are primarily used in the absence of a ligand.[7] So far, mechanistic studies of these reactions have primarily been focused on the C–H bond cleavage step of the Pd(II)–Pd(IV)–Pd(II) cycle,[8] which is the most common catalysis pathway. The oxidation of Pd(II) to Pd(IV) is often assumed to be fast and inconsequential. However, isotope experiments show that the C–H metallation step is often not the rate-limiting step for palladium-catalyzed reactions using a strong bidentate DG.[8c,9] In fact, the C–H palladation step could occur at room temperature without an external ligand for these DGs.[5a,10] Considering the reductive elimination is generally fast for a Pd(IV) species,[11] the oxidation of Pd(II) to Pd(IV) becomes particularly important for this type of sp^3 C–H functionalization reactions (Scheme 1).[12] So far, very few studies have been concerned with this part of the catalytic cycle from both experimental and theoretical standpoints.[6f,13] Herein, we report our mechanistic and computational findings of a drastic ligand effect on the oxidation of Pd for strong chelating group-directed sp^3 C–H fluorination reactions.

Scheme 1 shows the common mechanistic cycle for β-functionalization of aliphatic amides bearing a strong bidentate DG. Generally, fast chelation of the substrate to $Pd(OAc)_2$ is followed by a facile C–H palladation *via* the concerted metallation deprotonation (CMD) mechanism to give the key palladium bridged [5,5] metallacycle **B**.[5a,7f] The effects of DG and carboxylic anion have been extensively investigat-



Scheme 1. Catalytic cycle of sp^3 C–H functionalization reactions involving a strong chelating DG.

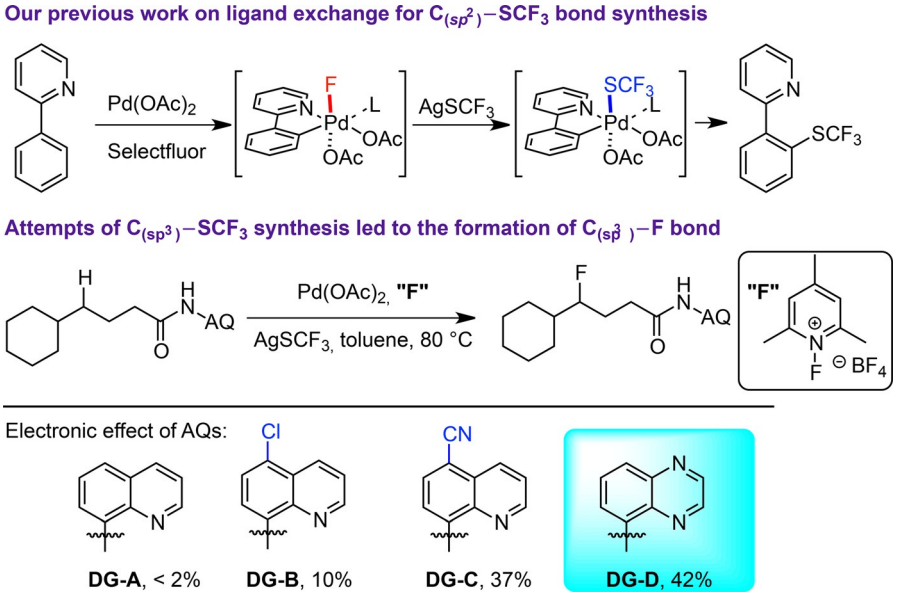
ed for the formation of this intermediate.[5a,c,14] The subsequent Pd(II) to Pd(IV) oxidation (Scheme 1, **B** to **C**), on the other hand, has been largely overlooked. Due to the high energy of Pd(IV), the oxidation of Pd is not easy. Often, experimentalists screen oxidants based on their redox potential. As a result, types of functionalization are quite limited.[7] A major part of the literature is concentrated on arylation, alkylation and oxygenation, etc. Many other seemingly viable bond formations have not been accomplished due to the problematic Pd oxidation step. In this work, we report our mechanistic studies of the effects of DG on this oxidation step that led to identification of quinoxaline as an external ligand to assist C–H fluorination reactions.

Results and Discussion

We recently published a ligand exchange strategy for C(sp^2)–SCF_3 bond synthesis by swopping a fluoride off a Pd(IV) center with a SCF_3 anion.[15] In this process, Selectfluor was used as a standalone oxidant. We wondered whether this ligand exchange strategy could be exploited for inert sp^3 C–H bond functionalization (Scheme 2). Interestingly, although the β-trifluoromethylthiolated product could not be obtained, the corresponding β-fluoro product was isolated in a small quantity using 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ("F") as the oxidant. This result indicated that the C–F reductive elimination might be faster than the ligand exchange in this scenario. When we removed $AgSCF_3$ from the reaction, the fluorination product was still observed. During this study, we found a very interesting correlation of yield and the electronics of the directing group. While DG-A resulted in only a trace amount of the fluorinated product, yield was significantly improved with substrates bearing a less electron-donating heterocycle as DG. The reaction using 8-aminoquinoxaline DG-D afforded the desired product in 42% yield.

We were intrigued by this substantial yield improvement using 8-aminoquinoxaline as DG. The key question is which step of the catalytic cycle is accelerated. In order to answer this question, we carried out a series of mechanistic studies. Firstly, a density functional theory (DFT) study on the C–H insertion step was conducted for both 8-aminoquinoline and 8-aminoquinoxaline phenylpropanamides (Figure 1).[16]

Although the more electron-donating 8-aminoquinoline DG provides better stabilization than 8-aminoquinoxaline for each species during the C–H cleavage process, the calculated free energy barriers for C–H palladation are 19.9 and 18.5 kcal mol^{-1} for 8-aminoquinoline (**Q1-TS1**) and 8-aminoquinoxaline (**Q2-TS1**) substrates, respectively. The slightly higher barrier for 8-aminoquinoline substrate, is attributed to the exergonic intermediate **Q1-Int1**. The activation free



Scheme 2. Initial investigations of the effect of DG on C–H fluorination reactions.

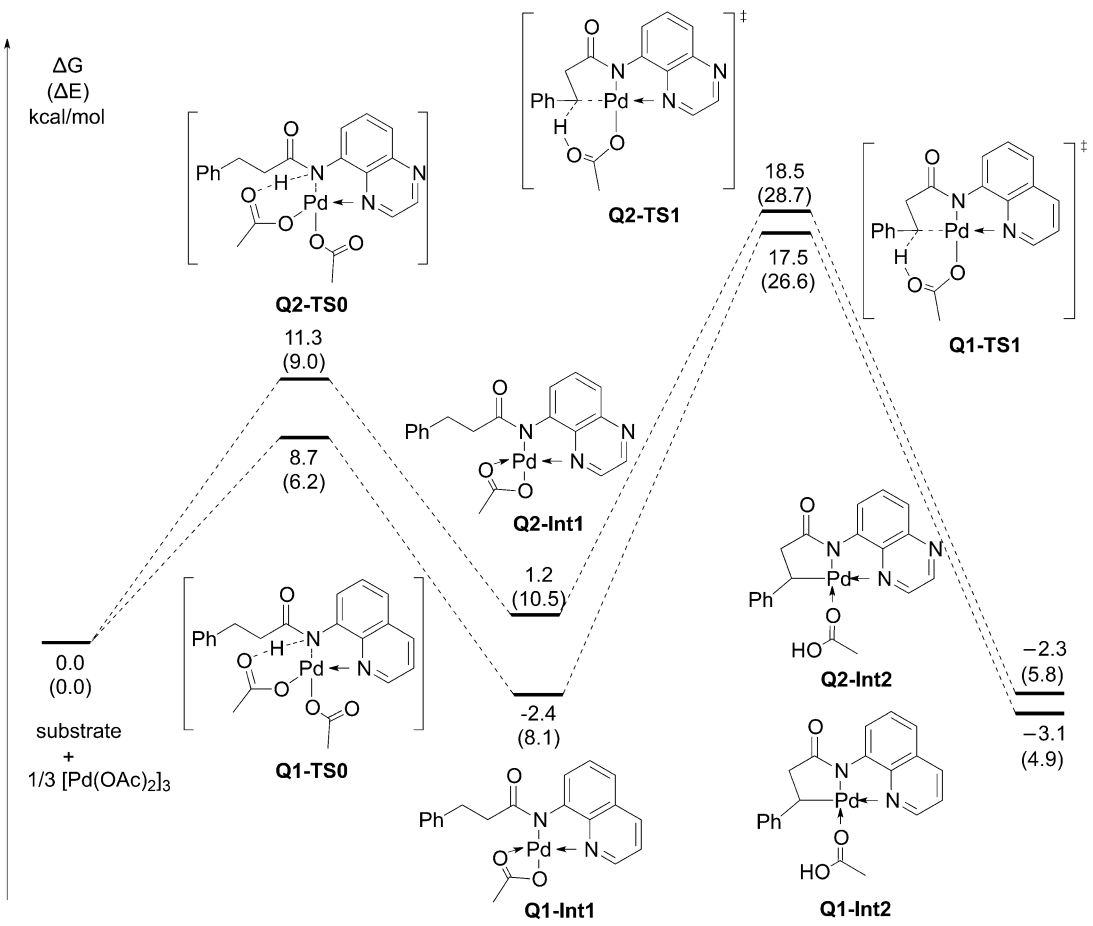
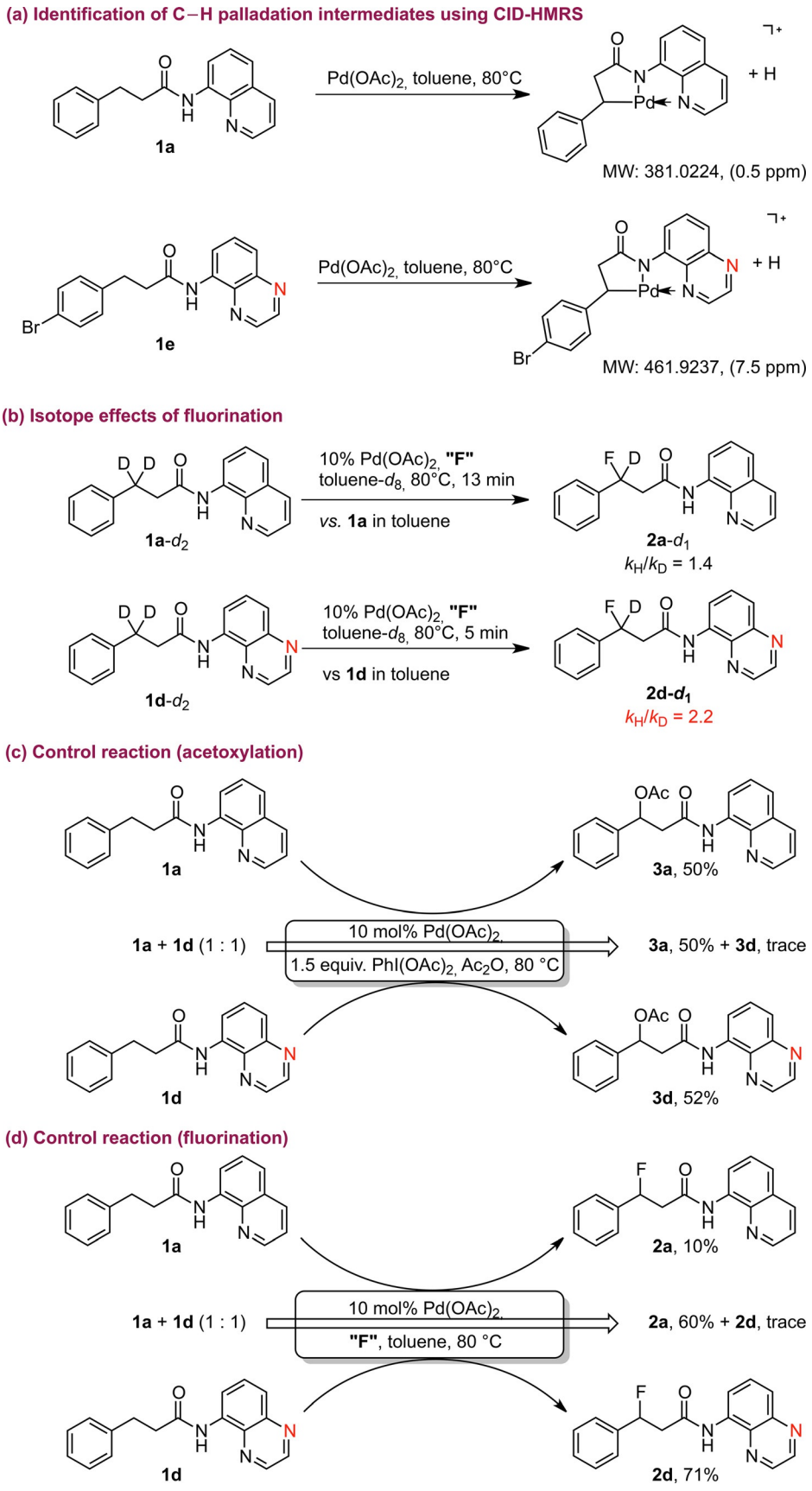


Figure 1. Free energy profile for the C–H insertion step calculated with M06.[16]

energy difference of the C–H activation is very small (1.4 kcal mol^{-1}). Therefore, the improved efficiency likely originates from later steps in the catalytic cycle.

Experimentally, the C–H palladation intermediate was identified for both substrates **1a** and **1e** with a high resolution mass spectrometer (HR-MS) by



Scheme 3. Mechanistic experiments for the role of DG.

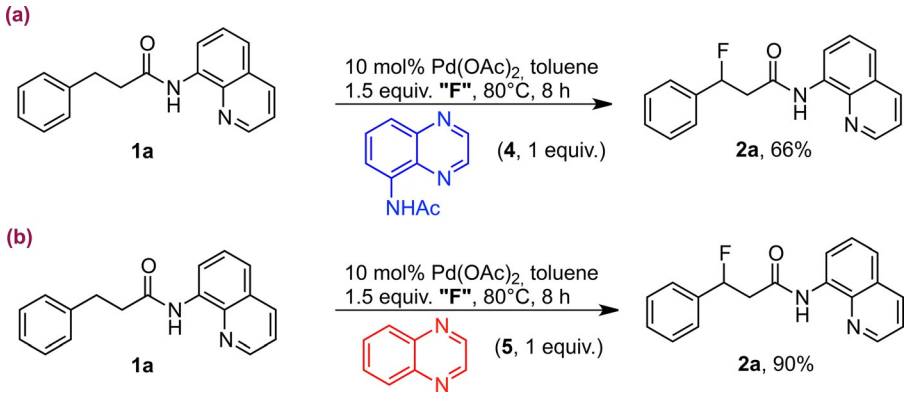
using collision-induced dissociation and ion-mobility techniques (Scheme 3a, see the Supporting Information for spectra),[17] suggesting that the C–H activation could occur smoothly using either DG under the reaction conditions (Scheme 3a). Secondly, we determined the kinetic isotope effect for substrates **1a** and **1d** (Scheme 3b). Interestingly, a smaller KIE value was obtained for **1a** compared to **1d** (1.4 *vs.* 2.2). This result indicates the C–H cleavage is the rate-limiting step for **1d** (KIE = 2.2), but may not for **1a** (KIE = 1.4). Based on these data, we proposed that Pd oxidation using *N*-fluoropyridinium salts is difficult (rate-limiting) for **1a** and the subsequent fluorination is suppressed. On the other hand, the analogue oxidation step is somehow accelerated for **1d**, making the C–H insertion step rate-limiting for this substrate. However, this rather small KIE difference is not definitive, theoretical calculations were performed and verified the shift of the rate-limiting step from **1a** to **1d** (*vide infra*).

In order to understand the reason behind this "likely" shift of rate-limiting step, we performed further experiments. Both **1a** and **1d** underwent smooth β-acetoxylation using a literature protocol,[7f] again suggesting that the C–H activation step is not a problem for either substrate. However, when a 1:1 mixture of **1a** and **1d** was subjected to the same reaction conditions, the acetoxylation occurred to **1a** exclusively, not **1d** (Scheme 3c). We believe that 8-aminoquinoline is a stronger chelator for Pd than 8-aminoquinoxaline, therefore attracting all metal catalyst towards the reaction of **1a**.

However, the situation becomes complicated for the β-fluorination reaction. Under the same conditions, **1a** reacted in very low conversion (10%), while **1d** afforded the fluorinated product **2d** in 71% yield. When a 1:1 mixture of **1a** and **1d** was used, it was very surprising that **1a** was fluorinated almost exclusively, although it did not work by itself (Scheme 3d). On the other hand, the fluorination of **1d** was suppressed in the presence of **1a**! This unexpected behavior using the substrate mixture has only one plausible explanation: **1d** acts as a promotor/ligand for the fluorination of **1a**, while **1a** acts as an inhibitor for the reaction of **1d**.

We suspected that the role of **1d** in promoting the reaction of **1a** as being a ligand to accelerate Pd oxidation. To test this idea, we replaced **1d** with *N*-(quinoxalin-5-yl)acetamide **4**, a close analogue without β-hydrogens. As expected, **4** promoted the β-fluorination of **1a** with similar efficiency as **1d** (Scheme 4a), confirming that both **1d** and **4** can serve as standalone ligands for this reaction. Considering that the Pd intermediates have only one vacant site left, we wondered whether the *N*,*N*-chelation control is required for this ligand. We were very pleased to find that the fluorination occurs in high yield when simple quinoxaline **5** was used! Product **2a** was isolated in 90% yield (Scheme 4b).

To understand the function of ligand **5**, we carried out theoretical calculations for the Pd oxidation and subsequent steps. Ligand **5** does not alter the potential energy surface for the C–H cleavage step, as the Pd center is fully coordinated during the CMD process (Figure 2, **Q1-Int1**, **Q1-TS1** and **Q1-Int2**). In the absence of quinoxaline (**5**), comparable relative free energies were calculated for **Q1-TS1** and **Q1-TS2-HOAc**. Although the ΔG for **Q1-TS1** is slighly higher (4.3 kcal mol^{-1}) than that for **Q1-TS2-HOAc**, both steps are mechanistically very different and computational errors would be too significant to draw a definitive conclusion on the rate-determining step. In fact, a small KIE (1.4, Scheme 3b) suggests that the C–H cleavage step might not be rate-limiting. In contrast, we found that **5** drastically lowers the energy of **Q1-Int2-Q** by about 10.0 kcal mol^{-1}, compared to the "ligand-free" complex **Q1-Int2**. In addition, the relative free energy of transition state for Pd oxidation **Q1-TS2-Q** and Pd(IV) intermediate **Q1-Int3-Q** is also stabilized significantly. The activation free energy for the oxidation of Pd(II) is 14.1 kcal mol^{-1} with **5** *vs.* 16.4 kcal mol^{-1} without **5**. Comparing the C–H cleav-



Scheme 4. Discovery of ligands that promote β-fluorination of C–H bonds.

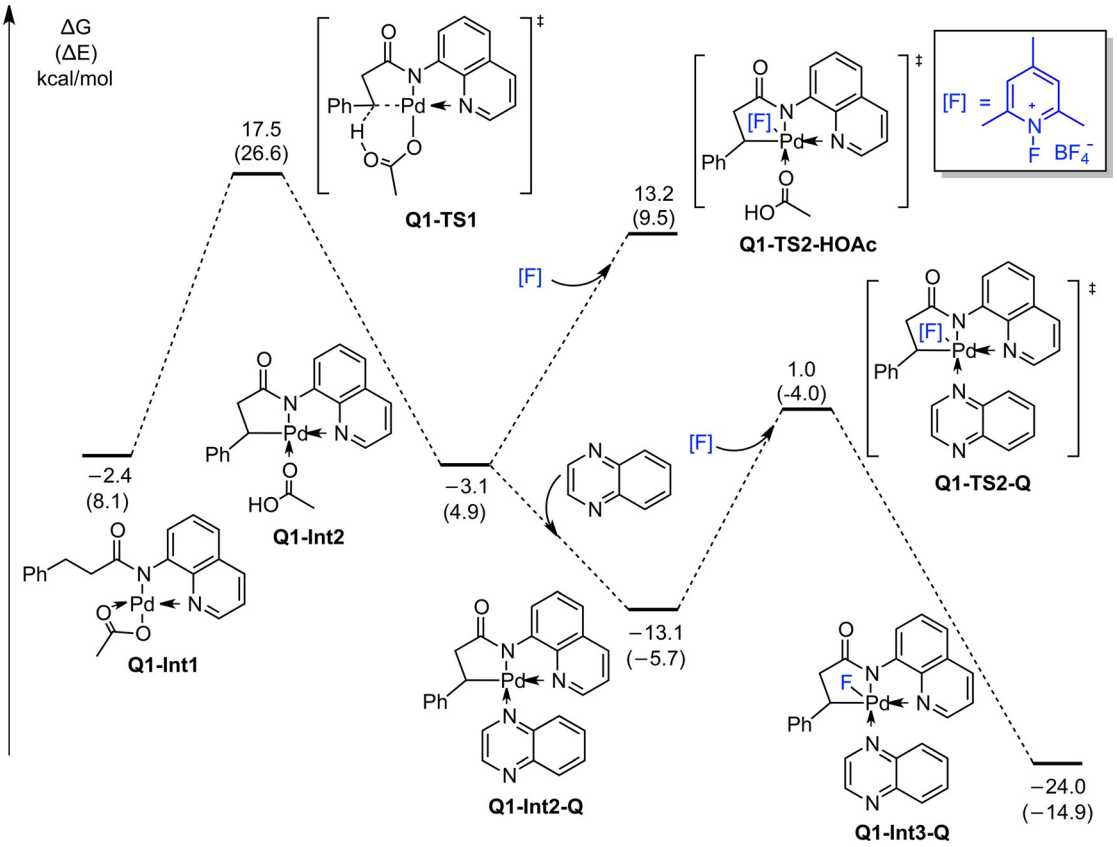
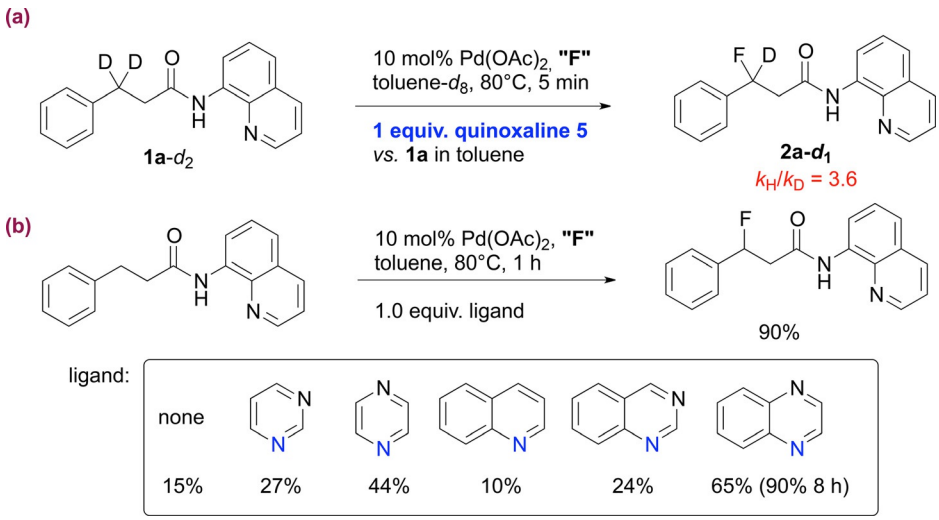


Figure 2. Free energy profile for for the oxidation of Pd(II) intermediates in the absence and presence of quinoxaline.

age and oxidation steps, **Q1-TS2-Q** is more stable than **Q1-TS1** by 16.5 kcal mol^{-1}. As a result, it is safe to conclude that the step of C–H bond activation becomes the rate-determining step. Therefore, the KIE of the fluorination of **1a** would become significant when **5** is used as ligand.

As predicted, we found a large primary isotope effect for the reaction of **1a** in the presence of **5** (Scheme 5a), confirming that the C–H cleavage step becomes rate-limiting in the presence of ligand **5**. In the absence of this important ligand, the oxidation of Pd is rate-limiting, and is very slow, resulting in very

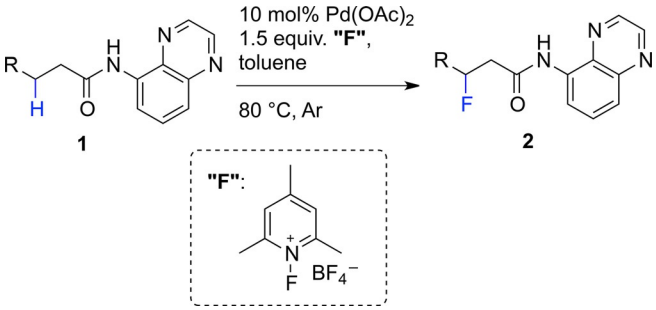


Scheme 5. Isotope and ligand effects.

poor yield (Scheme 3b). These data clearly show that quinoxaline shifts the rate-limiting step by lowering the activation energy of the oxidation step considerably. In addition to quinoxazline, other nitrogen-containing aryl ligands were also examined (Scheme 5b). Quinoxaline clearly stands out as the best promoter for the sp^3 C–H fluorination. Very interestingly, quinoline failed to improve this reaction. We suspect that the quinoline nitrogen is too basic and interferes by remaining on the palladium throughout the reaction.

The requirement of external ligand **5** to assist Pd oxidation is in agreement with very recent reports of β-fluorination where a stoichiometric amount of Ag salts was required to facilitate this rather difficult oxidation process.[4e,10,18] The use of either quinoxaline as ligand or 8-aminoquinoxaline as DG shows a clear advantage by eliminating precious metal oxidants. In the case of using 8-aminoquinoxaline as DG, the substrate itself serves as the ligand to assist the Pd oxidation and no external ligand is required anymore. The reaction scope was briefly examined for the 8-aminoquinoxaline-directed fluorination (Table 1). The reaction is general for various arylpropanamides. Noticeably decreased yield was observed for simple aliphatic amides. The use of quinoxaline as ligand shows a similar substrate scope for the 8-aminoquinoline substrates.

Table 1. Substrate scope for 8-aminoquinoxaline-directed fluorination.[a]



Entry	R, Product	Yield [%]	Entry	R, Product	Yield [%]
1	Ph, **2d**	71	9	*m*-Cl-C_6H_4, **2l**	53
2	*p*-Br-C_6H_4, **2e**	80	10	*m*-Br-C_6H_4, **2m**	87
3	*p*-F-C_6H_4, **2f**	90	11	*o*-Cl-C_6H_4, **2n**	69
4	*p*-Cl-C_6H_4, **2g**	71	12	*o*-Me-C_6H_4, **2o**	85
5	*p*-CF_3-C_6H_4, **2h**	68	13	2-naphthyl, **2p**	91
6	*p*-CN-$C_6H_4H_4$, **2i**	48	14[b]	$CyCH_2$, **2q**	58
7	*p*-NO_2-C_6H_4, **2j**	56	15[b]	Et, **2r**	45
8	*p*-Me-C_6H_4, **2k**	76	16[b]	*n*-Bu, **2s**	56

[a] The reactions were performed using **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (**"F"**, 1.5 equiv.) in toluene (3 mL) for 4–8 h at 80 °C under an argon atmosphere. Isolated yields are reported.

[b] 20 mol% $Pd(OAc)_2$ was used and the reaction was carried out at 110 °C.

Conclusions

In summary, we have identified a significant difference for sp^3 C–H fluorination reactions using different chelating directing groups. Computational and experimental investigation concludes a change of rate-limiting step using 8-aminoquinoline *vs.* 8-aminoquinoxaline as DG, by affecting the key Pd(II) to Pd(IV) oxidation step. This finding led to the discovery of a simple ligand capable of lowering the activation energy for the oxidation of Pd. This intriguing mechanistic journey provides new clues into oxidative C–H functionalization reactions. We expect these results will stimulate the development of new C–H functionalization reactions.

Experimental Section

General Methods and Materials

All reactions were carried out under an argon atmosphere (balloon) with dry solvents under anhydrous conditions. $Pd(OAc)_2$ was purchased from Sinocompound Technology Co., Ltd. 1-Fluoro-2,4,6-trimethylpyridin-1-ium tetrafluoroborate was purchased from TCI. All other reagents were purchased and used without further purification unless specified otherwise. Solvents for chromatography were of technical grade and distilled prior to use. Flash chromatography was performed using 200–300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance (254 nm). ^{1}H NMR and ^{13}C NMR data were recorded on Bruker 400 M nuclear resonance spectrometers unless otherwise specified, respectively. Chemical shifts (δ) in ppm are reported relative to the residual signals of chloroform (^{1}H 7.27 ppm or ^{13}C 77.16 ppm). Multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); and coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded with total proton decoupling. HR-MS (ESI) analysis was performed by The Analytical Instrumentation Center at Peking University, Shenzhen Graduate School and HR-MS data are reported with ion mass/charge (*m*/*z*) ratios as values in atomic mass units.

General Procedure for Starting Material (1a–1s) Synthesis

To an oven-dried flask, the acid (1.0 equiv.), DMF (1 drop) and DCM were added under Ar. Oxalyl chloride (1.5 equiv.) was added dropwise under ice bath cooling. The mixture was stirred for 3 h at room temperature and the solvent was removed under vacuum. The resulting acid chloride was used immediately without further purification.[19]

To a flask with the acid chloride and THF, a THF solvent of quinoxalin-5-amine[20] and NEt_3 was added dropwise under ice bath cooling. Then the mixture was stirred overnight at room temperature. Then the solvent was removed

and the residue was dissolved in DCM and washed with aqueous $NaHCO_3$ (3 times), 1 N HCl and brine. The organic phase was dried with Na_2SO_4, concentrated and purified by flash column to give the desired product.

3-Phenyl-*N*-(quinolin-8-yl)propanamide (1a):[21] white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.81 (s, 1H), 8.90–8.70 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63–7.48 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.31 (d, *J* = 4.4 Hz, 4H), 7.26–7.17 (m, 1H), 3.18 (t, *J* = 7.8 Hz, 2H), 2.92 (m, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.90, 148.23, 140.91, 138.44, 136.50, 134.56, 128.69, 128.54, 128.06, 127.56, 126.38, 121.72, 121.60, 116.64, 39.87, 31.62; HR-MS (ESI): *m/z* = 299.1155, calcd. for $C_{18}H_{16}N_2NaO$ ([M+Na]$^+$): 299.1160.

3-Phenyl-*N*-(quinoxalin-5-yl)propanamide (1d): white solid; ^{1}H NMR (300 MHz, chloroform-*d*): δ = 9.46 (s, 1H), 8.91 (d, *J* = 1.9 Hz, 1H), 8.83 (dd, *J* = 6.1, 2.9 Hz, 1H), 8.71 (d, *J* = 1.8 Hz, 1H), 7.86–7.72 (m, 2H), 7.30 (d, *J* = 4.4 Hz, 4H), 7.22 (m, 1H), 3.15 (t, *J* = 7.8 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, chloroform-*d*): δ = 170.91, 145.49, 143.00, 142.43, 140.68, 134.61, 133.30, 131.33, 128.75, 128.53, 126.48, 123.18, 117.22, 39.81, 31.53; HR-MS (ESI): *m/z* = 300.1108, calcd. for $C_{17}H_{15}N_3NaO$ ([M+Na]+): 300.1113.

3-(4-Bromophenyl)-*N*-(quinoxalin-5-yl)propanamide (1e): white solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.40 (s, 1H), 8.90 (d, *J* = 1.8 Hz, 1H), 8.79 (dd, *J* = 7.3, 1.8 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H), 7.83–7.71 (m, 2H), 7.46–7.35 (m, 2H), 7.21–7.11 (m, 2H), 3.09 (t, *J* = 7.6 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (126 MHz, chloroform-*d*): δ = 170.45, 145.51, 142.97, 142.44, 139.64, 134.46, 133.22, 131.78, 131.24, 130.32, 123.27, 120.26, 117.21, 39.46, 30.86; HR-MS (ESI): *m/z* = 378.0210, calcd. for $C_{17}H_{14}BrN_3NaO$ ([M+Na]$^+$): 378.0218.

3-(4-Fluorophenyl)-*N*-(quinoxalin-5-yl)propanamide (1f): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.42 (s, 1H), 8.90 (d, *J* = 1.8 Hz, 1H), 8.81 (dd, *J* = 6.9, 2.1 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H), 7.86–7.71 (m, 2H), 7.32–7.18 (m, 2H), 6.98 (t, *J* = 8.5 Hz, 2H), 3.12 (t, *J* = 7.6 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.64, 162.88, 160.45, 145.52, 143.01, 142.42, 136.30, 134.53, 133.26, 131.28, 130.00, 129.93, 123.26, 117.22, 115.60, 115.39, 39.85, 30.69; ^{19}F NMR (376 MHz, chloroform-*d*): δ = −116.92 (s, 1F); HR-MS (ESI): *m/z* = 318.1014, calcd. for $C_{17}H_{14}FN_3NaO$ ([M+Na]$^+$): 318.1019.

3-(4-Chlorophenyl)-*N*-(quinoxalin-5-yl)propanamide (1g): yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.41 (s, 1H), 8.90 (d, *J* = 1.9 Hz, 1H), 8.80 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.69 (d, *J* = 1.9 Hz, 1H), 7.84–7.74 (m, 2H), 7.29–7.19 (m, 4H), 3.11 (t, *J* = 7.6 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.49, 145.52, 142.99, 142.44, 139.13, 134.48, 133.23, 132.23, 131.26, 129.92, 128.83, 123.28, 117.21, 39.56, 30.81; HR-MS (ESI): *m/z* = 334.0716, calcd. for $C_{17}H_{14}ClN_3NaO$ ([M+Na]$^+$): 334.0723.

***N*-(Quinoxalin-5-yl)-3-[4-(trifluoromethyl)phenyl]propanamide (1h)**: white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.41 (s, 1H), 8.88 (d, *J* = 1.8 Hz, 1H), 8.79 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.66 (d, *J* = 1.8 Hz, 1H), 7.84–7.68 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 3.18 (t, *J* = 7.6 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.23, 145.47, 144.81, 142.90, 142.41, 134.38, 133.17, 131.19, 128.87, 128.61, 125.65, 125.61, 125.57, 125.54, 123.27, 117.19, 39.11, 31.12; HR-MS (ESI): *m/z* = 368.0981, calcd. for $C_{18}H_{14}F_3N_3NaO$ ([M+Na]$^+$): 368.0987

3-(4-Cyanophenyl)-*N*-(quinoxalin-5-yl)propanamide (1i): yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.41 (s, 1H), 8.87 (d, *J* = 1.9 Hz, 1H), 8.75 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.66 (d, *J* = 1.9 Hz, 1H), 7.83–7.66 (m, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.17 (t, *J* = 7.5 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 169.88, 146.30, 145.45, 142.80, 142.40, 134.23, 133.07, 132.40, 131.11, 129.33, 123.26, 118.94, 117.14, 110.24, 38.63, 31.23; HR-MS (ESI): *m/z* = 325.1067, calcd. for $C_{18}H_{14}N_4ONa$ ([M+Na]$^+$): 325.1065.

3-(4-Nitrophenyl)-*N*-(quinoxalin-5-yl)propanamide (1j): yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.44 (s, 1H), 8.91 (d, *J* = 1.8 Hz, 1H), 8.79 (dd, *J* = 7.3, 1.8 Hz, 1H), 8.70 (d, *J* = 1.8 Hz, 1H), 8.22–8.09 (m, 2H), 7.86–7.73 (m, 2H), 7.53–7.41 (m, 2H), 3.25 (t, *J* = 7.5 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, chloroform-*d*): δ = 169.83, 148.55, 146.82, 145.60, 143.01, 142.49, 134.31, 133.21, 131.26, 129.49, 123.99, 123.49, 117.30, 38.74, 31.10; HR-MS (ESI): *m/z* = 323.1147, calcd. for $C_{17}H_{15}N_4O_3$ ([M+H]$^+$): 323.1144.

***N*-(Quinoxalin-5-yl)-3-(*p*-tolyl)propanamide (1k):** white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.45 (s, 1H), 8.89 (d, *J* = 1.9 Hz, 1H), 8.82 (dd, *J* = 6.8, 2.3 Hz, 1H), 8.69 (d, *J* = 1.8 Hz, 1H), 7.86–7.70 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.87 (t, *J* = 7.7 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.97, 145.41, 142.93, 142.36, 137.52, 135.90, 134.59, 133.24, 131.26, 129.36, 128.34, 123.09, 117.16, 39.88, 31.07, 21.11; HR-MS (ESI): *m/z* = 314.1262, calcd. for $C_{18}H_{17}N_3ONa$ ([M+Na]$^+$): 314.1269.

3-(3-Chlorophenyl)-*N*-(Quinoxalin-5-yl)propanamide (1l): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.44 (s, 1H), 8.91 (d, *J* = 1.8 Hz, 1H), 8.81 (dd, *J* = 7.0, 2.1 Hz, 1H), 8.71 (d, *J* = 1.8 Hz, 1H), 7.85–7.73 (m, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.25–7.15 (m, 3H), 3.12 (t, *J* = 7.7 Hz, 2H), 2.88 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.41, 145.52, 142.99, 142.70, 142.47, 134.48, 134.46, 133.27, 131.29, 130.00, 128.68, 126.80, 126.69, 123.28, 117.25, 39.35, 31.08; HR-MS (ESI): *m/z* = 334.0716, calcd. for $C_{17}H_{14}ClN_3NaO$ ([M+Na]$^+$): 334.0723.

3-(3-Bromophenyl)-*N*-(quinoxalin-5-yl)propanamide (1m): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.43 (s, 1H), 8.91 (d, *J* = 1.9 Hz, 1H), 8.80 (dd, *J* = 6.9, 2.0 Hz, 1H), 8.71 (d, *J* = 1.9 Hz, 1H), 7.85–7.73 (m, 2H), 7.45 (t, *J* = 1.8 Hz, 1H), 7.33 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 3.11 (t, *J* = 7.7 Hz, 2H), 2.88 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.37, 145.52, 143.00, 142.46, 134.47, 133.26, 131.58, 131.27, 130.29, 129.62, 127.27, 123.28, 122.74, 117.24, 39.36, 31.05; HR-MS (ESI): *m/z* = 378.0214, calcd. for $C_{17}H_{14}BrN_3NaO$ ([M+Na]$^+$): 378.0218.

3-(2-Chlorophenyl)-*N*-(quinoxalin-5-yl)propanamide (1n): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.47 (s, 1H), 8.91 (d, *J* = 1.8 Hz, 1H), 8.83 (dd, *J* = 6.5, 2.5 Hz, 1H), 8.72 (d, *J* = 1.8 Hz, 1H), 7.83–7.73 (m, 2H), 7.40–7.31 (m, 2H), 7.24–7.13 (m, 2H), 3.28 (t, *J* = 7.7 Hz, 2H), 2.93 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.64, 145.52, 143.01, 142.47, 138.27, 134.61, 134.08, 133.30, 131.31, 130.85, 129.75, 128.07, 127.18, 123.21, 117.20, 37.76, 29.54; HR-MS (ESI): *m/z* = 334.0718, calcd. for $C_{17}H_{14}ClN_3NaO$ ([M+Na]$^+$): 334.0723.

***N*-(Quinoxalin-5-yl)-3-(*o*-tolyl)propanamide (1o):** white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.47 (s, 1H), 8.90 (d, J = 1.8 Hz, 1H), 8.84 (dd, J = 6.6, 2.4 Hz, 1H), 8.70 (d, J = 1.8 Hz, 1H), 7.84–7.72 (m, 2H), 7.25–7.20 (m, 1H), 7.15 (dtd, J = 8.6, 5.9, 2.7 Hz, 3H), 3.16 (t, J = 7.7 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 171.02, 145.47, 142.96, 142.41, 138.77, 136.12, 134.59, 133.26, 131.29, 130.49, 128.68, 126.58, 126.33, 123.15, 117.15, 38.42, 28.76, 19.48; HR-MS (ESI): m/z = 314.1265, calcd. for $C_{18}H_{17}N_3ONa$ ([M+Na]$^+$): 314.1269.

3-(Naphthalen-2-yl)-*N*-(quinoxalin-5-yl)propanamide (1p): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.42 (s, 1H), 8.91–8.76 (m, 2H), 8.52 (d, J = 1.8 Hz, 1H), 7.85–7.67 (m, 6H), 7.51–7.38 (m, 3H), 3.31 (t, J = 7.6 Hz, 2H), 2.98 (t, J = 7.7 Hz, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 170.88, 145.39, 142.89, 142.32, 138.09, 134.54, 133.76, 133.21, 132.32, 131.23, 128.40, 127.72, 127.60, 127.10, 126.79, 126.16, 125.52, 123.14, 117.20, 39.71, 31.72; HR-MS (ESI): m/z = 350.1261, calcd. for $C_{21}H_{17}N_3ONa$ ([M+Na]$^+$): 350.1269.

4-Cyclohexyl-*N*-(quinoxalin-5-yl)butanamide (1q): yellow solid; ^{1}H NMR (300 MHz, chloroform-*d*): δ = 9.49 (s, 1H), 8.92 (d, J = 1.9 Hz, 1H), 8.83 (dd, J = 6.0, 3.1 Hz, 1H), 8.74 (d, J = 1.9 Hz, 1H), 7.85–7.71 (m, 2H), 2.54 (t, J = 7.6 Hz, 2H), 1.92–1.57 (m, 9H), 1.31 (m, 4H), 0.99–0.84 (m, 2H); ^{13}C NMR (75 MHz, chloroform-*d*): δ = 172.07, 145.47, 143.02, 142.43, 134.76, 133.34, 131.36, 123.02, 117.14, 38.57, 37.61, 37.13, 33.40, 26.78, 26.48, 23.09; HR-MS (ESI): m/z = 320.1736, calcd. for $C_{18}H_{23}N_3NaO$ ([M+Na]$^+$): 320.1739.

***N*-(Quinoxalin-5-yl)pentanamide (1r):** yellow solid; ^{1}H NMR (300 MHz, chloroform-*d*): δ = 9.50 (s, 1H), 8.90 (dd, J = 10.8, 2.0 Hz, 1H), 8.83 (dd, J = 6.0, 3.1 Hz, 1H), 8.73 (dd, J = 10.9, 2.0 Hz, 1H), 7.84–7.70 (m, 2H), 2.65–2.46 (m, 2H), 1.89–1.71 (m, 2H), 1.57–1.34 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, chloroform-*d*): δ = 172.04, 145.48, 143.05, 142.44, 134.77, 133.34, 131.36, 123.04, 117.12, 38.05, 27.79, 22.54, 13.98; HR-MS (ESI): m/z = 252.1106, calcd. for $C_{13}H_{15}N_3NaO$ ([M+Na]$^+$): 252.1113.

***N*-(Quinoxalin-5-yl)heptanamide (1s):** yellow solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.49 (s, 1H), 8.91 (d, J = 1.8 Hz, 1H), 8.83 (dd, J = 6.9, 2.2 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.86–7.70 (m, 2H), 2.56 (t, J = 7.6 Hz, 2H), 1.82 (p, J = 7.6 Hz, 2H), 1.50–1.40 (m, 2H), 1.35 (tq, J = 6.2, 2.9 Hz, 4H), 0.90 (td, J = 5.8, 4.7, 2.1 Hz, 3H); ^{13}C NMR (126 MHz, chloroform-*d*): δ = 172.06, 145.44, 143.01, 142.44, 134.76, 133.35, 131.36, 123.01, 117.15, 38.31, 31.70, 29.07, 25.68, 22.64, 14.17; HR-MS (ESI): m/z = 280.1419, calcd. for $C_{15}H_{19}N_3NaO$ ([M+Na]$^+$): 280.1426.

2,2-D-3-Phenyl-*N*-(quinoxalin-5-yl)propanamide (1d-d_2): white solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.46 (s, 1H), 8.91 (d, J = 1.8 Hz, 1H), 8.83 (dd, J = 6.8, 2.3 Hz, 1H), 8.71 (d, J = 1.8 Hz, 1H), 7.83–7.74 (m, 2H), 7.34–7.28 (m, 4H), 7.26–7.18 (m, 1H), 2.88 (s, 2H); ^{13}C NMR (126 MHz, chloroform-*d*): δ = 170.92, 145.51, 143.04, 142.43, 134.64, 133.33, 131.33, 128.88, 128.76, 128.53, 126.49, 123.20, 117.23, 39.69, 29.85; HR-MS (ESI): m/z = 302.1239, calcd. for $C_{17}H_{13}D_2N_3NaO$ ([M+Na]$^+$): 302.1238.

General Procedure for C–H Fluorination

To a Schlenk tube were added SM (0.1 mmol), $Pd(OAc)_2$ (10 mol%), 1-fluoro-2,4,6-trimethylpyridin-1-ium tetrafluoroborate (1.5 equiv.) and toluene (3 mL) and the tube was degassed with argon 3 times. The mixture was stirred at 80 °C for 6 h and cooled to room temperature. Then the mixture was diluted with DCM, and filtered through a short pad of Celite. After concentration under vacuum, the crude reaction mixture was purified by silica gel flash chromatography.

3-Fluoro-3-phenyl-*N*-(quinolin-8-yl)propanamide (2a): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 10.00 (s, 1H), 8.81 (dt, J = 6.2, 1.7 Hz, 2H), 8.17 (dd, J = 8.2, 1.7 Hz, 1H), 7.61–7.50 (m, 2H), 7.50–7.31 (m, 6H), 6.20 (dd, J = 9.2, 3.6 Hz, 0.5H), 6.09 (dd, J = 9.1, 3.6 Hz, 0.5H), 3.27 (td, J = 15.2, 9.1 Hz, 1H), 3.04 (ddd, J = 34.1, 15.2, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 167.54, 167.51 (d, J = 3.0 Hz), 148.40, 139.20, 139.01 (d, J = 19.0 Hz), 138.47, 136.50, 134.37, 128.90, 128.84, 128.05, 127.49, 125.71, 125.64 (d, J = 7.0 Hz), 122.01, 121.81 (d, J = 20.0 Hz), 116.89, 92.19, 90.48 (d, J = 171.0 Hz), 46.46, 46.20 (d, J = 26.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −173.70 (s, 1F); HR-MS (ESI): m/z = 317.1058, calcd. for $C_{18}H_{15}N_2FNaO$ ([M+Na]$^+$): 317.1066.

3-Fluoro-3-phenyl-*N*-(quinoxalin-5-yl)propanamide (2d): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.70 (s, 1H), 8.92 (d, J = 1.9 Hz, 1H), 8.85 (dd, J = 7.4, 1.7 Hz, 1H), 8.75 (d, J = 1.9 Hz, 1H), 7.86–7.74 (m, 2H), 7.49–7.33 (m, 5H), 6.18 (dd, J = 9.1, 3.5 Hz, 0.5H), 6.06 (dd, J = 9.1, 3.5 Hz, 0.5H), 3.25 (td, J = 15.4, 9.1 Hz, 1H), 3.04 (ddd, J = 33.9, 15.3, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 167.58, 167.56 (d, J = 2.0 Hz), 145.59, 143.01, 142.61, 138.96, 138.77 (d, J = 19.0 Hz), 134.43, 133.38, 131.23, 128.99, 128.89, 125.64, 125.57 (d, J = 7.0 Hz), 123.62, 117.50, 92.14, 90.43 (d, J = 171 Hz), 46.43, 46.17 (d, J = 26.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −173.67 (s, 1F); HR-MS (ESI): m/z = 318.1014, calcd. for $C_{17}H_{14}N_3FNaO$ ([M+Na]$^+$): 318.1019.

3-(4-Bromophenyl)-3-fluoro-*N*-(quinoxalin-5-yl)propanamide (2e): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.65 (s, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.82 (dd, J = 7.5, 1.6 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.88–7.75 (m, 2H), 7.59–7.50 (m, 2H), 7.38–7.29 (m, 2H), 6.14 (dd, J = 8.7, 4.0 Hz, 0.5H), 6.02 (dd, J = 8.7, 4.0 Hz, 0.5H), 3.22 (td, J = 15.5, 8.7 Hz, 1H), 3.02 (ddd, J = 31.9, 15.2, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 167.14, 167.10 (d, J = 4.0 Hz), 145.63, 143.03, 142.64, 138.02, 137.82 (d, J = 20.0 Hz), 134.30, 133.34, 132.08, 131.82, 131.22, 127.36, 127.29 (d, J = 7.0 Hz), 123.75, 123.03, 117.54, 91.49, 89.77 (d, J = 172 Hz), 46.23, 45.97 (d, J = 26.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −174.67 (s, 1F); HR-MS (ESI): m/z = 396.0126, calcd. for $C_{17}H_{13}N_3FBrNaO$ ([M+Na]$^+$): 396.0124.

3-Fluoro-3-(4-fluorophenyl)-*N*-(quinoxalin-5-yl)propanamide (2f): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.67 (s, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.83 (dd, J = 7.5, 1.6 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.89–7.74 (m, 2H), 7.50–7.39 (m, 2H), 7.10 (t, J = 8.6 Hz, 2H), 6.16 (dd, J = 8.8, 3.9 Hz, 0.5H), 6.04 (dd, J = 8.8, 3.9 Hz, 0.5H), 3.25 (td, J = 15.3, 8.8 Hz, 1H), 3.02 (ddd, J = 32.2, 15.2, 3.9 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 167.30, 167.27 (d, J = 3.0 Hz), 145.62, 143.04, 142.62, 134.80, 134.59 (d, J = 21.0 Hz), 134.34, 133.35, 131.22, 127.71, 127.64, 127.62, 127.56, 123.71, 117.52, 116.01, 115.79, 91.55, 89.83 (d, J = 162.0 Hz), 46.32, 46.06 (d, J = 26.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −112.66 (s, 1F), −171.73 (s, 1F); HR-MS

(ESI): m/z = 336.0918, calcd. for $C_{17}H_{13}N_3F_2NaO$ ([M+Na]$^+$): 336.0924.

3-(4-Chlorophenyl)-3-fluoro-*N*-(quinoxalin-5-yl)propanamide (2g): white solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.65 (s, 1H), 8.92 (d, J = 1.8 Hz, 1H), 8.82 (dd, J = 7.6, 1.5 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.88–7.75 (m, 2H), 7.39 (s, 4H), 6.14 (dd, J = 8.7, 3.9 Hz, 0.5H), 6.05 (dd, J = 8.8, 4.0 Hz, 0.5H), 3.23 (td, J = 15.4, 8.8 Hz, 1H), 3.02 (ddd, J = 32.0, 15.2, 3.9 Hz, 1H); ^{13}C NMR (126 MHz, chloroform-*d*): δ = 167.16, 167.13(d, J = 3.0 Hz), 145.62, 143.03, 142.63, 137.48, 137.32 (d, J = 16.0 Hz), 134.88, 134.31, 133.34, 131.21, 129.12, 127.08, 127.02 (d, J = 6.0 Hz), 123.74, 117.53, 91.28, 89.91 (d, J = 137.0 Hz), 46.22, 46.02 (d, J = 20.0 Hz); ^{19}F NMR (376 MHz, Cchloroform-*d*): δ = −174.16 (s, 1F); HR-MS (ESI): m/z = 352.0625, calcd. for $C_{17}H_{13}N_3ClFNaO$ ([M+Na]$^+$): 352.0629.

3-Fluoro-*N*-(quinoxalin-5-yl)-3-[4-(trifluoromethyl)phenyl]propanamide (2h): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.65 (s, 1H), 8.93 (d, J = 1.9 Hz, 1H), 8.83 (dd, J = 7.5, 1.6 Hz, 1H), 8.74 (d, J = 1.9 Hz, 1H), 7.89–7.75 (m, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.64–7.56 (m, 2H), 6.25 (dd, J = 8.6, 4.0 Hz, 0.5H), 6.14 (dd, J = 8.7, 4.0 Hz, 0.5H), 3.24 (ddd, J = 16.2, 15.3, 8.6 Hz, 1H), 3.06 (ddd, J = 32.0, 15.3, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 166.94, 166.90 (d, J = 4.0 Hz), 145.67, 143.06, 142.65, 134.25, 133.34, 131.22, 125.98, 125.94, 125.91, 125.87, 125.80, 123.84, 117.57, 91.33, 89.60 (d, J = 173.0 Hz), 46.28, 46.02 (d, J = 26.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −62.71 (s, 1F), −177.49 (s, 1F); HR-MS (ESI): m/z = 386.0887, calcd. for $C_{13}H_{13}N_3F_4NaO$ ([M+Na]$^+$): 386.0892.

3-(4-Cyanophenyl)-3-fluoro-*N*-(quinoxalin-5-yl)propanamide (2i): white solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.63 (s, 1H), 8.94 (d, J = 1.9 Hz, 1H), 8.81 (dd, J = 7.6, 1.3 Hz, 1H), 8.74 (d, J = 1.9 Hz, 1H), 7.90–7.75 (m, 2H), 7.72 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.1 Hz, 2H), 6.24 (dd, J = 8.5, 4.1 Hz, 0.5H), 6.14 (dd, J = 8.5, 4.1 Hz, 0.5H), 3.23 (td, J = 15.9, 8.5 Hz, 1H), 3.06 (ddd, J = 31.2, 15.4, 4.2 Hz, 1H); ^{13}C NMR (126 MHz, chloroform-*d*): δ = 166.62, 166.58 (d, J = 5.0 Hz), 145.70, 144.18, 144.02 (d, J = 20.0 Hz), 143.06, 142.66, 134.16, 133.30, 132.74, 131.20, 126.17, 126.11 (d, J = 7.6 Hz), 123.92, 118.44, 117.58, 112.87, 90.90, 89.51 (d, J = 175,1 Hz), 46.02, 45.82 (d, J = 25.2 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −178.97 (s, 1F); HR-MS (ESI): m/z = 343.0970, calcd. for $C_{18}H_{13}N_4FNaO$ ([M+Na]$^+$): 343.0971.

3-Fluoro-3-(4-nitrophenyl)-*N*-(quinoxalin-5-yl)propanamide (2j): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.65 (s, 1H), 8.94 (d, J = 1.9 Hz, 1H), 8.82 (d, J = 7.5 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), 8.28 (d, J = 8.4 Hz, 2H), 7.83 (dt, J = 16.1, 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 6.31 (dd, J = 8.4, 4.2 Hz, 0.5H), 6.19 (dd, J = 8.4, 4.2 Hz, 0.5H), 3.25 (td, J = 15.9, 8.4 Hz, 1H), 3.08 (ddd, J = 30.9, 15.3, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 166.54, 166.50 (d, J = 4.0 Hz), 148.22, 146.06, 145.86 (d, J = 20.0 Hz), 145.72, 143.03, 142.67, 134.11, 133.29, 131.23, 126.38, 126.30 (d, J = 8.0 Hz), 124.17, 123.94, 117.60, 90.93, 89.19 (d, J = 174.0 Hz), 46.06, 45.81 (d, J = 25.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −178.91 (s, 1F); HR-MS (ESI): m/z = 363.0861, calcd. for $C_{17}H_{13}N_4FNaO_3$ ([M+Na]$^+$): 363.0869.

3-Fluoro-*N*-(quinoxalin-5-yl)-3-(*p*-tolyl)propanamide (2k): white solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.71 (s, 1H), 8.92 (d, J = 1.9 Hz, 1H), 8.84 (dd, J = 7.4, 1.5 Hz, 1H), 8.75 (d, J = 1.9 Hz, 1H), 7.89–7.72 (m, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.22 (d, J = 7.9 Hz, 2H), 6.12 (dd, J = 9.0, 3.6 Hz, 0,5H), 6.03 (dd, J = 9.1, 3.6 Hz, 0.5H), 3.25 (td, J = 15.3, 9.0 Hz, 1H), 3.02 (ddd, J = 33.6, 15.2, 3.6 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, chloroform-*d*): δ = 167.70, 167.68 (d, J = 2.0 Hz), 145.57, 143.04, 142.60, 138.94, 135.95, 135.79 (d, J = 16.0 Hz), 134.49, 133.41, 131.23, 129.55, 125.74, 125.69 (d, J = 5.0 Hz), 123.59, 117.51, 91.98, 90.63 (d, J = 135.0 Hz), 46.32, 46.12 (d, J = 20.0 Hz), 21.35; ^{19}F NMR (376 MHz, chloroform-*d*): δ = −171.59 (s, 1F); HR-MS (ESI): m/z = 332.1173, calcd. for $C_{18}H_{16}N_3FNaO$ ([M+Na]$^+$): 332.1175.

3-(3-Chlorophenyl)-3-fluoro-*N*-(quinoxalin-5-yl)propanamide (2l): white solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.66 (s, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.83 (d, J = 7.5 Hz, 1H), 8.75 (d, J = 1.9 Hz, 1H), 7.92–7.74 (m, 2H), 7.48 (s, 1H), 7.33 (d, J = 4.6 Hz, 3H), 6.15 (dd, J = 8.9, 3.8 Hz, 0.5H), 6.05 (dd, J = 9.0, 3.7 Hz, 0.5H), 3.22 (td, J = 15.5, 8.9 Hz, 1H), 3.03 (ddd, J = 33.1, 15.2, 3.8 Hz, 1H); ^{13}C NMR (126 MHz, chloroform-*d*): δ = 167.08, 167.06 (d, J = 2.5 Hz), 145.64, 143.04, 142.64, 141.02, 140.85 (d, J = 21.4 Hz), 134.95, 134.32, 133.36, 131.22, 130.22, 129.12, 125.82, 125.76 (d, J = 7.6 Hz), 123.77, 123.75, 123.72, 117.55, 91.14, 89.76 (d, J = 173.9 Hz), 46.23, 46.03 (d, J = 25.2 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −175.46 (s, 1F); HR-MS (ESI): m/z = 352.0623, calcd. for $C_{17}H_{13}N_3ClFNaO$ ([M+Na]$^+$): 352.0629.

3-(3-Bromophenyl)-3-fluoro-*N*-(quinoxalin-5-yl)propanamide (2m): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.65 (s, 1H), 8.92 (d, J = 1.8 Hz, 1H), 8.82 (dd, J = 7.5, 1.6 Hz, 1H), 8.74 (d, J = 1.8 Hz, 1H), 7.89–7.72 (m, 2H), 7.62 (d, J = 1.8 Hz, 1H), 7.49 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.31–7.22 (m, 1H), 6.14 (dd, J = 8.9, 3.7 Hz, 0.5H), 6.03 (dd, J = 9.0, 3.7 Hz, 0.5H), 3.21 (td, J = 15.4, 8.9 Hz, 1H), 3.02 (ddd, J = 33.3, 15.3, 3.7 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 167.07, 167.04 (d, J = 3.0 Hz), 145.62, 142.98, 142.63, 141.21, 141.02 (d, J = 19.0 Hz), 134.26, 133.30, 132.03, 131.19, 130.47, 128.69, 128.61 (d, J = 8.0 Hz), 124.25, 124.18 (d, J = 7.0 Hz), 123.71, 122.99, 117.51, 91.22, 89.49 (d, J = 173.0 Hz), 46.24, 45.99 (d, J = 25.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −175.45 (s, 1F): HR-MS (ESI): m/z = 396.0119, calcd. for $C_{17}H_{13}N_3FBrNaO$ ([M+Na]$^+$): 396.0124.

3-(2-Chlorophenyl)-3-fluoro-*N*-(quinoxalin-5-yl)propanamide (2n): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ = 9.72 (s, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.86 (dd, J = 7.3, 1.7 Hz, 1H), 8.75 (d, J = 1.8 Hz, 1H), 7.91–7.72 (m, 2H), 7.61 (dd, J = 7.5, 1.9 Hz, 1H), 7.44–7.27 (m, 3H), 6.52 (dd, J = 9.3, 2.6 Hz, 0.5H), 6.41 (dd, J = 9.1, 2.7 Hz, 0.5H), 3.20 (ddd, J = 37.3, 15.8, 3.0 Hz, 1H), 3.11–3.00 (m, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ = 167.21, 145.58, 143.01, 142.61, 136.84, 136.62 (d, J = 22.0 Hz), 134.43, 133.35, 131.27, 131.07, 131.01 (d, J = 6.0 Hz), 129.88, 129.85, 127.42, 126.69, 126.59 (d, J = 10.0 Hz), 123.58, 117.49, 89.34, 87.61 (d, J = 173.0 Hz), 44.75, 44.50 (d, J = 25.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ = −181.80 (s, 1F); HR-MS (ESI): m/z = 352.0621, calcd. for $C_{17}H_{13}N_3ClFNaO$ ([M+Na]$^+$): 352.0629.

3-Fluoro-*N*-(quinoxalin-5-yl)-3-(*o*-tolyl)propanamide (2o): white solid; ^{1}H NMR (500 MHz, chloroform-*d*): δ = 9.75 (s, 1H), 8.93 (d, J = 1.8 Hz, 1H), 8.87 (dd, J = 7.6, 1.5 Hz, 1H), 8.76 (d, J = 1.9 Hz, 1H), 7.88–7.76 (m, 2H), 7.57–7.47 (m, 1H), 7.32–7.24 (m, 2H), 7.23–7.17 (m, 1H), 6.40 (dd, J = 9.4, 2.9 Hz, 0.5H), 6.30 (dd, J = 9.3, 2.9 Hz, 0.5H), 3.22 (td, J =

15.6, 9.3 Hz, 1H), 3.01 (ddd, J=35.9, 15.4, 2.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, chloroform-*d*): δ=167.81, 145.54, 142.96, 142.63, 137.04, 136.89 (d, J=18.9 Hz), 134.73, 134.69 (d, J=5.0 Hz), 134.46, 133.39, 131.23, 130.90, 128.81, 126.52, 125.24, 125.18 (d, J=7.5 Hz), 123.57, 117.49, 89.45, 88.09 (d, J=171.4 Hz), 45.34, 45.14 (d, J=25.2 Hz), 19.04; ^{19}F NMR (376 MHz, chloroform-*d*): δ=−175.34 (s, 1F); HR-MS (ESI): m/z=332.1168, calcd. for $C_{18}H_{16}N_3FNaO$ ([M+Na]$^+$): 332.1175.

3-Fluoro-3-(naphthalen-2-yl)-*N*-(quinoxalin-5-yl)propanamide (2p): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ=9.70 (s, 1H), 8.91 (d, J=1.8 Hz, 1H), 8.86 (dd, J=7.2, 1.8 Hz, 1H), 8.67 (d, J=1.8 Hz, 1H), 7.98–7.75 (m, 6H), 7.54 (ddd, J=14.6, 7.4, 2.5 Hz, 3H), 6.35 (dd, J=8.9, 3.8 Hz, 0.5H), 6.23 (dd, J=8.9, 3.7 Hz, 0.5H), 3.35 (td, J=15.4, 8.9 Hz, 1H), 3.14 (ddd, J=32.9, 15.2, 3.8 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*): δ=167.53, 167.50 (d, J=3.0 Hz), 145.58, 143.00, 142.58, 136.27, 134.41, 133.57, 133.36, 133.23, 131.23, 128.92, 128.33, 127.92, 126.72, 125.10, 125.02 (d, J=8.0 Hz), 123.64, 123.05, 123.00 (d, J=5.0 Hz), 117.52, 92.33, 90.61 (d, J=172.0 Hz), 46.47, 46.21 (d, J=26.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ=−173.38 (s, 1F); HR-MS (ESI): m/z=368.1170, calcd. for $C_{21}H_{14}N_3FNaO$ ([M+Na]$^+$): 368.1175.

4-Cyclohexyl-3-fluoro-*N*-(quinoxalin-5-yl)butanamide (2q): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ=9.72 (s, 1H), 8.92 (d, J=1.8 Hz, 1H), 8.83 (dd, J=7.3, 1.7 Hz, 1H), 8.76 (d, J=1.8 Hz, 1H), 7.90–7.70 (m, 2H), 5.28 (td, J=9.0, 8.1, 4.0 Hz, 0.5H), 5.20–5.10 (m, 0.5H), 2.96–2.68 (m, 2H), 1.85 (m, 1H), 1.73 (m, J=13.9, 12.3, 9.7, 6.2 Hz, 5H), 1.58–1.44 (m, 2H), 1.24–1.07 (m, 3H), 0.97 (m, 2H); ^{13}C NMR (101 MHz, chloroform-*d*): δ=168.42, 168.39 (d, J=3.0 Hz), 145.55, 143.04, 142.66, 134.59, 133.46, 131.25, 123.50, 117.44, 90.39, 88.71(d, J=168.0 Hz), 44.91, 44.68 (d, J=23.0 Hz), 42.89, 42.69 (d, J=20.0 Hz), 34.08, 33.95, 32.87, 26.55, 26.37, 26.21; ^{19}F NMR (376 MHz, chloroform-*d*): δ=−178.47 (s, 1F); HR-MS (ESI): m/z=338.1644, calcd. for $C_{18}H_{22}N_3FNaO$ ([M+Na]$^+$): 338.1645.

3-Fluoro-*N*-(quinoxalin-5-yl)pentanamide (2r): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ=9.73 (s, 1H), 8.92 (d, J=1.9 Hz, 1H), 8.83 (dd, J=7.3, 1.7 Hz, 1H), 8.76 (d, J=1.9 Hz, 1H), 7.85–7.73 (m, 2H), 5.11 (m, 0.5H), 4.98 (m, 0.5H), 2.98–2.73 (m, 2H), 1.90–1.74 (m, 2H), 1.07 (t, J=7.5 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-*d*): δ=168.40, 168.37 (d, J=3.0 Hz), 145.55, 143.02, 142.65, 134.57, 133.44, 131.24, 123.50, 117.44, 93.26, 91.58 (d, J=168.0 Hz), 43.97, 43.75 (d, J=22.0 Hz), 28.33, 28.12 (d, J=21.0 Hz), 9.41, 9.35 (d, J=6.0 Hz); ^{19}F NMR (376 MHz, chloroform-*d*): δ=−179.67 (s, 1F): HR-MS (ESI): m/z=270.1011, calcd. for $C_{13}H_{14}N_3FNaO$ ([M+Na]$^+$): 270.1019.

3-Fluoro-*N*-(quinoxalin-5-yl)heptanamide (2s): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ=9.72 (s, 1H), 8.92 (d, J=1.8 Hz, 1H), 8.83 (dd, J=7.3, 1.7 Hz, 1H), 8.76 (d, J=1.8 Hz, 1H), 7.88–7.72 (m, 2H), 5.16 (tt, J=8.1, 4.2 Hz, 0.5H), 5.10–4.94 (m, 0.5H), 3.00–2.72 (m, 2H), 1.93–1.70 (m, 2H), 1.60–1.36 (m, 4H), 0.93 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-*d*): δ=168.40, 168.37 (d, J=3.0 Hz), 145.54, 143.02, 142.64, 134.57, 133.43, 131.23, 123.49, 117.42, 92.20, 90.52 (d, J=168.0 Hz), 44.38, 44.16 (d, J=22.0 Hz), 34.93, 34.72 (d, J=21.0 Hz), 27.22, 27.18 (d, J=4.0 Hz), 22.54, 14.07; ^{19}F NMR (376 MHz, chloroform-*d*): δ=−178.57 (s, 1F); HR-MS (ESI): m/z=298.1324, calcd. for $C_{15}H_{18}N_3FNaO$ ([M+Na]$^+$): 298.1332.

General Procedure for C−H Acetoxylation

To a 2-dram vial equipped with a stirrer was added SM, $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (1.5 equiv.), acetic anhydride (2.5 equiv.) and *o*-dichlorobenzene. The mixture was stirred at 80 °C for 12 h. After completion, the reaction mixture was concentrated under vacuum. Purification of the residue was done by flash chromatography.

3-Oxo-1-phenyl-3-(quinolin-8-ylamino)propyl acetate (3a): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ=9.99 (s, 1H), 8.86–8.72 (m, 2H), 8.17 (dd, J=8.3, 1.7 Hz, 1H), 7.60–7.49 (m, 2H), 7.46 (dt, J=8.0, 3.0 Hz, 3H), 7.37 (t, J=7.3 Hz, 2H), 7.31 (dd, J=8.5, 6.0 Hz, 1H), 6.33 (dd, J=9.1, 4.2 Hz, 1H), 3.22 (dd, J=15.1, 9.1 Hz, 1H), 3.00 (dd, J=15.1, 4.2 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*): δ=169.94, 167.74, 148.24, 139.75, 138.44, 136.55, 134.40, 128.82, 128.42, 128.06, 127.56, 126.45, 121.84, 121.77, 116.86, 72.85, 45.28, 21.32; HR-MS (ESI): m/z=357.1211, calcd. for $C_{20}H_{18}N_2NaO_3$ ([M+Na]$^+$): 357.1215.

3-Oxo-1-phenyl-3-(quinoxalin-5-ylamino)propyl acetate (3d): white solid; ^{1}H NMR (400 MHz, chloroform-*d*): δ=9.66 (s, 1H), 8.93 (d, J=1.9 Hz, 1H), 8.80 (dd, J=7.5, 1.6 Hz, 1H), 8.73 (d, J=1.9 Hz, 1H), 7.87–7.72 (m, 2H), 7.49–7.41 (m, 2H), 7.40–7.33 (m, 2H), 7.33–7.27 (m, 1H), 6.32 (dd, J=8.9, 4.4 Hz, 1H), 3.21 (dd, J=15.1, 8.9 Hz, 1H), 3.00 (dd, J=15.1, 4.4 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR (101 MHz, chloroform-*d*): δ=169.86, 167.77, 145.51, 142.96, 142.45, 139.50, 134.42, 133.31, 131.34, 128.87, 128.51, 126.40, 123.40, 117.49, 72.74, 45.19, 21.29; HR-MS (ESI): m/z=358.1162, calcd. for $C_{29}H_{17}N_3NaO_3$ ([M+Na]$^+$): 358.1168.

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