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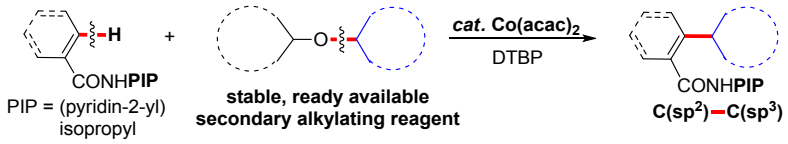
Cobalt-Catalyzed Secondary Alkylation of Arenes and Olefins with Alkyl Ethers through Cleavage of C(sp²)–H and C(sp³)–O Bonds

Xunqing Dong,† Qun Li,† Guigen Li*,†,‡ and Hongjian Lu*,†

†Institute of Chemistry and BioMedical Sciences, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China

‡Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA



ABSTRACT: A novel cobalt-catalyzed C–H alkylation of arenes and olefins is achieved with (pyridin-2-yl)isopropyl amine as a *N*,*N*-bidentate directing group. Different linear, branched and cyclic alkyl ethers were used as practical secondary alkylating reagents through cleavage of C(sp³)–O bond, providing an efficient approach to the synthesis of verstile *o*-alkylated arylamides and tetrasubstituted acrylamides. Mechanistic studies indicate that cleavage of the inert C(sp³)–O bond involves a cobalt-promoted radical process and that cleavage of the inert C(sp²)–H bond by a cobalt catalyst is a rate-limiting step.

Introduction

By avoiding the pre-functionalization of starting materials, transition metal

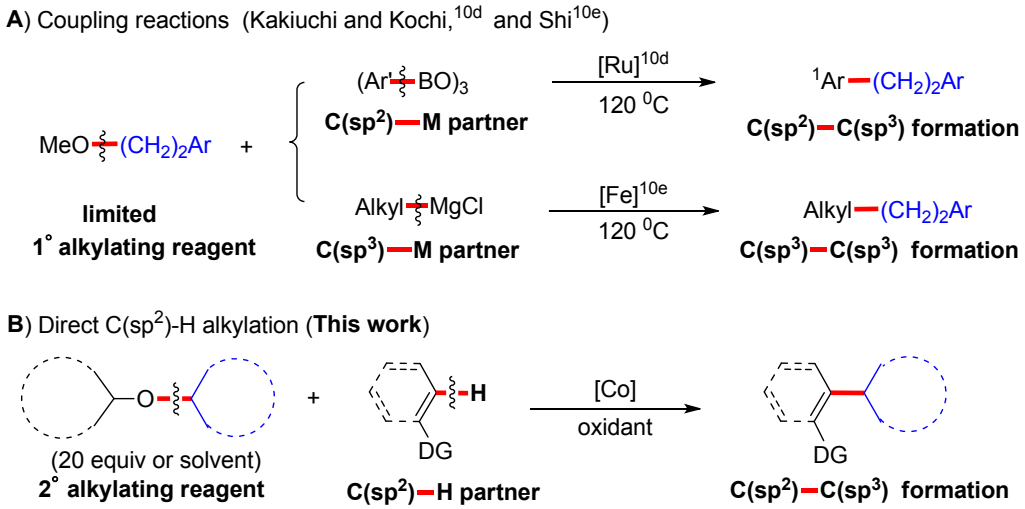
catalyzed C–H functionalization can be performed in a step- and atom-economic manner, and this has attracted attention in organic synthesis.[1] The alkylation reaction of C(sp^2)–H bond provides an efficient strategy for the construction of C(sp^2)–C(sp^3) bonds.[1,2] The most commonly encountered alkylating reagents include nucleophilic organometallic reagents[3] and electrophilic alkyl halides.[4] These reagents have some disadvantages, such as the requirement of pre-preparation, environmental unfriendliness, propensity for β-H elimination, instability and high reactivity. To avoid these disadvantages, other alkylating reagents have been developed. For example, the olefins have emerged as efficient alkylating reagents.[2b,5] However, it is generally necessary to use noble metal catalysts or ligands to control the reactivity and the regioselectivity. Alcohols and alkanes have been also promoted as green alkylating reagents. Alcohols have a limited substance scope, require noble metal catalysts and have been used infrequently.[6] Alkanes have site-selective issues and low regioselectivity were achieved in linear alkanes in most cases.[7] Thus, cheap and stable alkylating reagents with good site-selectivity still await development in catalytic C–H alkylation reactions.

Alkyl ethers, common in industry and nature, are readily accessible chemicals and often used as solvents in organic reactions. Thus, it is of interest to use alkyl ethers as alkylating reagents formed by the cleavage of inert C(sp^3)–O bonds.[8]

But the C(sp^3)–O bonds are extremely unreactive chemical bonds and are very stable under basic and reductive conditions. Nevertheless, transition metal-catalyzed cross-coupling reactions involving cleavage of C–O bonds have potential utility and have seen remarkable progress.[9] In most cases, aryl or benzyl(allyl) ethers were used as aryl or benzyl(allyl) coupling partners, and reactive organometallic reagents, such as organoboron, organozinc or Grignard reagents, have to be used as a second coupling partner due to the low reactivity of C–O bonds. Only a few examples have been provided in which unactivated alkyl ethers have been used as alkyl coupling partners in reactions involving the cleavage of C(sp^3)–O bonds.[10] Kakiuchi and Kochi have reported pioneering work involving Ru-catalyzed C(sp^2)–C(sp^3) coupling of alkyl ethers with triarylboroxines,[10d] and Shi has developed an Fe-promoted C(sp^3)–C(sp^3) coupling of alkyl ethers with Grignard reagents[10e] (Scheme 1A). The substrate scope of alkyl ethers in both cases is limited to 2-methoxyethyl aryl derivatives. Thus, use of chemically stable and convenient counterparts, such as C(sp^2)–H bonds instead of organometallic reagents to couple with common alkyl ethers would contribute significantly to the development of catalytic C(sp^2)–C(sp^3) bond-forming methods. In this paper, we report a cobalt-catalyzed alkylation of arylamides and acrylamides *via* inert C(sp^2)–H and C(sp^3)–O bond cleavages, in which large excess amount of secondary alkyl ethers were used as alkylating

reagents (Scheme 1B).[11]

Scheme 1. Metal-catalyzed C–C formation using alkyl ethers as alkylating reagents by cleavage of C(sp^3)–O bonds

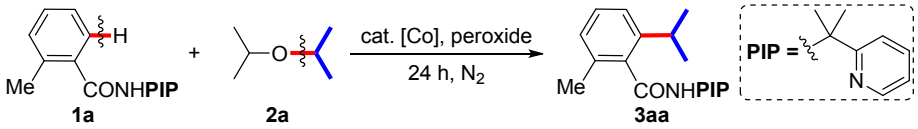


Results and Discussion

Cobalt-catalyzed C−H alkylation has met with remarkable success on account of its economy, low toxicity and interesting reaction modes.[12] Inspired by our recent work on cobalt-catalyzed C−H bond functionalization,[13,14] our study began with the reaction between *o*-methylbenzamide **1a** with (pyridin-2-yl)isopropyl (PIP) amine as the bidentate directing group[15] and isopropyl ether **2a** as an alkylating reagent to identify cobalt catalysts under oxidative conditions (Table 1). Both the counteranion of the cobalt salt (entries 1-7) and oxidants (entries 8-10) play a crucial role, and the valence state of cobalt complex has no influence on the reaction (entries 3-4). After screening the solvents and temperatures (entries

11-18), the optimal conditions were achieved with commercially available $Co(acac)_2$ and DTBP as catalyst and oxidant respectively (entry 3). Reducing the catalyst loading, the yield of **3aa** was decreased slightly (entries 19 and 20). When the reaction was performed in 5.0 mmol scale, **3aa** was still obtained in 78% isolated yield (entry 21). When 8-quinolinylbenzamide was used as substrate, the reaction was complicated and few desired products (less than 10%) could be observed.

Table 1. Optimization of Reaction Conditions[a]

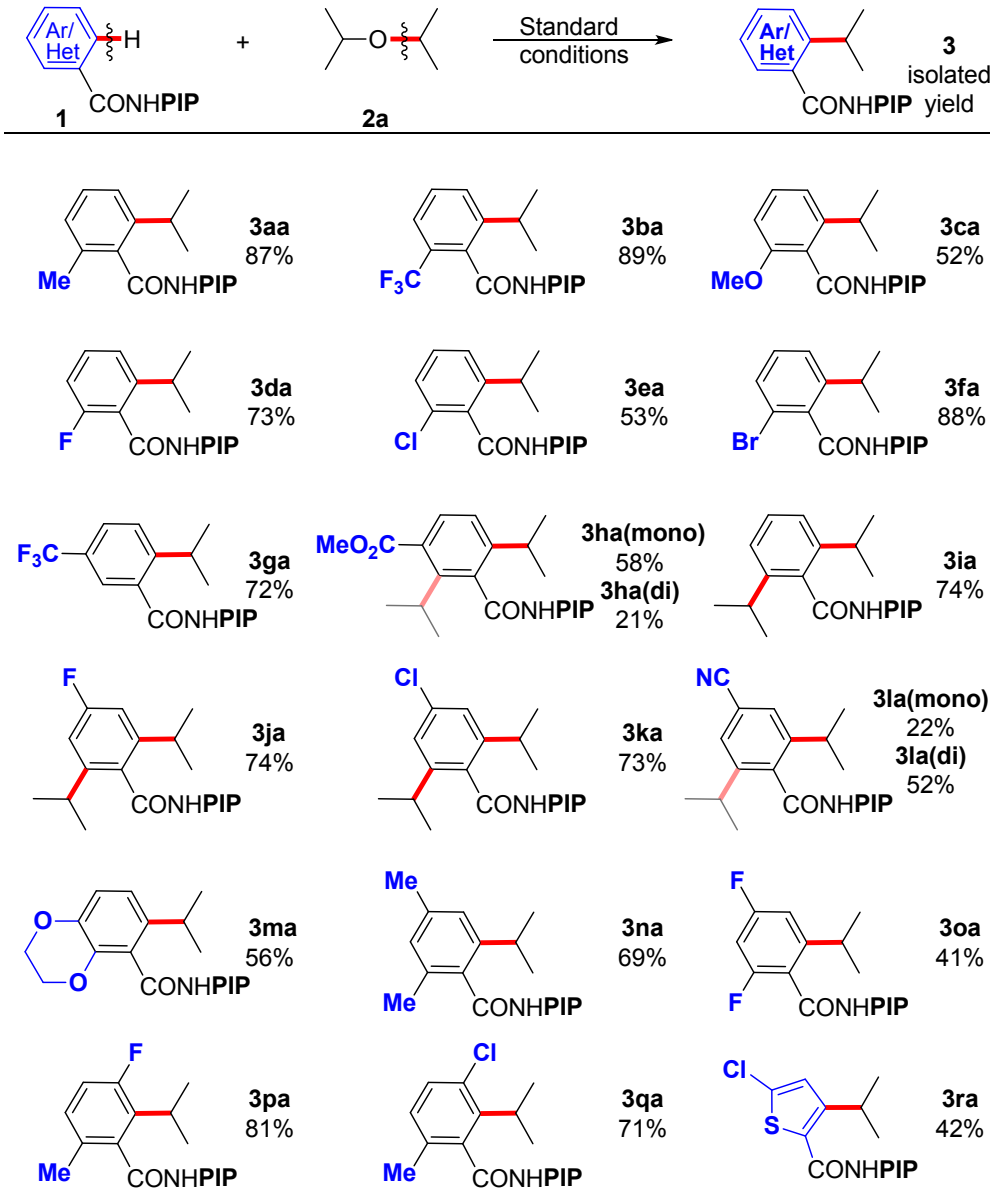


entry	cat.[Co]	peroxide	solvent	temp. (°C)	**3aa** yield (%)[b]
1	$Co(OAc)_2{\cdot}4H_2O$	DTBP	Benzene	140	0
2	$CoCl_2$	DTBP	Benzene	140	9
3	**$Co(acac)_2$**	**DTBP**	**Benzene**	**140**	**87**[c]
4	$Co(acac)_3$	DTBP	Benzene	140	85
5	CoF_3	DTBP	Benzene	140	trace
6	$Co(Cp^*)(CO)I_2$	DTBP	Benzene	140	trace
7	Co(TPP)Cl	DTBP	Benzene	140	0
8	$Co(acac)_2$	DCP	Benzene	140	42
9	$Co(acac)_2$	DBHP	Benzene	140	6
10	$Co(acac)_2$	TBHP	Benzene	140	trace
11	$Co(acac)_2$	DCP	$PhCF_3$	140	23
12	$Co(acac)_2$	DTBP	*t*-BuPh	140	66
13	$Co(acac)_2$	DTBP	PhCl	140	55
14	$Co(acac)_2$	DTBP	$PhCF_3$	140	56
16	$Co(acac)_2$	DTBP	Benzene	120	63

17	$Co(acac)_2$	DTBP	Benzene	100	32
18	$Co(acac)_2$	DTBP	Benzene	160	54
19	$Co(acac)_2$ [d]	DTBP	Benzene	140	84
20	$Co(acac)_2$ [e]	DTBP	Benzene	140	69
21[f]	$Co(acac)_2$	DTBP	Benzene	140	78[c]

[a] Reaction Conditions: **1a** (0.2 mmol), **2a** (4.0 mmol), [Co] (20 mol %), peroxide (0.8 mmol), solvent (1.0 mL), N_2, 24 h. [b] Crude ^1H NMR yield determined by using CH_2Br_2 as an internal standard. [c] Isolated yield. [d] [Co] (10 mol %). [e] [Co] (5 mol %). [f] **1a** (5.0 mmol), **2a** (75.0 mmol), $Co(acac)_2$ (10 mol %), DTBP (15.0 mmol), benzene (25 mL), N_2, 140 °C, 24 h.

Scheme 2. The scope of arylamides[a]

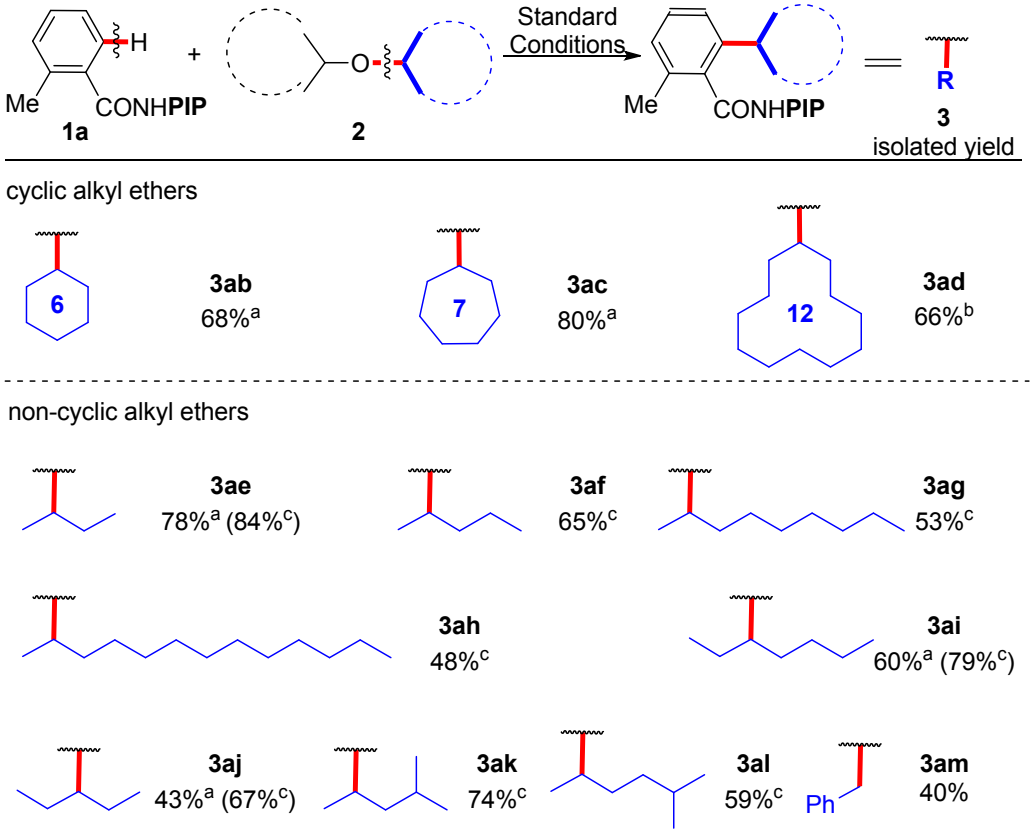


[a] Standard conditions: **1** (0.2 mmol), **2** (4.0 mmol), $Co(acac)_2$ (20 mol %), DTBP (0.8 mmol), benzene (1.0 mL), N_2, 140 °C, 24 h.

Investigation of the scope of arylamides gave the results shown in Scheme 2. Both electron-donating groups such as Me and OMe, and electron-withdrawing groups such as CF_3, F, Cl and Br in the *o*-position of benzamides were tolerated,

producing the mono-alkylated products **3aa-fa** in moderate to high yield. Due to the electron density and steric effects, substituents in the *m*-position of benzamides are able to control the reactivity and selectivity of substrates.[16] When there is CF_3 group in the *m*-position, mono C−H alkylation takes place selectively at the less-hindered position (**3ga**). Mixtures of the major mono-alkylated and the minor di-alkylated compounds were produced when the *m*-position was substituted by a CO_2Me group (**3ha**). Benzamide or *p*-substituted benzamides provided di-alkylated products (**3ia-ka**), while *p*-cyanobenzamide gives a mixture of mono- and di-alkylated compounds, the latter being predominant (**3la)**. Tetrasubstituted benzamides were obtained when trisubstituted substrates were used (**3ma-oa**). When the halogen group was in the *o*-position relative to the reaction site, the reaction still proceeded well (**3pa-qa)**, showing that the efficiency of the reaction is not influenced significantly by steric hindrance. Heteroarylamides such as 5-chlorothiophene-1-carboxamide are also tolerated (**3ra**).

Scheme 3. The scope of alkyl ethers

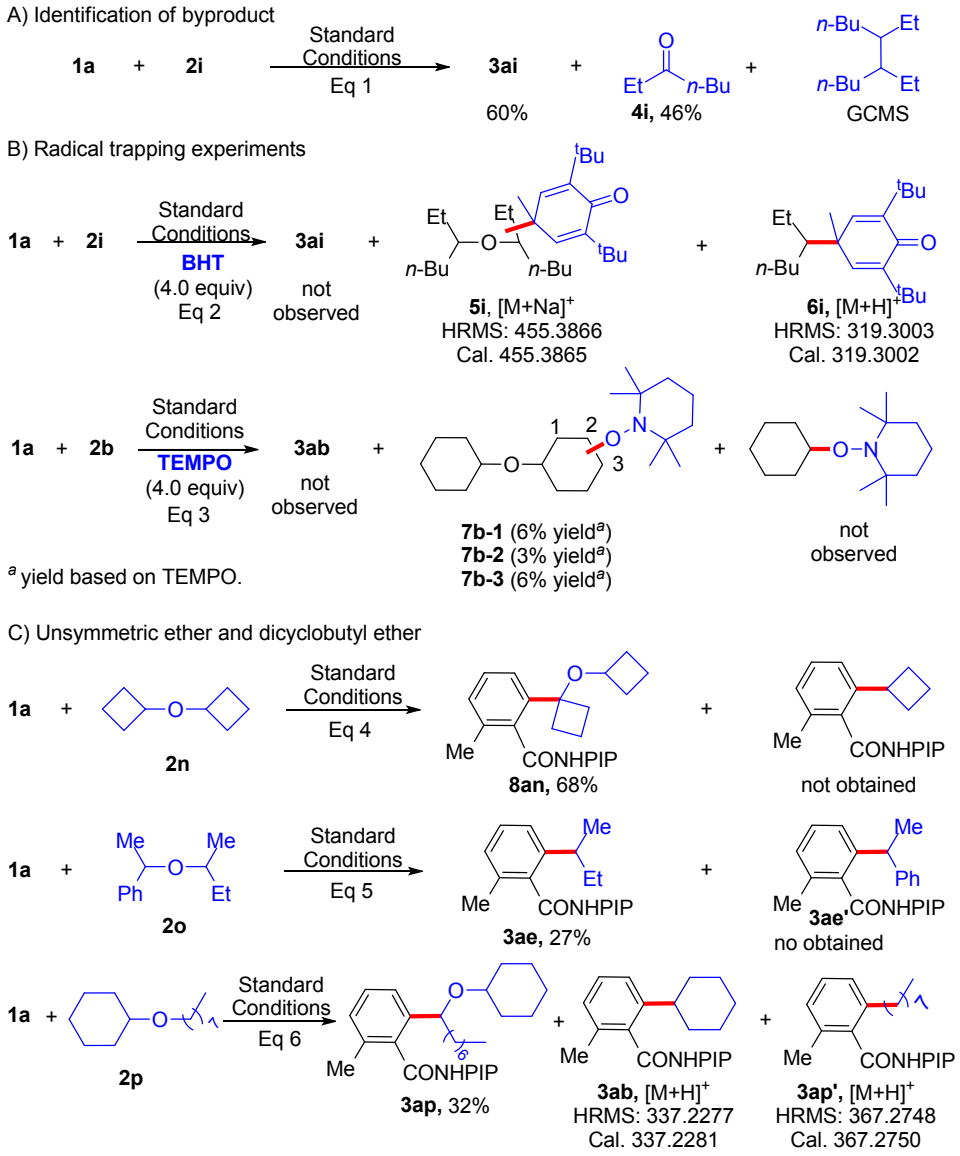


[a] **2** (2.0 mmol). [b] **2d** (0.6 mmol), benzene (2.0 mL), 48 h. [c] Using **2** (1.0 mL) without benzene.

Next, the scope of alkyl ethers was examined (Scheme 3). Cyclic alkyl ethers with varying ring size, such as cyclohexyl, cycloheptyl and even cyclododecyl ethers can be used as efficient cyclic alkylating reagents, leading to the target products **3ab-ad** in good yields. Different linear alkyl ethers, such as 2-butyl and 2-pentyl ethers were tested, and the desired products **3ae-af** were achieved, also in good yields. This strategy can also be used with longer alkyl chain ethers such as 2-nonyl and 2-tridecyl ethers (**3ag-ah**). More sterically hindered substrates, such as 3-heptyl and 3-pentyl ethers were also compatible with the reaction

(**3ai**-**aj**). Branched alkyl ethers, whose tertiary C–H bonds could be easily broken in radical reactions, were tolerated (**3ak**-**al**), showing the generality of this reaction. It could be noted that the single desired product was afforded without obvious sideproducts from cross-dehydrogenative coupling (CDC) reactions,[8] and the yield was significantly improved when ether was used as the solvent (Scheme 3, note c). When dibenzyl ether was used, the desired product **3am** was obtained only in moderate yield.

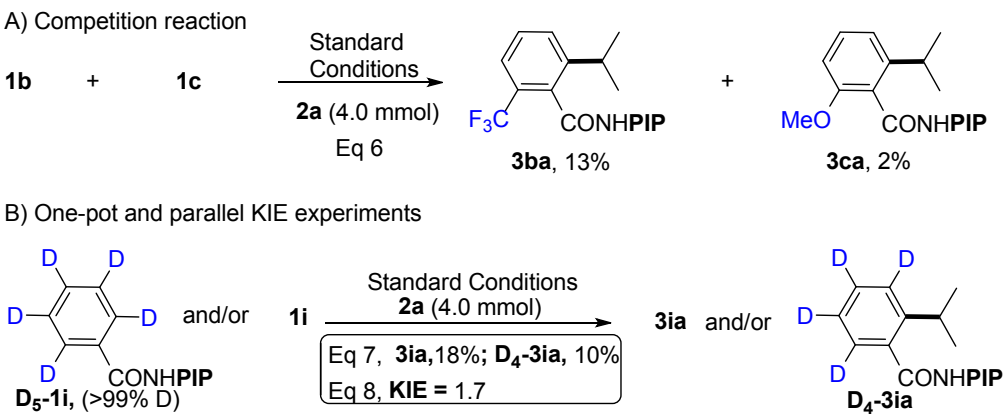
Scheme 4. Mechanistic studies of C(sp^3)−O bond cleavage



A series of control experiments were performed in an effort to clarify the mechanism of the C−O bond cleavage (Scheme 4). In the reaction of **1a** with **2i**, the ketone **4i** was obtained in 46% GC yield and the product from homocoupling of alkyl radicals was observed by GCMS (Eq 1). When adding butylated hydroxytoluene (BHT), a radical scavenger, to the reaction, the desired product **3ai** was not observed but products **5i** and **6i** were detected by HRMS (Eq 2),

implying that both alkyl radical and *α*-alkyl radical of the ether may exist in the reaction. When active radical scavenger (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) was added, products **7b** were obtained in 15% isolated yield, while products arising from capture of the *α*-alkyl radical of ether were not detected by either HRMS or GCMS possibly due to the steric hindrance in *α*-position of ether **2b** (Eq 3). When cyclic butyl ether **2n** was subjected to the reaction (Eq 4), no obvious desired C−H alkylation product was observed and the product **8an** was isolated in good yield possibly due to the less sterically hindrance in *α*-position of **2n** than that of other ethers. The asymmetric ether **2o** was also used, the alkylation product **3ae** was obtained and **3ae'** was not observed possibly due to the steric hindrance and low reactivity of 1-phenylethyl radical if it was formed [14c] (Eq 5). When cyclohexyloctyl ether **2p** was subjected to the reaction, the product **3ap** formed from direct C−C coupling was isolated [14c] and the alkylating products **3ab** and **3ap'** were only observed by HRMS (Eq 6).

Scheme 5. Mechanistic studies of C(sp^2)−H bond cleavage



Several experiments were designed to reveal the mechanism of C(sp^2)−H bond cleavage (Scheme 5). The electronic effect on the phenyl ring was investigated through the competition between **1b** and **1c** and it was found that the electron-deficient benzamide **1b** was more reactive (Eq 6). When the deuterated benzamide **D_5-1i** was subjected to the reaction for 6 h, 52% of **D_5-1i** was recovered without observation of obvious H/D exchange. Then, kinetic isotope effects (KIE) were observed in competition experiments between substrates **1i** and **D_5-1i** in one pot (**3ia**/**D_4-3ia** = 1.8, Eq 7) or parallel experiments (KIE = 1.7, Eq 8), implying that C(sp^2)−H bond cleavage induced by cobalt is likely to be a rate-limiting step.

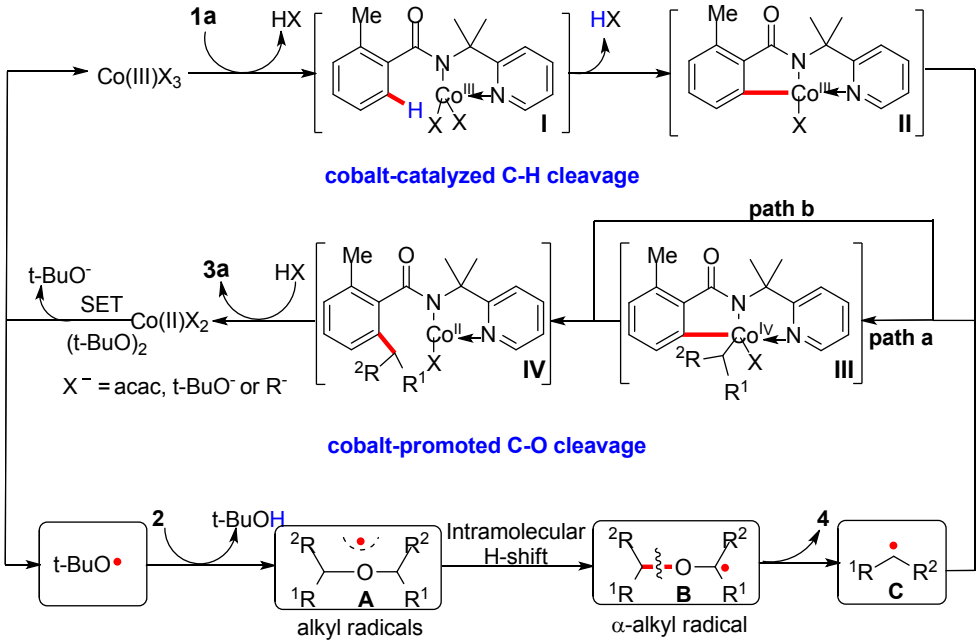
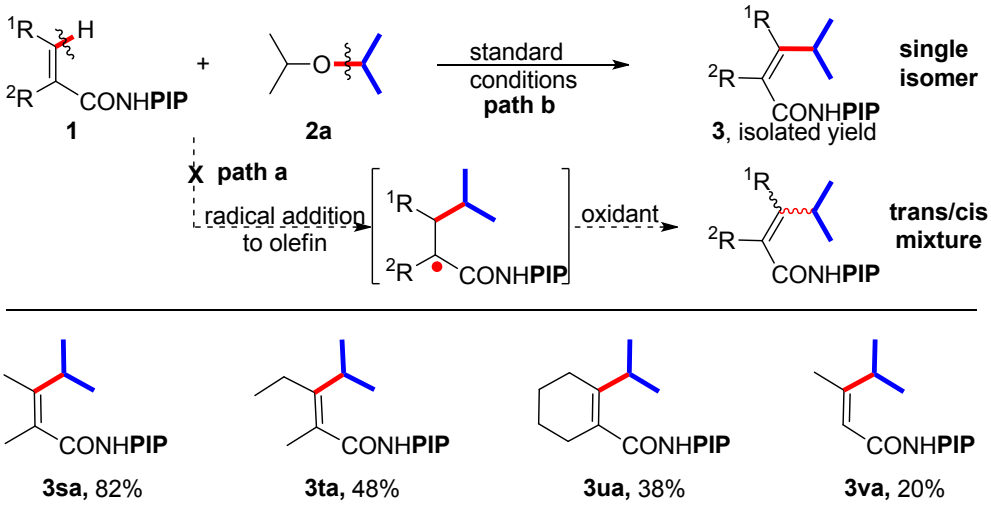


Figure 1. Possible Catalytic Cycles.

Based on these experimental results and previous reports,[12] a conceivable catalytic cycle involving high-valent Co-catalyzed C(sp^2)–H cleavage and Co-promoted C(sp^3)–O cleavage is proposed (Figure 1). Initially, an intermolecular single electron transfer (SET) process between Co(II)X_2 and DTBP provides a high-valent Co(III) species and the alkoxy radical *t*-BuO•. Coordination of **1a** with the Co(III) species by a ligand exchange process generates intermediate **I**, and the subsequent C(sp^2)−H cleavage forms intermediate **II**. Meanwhile *t*-BuO• abstracts a hydrogen atom from the ether to generate alkyl radicals **A**. Intramolecular hydrogen shift of **A** forms *α*-alkyl radical **B**. Homolytic cleavage of **B** gives the ketone **4** and the active alkyl radical **C**. **C** is promptly captured by the cobalt center of **II** to provide the Co(IV) species **III.** This is followed by rapid reductive elimination of **III** as a result of the instability of high-valent Co(IV), generating the Co(II) species **IV** (Path a).[14] Alternatively, a radical substitution reaction of radical **C** with Co(III) species **II** forms **IV** directly (Path b).[17] Finally, protonation of **IV** gives the product **3a** and Co(II) species, which can be re-oxidized to continue the catalytic cycle.

Scheme 6. Synthesis of (*Z*) tetra- and tri-substituted acrylamides



Based on this proposed mechanism, direct addition of the alkyl radical to the double bond, which may lead to a *trans*- and *cis*-acrylamide mixture, would be a major issue when acrylamides are used (path a, Scheme 6). In fact, when (*E*)-2-methylbut-2-enamide was subjected to the reaction, (*Z*)-**3sa** alone was obtained in high yield, showing that the alkyl radical **B** reacts with Co species **II** (Figure 1) at a much faster rate than **B** reacts directly with double bonds. When other trisubstituted and cyclic substrates were used, the desired tetrasubstituted acrylamides **3ta-ua** with *Z* configuration were produced, albeit in moderate yields. The trisubstitued acrylamide **3va** with a *Z* configuration could also be obtained, but with low yield possibly due to the high reactivity of the double bond.

Conclusions

In summary, Co-catalyzed direct secondary alkylation of arenes and olefins with alkyl ethers has been achieved. This reaction represents the first example of the use of stable alkyl ethers as alkylating reagents in metal-catalyzed C−H alkylation reactions through cleavage of inert C(sp^3)−O bonds. It shows good compatibility with synthetically relevant functional groups in arenes, and high site selectivity with different alkylating reagents including linear, branched and cyclic alkyl ethers. The reaction thus provides a novel practical tool for the preparation of *o*-alkyl arylamides and tetrasubstituted acrylamides. Preliminary mechanistic studies suggest that a high-valent cobalt species generated *in situ* catalyzes the cleavage of C(sp^2)−H bonds and cobalt promotes C(sp^3)−O bond cleavage under oxidative conditions *via* a radical process. The strategy developed here may lead to new types of alkylation reaction which uses convenient alkyl ethers as alkylating reagents.

EXPERIMENTAL SECTION

General Information. Thin layer chromatography (TLC) was performed on pre-coated silica gel GF254 plates. Visualization of TLC was achieved by using UV light (254 nm). Column chromatography was performed on silica gel (300-400 mesh) using a proper eluent. ^{1}H NMR was recorded on FT AM 400 (400 MHz). Chemical shifts were reported in parts per million (ppm) referenced to chloroform-d ($CDCl_3$) at 7.26 ppm. The following abbreviations were

used to describe peak splitting patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, td = triplet of doublet, ddd = doublet of doublet of doublet, m = multiplet. Coupling constants, J, were reported in hertz (Hz). The fully decoupled ^{13}C NMR was recorded on FT AM 400 (100 MHz). Chemical shifts were reported in ppm referenced to the center of a triplet at 77.0 ppm of chloroform-d. Infrared (IR) spectra were recorded neat in KBr cell. Frequencies are given in centimeter inverse (cm^{-1}) and only selected absorbance is reported. High resolution mass spectra were obtained by using the UHD Accurate-Mass Q-TOF equipped with ESI or APCI.Unless otherwise mentioned, all commercial reagents and solvents were obtained from commercial suppliers and used without further purification. Starting compounds **1a-1c**,[14c] **1d**,[18a] **1e-1j**,[14c] **1k**,[18b] **1l**,[14c] **1m**,[14a] **1n**,[18c] **1o**,[14a] **1p**,[14a] **1r**,[14c] **1s**,[18d] **1u**,[14a] and D_5-**1i**[14c] were known compounds, while **1q**, **1t**, **1v** were unknown compounds, all of whose were prepared according the general procedure. Starting compound **2b,**[18e] **2c,**[18e] **2d,**[18f] **2**j,[18g] **2o**[18h] and **2p**[18e] were known compounds, while **2f**, **2g**, **2h**, **2i**, **2k**, **2l**, **2n** were unknown compounds, all of whose were prepared according the general procedure. **2a**, **2e** and **2m** were commercial available.

General procedure for the synthesis of compounds 1[14c]

Method one: To a 50 mL flask was added pre-prepared 2-(Pyridin-2-yl)isopropyl amine ($PIPNH_2$) (2.0 mmol) and Et_3N (2.2 mmol), then Substituted-benzoyl chloride (2.2 mmol) was added slowly at 0 ^oC. The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduce pressure, then the residue was purified by column chromatography on silica gel to afford product **1.**

Method two: To a 50 mL flask was added HOBt (2.2 mmol), EDCI (2.2 mmol) and Substituted-benzoic acid (2.2 mmol), after charged with nitrogen, DCM (20 mL), pre-prepared $PIPNH_2$ (2.0 mmol) was added, then the reaction was stirred at rt overnight. The solvent was removed under reduce pressure, then the residue was purified by column chromatography on silica gel to afford product **1.**

5-chloro-2-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (1q): TLC R_f = 0.5 (EtOAc/PE = 1:5); white solid, 473 mg, 82% (Method two); m.p.: 98-99 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.3 Hz, 1H), 8.19 (s, 1H), 7.74 (td, *J* = 8.0, 1.7 Hz, 1H), 7.48–7.42 (m, 2H), 7.26 (t, *J* = 2.9 Hz, 1H), 7.20 (dd, *J* = 6.9, 5.1 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 2.42 (s, 3H), 1.88 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.8, 164.2, 147.6, 139.3, 137.2, 134.2, 132.2, 131.3, 129.3, 126.9, 122.0, 119.4, 57.1, 27.5, 19.3; IR (neat): 3012, 3005, 2988, 1647, 1473, 1275, 1260, 771, 763, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{18}ClN_2O$ $[M+H]^+$: 289.1108, found: 289.1110.

(*E*)-2-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pent-2-enamide (1t): TLC R_f = 0.4 (EtOAc/PE = 1:3); white solid, 450 mg, 97% (Method two); m.p.: 90-91 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.14 (s, 1H), 7.72 (td, *J* = 7.9, 1.7 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 6.9, 5.3 Hz, 1H), 6.42 (td, *J* = 7.2, 1.2 Hz, 1H), 2.18 (p, *J* = 7.4 Hz, 2H), 1.91 (s, 3H), 1.79 (s, 6H), 1.05 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.5, 165.0, 147.6, 137.1, 131.4, 121.8, 119.5, 56.4, 27.5, 21.7, 13.4, 12.6; IR (neat): 3349, 3000, 2971, 2933, 2873, 1663, 1507, 1275, 1260, 787, 765, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1655, found: 233.1658.

(E)-*N*-(2-(pyridin-2-yl)propan-2-yl)but-2-enamide (1v): TLC R_f = 0.4 (EtOAc/PE = 1:2); white solid, 379 mg, 93% (Method two); m.p.: 108-109 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.4 Hz, 1H), 7.81–7.66 (m, 2H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 6.9, 5.2 Hz, 1H), 6.81 (dq, *J* = 13.8, 6.8 Hz, 1H), 5.95 (d, *J* = 15.1 Hz, 1H), 1.85 (d, *J* = 5.9 Hz, 3H), 1.78 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.1, 164.6, 147.6, 138.6, 137.1, 126.6, 121.8, 119.5, 56.4, 27.6, 17.6; IR (neat): 3305, 3005, 2987, 2937, 1634, 1474, 1275, 1260, 787, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{12}H_{17}N_2O$ $[M+H]^+$: 205.1342, found: 205.1343.

General procedure for the synthesis of compounds 2:[18e] a solution of 2.0 mmol trimethylsilyl triflate and 40.0 mmol triethylsilane in 20 mL of CH_2C1_2 was added to a 100 mL flask with magnetic stir bar after charged with nitrogen, then the ketone (20.0 mmol) in 20 mL of CH_2C1_2 was added slowly at 0 °C. Then the reaction was allowed to stir at room temperature for 2 hours. The solvent was removed under reduce pressure, then the residue was purified by column chromatography on silica gel to afford product **2.**

Oxydicyclohexane (2b): TLC R_f = 0.6 (EtOAc/PE = 1:50); colorless oil, 561 mg, 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.29 (dt, *J* = 8.9, 4.0 Hz, 1H), 1.86 (m, 2H), 1.73 (m, 2H), 1.53 (m, 1H), 1.19 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 74.8, 33.5, 26.0, 24.7; HRMS (ESI) Calcd. for $C_{12}H_{23}O$ $[M+H]^+$: 183.1749, found: 183.1747.

Oxydicycloheptane (2c): TLC R_f = 0.5 (EtOAc/PE = 1:20); colorless oil, 1.40 g, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.37 (tt, *J* = 8.4, 4.2 Hz, 1H), 1.85–1.73 (m, 2H), 1.67–1.55 (m, 2H), 1.55–1.43 (m, 6H), 1.37–1.24 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 77.4, 34.8, 28.2, 23.1; HRMS (ESI) Calcd. for $C_{14}H_{27}O$ $[M+H]^+$: 211.2063, found: 211.2057.

Oxydicyclododecane (2d): TLC R_f = 0.6 (EtOAc/PE = 1:40); colorless oil, 3.19 g, 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50–3.41 (m, 1H), 1.65–1.52 (m, 2H), 1.49–1.23 (m, 20H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 73.9, 30.0, 24.5, 23.9, 23.5, 23.3, 21.1; HRMS (ESI) Calcd. for $C_{24}H_{46}NaO$ $[M+Na]^+$: 373.3447, found: 373.3437.

2-(pentan-2-yloxy)pentane (2f): TLC R_f = 0.5 (CH_2Cl_2/PE = 1:20); colorless oil, 820 mg, 52%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (dt, *J* = 11.9, 6.0 Hz, 1H), 1.50–1.25 (m, 4H), 1.09 (dd, *J* = 11.0, 6.1 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 73.2, 72.6, 39.8, 39.5, 21.1, 20.4, 19.0, 18.9, 14.23, 14.16; HRMS (ESI) Calcd. for $C_{10}H_{22}NaO$ $[M+Na]^+$: 181.1569, found: 181.1575.

2-(nonan-2-yloxy)nonane (2g): TLC R_f = 0.6 (PE); colorless oil, 2.30 g, 85%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (dt, *J* = 11.9, 6.0 Hz, 1H), 1.45 (dd, *J* = 13.2, 6.3 Hz, 1H), 1.39–1.21 (m, 11H), 1.09 (dd, *J* = 10.1, 6.1 Hz, 3H), 0.87 (t, *J* = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 73.4, 72.9, 37.5, 37.2, 31.9, 29.78, 29.74, 29.3, 25.9, 25.7, 22.7, 21.1, 20.4, 14.1; HRMS (ESI) Calcd. for $C_{18}H_{39}O$ $[M+H]^+$: 271.3002, found: 271.3001.

2-(tridecan-2-yloxy)tridecane (2h): TLC R_f = 0.4 (PE); colorless oil, 3.60 g, 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (dt, *J* = 11.9, 6.1 Hz, 1H), 1.51–1.43 (m, 1H), 1.40–1.20 (m, 19H), 1.09 (dd, *J* = 10.2, 6.1 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 73.4, 72.9, 37.6, 37.2, 31.9, 29.83, 29.79, 29.70, 29.68, 29.66, 29.37, 29.36, 25.9, 25.7, 22.7, 21.1, 20.5, 14.1; HRMS (ESI) Calcd. for $C_{26}H_{55}O$ $[M+H]^+$: 383.4254, found: 383.4260.

3-(heptan-3-yloxy)heptane (2i): TLC R_f = 0.6 (CH_2Cl_2/PE = 1:30); colorless oil, 2.05 g, 95%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.24–3.12 (m, 1H), 1.54–1.36 (m, 4H), 1.36–1.20 (m, 4H), 0.95–0.81 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 78.21, 78.16, 33.6, 33.5, 27.8, 27.6, 26.8, 26.7, 23.0, 14.1, 9.7, 9.6; HRMS (ESI) Calcd. for $C_{14}H_{30}NaO$ $[M+Na]^+$: 237.2195, found: 237.2200.

3-(pentan-3-yloxy)pentane (2j): TLC R_f = 0.6 (CH_2Cl_2/PE = 1:10); colorless oil, 1.30 g, 82%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.14 (m, 1H), 1.52–1.42 (m, 4H), 0.89 (t, J = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 79.5, 26.4, 9.7; HRMS (ESI) Calcd. for $C_{10}H_{22}NaO$ $[M+Na]^+$: 181.1569, found: 181.1577.

2-methyl-4-((4-methylpentan-2-yl)oxy)pentane (2k): TLC R_f = 0.7 (EtOAc/PE = 1:40); colorless oil, 1.04 g, 56%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.48 (ddd, J = 9.6, 6.9, 4.8 Hz, 1H), 1.76–1.64 (m, 1H), 1.43 (td, J = 13.8, 7.2 Hz, 1H), 1.18–1.03 (m, 4H), 0.88 (dd, J = 9.8, 4.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 71.8, 70.5, 47.2, 47.0, 24.52, 24.45, 23.0, 22.9, 22.85, 22.6, 21.6, 20.6; HRMS (ESI) Calcd. for $C_{12}H_{26}NaO$ $[M+Na]^+$: 209.1882, found: 209.1880.

2-methyl-5-((5-methylhexan-2-yl)oxy)hexane (2l): TLC R_f = 0.4 (PE); colorless oil, 1.93 g, 91%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.38 (dq, J = 13.1, 6.4 Hz, 1H), 1.57–1.41 (m, 2H), 1.41–1.31 (m, 1H), 1.30–1.20 (m, 1H), 1.20–1.05 (m, 4H), 0.88 (t, J = 10.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 73.7, 73.2, 35.3, 35.0, 34.9, 34.8, 28.16, 28.15, 22.69, 22.66, 22.56, 21.1, 20.4; HRMS (ESI) Calcd. for $C_{14}H_{30}NaO$ $[M+Na]^+$: 237.2195, found: 237.2197.

Oxydicyclobutane (2n): TLC R_f = 0.6 (CH_2Cl_2/PE = 1:10); colorless oil, 718 mg, 57%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (p, J = 7.4 Hz, 1H), 2.20–2.08 (m, 2H), 1.90 (qd, J = 10.3, 2.7 Hz, 2H), 1.65 (q, J = 10.1 Hz, 1H), 1.45 (qt, J = 10.7, 8.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 70.8, 30.8, 12.8; HRMS (ESI) Calcd. for $C_8H_{15}O$ $[M+H]^+$: 127.1124, found: 127.1126.

(Octyloxy)cyclohexane (2p):[18e] To a 100 mL flask with magnetic stir bar was added 30.0 mmol 1-Octanol, 60.0 mmol Imidazole and 30 mL of CH_2C1_2, then 36.0 mmol TMSCl was added slowly at 0 °C. The reaction was allowed to stir at room temperature for 2 hours. The solvent was removed under reduce pressure, then the residue was purified by column chromatography on silica gel to afford trimethyl(octyloxy)silane. To a 100 mL two-neck flask with magnetic stirring bar, and nitrogen inlet

was added powdered iodine (0.70 mmol) and hexamethyldisilane (0.77 mmol) in 14 mL of CH_2C1_2. The solution was stirred at room temperature for 10 min and then cooled to 0 °C and a solution of Cyclohexanone (14.0 mmol) and trimethyl(octyloxy)silane (14.0 mmol) in 20 mL of CH_2C1_2 was added via syringe. The reaction was stirred for 10 min more at 0 °C, then triethylsilane was added slowly via syringe until the color changes from violet to red-gold, during of which the solution was warmed from 0 °C to 24 °C, and then the reaction was stirred at room temperature for 2 hours. The solvent was removed under reduce pressure, then the residue was purified by column chromatography on silica gel to afford product **2p** as colorless oil, 1.98 g, 31% (based on 1-Octanol); TLC R_f = 0.5 (AcOEt/PE = 1:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.42 (t, *J* = 6.8 Hz, 2H), 3.24–3.13 (m, 1H), 1.94–1.85 (m, 2H), 1.73 (m, 2H), 1.53 (m, 2H), 1.36–1.18 (m, 16H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 77.4, 68.0, 32.4, 31.8, 30.3, 29.5, 29.3, 26.3, 25.9, 24.3, 22.7, 14.1; HRMS (ESI) Calcd. for $C_{14}H_{28}NaO$ $[M+Na]^+$: 235.2038, found: 235.2034.

General procedure for the synthesis of compounds 3: A screw capped 25 mL oven-dried Schlenk tube was charged with Teflon spinbar, benzamide **1** (0.2 mmol) and $Co(acac)_2$ (10.3 mg, 0.04 mmol, 20 mol %), then ether **2** (4.0 mmol), DTBP (117.0 mg, 0.8 mmol, 4.0 equiv) and benzene (1.0 mL) were injected by syringe behind the tube was evacuated and filled with N_2. The reaction mixture was stirred intensively at 140 °C for 24 h. Then the reaction mixture was cooled to room temperature, disposed under reduced pressure and the residue was purified by chromatography on silica gel (EtOAc/PE) to give the desired product **3**.

2-isopropyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3aa): TLC R_f = 0.5 (EtOAc/PE = 1:5); white solid; 51.5 mg, yield: 87%; m.p.: 118-119 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.3 Hz, 1H), 8.10 (s, 1H), 7.73 (td, *J* = 7.9, 1.7 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 5.0, 4.1 Hz, 2H), 7.03 (d, *J* = 7.3 Hz, 1H), 3.16 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.37 (s, 3H), 1.92 (s, 6H), 1.26 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.5, 145.2, 137.9, 137.1, 134.0, 128.5, 127.5, 122.8, 121.9, 119.4, 57.1, 30.6, 27.4, 24.4, 19.3.; IR (neat): 3333, 3063, 2963, 2929, 2868, 1660, 1594, 1501, 788, 764 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1968, found: 297.1973.

2-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)-6-(trifluoromethyl)benzamide (3ba): TLC R_f = 0.7 (EtOAc/PE = 1:5); white solid; 62.3 mg, yield: 89%; m.p.: 73-74 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 – 8.39 (m, 1H), 8.35 (s, 1H), 7.73 (td, *J* = 7.9, 1.7 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.0 Hz, 1H), 7.45 (dd, *J* = 7.6, 7.0 Hz, 2H), 7.19 – 7.15 (m, 1H), 3.27 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.91 (d, *J* = 20.2 Hz, 6H), 1.27 (t, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 164.0, 147.5, 147.3, 137.2, 135.5, 129.5, 128.8, 126.8 (q, $^2J_{C\text{-}F}$ = 30 Hz), 125.4, 123.5 (q, $^3J_{C\text{-}F}$ = 5 Hz), 122.7, 120.7 (d, $^1J_{C\text{-}F}$ = 251 Hz, CF_3), 57.3, 30.2, 27.1, 26.8, 24.6, 24.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.47; IR (neat): 3324, 3058, 2969, 2933, 2872, 1669, 1594, 1505, 1128, 765, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{22}F_3N_2O$ $[M+H]^+$: 351.1685, found: 351.1684.

2-isopropyl-6-methoxy-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ca): TLC R_f = 0.4 (EtOAc/PE = 1:5); white solid; 33.1 mg, yield: 53%; m.p.: 121-122 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.40 (m, 1H), 7.76 (s, 1H), 7.71 – 7.65 (m, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.11 (m, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 3.79 (s, 3H), 3.17 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.2, 164.5, 155.9, 147.6, 147.4, 136.9, 129.6, 127.5, 121.7, 119.5, 117.7, 108.4, 57.4, 55.9, 30.3, 27.7, 24.2; IR (neat): 3308, 3065, 2967, 2868, 2837, 1655, 1596, 1514, 787, 752 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1917, found: 313.1916.

2-fluoro-6-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3da): TLC R_f = 0.6 (EtOAc/PE = 1:5); white solid; 43.8 mg, yield: 73%; m.p.: 91-92 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.6 Hz, 1H), 8.12 (s, 1H), 7.73 (td, *J* = 8.0, 1.6 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.18 (dd, *J* = 7.0, 5.2 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.93 (t, *J* = 8.6 Hz, 1H), 3.24 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.90 (s, 6H), 1.27 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.5, 164.1, 158.9 (d, $^1J_{C\text{-}F}$ = 246 Hz), 148.8 (d, $^4J_{C\text{-}F}$ = 3 Hz), 147.5, 137.1, 130.1 (d, $^3J_{C\text{-}F}$ = 9 Hz), 125.8 (d, $^2J_{C\text{-}F}$ = 18 Hz), 121.9, 121.2 (d, $^4J_{C\text{-}F}$ = 3 Hz), 119.4, 112.8 (d, $^2J_{C\text{-}F}$ = 22 Hz), 57.4, 30.32, 30.31, 27.5, 24.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.33； IR (neat): 3321, 2967, 2931, 2870, 1666, 1614, 1504, 1472, 787, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{22}FN_2O$ $[M+H]^+$: 301.1717, found: 301.1718.

2-chloro-6-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ea): TLC R_f = 0.6 (EtOAc/PE = 1:5); primrose solid; 33.5 mg, yield: 53%; m.p.: 100-101 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.3 Hz, 1H), 8.19 (s, 1H), 7.73 (td, *J* = 8.0, 1.7 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.26 (dd, *J* = 6.2, 3.1 Hz, 2H), 7.22 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.20 – 7.16 (m, 1H), 3.18 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.92 (s, 6H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 164.1, 147.9, 147.4, 137.2, 136.9, 130.5, 129.7, 126.8, 124.0, 121.9, 119.5, 57.4, 30.9, 27.3, 24.3; IR (neat): 3322, 3058, 2966, 2931, 2870, 1664, 1592, 1472, 788, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{22}ClN_2O$ $[M+H]^+$: 317.1421, found: 317.1426.

2-bromo-6-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3fa): TLC R_f = 0.7 (EtOAc/PE = 1:5); primrose solid; 63.3 mg, yield: 88%; m.p.: 95-96 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.6 Hz, 1H), 8.20 (s, 1H), 7.73 (td, *J* = 7.9, 1.6 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 2H), 3.17 (dd, *J* = 13.8, 6.9 Hz, 1H), 1.93 (s, 6H), 1.26 (d, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.0, 164.1, 148.1, 147.4, 138.8, 137.2, 130.0, 124.6, 122.8, 121.9, 119.6, 119.5, 57.4, 31.1, 27.3, 24.3; IR (neat): 3323, 2966, 2931, 2867, 1665, 1592, 1502, 787, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{22}BrN_2O$ $[M+H]^+$: 361.0916, found: 361.0918.

2-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)-5-(trifluoromethyl)benzamide (3ga): TLC R_f = 0.7 (EtOAc/PE = 1:5); white solid; 50.4 mg, yield: 72%; m.p.: 85-86 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.41 (m, 1H), 8.27 (s, 1H), 7.74 (td, *J* = 8.1 Hz, 1H), 7.64 (s, 1H), 7.63-7.60 (d, *J* =12.0 Hz, 1H), 7.47 (t, *J* = 8.8 Hz, 2H), 7.20 (dd, *J* = 6.9, 5.1 Hz, 1H), 3.45 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.90 (s, 6H), 1.29 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.3, 164.0, 150.5, 147.5, 138.0, 137.3, 128.0 (q, $^2J_{C\text{-}F}$ = 32 Hz), 126.6, 126.2 (q, $^3J_{C\text{-}F}$ = 3 Hz), 125.4, 123.8 (q, $^3J_{C\text{-}F}$ = 3 Hz), 122.7, 120.7 (d, $^1J_{C\text{-}F}$ = 266 Hz, CF_3), 57.2, 30.0, 27.4, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.37; IR (neat): 3315, 3061, 2970, 2933, 2873, 1664, 1617, 1473, 1125, 837, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{22}F_3N_2O$ $[M+H]^+$: 351.1685, found: 351.1688.

methyl 4-isopropyl-3-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)benzoate (3ha(mono)): TLC R_f = 0.7 (EtOAc/PE = 1:5); primrose solid; 44.2 mg, yield: 58%; m.p.: 88-89 ℃; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.44 (d, *J* = 4.3 Hz, 1H), 8.19 (s, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 8.01 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.73 (td, *J* = 8.0, 1.7 Hz, 1H), 7.44 (t, *J* = 8.7 Hz, 2H), 7.20 – 7.15 (m, 1H), 3.90 (s, 3H), 3.45 (dt, *J* = 13.7, 6.8 Hz, 1H), 1.89 (s, 6H), 1.27 (d, *J* = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.7, 166.6, 164.1, 151.9, 147.6, 137.7, 137.2, 130.5, 128.0, 127.6, 126.2, 122.0, 119.4, 57.2, 52.1, 30.1, 27.4, 23.9; IR (neat): 3324, 3057, 2967, 2870, 1723, 1664, 1473, 1255, 786, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1866, found: 341.1868.

methyl 2,4-diisopropyl-3-((2-(pyridin-2-yl)propan-2-yl)carbamoyl)benzoate (3ha(di)): TLC R_f = 0.5 (EtOAc/PE = 1:5); primrose solid; 16.0 mg, yield: 21%; m.p.: 93-94 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.2 Hz, 1H), 8.29 (s, 1H), 7.73 (td, *J* = 8.0, 1.7 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.18 (dd, *J* = 7.0, 5.3 Hz, 1H), 3.89 (s, 3H), 3.37 (dt, *J* = 14.3, 7.1 Hz, 1H), 3.14 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.91 (s, 6H), 1.39 (d, *J* = 7.2 Hz, 3H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 170.9, 168.7, 164.0, 148.3, 147.4, 142.5, 138.6, 137.2, 130.1, 129.6, 123.1, 122.0, 119.4, 57.2, 52.2, 31.8, 30.7, 27.2, 27.1, 24.6, 23.9, 22.6, 21.8; IR (neat): 3326, 2965, 2931, 2867, 1728, 1660, 1471, 1275, 1123, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{31}N_2O_3$ $[M+H]^+$: 383.2335, found: 383.2338.

2-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ia): TLC R_f = 0.7 (EtOAc/PE = 1:5); Colorless crystal; 47.9 mg, yield: 74%; m.p.: 140-141 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42–8.38 (m, 1H), 8.16 (s, 1H), 7.72 (m, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.16 (m, 1H), 3.17 (m, 2H), 1.93 (s, 6H), 1.27 (m, 12H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.4, 145.0, 137.1,137.0, 128.8, 122.8, 121.9, 119.4, 57.1, 30.6, 27.3, 24.8, 24.2; IR (neat): 3333, 3063, 2964, 2929, 2868, 1660, 1594, 1501, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{29}N_2O$ $[M+H]^+$: 325.2281, found: 325.2285.

4-fluoro-2,6-diisopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ja): TLC R_f = 0.6 (EtOAc/PE = 1:5); white solid; 50.6 mg, yield: 74%; m.p.: 103-104 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.5 Hz, 1H), 8.24 (s, 1H), 7.77–7.71 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.19 (dd, *J* = 6.9, 5.3 Hz, 1H), 6.86 (d, *J* = 10.2 Hz, 2H), 3.18 (dt, *J* = 13.4, 6.7 Hz, 2H), 1.92 (s, 6H), 1.28–1.23 (m, 12H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.6, 164.1, 163.3 (d, $^1J_{C-F}$ = 245 Hz), 148.0 (d, $^3J_{C-F}$ = 7

Hz), 147.4, 137.2, 133.1 (d, $^4J_{C\text{-}F}$ = 3 Hz), 122.0, 119.4, 109.8 (d, $^2J_{C\text{-}F}$ = 22 Hz), 57.1, 30.7, 27.3, 24.6, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.50; IR (neat): 3334, 2965, 2932, 2871, 1660, 1597, 1470, 1167, 786, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{28}FN_2O$ $[M+H]^+$: 343.2186, found: 343.2189.

4-chloro-2,6-diisopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ka): TLC R_f = 0.7 (EtOAc/PE = 1:5); white solid; 52.3 mg, yield: 73%; m.p.: 150-151 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.4 Hz, 1H), 8.25 (s, 1H), 7.73 (dd, *J* = 11.1, 4.4 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.17 (dd, *J* = 6.9, 5.4 Hz, 1H), 7.13 (s, 2H), 3.12 (dq, *J* = 13.5, 6.7 Hz, 2H), 1.90 (s, 6H), 1.24 (dd, *J* = 6.4, 4.6 Hz, 12H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.4, 164.0, 147.4,147.3, 137.2, 135.4, 134.7, 123.3, 122.0, 119.4, 57.1, 30.7, 27.3, 24.6, 24.0; IR (neat): 3325, 2964, 2932, 2870, 1661, 1580, 1500, 900, 764, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{28}ClN_2O$ $[M+H]^+$: 359.1891, found: 359.1893.

4-cyano-2-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3la(mono)): TLC R_f = 0.5 (EtOAc/PE = 1:5); primrose solid; 13.5 mg, yield: 22%; m.p.: 180-181 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.3 Hz, 1H), 8.35 (s, 1H), 7.76 (td, *J* = 7.9, 1.7 Hz, 1H), 7.65 (s, 1H), 7.54–7.47 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.21 (dd, *J* = 6.7, 5.0 Hz, 1H), 3.42 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.89 (s, 6H), 1.27 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.8, 163.8, 147.8, 147.5, 141.5, 137.4, 130.2, 129.4, 127.6, 122.2, 119.5, 118.7, 113.3, 57.2, 29.9, 27.4, 23.9; IR (neat): 3251, 3054, 2970, 2921, 2851, 2231, 1640, 1592, 1543, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{22}N_3O$ $[M+H]^+$: 308.1764, found: 308.1769.

4-cyano-2,6-diisopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3la(di)): TLC R_f = 0.7 (EtOAc/PE = 1:5); white solid; 36.3 mg, yield: 52%; m.p.: 149-150 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.6 Hz, 1H), 8.35 (s, 1H), 7.75 (dd, *J* = 11.1, 4.3 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 3H), 7.19 (dd, *J* = 6.9, 5.4 Hz, 1H), 3.15 (dt, *J* = 13.6, 6.8 Hz, 2H), 1.90 (s, 6H), 1.25 (dd, *J* = 6.6, 3.9 Hz, 12H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.30, 163.7, 147.4, 146.6, 140.9, 137.4, 127.1, 122.1, 119.4, 119.2, 112.8, 57.3, 30.6, 27.3, 24.5, 23.9; IR (neat): 3320, 2966, 2933, 2871, 2229, 1663, 1594, 1503, 1470, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{28}N_3O$ $[M+H]^+$: 350.2233, found: 350.2234.

6-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)-2,3-dihydrobenzo[b][1,4]dioxine-5-carboxamide (3ma): TLC R_f = 0.3 (EtOAc/PE = 1:5); primrose oil; 38.1 mg, yield: 56 %; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.45 (dd, *J* = 4.8, 0.7 Hz, 1H), 7.94 (s, 1H), 7.71 (td, *J* = 7.9, 1.8 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.19–7.15 (m, 1H), 6.83 (dd, *J* = 20.3, 8.5 Hz, 2H), 4.25 (m, 4H), 3.10 (m, 1H), 1.89 (s, 6H), 1.22 (d, *J* = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 164.4, 147.5, 141.3, 139.9, 139.1, 137.0, 127.3, 121.8, 119.5, 118.0, 117.5, 64.5, 64.1, 57.4, 29.8, 27.6, 24.4; IR (neat): 3326, 3053, 2969, 2931, 2874, 1655, 1590, 1487, 1286, 1086, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{25}N_2O_3$ $[M+H]^+$: 341.1866, found: 341.1868.

2-isopropyl-4,6-dimethyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3na): TLC R_f = 0.6 (EtOAc/PE = 1:5); white solid; 42.8 mg, yield: 69%; m.p.: 80-81 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.3 Hz, 1H), 8.08 (s, 1H), 7.72 (td, *J* = 8.0, 1.7 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.17 (dd, *J* = 7.0, 5.3 Hz, 1H), 6.98 (s, 1H), 6.86 (s, 1H), 3.15 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 1.92 (s, 6H), 1.25 (d, *J* = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.6, 164.4, 147.5, 145.2, 138.1, 137.1, 135.3, 134.0, 128.3, 123.3, 121.9, 119.4, 57.0, 30.5, 27.4, 24.4, 21.4, 19.2; IR (neat): 3336, 2964, 2927, 2868, 1656, 1609, 1501, 1470, 877, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2124, found: 311.2126.

2,4-difluoro-6-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3oa): TLC R_f = 0.6 (EtOAc/PE = 1:5); white solid; 26.1 mg, yield: 41 %; m.p.: 84-85 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.2 Hz, 1H), 8.19 (s, 1H), 8.07 (m, 1H), 7.71 (td, *J* = 8.0, 1.7 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.18 (dt, *J* = 14.4, 6.3 Hz, 1H), 6.89–6.81 (m, 1H), 3.26 (dt, *J* = 13.6, 6.6 Hz, 1H), 1.85 (s, 6H), 1.23 (d, *J* = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.1, 163.7, 151.0 (d, $^4J_{C\text{-}F}$ = 4 Hz), 150.9 (d, $^4J_{C\text{-}F}$ = 4 Hz), 147.6, 137.3, 120.8 (d, $^1J_{C\text{-}F}$ = 256 Hz), 108.7 (d, $^4J_{C\text{-}F}$ = 3 Hz), 108.5 (d, $^4J_{C\text{-}F}$ = 3 Hz), 101.7, 101.44, 101.18, 57.5, 30.5, 27.5, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.74, -108.76, -113.34, -113.36; IR (neat): 3330, 3057, 2976, 2934, 2871, 1664, 1593, 1473, 1108, 768, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{21}F_2N_2O$ $[M+H]^+$: 319.1623, found: 319.1621.

3-fluoro-2-isopropyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3pa): TLC R_f = 0.5 (EtOAc/PE = 1:5); white solid; 50.9 mg, yield: 81%; m.p.: 111-112 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.3 Hz, 1H), 8.15 (s, 1H), 7.73 (td, *J* = 8.0, 1.6 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.21–7.15 (m, 1H), 6.98 (dd, *J* = 8.3, 5.0 Hz, 1H), 6.90 (dd, *J* = 11.5, 8.4 Hz, 1H), 3.11 (dt, *J* = 14.0,

7.0 Hz, 1H), 2.32 (s, 3H), 1.91 (s, 6H), 1.35 (d, J = 7.0 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.3 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 164.1, 160.4 (d, $^{1}J_{C\text{-}F}$ = 246 Hz), 147.5, 139.4(d, $^{3}J_{C\text{-}F}$ = 6 Hz), 137.2, 131.4, 131.2, 129.7 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 128.8 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 122.0, 119.4, 116.0 (d, $^{2}J_{C\text{-}F}$ = 23 Hz), 57.1, 30.3, 27.3, 21.6, 18.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.47; IR (neat): 3323, 2974, 2932, 2875, 1663, 1563, 1502, 1473, 814, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{24}FN_2O$ $[M+H]^+$: 315.1873, found: 315.1874.

3-chloro-2-isopropyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3qa): TLC R_f = 0.5 (EtOAc/PE = 1:5); white solid; 46.8 mg, yield: 71%; m.p.: 120-121 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 4.8 Hz, 1H), 8.17 (s, 1H), 7.73 (td, J = 8.0, 1.7 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.23–7.16 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 3.39 (d, J = 6.0 Hz, 1H), 2.32 (s, 3H), 1.91 (s, 6H), 1.43 (dd, J = 6.9, 4.5 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.6, 164.0, 147.4, 140.6, 140.3, 137.2, 133.3, 131.2, 130.9, 128.9, 122.0, 119.4, 57.1, 32.3, 27.2, 20.7, 20.4, 19.0; IR (neat): 3321, 2974, 2931, 2873, 1663, 1593, 1501, 1472, 1125, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{19}H_{24}ClN_2O$ $[M+H]^+$: 331.1578, found: 331.1580.

5-chloro-3-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)thiophene-2-carboxamide (3ra): TLC R_f = 0.7 (EtOAc/PE = 1:5); primrose solid; 27.1 mg, yield: 42 %; m.p.: 74-75 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.51 (d, J = 4.8 Hz, 1H), 7.75 (td, J = 7.9, 1.7 Hz, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.22 (dd, J = 7.2, 5.2 Hz, 1H), 6.86 (s, 1H), 3.70 (m, 1H), 1.84 (s, 6H), 1.26 (d, J = 6.9 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 164.2, 161.2, 150.7, 147.4, 137.4, 131.5, 131.5, 126.6, 122.0, 119.4, 57.3, 28.3, 27.5, 23.7; IR (neat): 3302, 2969, 2926, 2869, 2379, 2316, 1655, 1484, 848, 786 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{20}ClN_2OS$ $[M+H]^+$: 323.0986, found: 323.0980.

(Z)-2,3,4-trimethyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pent-2-enamide (3sa): TLC R_f = 0.5 (EtOAc/PE = 1:5); white solid; 42.6 mg, yield: 82 %; m.p.: 83-84 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 4.8 Hz, 1H), 7.77–7.68 (m, 2H), 7.41 (d, J = 8.1 Hz, 1H), 7.17 (dd, J = 7.3, 4.9 Hz, 1H), 2.94 (dt, J = 13.6, 6.8 Hz, 1H), 1.84 (s, 3H), 1.79 (s, 6H), 1.57 (s, 3H), 1.00 (d, J = 6.8 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 172.0, 164.6, 147.5, 139.2, 137.0, 127.4, 121.8, 119.4, 56.5, 32.1,

27.5, 21.0, 16.3, 11.2; IR (neat): 3336, 2963, 2871, 2374, 2362, 2339, 2320, 1657, 1468, 871 cm^{-1}; HRMS (ESI) Calcd. for $C_{16}H_{25}N_2O$ $[M+H]^+$: 261.1968, found: 261.1966.

(Z)-3-ethyl-2,4-dimethyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pent-2-enamide (3ta): TLC R_f = 0.5 (EtOAc/PE = 1:3); Colorless oil; 26.3 mg, yield: 48 %; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 4.8 Hz, 1H), 7.74–7.64 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.17 (dd, *J* = 7.3, 5.0 Hz, 1H), 2.94 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.02 (q, *J* = 7.6 Hz, 2H), 1.86 (s, 3H), 1.79 (s, 6H), 1.03 (dd, *J* = 13.5, 7.2 Hz, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.1, 164.6, 147.5, 144.6, 137.0, 128.2, 121.7, 119.4, 56.5, 32.5, 27.5, 21.4, 19.5, 16.0, 14.2; IR (neat): 3343, 3053, 2967, 2933, 2873, 1652, 1499, 1472, 787, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2124, found: 275.2120.

2-isopropyl-*N*-(2-(pyridin-2-yl)propan-2-yl)cyclohex-1-enecarboxamide (3ua): TLC R_f = 0.5 (EtOAc/PE = 1:4); white solid; 21.8 mg, yield: 38 %; m.p.: 85-86 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51–8.47 (m, 1H), 7.75–7.67 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.19–7.15 (m, 1H), 2.95 (dt, *J* = 13.7, 6.8 Hz, 1H), 2.25 (d, *J* = 2.0 Hz, 2H), 1.98 (d, *J* = 1.9 Hz, 2H), 1.79 (s, 6H), 1.64–1.58 (m, 4H), 1.00 (d, *J* = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.6, 164.7, 147.5, 140.9, 137.0, 129.6, 121.8, 119.4, 56.5, 31.3, 27.5, 27.3, 22.51, 22.49, 22.1, 21.0; IR (neat): 3344, 2961, 2931, 2867, 2837, 1648, 1498, 1471, 787, 748 cm^{-1}; HRMS (ESI) Calcd. for $C_{18}H_{27}N_2O$ $[M+H]^+$: 287.2124, found: 287.2123.

(*Z*)-3,4-dimethyl-*N*-(2-(pyridin-2-yl)propan-2-yl)pent-2-enamide (3va): TLC R_f = 0.5 (EtOAc/PE = 1:3); white solid; 9.9 mg, yield: 20 %; m.p.: 43-44 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 1H), 7.70 (td, *J* = 7.9, 1.7 Hz, 1H), 7.55 (s, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.17 (dd, *J* = 7.0, 5.3 Hz, 1H), 5.66 (d, *J* = 29.8 Hz, 1H), 3.90 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.77 (s, 6H), 1.74 (d, *J* = 1.1 Hz, 3H), 1.04 (dd, *J* = 14.8, 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 164.8, 157.3, 147.6, 137.0, 121.7, 119.6, 119.5, 56.4, 28.8, 27.7, 20.8, 18.6; IR (neat): 3325, 3044,2987, 1655, 1502, 1473, 1275, 1261, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{15}H_{23}N_2O$ $[M+H]^+$: 247.1811, found: 247.1808.

2-cyclohexyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ab): TLC R_f = 0.6 (EtOAc/PE = 1:5); primrose solid; 45.7 mg, yield: 68 %; m.p.: 75-76 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.7 Hz, 1H), 8.02 (s, 1H), 7.76–7.70 (m, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H),

7.20–7.16 (m, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 2.75 (ddd, *J* = 11.7, 7.5, 3.1 Hz, 1H), 2.37 (s, 3H), 1.93 (s, 6H), 1.92–1.87 (m, 2H), 1.76 (s, 2H), 1.67 (s, 2H), 1.43 (dd, *J* = 24.2, 12.1 Hz, 2H), 1.27–1.23 (m, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.5, 144.2, 138.1, 137.1, 134.1, 128.4, 127.4, 123.5, 121.9, 119.4, 57.0, 41.2, 27.4, 27.0, 26.2, 19.3; IR (neat): 3326, 2927, 2852, 1659, 1593, 1472, 1275, 1124, 786, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{29}N_2O$ $[M+H]^+$: 337.2281, found: 337.2283.

2-cycloheptyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ac): TLC R_f = 0.7 (EtOAc/PE = 1:5); white solid; 56.0 mg, yield: 80 %; m.p.: 95-96 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 4.8 Hz, 1H), 8.05 (s, 1H), 7.73 (td, *J* = 7.9, 1.7 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.24–7.16 (m, 2H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 2.95–2.80 (m, 1H), 2.36 (s, 3H), 1.93 (s, 6H), 1.77–1.37 (m, 12H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.5, 146.3, 137.2, 137.1， 134.0, 128.5, 127.1, 123.6, 121.9, 119.5, 57.0, 42.8, 27.8, 27.5, 27.4, 19.3; IR (neat): 3334, 2926, 2855, 1659, 1593, 1500, 1471, 1123, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{31}N_2O$ $[M+H]^+$: 351.2437, found: 351.2440.

2-cyclododecyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ad): TLC R_f = 0.6 (EtOAc/PE = 1:3); primrose solid; 55.5 mg, yield: 66 %; m.p.: 83-84 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.2 Hz, 1H), 8.16 (s, 1H), 7.75 (td, *J* = 7.9, 1.7 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.22–7.16 (m, 2H), 7.04 (d, *J* = 7.3 Hz, 1H), 3.06 (p, *J* = 6.6 Hz, 1H), 2.38 (s, 3H), 1.98 (s, 6H), 1.78 (s, 2H), 1.55 (dd, *J* = 13.0, 6.9 Hz, 2H), 1.44–1.20 (m, 18H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.4, 164.3, 147.4, 144.2, 138.9, 137.1, 134.1, 128.3, 127.4, 124.4, 121.9, 119.4, 57.0, 36.5, 32.1, 27.3, 24.1, 23.9, 23.3, 23.2, 19.4; IR (neat): 3336, 3062, 2931, 2861, 1659, 1499, 1470, 1444, 765, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{28}H_{40}N_2NaO$ $[M+Na]^+$: 443.3039, found: 443.3038.

2-(sec-butyl)-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ae): TLC R_f = 0.6 (EtOAc/PE = 1:5); primrose solid; 52.1 mg, yield: 84 %; m.p.: 91-92 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.4 Hz, 1H), 8.07 (s, 1H), 7.72 (td, *J* = 8.0, 1.7 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.16 (dd, *J* = 6.9, 5.3 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 2.87 (dd, *J* =

14.0, 6.9 Hz, 1H), 2.37 (s, 3H), 1.92 (s, 6H), 1.68 (dt, *J* = 14.8, 7.4 Hz, 1H), 1.60–1.52 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.5, 144.2, 138.5, 137.1, 134.0, 128.5, 127.4, 123.0, 121.9, 119.4, 57.0, 37.7, 31.1, 27.4, 22.4, 19.3, 12.5; IR (neat): 3335, 3064, 2964, 2930, 2872, 1660, 1594, 1500, 787, 766 cm^{-1}; HRMS (ESI) Calcd. for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2124, found: 311.2125.

2-methyl-6-(pentan-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3af): TLC R_f = 0.4 (EtOAc/PE = 1:5); primrose oil; 42.1 mg, yield: 65 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.5 Hz, 1H), 8.11 (s, 1H), 7.72 (td, *J* = 7.9, 1.7 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.19–7.15 (m, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 2.96 (h, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 1.92 (s, 6H), 1.70–1.61 (m, 1H), 1.52 (dt, *J* = 16.6, 6.3 Hz, 1H), 1.35–1.27 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.16 (ddd, *J* = 15.9, 9.3, 4.4 Hz, 1H), 0.81 (t, *J* = 6.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.4, 144.4, 138.4, 137.1, 134.0, 128.5, 127.4, 123.1, 121.9, 119.4, 57.0, 40.6, 35.8, 27.3, 22.9, 21.0, 19.3, 14.2; IR (neat): 3335, 2958, 2929, 2870, 1660, 1500, 1470, 1275, 787, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{28}N_2NaO$ $[M+Na]^+$: 347.2100, found: 347.2101.

2-methyl-6-(nonan-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ag): TLC R_f = 0.6 (EtOAc/PE = 1:4); primrose oil; 40.3 mg, yield: 53 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.4 Hz, 1H), 8.08 (s, 1H), 7.75–7.70 (m, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.2, 5.0 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 2.94 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.37 (s, 3H), 1.92 (s, 6H), 1.69–1.62 (m, 1H), 1.54–1.48 (m, 1H), 1.22 (dd, *J* = 23.6, 16.8 Hz, 13H), 0.81 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.4, 144.5, 138.4, 137.1, 134.0, 128.4, 127.3, 123.1, 121.9, 119.4, 57.0, 38.4, 36.1, 31.8, 29.7, 29.2, 27.4, 27.3, 22.9, 22.7, 22.6, 19.3, 14.1; IR (neat): 3337, 2957, 2926, 2855, 1661, 1594, 1500, 1470, 787, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{25}H_{37}N_2O$ $[M+H]^+$: 381.2907, found: 381.2906.

2-methyl-6-(tridecan-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ah): TLC R_f = 0.6 (EtOAc/PE = 1:4); primrose oil; 46.3 mg, yield: 53 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.4 Hz, 1H), 8.10 (s, 1H), 7.72 (td, *J* = 7.9, 1.7 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.19–7.15 (m, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 2.94 (dt, *J* = 14.1, 7.0 Hz, 1H),

2.37 (s, 3H), 1.92 (s, 6H), 1.65 (ddd, *J* = 13.1, 9.1, 4.0 Hz, 1H), 1.54–1.47 (m, 1H), 1.27–1.14 (m, 21H), 0.87 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.4, 144.5, 138.4, 137.1, 134.0, 128.4, 127.3, 123.1, 121.9, 119.4, 57.0, 36.1, 31.9, 29.8, 29.6, 29.5, 29.3, 27.3, 22.9, 22.7, 19.3, 14.1; IR (neat): 3337, 2956, 2925, 2853, 1661, 1594, 1500, 1469, 787, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{29}H_{45}N_2O$ $[M+H]^+$: 437.3533, found: 437.3533.

2-(heptan-3-yl)-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ai): TLC R_f = 0.6 (EtOAc/PE = 1:5); primrose oil; 55.6 mg, yield: 79 %; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.7 Hz, 1H), 8.05 (s, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.3, 5.0 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 2.85–2.62 (m, 1H), 2.37 (s, 3H), 1.92 (s, 6H), 1.70–1.50 (m, 4H), 1.23 (dd, *J* = 14.3, 5.8 Hz, 4H), 0.78 (t, *J* = 7.3 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.2, 164.3, 147.4, 142.8, 139.4, 137.0, 133.9, 128.3, 127.3, 123.2, 121.8, 119.4, 57.0, 43.4, 36.6, 29.9, 27.3, 23.0, 19.4, 14.0, 12.3; IR (neat): 3337, 2959, 2929, 2858, 1661, 1594, 1499, 1470, 787, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{33}N_2O$ $[M+H]^+$: 353.2594, found: 353.2590.

2-methyl-6-(pentan-3-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3aj): TLC R_f = 0.7 (EtOAc/PE = 1:5); primrose solid; 43.4 mg, yield: 67 %; m.p.: 72-73 ℃; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.8, 0.6 Hz, 1H), 8.06 (s, 1H), 7.75 (td, *J* = 7.9, 1.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.19 (ddd, *J* = 7.4, 4.9, 0.8 Hz, 1H), 7.07 (dd, *J* = 14.8, 7.6 Hz, 2H), 2.69 (tt, *J* = 8.7, 5.8 Hz, 1H), 2.40 (s, 3H), 1.94 (s, 6H), 1.67 (ddd, *J* = 27.9, 17.3, 10.2 Hz, 4H), 0.81 (t, J = 7.4 Hz, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.2, 164.3, 147.4, 142.5, 139.6, 137.0, 133.9, 128.3, 127.3, 123.2, 121.9, 119.5, 57.0, 44.9, 29.5, 27.4, 19.4, 12.3; IR (neat): 3336, 2963, 2930, 2873, 1660, 1500, 1471, 1123, 765, 749 cm^{-1}; HRMS (ESI) Calcd. for $C_{21}H_{29}N_2O$ $[M+H]^+$: 325.2281, found: 325.2285.

2-methyl-6-(4-methylpentan-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ak): TLC R_f = 0.6 (EtOAc/PE = 1:4); primrose oil; 50.1 mg, yield: 74 %; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.7 Hz, 1H), 8.13 (s, 1H), 7.72 (td, *J* = 7.8, 1.7 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.2, 5.0 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 3.05 (dd, *J* = 14.1,

7.1 Hz, 1H), 2.37 (s, 3H), 1.93 (d, *J* = 3.2 Hz, 6H), 1.64–1.57 (m, 1H), 1.50 (s, 1H), 1.38 (d, *J* = 5.1 Hz, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.86–0.76 (m, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.2, 164.3, 147.4, 144.5, 138.4, 137.1, 134.1, 128.5, 127.4, 123.2, 121.9, 119.4, 57.0, 47.4, 33.8, 27.3, 25.7, 23.2, 22.7, 19.3, 14.1; IR (neat): 3335, 3064, 2956, 2928, 2867, 1660, 1500, 1470, 787, 765, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{22}H_{30}N_2NaO$ $[M+Na]^+$: 361.2256, found: 361.2257.

2-methyl-6-(5-methylhexan-2-yl)-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3al): TLC R_f = 0.6 (EtOAc/PE = 1:4); primrose oil; 41.6 mg, yield: 59 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.7 Hz, 1H), 8.09 (s, 1H), 7.72 (td, *J* = 7.9, 1.7 Hz, 1H), 7.47–7.43 (m, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.16 (dd, *J* = 7.3, 5.0 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 1H), 2.90 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.37 (s, 3H), 1.92 (s, 6H), 1.66 (ddd, *J* = 11.5, 7.7, 2.5 Hz, 1H), 1.52 (dd, *J* = 12.5, 6.2 Hz, 1H), 1.27–1.14 (m, 5H), 0.87 (dd, *J* = 15.7, 8.6 Hz, 3H), 0.76 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.3, 164.3, 147.4, 144.4, 138.5, 137.1, 134.0, 128.5, 127.3, 123.0, 121.9, 119.4, 57.0, 36.3, 36.1, 28.1, 27.4, 27.3, 23.0, 22.6, 22.5, 19.3; IR (neat): 3336, 3063, 2955, 2928, 2868, 1600, 1500, 1470, 787, 764, 750 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{32}N_2NaO$ $[M+Na]^+$: 375.2413, found: 375.2412.

2-benzyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3am): TLC R_f = 0.3 (EA:PE = 1:5); primrose solid; yield: 40 %; m.p.: 115-116 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.7 Hz, 1H), 7.98 (s, 1H), 7.73 (dd, *J* = 11.1, 4.3 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.27–7.16 (m, 7H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 4.12 (s, 2H), 2.44 (s, 3H), 1.88 (s, 6H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 169.0, 164.2, 147.5, 141.0, 138.7, 137.10, 137.05, 134.6, 129.0, 128.44, 128.36, 128.1, 127.5, 125.9, 121.9, 119.4, 57.1, 38.6, 27.3, 19.4; IR (neat): 3326, 3060, 3025, 2975, 2927, 1659, 1497, 1472, 768, 725 cm^{-1}; HRMS (ESI) Calcd. for $C_{23}H_{25}N_2O$ $[M+H]^+$: 345.1968, found: 345.1971.

2-(1-(cyclohexyloxy)octyl)-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (3ap): TLC R_f = 0.5 (EtOAc/PE = 1:6); primrose oil; 29.7 mg, yield: 32 %; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.2 Hz, 1H), 8.17 (s, 1H), 7.74 (td, *J* = 7.9, 1.8 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.18 (dd, *J* = 6.6, 5.0 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 4.67–4.57 (m, 1H), 3.16 (m, 1H), 2.37 (s, 3H), 1.92 (s, 6H), 1.73-1.46 (m, 8H), 1.25-1.07 (m, 14H), 0.82 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.7, 164.2, 147.4, 141.5, 137.5, 137.2, 133.6, 128.6,

128.5, 123.7, 121.9, 119.4, 75.2, 74.8, 57.0, 39.4, 33.7, 31.8, 31.5, 29.7, 29.5, 29.2, 27.3, 26.6, 25.9, 24.3, 24.0, 22.6, 19.1, 14.1; IR (neat): 3335, 3058, 2976, 2942, 2872, 1717, 1501, 1445, 776, 745 cm^{-1}; HRMS (ESI) Calcd. for $C_{30}H_{45}N_2O_2$ $[M+H]^+$: 465.3482, found: 465.3484.

Product **7b-1:** colorless oil, 31.2 mg, yield 6%; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04–3.97 (m, 1H), 3.79–3.70 (m, 1H), 3.37–3.25 (m, 1H), 1.87-1.80 (m, 2H), 1.78–1.67 (m, 4H), 1.65–1.47 (m, 6H), 1.47-1.38 (m, 6H), 1.30–1.18 (m, 6H), 1.13 (s, 12H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 78.9, 74.3, 71.4, 59.7, 40.3, 37.5, 33.1, 32.0, 31.7, 25.9, 24.3, 19.9, 17.2; HRMS (ESI) Calcd. for $C_{21}H_{40}NO_2$ $[M+H]^+$: 338.3060, found: 338.3062.

Product **7b-2:** colorless oil, 14.8 mg, yield 3%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78–3.70 (m, 1H), 3.51–3.43 (m, 1H), 3.41–3.33 (m, 1H), 2.22– 2.13 (m, 1H), 1.98–1.87 (m, 2H), 1.85-1.79 (m, 1H), 1.77–1.70 (m, 2H), 1.65–1.53 (m, 4H), 1.48–1.41 (m, 4H), 1.32–1.06 (m, 22H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 83.7, 77.2, 76.2, 40.5, 33.2, 33.1, 31.4, 29.8, 29.7, 26.0, 24.5, 24.4, 23.5, 23.3, 17.3; HRMS (ESI) Calcd. for $C_{21}H_{40}NO_2$ $[M+H]^+$: 338.3060, found: 338.3064.

Product **7b-3:** colorless oil, 30.8 mg, yield 6%; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67–3.58 (m, 1H), 3.37–3.23 (m, 2H), 2.17–2.06 (m, 2H), 2.00–1.90 (m, 2H), 1.88–1.80 (m, 2H), 1.75–1.68 (m, 2H), 1.59–1.48 (m, 2H), 1.47–1.42 (m, 4H), 1.29–1.17 (m, 10H), 1.11 (s, 12H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 81.2, 75.0, 74.4, 59.7, 40.2, 34.4, 33.3, 31.4, 30.4, 25.8, 24.5, 20.3, 17.3; HRMS (ESI) Calcd. for $C_{21}H_{40}NO_2$ $[M+H]^+$: 338.3060, found: 338.3063.

2-cyclobutyl-6-methyl-*N*-(2-(pyridin-2-yl)propan-2-yl)benzamide (8an): TLC R_f = 0.5 (EtOAc/PE = 1:5); primrose oil; 51.4 mg, yield: 68 %; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.2 Hz, 1H), 8.13 (s, 1H), 7.71 (td, *J* = 7.9, 1.7 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.23–7.18 (m, 2H), 7.15 (td, *J* = 6.9, 2.1 Hz, 2H), 3.86–3.78 (m, 1H), 2.65–2.57 (m, 2H), 2.45–2.36 (m, 2H), 2.35 (s, 3H), 1.95–1.77 (m, 10H), 1.67–1.60 (m, 1H), 1.53 (dd, *J* = 11.1, 5.6 Hz, 1H), 1.36–1.23 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9, 164.8, 147.5, 139.2, 137.7, 136.8, 136.8, 129.9, 127.5, 124.6, 121.8, 119.7, 82.1, 67.7, 57.2, 32.6, 27.3, 19.7, 14.5, 13.5; IR (neat): 3343, 3056, 2978, 2939, 2871, 1711, 1502, 1443, 788, 742 cm^{-1}; HRMS (ESI) Calcd. for $C_{24}H_{30}N_2NaO_2$ $[M+Na]^+$: 401.2205, found: 401.2207.

Supporting Information

Radical trapping experiment, KIE and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* Email: hongjianlu@nju.edu.cn ; guigenli@nju.edu.cn

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