JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00207 • Publication Date (Web): 02 Mar 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Cobalt-catalyzed, directed C-H functionalization/annulation of phenylglycinol derivatives with alkynes

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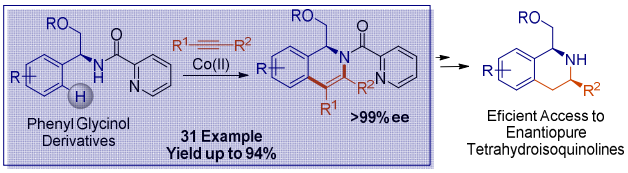
Supporting Information Placeholder



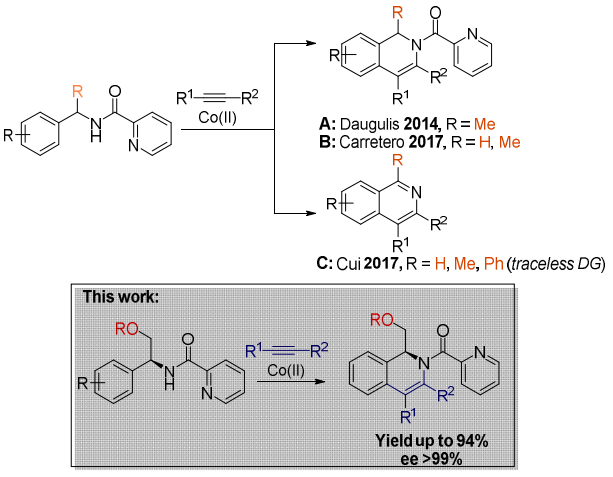
ABSTRACT: A new method for cobalt catalyzed C(sp^2)-H functionalization of phenylglycinol derivatives with terminal and internal alkynes directed by picolinamide auxiliary has been developed. This method offers an efficient and highly regioselective route for the synthesis of 1-hydroxymethyltetrahydroisoquinolines. The reaction employs commercially available Co(II) catalyst in the presence of Mn(III) cooxidant and oxygen as a terminal oxidant, and proceeds with full preservation of original stereochemistry.

INTRODUCTION

Transition metal catalyzed C-H bond functionalization during the past decades has become an important tool that allows simplification of synthetic schemes and allows the use of less complex starting materials.[1] In the past few years, C-H functionalization using 3d-transition metals has emerged as an attractive alternative to noble metals.[2a] Due to its earth-abundance, lower toxicity and unique catalytic activity cobalt has stood out as one of the promising alternatives.[2] In 2014 Daugulis group demonstrated that simple Co(II) salts in combination with bidentate directing group assistance can be efficiently exploited for C-H functionalization as high-valent cobalt(III) precursors.[3] Since the discovery a large number of other C-H functionalization reactions based on this approach have been reported showing the potential of this methodology starting from readily available Co(II) salts and co-oxidants (e.g. C-H functionalization with alkynes,[4a-c] alkenes,[4d-f] allenes,[4g-h] isonitriles,[4i] carbonylation,[4j-l] etc.).[4]

There is no literature precedent for the Co-catalyzed C-H functionalization of phenylglycinol derivatives. Although, several reports has been devoted to benzylamine derivatives. In 2014 Daugulis group demonstrated the first example of cobalt(II) catalyzed 1-methylbenzylamine derived picolinamide reaction with 2-butyne yielding cyclized product in moderate yield (Scheme 1, A).[3] In 2017 Carretero group published an extended study and improved methodology for cobalt catalyzed, picolinamide-directed C-H functionalization/alkyne annulation of benzylamine derivatives (Scheme 1, B).[5a] The same year Cui group demonstrated the cobalt-catalyzed annulation of benzylamides with alkynes to synthesize isoquinolines by using picolinamide as a traceless directing group (Scheme 1, C).[5b] Despite the significant progress made in picolinamide directed benzylamide alkynylation and annulation, the methodology developed so far unfortunately lack the substituent diversity at benzylamine benzylic position (Scheme 1).[6] Typically only methyl substituted or non-substituted benzylamine derivatives were exploited that may limit the use of developed methodology in total synthesis or synthesis of pharmaceutically relevant targets.

Scheme 1. Cobalt(II) catalyzed C-H functionalization with alkynes



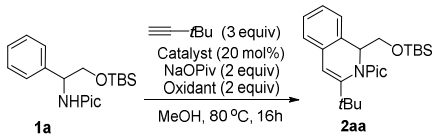
1-Substituted tetrahydroisoquinoline is a structural backbone of a large number of alkaloids that commonly possess a broad range of biological activity.[7] 1-Substituted 1,2-

dihydroisoquinoline derivatives are especially valuable as intermediates in the synthesis of alkaloid natural products, that has led to increasing interest for their synthesis.[8] Herein we report an efficient method for the synthesis of 1-hydroxymethyl-1,2-dihydroisoquinolines via cobalt catalyzed C-H annulation of phenylglycinol derivatives using terminal and internal alkynes.

RESULTS AND DISCUSSION

For optimization studies model reaction between phenylglycinol derivative **1a** and 3,3-dimethyl-1-butyne was chosen. During the optimization studies, a range of cobalt catalysts, oxidants, base additives and reaction solvents were evaluated. Treatment of **1a** with 3,3-dimethyl-1-butyne in the presence of $Co(OAc)_2$ catalyst, NaOPiv base and AgOAc oxidant in MeOH at 80 °C led to regioselective formation of **2aa** in 5% yield (Table 1, entry 1).[9] Screening of alternative oxidants showed, that product **2aa** yield can be slightly improved by using of $Mn(OAc)_3 \cdot 2\ H_2O$ in combination with oxygen (entries 2-5). Reducing the amount of NaOPiv enhanced the product **2aa** yield to 28% (entry 7). The results in entries 8 and 9 indicated that MeOH is the solvent of choice. Studies using alternative Co(II) and Co(III) salts identified $Co(dpm)_2$ catalyst as the crucial factor for successful reaction, yielding the product **2aa** in 84% yield as single regioisomer (entries 9-13). Control experiments excluding catalyst (entry 14) and oxidant (entry 6) showed no product **2aa** formation.

Table 1. Optimization of reaction conditions[a]



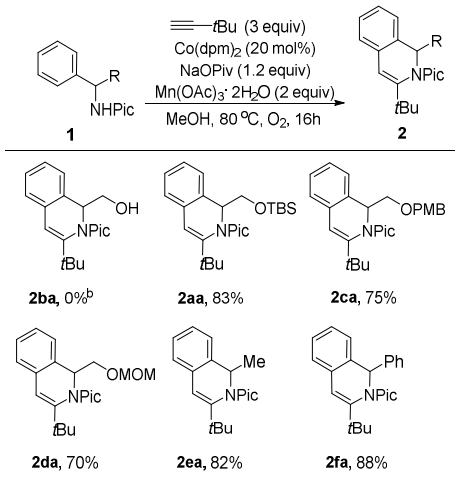
entry	catalyst	oxidant	yield, %[b]
1	$Co(OAc)_2$	AgOAc	5
2	$Co(OAc)_2$	MnO_2	4
3	$Co(OAc)_2$	$Mn(OAc)_2 \cdot 4H_2O$	5
4	$Co(OAc)_2$	$Mn(OAc)_3 \cdot 2H_2O$	12
5	$Co(OAc)_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	16
6	$Co(OAc)_2$	-	-
7[c]	$Co(OAc)_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	28
8[c,d]	$Co(OAc)_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	1
9[c,e]	$Co(OAc)_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	13
10[c]	$CoCl_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	-
11[c]	$Co(acac)_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	30
12[c]	$Co(dpm)_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	82
13[c,f]	$Co(dpm)_2$	$Mn(OAc)_3 \cdot 2H_2O/O_2$	84
14	-	$Mn(OAc)_3 \cdot 2H_2O/O_2$	-

[a] Reaction conditions: **1a** (0.1 mmol), 3,3-dimethyl-1-butyne (0.3 mmol, 3 equiv), catalyst (0.02 mmol, 20 mol%), NaOPiv (0.2 mmol, 2 equiv), $Mn(OAc)_3 \cdot 2H_2O$ (0.2 mmol, 2 equiv), MeOH (1 mL), 80 °C. [b] NMR yield using triphenylmethane as an internal standard. [c] NaOPiv (0.12 mmol, 1.2 equiv). [d] Solvent: EtOH (1 mL). [e] Solvent: CF_3CH_2OH (1 mL). [f] Time: 24h. Pic – picolinyl. $Co(dpm)_2$ – bis(2,2,6,6-tetramethyl-3,5-heptanedionato)cobalt(II), CAS: 13986-53-3.

With the optimized conditions in hand, we next examined the substrate scope with respect to picolinamides **1** (Scheme 2). We found that *O*-unprotected phenylglycinol picolinamide **1b** completely decomposed under the reaction conditions, and product **2ba** did not form. TBS, PMB and MOM protected phenylglycinol derivatives gave corresponding products (**2aa**, **2ca**, **2da**, respectively) in very good yields (70 – 83%) as single regioisomers (regiochemistry of products was confirmed by 2D-NOESY experiments, see SI for details). We were pleased to find that under optimized reaction conditions benzamide derivatives gave products in excellent yields (**2ea** and **2fa**) as well.

Subsequently, the scope of phenylglycinol derivatives **1** with diverse functional groups was examined under the optimized conditions (Scheme 3). As shown in Scheme 3, we found that reactions were successful on phenylglycinol derivatives **1** with *para*-, *meta*- and *ortho*-substitution patterns. Using *meta*-substituted substrates (**2ia**, **2ja**), we observed that reaction favors less hindered C-H bonds, yielding products in excellent regioselectivity that is consistent with literature examples.[3,5a]

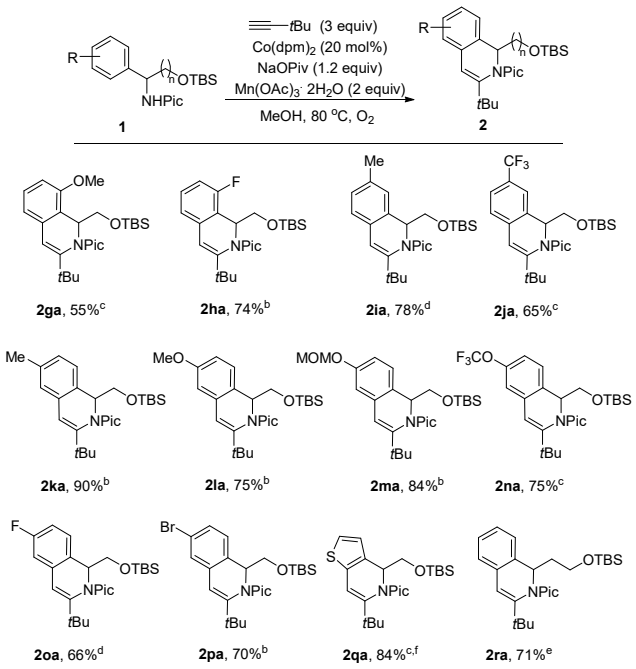
Scheme 2. Reaction scope with respect to picolinamides 1[a]



[a] Reaction conditions: **1** (0.5 mmol), 3,3-dimethyl-1-butyne (1.5 mmol, 3 equiv), catalyst (0.1 mmol, 20 mol%), NaOPiv (0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2H_2O$ (1.0 mmol, 2 equiv), MeOH (5 mL), O_2, 80 °C; Isolated yields are given. [b] Decomposition of substrate **1b**.

Different functional groups on phenylglycinol derivatives **1** were tolerated, including electron-donating groups, such as alkyl (**2ia**, **2ka**), methoxy (**2ga**, **2la**), methoxymethyl ether (**2ma**), as well as electron-withdrawing groups, such as trifluoromethyl (**2ja**) and trifluoromethoxy group (**2na**). Fluoro and bromo functionalities are compatible with reaction conditions (**2ha**, **2oa**, **2pa**). β-Phenylalaninol derivative **1r** was also competent substrate and gave corresponding product **2ra** in very good yield. Moreover, the reaction worked not only with benzyl amides but also with thiophene amino alcohol derivative **1q** and gave product **2qa** in very good yield. Unfortunately, using substrate **1q** C-H functionalization with 3,3-dimethyl-1-butyne was not selective and both regioisomers (thiophene 2nd vs 4th position) were obtained as 2.5/1 mixture.

Scheme 3. Reaction scope with respect to phenylglycinol derivatives 1[a]

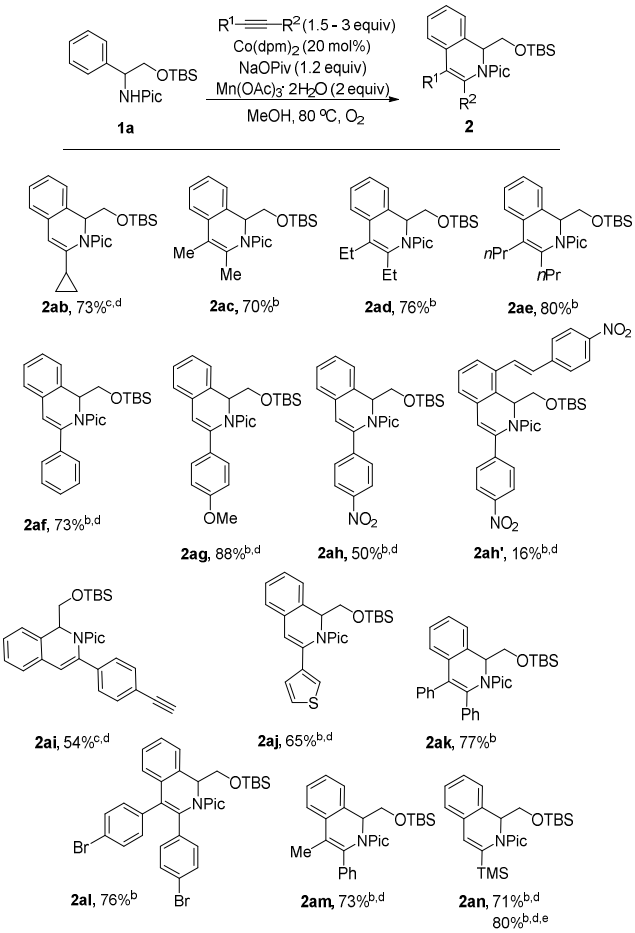


[a] Reaction conditions: **1** (0.5 mmol), 3,3-dimethyl-1-butyne (1.5 mmol, 3 equiv), catalyst (0.1 mmol, 20 mol%), NaOPiv (0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2H_2O$ (1.0 mmol, 2 equiv), MeOH (5 mL), O_2, 80 °C; Isolated yields are given; All products were isolated as single regioisomers unless stated. [b] Time: 16 -17 h. [c] Time: 20 h. [d] Time: 24 h. [e] Time: 40 h. [f] Isolated as 2.5:1 mixture of thiophene regioisomers, major product shown.

Thereafter, we investigated the reaction scope with respect to alkynes (Scheme 4). Both internal and terminal alkynes were competent reagents for C-H functionalization. Cyclopropylacetylene was compatible with reaction conditions and afforded product **2ab** as single regioisomer in 73% yield. Dialkyl-substituted alkynes reacted smoothly and gave corresponding products in high yields (70 – 80%; **2ac**, **2ad**, **2ae**). Terminal alkynes with either aromatic or heteroaromatic substituent gave products as single regioisomers (**2af**-**2aj**). Interestingly, 4-nitrophenylacetylene afforded mono C-H alkenylation/cyclization product **2ah** (50%) and bisalkenylation product **2ah'** (16%). In the case of *p*-diethynylbenzene, product **2ai** was isolated in 54% yield. 3-Ethynylthiophene and trimethylsilylacetylene were competent substrates and selectively formed products **2aj** and **2an**, as well as 1-phenyl-1-propyne – **2am**. Diarylacetylenes displayed excellent reactivity under the reaction conditions (**2ak**, **2al**). The synthetic application of the developed methodology was demonstrated through gram-scale synthesis of annulation product **2an** which was obtained in excellent yield – 80%.

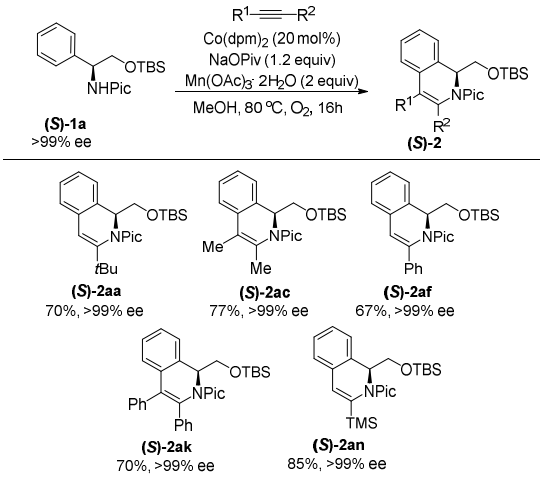
To find out whether stereochemical integrity for α-position of phenylglycinol derivative **1** is preserved during the reaction, enantiopure (*S*)-phenylglycinol derivative **(*S*)-1a** was tested under the optimized reaction conditions (Scheme 5). Aliphatic and aromatic terminal and internal alkynes were tested (**2aa**, **2ac**, **2af**, **2ak, 2an**). We were pleased to find that stereocenter was preserved completely and no loss of enantiopurity was detected exploiting either terminal or internal alkynes.

Scheme 4. Reaction scope with respect to alkynes[a]



[a] Reaction conditions: **1a** (0.5 mmol), alkyne (0.75 - 1.5 mmol, 1.5 - 3 equiv), catalyst (0.1 mmol, 20 mol%), NaOPiv (0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2H_2O$ (1.0 mmol, 2 equiv), MeOH (5 mL), O_2, 80 °C; Isolated yields are given; [b] Time: 16 -17 h. [c] Time: 20 h. [d] Isolated as single regioisomer; [e] Gram-scale synthesis, starting from 1 g picolinamide **1a**.

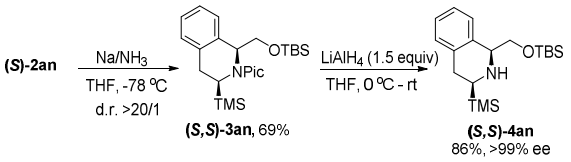
Scheme 5. Preservation of stereochemistry



The application of developed methodology was shown by accessing valuable tetrahydroisoquinoline derivative **(*S*,*S*)-4an** (Scheme 6). Reduction of enantiopure **(*S*)-2an** using Na/NH_3

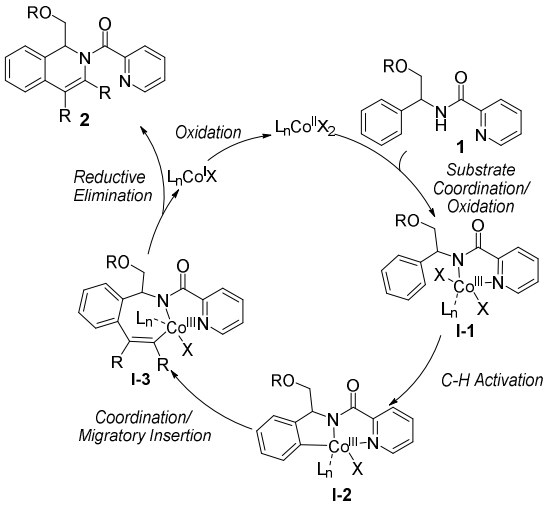
proceeded in highly diastereoselective manner (>20/1) and gave tetrahydroisoquinoline **(*S*,*S*)-3an**. Subsequent directing group removal using $LiAlH_4$ gave corresponding tetrahydroisoquinoline **(*S*,*S*)-4an** in good yield and without the loss of enantiopurity.

Scheme 6. Synthesis of tetrahydroisoquinoline (*S*,*S*)-4an



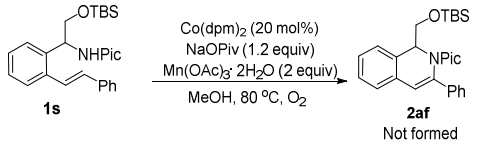
Based on literature data[3,5a,10] and experimental observations,[9] possible reaction mechanism was proposed (Scheme 7).

Scheme 7. Mechanistical considerations



Accordingly, oxidation of Co(II) catalyst in presence of substrate **1** would generate Co(III) species **I-1**.[5a] C-H bond activation would form intermediate **I-2**. Coordination, followed by insertion of alkyne into Co-Ar bond would result in formation of **I-3**. Subsequent reductive elimination would form dihydroisoquinoline **2** and Co(I) species which is reoxidized to Co(II) and returned to catalytic cycle. Protodemetallation pathway from **I-3** was excluded as no cyclization product **2af** formation was observed under standard reaction conditions (Scheme 8).[9]

Scheme 8. Possible cyclization of picolinamide 1s



In conclusion, we have developed a general method for cobalt catalyzed C-H functionalization of phenylglycinol derivatives with terminal and internal alkynes, directed by picolinamide auxiliary. The reactions proceed in the presence of commercially available cobalt(II) tetramethylheptanedionate catalyst, NaOPiv base, O_2 oxidant, and $Mn(OAc)_3 \cdot 2H_2O$ cooxidant. Major advantages of the methodology are substituent diversity at benzylamine benzylic position, excellent regioselectivity and full preservation of original stereochemistry.

EXPERIMENTAL SECTION

General Comments. Reactions were performed using standard glassware or were run in 4 mL vials with PTFE/Liner screw caps and 30 mL vials using w/polyseal screw caps. Reactions were heated using Chemglass aluminium reaction blocks. Column chromatography was performed using Kieselgel silicagel (35 - 70 and 60 - 200 μm). Thin layer chromatography (TLC) was performed on silica gel using Merck TLC Silica gel 60 F254 Aluminum sheets and was visualized by UV lamp, staining with $KMnO_4$. ^1H, ^{13}C, ^{19}F and 2D-NMR spectra were recorded on 400 MHz Bruker spectrometer using residual solvent peak as a reference. Compounds for HRMS were analyzed by positive mode electrospray ionization (ESI) using Waters Synapt G2-Si mass spectrometer. HPLC data were obtained using Waters Alliance 2695 HPLC system with a Phenomenex Lux Amylose-1 (4.6 x 150 mm) or Chiralpac IC-1 (4.6 x 250 mm) column (conditions specified on attached HPLC chromatograms). IR spectra were obtained using a Shimadzu IR Prestige-21 FT-IR spectrometer. Optical rotations were measured at 20 °C on a Rudolph Research Analytical Autopol VI Polarimeter, cell lenght 50 mm, using solvent and concentration stated, at 589 nm. All procedures were performed under ambient air unless otherwise noted. Reagents and starting materials were obtained from commercial sources and used without further purification unless otherwise noted.

Substrate synthesis. Amide substrates 1a-c,g-q,s were synthesized through methyl-2-aryl-2-(picolinamido)acetates (**5a,g-q,s**). Corresponding methyl-2-aryl-2-(picolinamido)acetates were synthesized in two steps from commercially available amino acids.

Methyl 2-phenyl-2-(picolinamido)acetate (5a). Procedure A. **Step 1**: 2-Amino-2-phenylacetic acid (6.00 g, 39.69 mmol, 1 equiv) was suspended in MeOH (48 mL) under an argon atmosphere. The solution was cooled to 0 °C and oxalyl chloride (6.9 mL, 79.38 mmol, 2 equiv) was slowly added dropwise. The reaction mixture was stirred overnight at room temperature. Solvent was evaporated under vacuum to obtain crude product as a pale solid. Crude product was used in the next step without further purification**. Step 2**: Under an argon atmosphere methyl 2-amino-2-phenylacetate hydrogen chloride (39.69 mmol, 1 equiv), picolinic acid (5.12 g, 41.58 mmol, 1.05 equiv) and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (30.03 g, 79.38 mmol, 2 equiv) were dissolved in DMF (48 mL). Pyridine (9.6 mL, 119.07 mmol, 3 equiv) was added to the solution directly. Reaction mixture was stirred at room temperature overnight. Then reaction mixture was diluted with EtOAc (60 mL) and H_2O (40 mL), filtered. Organic phase was separated and aqueous phase was extracted with EtOAc (50 mL), combined organic phase was washed with dist. H_2O (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered. Solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether/EtOAc (3/1) as an eluent to give corresponding product 8.07 g (75%) as a white solid. This compound is known.[11] ^1H-NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 8.4 Hz, 1H), 8.56 (d, J = 4.1 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.81 (td,

J = 7.7, 1.7 Hz, 1H), 7.48 – 7.35 (m, 2H), 7.35 – 7.27 (m, 1H), 7.05 – 6.81 (m, 2H), 6.00 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 3.73 (s, 3H).

Methyl 2-(2-methoxyphenyl)-2-(picolinamido)acetate (5g). Synthesized according to procedure A. **Step 1**: (2-Methoxyphenyl)glycine (1.28 g, 7.10 mmol, 1 equiv), $C_2O_2Cl_2$ (1.2 mL, 14.20 mmol, 2 equiv), MeOH (12 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (873 mg, 7.10 mmol, 1 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (5.38 g, 14.20 mmol, 2 equiv), DMF (15 mL), pyridine (1.7 mL, 21.30 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 900 mg (42%) of product was obtained as a colorless oil. This compound is known.[11] ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 4.1 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 – 7.35 (m, 2H), 7.35 – 7.27 (m, 1H), 7.05 – 6.81 (m, 2H), 6.00 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 3.73 (s, 3H).

Methyl 2-(2-fluorophenyl)-2-(picolinamido)acetate (5h). Synthesized according to procedure A. **Step 1**: (2-Fluorophenyl)glycine hydrochloride (1.84 g, 9.00 mmol, 1 equiv), $C_2O_2Cl_2$ (1.6 mL, 18.00 mmol, 2 equiv), MeOH (10 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (1.16 g, 9.50 mmol, 1.04 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (6.80 g, 18.00 mmol, 2 equiv), DMF (18 mL), pyridine (2.2 mL, 27.00 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 1.50 g (58%) of product was obtained as a colorless oil. R_f = 0.36 (petroleum ether/EtOAc 2:1).^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.98 (d, *J* = 7.4 Hz, 1H), 8.58 (d, *J* = 4.7 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.6 Hz, 1H), 7.52 – 7.38 (m, 2H), 7.39 – 7.27 (m, 1H), 7.20 – 7.05 (m, 2H), 6.02 (d, *J* = 7.9 Hz, 1H), 3.78 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 163.9, 160.7 (d, $J_{C\text{-}F}$ = 248.5 Hz), 149.3, 148.5, 137.4, 130.5 (d, $J_{C\text{-}F}$ = 8.3 Hz), 129.9 (d, $J_{C\text{-}F}$ = 3.5 Hz), 126.6, 124.7 (d, $J_{C\text{-}F}$ = 3.6 Hz), 124.4 (d, $J_{C\text{-}F}$ = 14.3 Hz), 122.5, 116.1 (d, $J_{C\text{-}F}$ = 21.3 Hz), 53.1, 51.5 (d, $J_{C\text{-}F}$ = 2.6 Hz). ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -117.06. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{15}H_{14}N_2O_3F$ 289.0988; found: 289.0999. FT-IR (thin film, cm^{-1}) υ 3387, 2955, 1750, 1683, 1510, 1233.

Methyl 2-(3-methylphenyl)-2-(picolinamido)acetate (5i). Synthesized from commercially available methyl amino(3-methylphenyl)acetate hydrochloride using procedure A, **Step 2**: Amino(3-methylphenyl)acetate hydrochloride (1.0 g, 4.6 mmol), picolinic acid (599 mg, 4.8 mmol, 1.05 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (3.52 g, 9.20 mmol, 2 equiv), DMF (10 mL), pyridine (1.1 mL, 13.80 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 1.00 g (76%) of product was obtained as a colorless oil. R_f = 0.59 (petroleum ether/EtOAc 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.93 (d, *J* = 7.0 Hz, 1H), 8.60 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.85 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.32 – 7.23 (m, 3H), 7.20 – 7.11 (m, 1H), 5.75 (d, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 2.38 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 163.9, 149.4, 148.4, 138.9, 137.4, 136.5, 129.5, 129.0, 128.2, 126.5, 124.6, 122.5, 56.7, 52.9, 21.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{16}H_{17}N_2O_3$ 285.1239; found: 285.1250. FT-IR (thin film, cm^{-1}) υ 3388, 2953, 1744, 1685, 1512, 1437, 1202.

Methyl 2-(3-trifluoromethylphenyl)-2-(picolinamido)acetate (5j). Synthesized according to procedure A. **Step 1**: 2-(3-Trifluoromethylphenyl)glycine (1.21 g, 5.50 mmol, 1 equiv), $C_2O_2Cl_2$ (0.95 mL, 11.00 mmol, 2 equiv), MeOH (12 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (679 mg, 5.50 mmol, 1 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (4.18 g, 11.00 mmol, 2 equiv), DMF (15 mL), pyridine (1.34 mL, 16.50 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 1.12 g (59%) of product was obtained as a colorless oil. R_f = 0.22 (petroleum ether/EtOAc 3:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 9.07 (d, *J* = 7.0 Hz, 1H), 8.62 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.15 (d, *J* = 7.8, 1.0 Hz, 1H), 7.85 (td, *J* = 7.7, 1.7 Hz, 1H), 7.73 (s, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.43 (m, 2H), 5.84 (d, *J* = 7.4 Hz, 1H), 3.80 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 164.0, 149.2, 148.5, 137.9, 137.5, 131.5 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.9 (q, $J_{C\text{-}F}$ = 1.2 Hz), 129.6, 126.8, 125.6 (q, $J_{C\text{-}F}$ = 3.6 Hz), 124.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.0 (q, $J_{C\text{-}F}$ = 272.5 Hz), 122.5, 56.4, 53.3. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -62.60. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{16}H_{14}N_2O_3F_3$ 339.0957; found: 339.0957. FT-IR (thin film, cm^{-1}) υ 2957, 1748, 1684, 1330, 1168, 1127.

Methyl 2-(4-methylphenyl)-2-(picolinamido)acetate (5k). Synthesized according to procedure A. **Step 1**: (4-Methylphenyl)glycine hydrochloride (1.4 g, 7.0 mmol, 1 equiv), $C_2O_2Cl_2$ (1.2 mL, 14.0 mmol, 2 equiv), MeOH (8 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (903 mg, 7.3 mmol, 1.04 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluoro-phosphate (5.30 g, 14.0 mmol, 2 equiv), DMF (14 mL), pyridine (1.7 mL, 21.0 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 750 mg (38%) of product was obtained as a colorless oil. R_f = 0.40 (petroleum ether/EtOAc 2:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.90 (d, *J* = 6.8 Hz, 1H), 8.62 – 8.45 (m, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.50 – 7.37 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.73 (d, *J* = 7.5 Hz, 1H), 3.76 (s, 3H), 2.34 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.4, 163.9, 149.5, 148.4, 138.6, 137.4, 133.7, 129.8, 127.4, 126.5, 122.5, 56.5, 52.9, 21.3. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{16}H_{17}N_2O_3$ 285.1239; found: 285.1243. FT-IR (thin film, cm^{-1}) υ 3388, 2951, 1743, 1684, 1507, 1437, 1180.

Methyl 2-(4-hydroxyphenyl)-2-(picolinamido)acetate (5lm). Synthesized according to procedure A. **Step 1**: 4-Hydroxyphenylglycine (1.50 g, 9.0 mmol, 1 equiv), $C_2O_2Cl_2$ (1.6 mL, 18.0 mmol, 2 equiv), MeOH (10 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (1.16 g, 9.45 mmol, 1.05 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluoro-phosphate (6.80 g, 18.0 mmol, 2 equiv), DMF (18 mL), pyridine (2.2 mL, 27.0 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 1.2 g (47%) of product was obtained as a colorless oil. This compound is known.[12] ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.97 (d, *J* = 7.2 Hz, 1H), 8.59 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.16 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.85 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.30 – 7.21 (m, 2H), 6.79 – 6.67 (m, 2H), 5.67 (d, *J* = 7.3 Hz, 1H), 3.76 (s, 3H).

Methyl 2-(4-methoxyphenyl)-2-(picolinamido)acetate (5l). To a solution of methyl 2-(4-hydroxy-phenyl)-2-(picolinamido)acetate (**5lm**) (500 mg, 1.75 mmol) in DMF (8 mL), NaH (60% dispersion in mineral oil, 105 mg, 2.62 mmol, 1.5 equiv) was added at 0 °C. The reaction was stirred at the same temperature for 5 min and then MeI (142 µL, 2.27 mmol 1.3 equiv) was added and further stirred for

30 min at the same temperature. The reaction mixture was quenched with ice water and then extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with dist. H_2O (20 mL), brine (20 mL) and then dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 270 mg (52%) of product was obtained as a colorless oil. R_f = 0.25 (petroleum ether/EtOAc 2:1). ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, ppm) δ 8.86 (d, *J* = 7.4 Hz, 1H), 8.61 (d, *J* = 4.1 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.45 – 7.32 (m, 2H), 6.96 – 6.89 (m, 2H), 5.68 (d, *J* = 7.4 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 163.9, 159.9, 149.5, 148.4, 137.4, 128.8, 128.7, 126.5, 122.5, 114.5, 56.2, 55.5, 52.9. HR-MS (ESI-TOF) m/z: Calcd. for $[M+Na]^+$: $C_{16}H_{16}N_2O_4Na$ 323.1002; found: 323.1015. FT-IR (thin film, cm^{-1}) υ 3385, 3007, 2954, 1745, 1682, 1513, 1259, 1179.

Methyl 2-(4-(methoxymethoxy)phenyl)-2-(picolinamido)acetate (5m). To a solution of methyl 2-(4-hydroxy-phenyl)-2-(picolinamido)acetate (**5lm**) (1.0 g, 3.49 mmol) in DMF (15 mL), NaH (60% dispersion in mineral oil, 210 mg, 5.24 mmol, 1.5 equiv) was added at 0 °C. The reaction was stirred at the same temperature for 5 min and then MOMCl (0.35 mL, 4.54 mmol 1.3 equiv) was added and further stirred for 30 min at the same temperature. The reaction mixture was quenched with ice water and then extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with dist. H_2O (20 mL), brine (20 mL) and then dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 550 mg (48%) of product was obtained as a colorless oil. R_f = 0.33 (petroleum ether/EtOAc 2:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.88 (d, *J* = 7.1 Hz, 1H), 8.58 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.15 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.06 – 7.01 (m, 2H), 5.71 (d, *J* = 7.4 Hz, 1H), 5.16 (s, 2H), 3.77 (s, 3H), 3.46 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.4, 163.9, 157.5, 149.4, 148.4, 137.4, 129.9, 128.8, 126.6, 122.5, 116.8, 94.5, 56.2, 56.1, 52.9. HR-MS (ESI-TOF) m/z: Calcd. for $[M+Na]^+$: $C_{17}H_{18}N_2O_5Na$ 353.1113; found: 353.1117. FT-IR (thin film, cm^{-1}) υ 3386, 2954, 1751, 1683, 1508, 1236, 1153.

Methyl 2-(4-trifluoromethoxyphenyl)-2-(picolinamido)acetate (5n). Synthesized according to procedure A. **Step 1**: (4-Trifluoromethoxyphenyl)glycine (1.0 g, 4.3 mmol, 1 equiv), $C_2O_2Cl_2$ (0.74 mL, 8.6 mmol, 2 equiv), MeOH (5 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (550 mg, 4.5 mmol, 1.05 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexa-fluorophosphate (3.23 g, 8.6 mmol, 2 equiv), DMF (8 mL), pyridine (1.0 mL, 12.9 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 1.3 g (82%) of product was obtained as a colorless oil. R_f = 0.42 (petroleum ether/EtOAc 2:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 9.01 (d, *J* = 7.2 Hz, 1H), 8.60 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.14 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.25 – 7.17 (m, 2H), 5.79 (d, *J* = 7.5 Hz, 1H), 3.79 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 170.8, 164.0, 149.4 (q, J_{C-F} = 1.6 Hz), 149.2, 148.5, 137.5, 135.4, 129.0, 126.7, 122.5, 121.5, 120.5 (q, J_{C-F} = 257.6 Hz), 56.0, 53.2. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -57.84. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{16}H_{14}N_2O_4F_3$ 355.0906; found: 355.0906. FT-IR (thin film, cm^{-1}) υ 3384, 2957, 1743, 1675, 1505, 1436, 1261, 1221, 1162.

Methyl 2-(4-fluorophenyl)-2-(picolinamido)acetate (5o). Synthesized according to procedure A. **Step 1**: 2-(4-Fluorophenyl)glycine (1.0 g, 5.9 mmol, 1 equiv), $C_2O_2Cl_2$ (1.5 mL, 17.7 mmol, 3 equiv), MeOH (9 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (762 mg, 6.2 mmol, 1.05 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexa-fluorophosphate (4.48 g, 11.8 mmol, 2 equiv), DMF (12 mL), pyridine (1.4 mL, 17.7 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 1.3 g (76%) of product was obtained as a colorless oil. R_f = 0.37 (eluent petroleum ether/EtOAc = 2/1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.96 (d, *J* = 6.8 Hz, 1H), 8.65 – 8.54 (m, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.89 – 7.76 (m, 1H), 7.50 – 7.40 (m, 3H), 7.12 – 7.00 (m, 2H), 5.75 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.1, 163.9, 162.9 (d, J_{C-F} = 247.4 Hz), 149.3, 148.5, 137.5, 132.6 (d, J_{C-F} = 3.3 Hz), 129.3 (d, J_{C-F} = 8.4 Hz), 126.7, 122.5, 116.1 (d, J_{C-F} = 21.8 Hz), 56.0, 53.1. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -113.28. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{15}FH_{14}N_2O_3$ 289.0988; found: 289.1002. FT-IR (thin film, cm^{-1}) υ 3386, 2955, 1744, 1683, 1507, 1437, 1225, 1161.

Methyl 2-(4-bromophenyl)-2-(picolinamido)acetate (5p). Synthesized according to procedure A. **Step 1**: 2-(4-Bromophenyl)glycine (1.59 g, 6.0 mmol, 1 equiv), $C_2O_2Cl_2$ (1.6 mL, 18.0 mmol, 3 equiv), MeOH (10 mL). **Step 2**: Crude reaction mixture from Step 1, picolinic acid (775 mg, 6.3 mmol, 1.05 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexa-fluorophosphate (4.55 g, 12.0 mmol, 2 equiv), DMF (12 mL), pyridine (1.5 mL, 18.0 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 700 mg (33%) of product was obtained as a colorless oil. R_f = 0.40 (eluent petroleum ether/EtOAc = 2/1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.99 (d, *J* = 7.0 Hz, 1H), 8.60 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.14 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.38 – 7.33 (m, 2H), 5.73 (d, *J* = 7.4 Hz, 1H), 3.77 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 170.8, 163.9, 149.2, 148.4, 137.5, 135.8, 132.3, 129.2, 126.7, 122.8, 122.5, 56.2, 53.1. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{15}BrH_{14}N_2O_3$ 349.0188; found: 349.0190. FT-IR (thin film, cm^{-1}) υ 3378, 2954, 1748, 1680, 1507, 1173.

Methyl 2-(picolinamido)-2-(thiophen-3-yl)acetate (5q). Synthesized according to procedure A. **Step 1**: 2-Amino-2-(thiophen-3-yl)acetic acid hydrochloride (1.23 g, 7.8 mmol, 1 equiv), $C_2O_2Cl_2$ (1.36 mL, 15.6 mmol, 2 equiv), MeOH (15 mL). Step 2: Crude reaction mixture from Step 1, picolinic acid (965 mg, 7.8 mmol, 1.0 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexa-fluorophosphate (5.95 g, 15.6 mmol, 2 equiv), DMF (24 mL), pyridine (1.89 mL, 23.4 mmol, 3 equiv). After column chromatography (gradient hexanes/EtOAc from 3:1 to 2:1) 280 mg (13%) of product was obtained as a colorless oil. R_f = 0.51 (eluent petroleum ether/EtOAc = 1/1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.84 (d, *J* = 7.2 Hz, 1H), 8.58 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.33 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 (dd, *J* = 5.0, 1.3 Hz, 1H), 5.92 (d, *J* = 7.9 Hz, 1H), 3.80 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 170.9, 164.0, 149.4, 148.4, 137.4, 136.6, 126.9, 126.6, 126.5, 123.5, 122.5, 53.0, 52.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{13}H_{13}N_2O_3S$ 277.0647; found: 277.0655. FT-IR

(thin film, cm^{-1}) υ 3387, 3098, 2954, 1752, 1679, 1514, 1212, 1164.

Methyl (*E*)-2-(picolinamido)-2-(2-styrylphenyl)acetate (5s). Step 1: To a stirred solution of ammonium chloride (0.58 g, 10.87 mmol, 1.3 equiv) in 25 mL of ammonium hydroxide solution (25% NH_3 in water), sodium cyanide (0.52 g, 10.45 mmol, 1.25 equiv) carefully was added, followed by dropwise (over 30 min) addition of (*E*)-2-styrylbenzaldehyde[11] (1.74 g, 8.36 mmol, 1 equiv) solution in *i*PrOH (10 mL). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude mixture was diluted with water (pH > 10) and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product, which was used in next step without further purification. **Step 2**: To a stirred solution of crude product from Step 1 in 1,4-dioxane (5 mL), concentrated hydrochloric acid (37%, 5.2 mL, 167.23 mmol, 20 equiv) was added dropwise and resulting mixture was refluxed for 5 h. The solvent was removed under reduced pressure to afford the crude product, which was used in next step without further purification. **Step 3**: The crude product from Step 2 was suspended in MeOH (24 mL) under an argon atmosphere. The solution was cooled to 0 °C and oxalyl chloride (1.5 mL, 16.72 mmol, 2 equiv) was slowly added dropwise. The reaction mixture was stirred overnight at room temperature. Solvent was evaporated under vacuum, the residue was dissolved in dist. H_2O (50 mL), extracted with EtOAc (50 mL). Using 1M NaOH the pH of aqueous phase was adjusted to ~8. Aqueous phase was extracted with EtOAc (3 x 50 mL). Combined organic phase was dried over Na_2SO_4, filtered. Solvent was evaporated under reduced pressure to afford the crude product as a yellowish oil. Crude product was used in the next step without further purification. **Step 4**: Under argon atmosphere crude product from Step 3, picolinic acid (1.08 g, 8.78 mmol, 1.05 equiv) and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (6.34 g, 16.72 mmol, 2 equiv) were dissolved in DMF (10 mL). Pyridine (1.4 mL, 16.72 mmol, 2 equiv) was added to the solution directly. Reaction mixture was stirred at room temperature overnight. Then reaction mixture was diluted with EtOAc (50 mL) and H_2O (40 mL), filtered. Organic phase was separated and aqueous phase was extracted with EtOAc (50 mL), combined organic phase was washed with dist. H2O (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered. Solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether/EtOAc (3/1) as an eluent to give corresponding product 1.04 g (34% over 4 steps) as a yellowish oil. R_f = 0.28 (petroleum ether/EtOAc 3:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.92 (d, *J* = 7.5 Hz, 1H), 8.52 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.61 – 7.54 (m, 2H), 7.44 – 7.35 (m, 5H), 7.33 – 7.26 (m, 2H), 7.03 (d, *J* = 16.0 Hz, 1H), 6.16 (d, *J* = 7.7 Hz, 1H), 3.76 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.6, 163.9, 149.4, 148.4, 137.4, 137.3, 134.2, 132.7, 129.0, 128.8, 128.4, 128.0, 127.9, 127.1, 127.0, 126.6, 125.4, 122.5, 53.9, 53.0. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{23}H_{21}N_2O_3$ 373.1552; found: 373.1561. FT-IR (thin film, cm^{-1}) υ 3389, 1743, 1680, 1507, 1220.

Synthesis and characterization of picolinamides 1.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (1a).** Procedure B. **Step 1**: Methyl 2-phenyl-2-(picolinamido)acetate (1.50 g, 5.55 mmol, 1 equiv) was dissolved in THF (20 mL) under an argon atmosphere. The solution was cooled in water/ice bath to 0 °C and lithium borohydride (4 M in THF, 1.8 mL, 7.21 mmol, 1.3 equiv) was added slowly dropwise, then reaction mixture was stirred at room temperature for 3 h. The reaction was monitored by TLC to achieve full conversion, then cooled in water/ice bath and quenched by 15% citric acid solution in water. Organic solvent was evaporated in vacuum and water phase was extracted by DCM (2 x 30 mL). Combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product, which was used in next step without further purification. **Step 2**: To the solution of *N*-(2-hydroxy-1-phenylethyl)picolinamide (5.55 mmol, 1 equiv) in DMF (18 mL) under an argon atmosphere imidazole (1.10 g, 7.21 mmol, 1.3 equiv) and tert-butyldimethylsilyl chloride (491 mg, 7.21 mmol, 1.3 equiv) were added. The reaction mixture was stirred at room temperature to achieve full conversion, then was diluted with EtOAc (30 mL) and H_2O (20 mL). Organic phase was separated and water phase was extracted with EtOAc (20 mL), combined organic phase was washed with dist. H_2O (20 mL) and brine (20 mL). Combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether/EtOAc (6/1) as an eluent to give corresponding product 1.6 g (81%) as colorless oil. R_f = 0.34 (petroleum ether/EtOAc 4:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.86 (d, *J* = 7.7 Hz, 1H), 8.58 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.36 – 7.29 (m, 2H), 7.28 – 7.22 (m, 1H), 5.22 (dt, *J* = 8.7, 4.6 Hz, 1H), 4.01 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.94 (dd, *J* = 10.2, 4.6 Hz, 1H), 0.87 (s, 9H), -0.01 (s, 3H), -0.05 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 150.1, 148.2, 140.3, 137.4, 128.5, 127.5, 127.2, 126.3, 122.4, 66.4, 54.9, 25.9, 18.4, -5.4, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{20}H_{29}N_2O_2Si$ 357.1998; found: 357.2007. FT-IR (thin film, cm^{-1}) υ 3386, 2954, 2927, 2856, 1681, 1517, 1254, 1107.

***N*-(2-Hydroxy-1-phenylethyl)picolinamide (1b).** Synthesized according to procedure B. **Step 1**: Methyl 2-phenyl-2-(picolinamido)acetate (1.10 g, 4.07 mmol, 1 equiv), LiBH4 (4 M in THF 1.32 mL, 5.29 mmol, 1.3 equiv), THF (15 mL). After column chromatography (gradient hexanes/EtOAc from 1:1 to EtOAc) 880 mg (89%) of product was obtained as a colorless oil. This compound is known.[13] ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.70 (d, *J* = 6.5 Hz, 1H), 8.63 – 8.48 (m, 1H), 8.23 – 8.09 (m, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.51 – 7.22 (m, 6H), 5.32 – 5.18 (m, 1H), 4.11 – 3.89 (m, 2H), 3.07 (s, 1H).

***N*-(2-((4-Methoxybenzyl)oxy)-1-phenylethyl)picolinamide (1c).** To a solution of *N*-(2-hydroxy-1-phenylethyl)picolinamide (300 mg, 1.24 mmol) in DMF (4 mL), NaH (60% dispersion in mineral oil, 74 mg, 1.86 mmol, 1.5 equiv) was added at 0 °C. The reaction was stirred at the same temperature for 5 min and then PMBCl (0.22 mL, 1.61 mmol 1.3 equiv) was added and further stirred for 30 min at the same temperature. The reaction mixture was quenched with ice water and then extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with dist. H_2O (10 mL), brine (10 mL) and then dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. After column chromatography (gradient hexanes/EtOAc from 5:1 to 3:1) 380 mg (85%) of product was obtained as a colorless oil. R_f = 0.10 (petroleum ether/EtOAc 4:1). ^{1}H-NMR (400 MHz,

$CDCl_3$, ppm) δ 8.75 (d, *J* = 8.0 Hz, 1H), 8.58 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.38 – 7.30 (m, 2H), 7.31 – 7.23 (m, 1H), 7.24 – 7.18 (m, 2H), 6.87 – 6.81 (m, 2H), 5.39 (dt, *J* = 8.2, 5.2 Hz, 1H), 4.59 – 4.46 (m, 2H), 3.83 (d, *J* = 5.3 Hz, 2H), 3.79 (s, 3H). $^{13}C\{1H\}$NMR (100 MHz, $CDCl_3$, ppm) δ 164.0, 159.3, 150.0, 148.2, 139.9, 137.4, 130.1, 129.4, 128.6, 127.5, 127.1, 126.3, 122.4, 113.9, 72.8, 72.3, 53.3, 53.1. HR-MS (ESI-TOF) m/z: Calcd. for $[M+Na]^+$: $C_{22}H_{22}N_2O_3Na$ 385.1528; found: 385.1530. FT-IR (thin film, cm^{-1}) υ 3393, 2862, 1683, 1512, 1250, 1096.

***N*-(2-(Methoxymethoxy)-1-phenylethyl)picolinamide (1d).** To a solution of *N*-(2-hydroxy-1-phenylethyl)picolinamide (300 mg, 1.24 mmol) in DMF (4 mL), NaH (60% dispersion in mineral oil, 74 mg, 1.86 mmol, 1.5 equiv) was added at 0 °C. The reaction was stirred at the same temperature for 5 min and then MOMCl (0.12 mL, 1.61 mmol 1.3 equiv) was added and further stirred for 30 min at the same temperature. The reaction mixture was quenched with ice water and then extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with dist. H_2O (10 mL), brine (10 mL) and then dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. After column chromatography (gradient hexanes/EtOAc from 2:1 to 1:1) 185 mg (52%) of product was obtained as a colorless oil. R_f = 0.29 (petroleum ether/EtOAc 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.71 (d, *J* = 8.0 Hz, 1H), 8.53 – 8.42 (m, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.79 – 7.67 (m, 1H), 7.43 – 7.30 (m, 3H), 7.32 – 7.22 (m, 2H), 7.23 – 7.14 (m, 1H), 5.34 (dt, *J* = 8.5, 5.1 Hz, 1H), 4.63 – 4.52 (m, 2H), 3.92 – 3.82 (m, 2H), 3.20 (s, 3H). $^{13}C\{1H\}$NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 149.8, 148.1, 139.7, 137.3, 128.6, 127.5, 126.9, 126.3, 122.3, 96.5, 70.4, 55.4, 53.0. HR-MS (ESI-TOF) m/z: Calcd. for $[M+Na]^+$: $C_{16}H_{18}N_2O_3Na$ 309.1215; found: 309.1217. FT-IR (thin film, cm^{-1}) υ 3390, 2932, 2887, 1680, 1518, 1151, 1041.

***N*-(1-Phenylethyl)picolinamide (1e).** Under an argon atmosphere phenylethylamine (1.50 g, 12.38 mmol, 1 equiv), picolinic acid (1.60 g, 13.00 mmol, 1.05 equiv) and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (9.39 g, 24.76 mmol, 2 equiv) were dissolved in DMF (24 mL). Pyridine (3.0 mL, 37.14 mmol, 3 equiv) was added to the solution directly. Reaction mixture was stirred at room temperature overnight. Reaction was monitored by TLC to achieve full conversion, and then was diluted with EtOAc (50 mL) and H_2O (50 mL), filtered. Organic phase was separated and aqueous phase was extracted with EtOAc (50 mL), combined organic phase was washed with dist. H_2O (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered. Solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether/EtOAc (2/1) as an eluent to give corresponding product 2.05 g (73%) as colorless oil. This compound is known.[3] ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.53 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.34 (d, *J* = 6.6 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.38 – 7.33 (m, 2H), 7.26 (tt, *J* = 6.9, 1.3 Hz, 1H), 5.38 – 5.28 (m, 1H), 1.63 (d, *J* = 6.9 Hz, 3H).

***N*-Benzhydrylpicolinamide (1f).** Under an argon atmosphere diphenylmethanamine (0.66 mL, 3.82 mmol, 1 equiv), picolinic acid (470 mg, 3.82 mmol, 1 equiv) and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (2.90 g, 7.64 mmol, 2 equiv) were dissolved in DMF (15 mL). Pyridine (0.62 mL, 7.64 mmol, 2 equiv) was added to the solution directly. Reaction mixture was stirred at room temperature overnight. Reaction was monitored by TLC to achieve full conversion, and then was diluted with EtOAc (30 mL) and H_2O (30 mL), filtered. Organic phase was separated and aqueous phase was extracted with EtOAc (30 mL), combined organic phase was washed with dist. H_2O (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered. Solvent was evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether/EtOAc (3/1) as an eluent to give corresponding product 931 mg (85%) as white powder. This compound is known.[14] ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.75 (d, *J* = 8.1 Hz, 1H), 8.57 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.24 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.40 – 7.20 (m, 10H), 6.47 (d, *J* = 8.6 Hz, 1H).

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(2-methoxyphenyl) ethyl)picolinamide (1g).** Synthesized according to procedure B. **Step 1**: Methyl 2-(2-methoxyphenyl)-2-(picolinamido)-acetate (0.90 g, 2.99 mmol, 1 equiv), $LiBH_4$ (4 M in THF 0.97 mL, 3.89 mmol, 1.3 equiv), THF (24 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (265 mg, 3.89 mmol, 1.3 equiv), TBSCl (587 mg, 3.89 mmol, 1.3 equiv), DMF (12 mL). After column chromatography (hexanes/EtOAc 6:1) 627 mg (54%) of product was obtained as a colorless oil. R_f = 0.38 (petroleum ether/EtOAc 3:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 9.02 (d, *J* = 8.6 Hz, 1H), 8.59 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.22 (td, *J* = 7.9, 1.7 Hz, 1H), 6.94 – 6.85 (m, 2H), 5.53 (dt, *J* = 9.0, 5.1 Hz, 1H), 3.98 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.94 – 3.86 (m, 4H), 0.83 (s, 9H), -0.06 (s, 3H), -0.10 (s, 3H). $^{13}C\{1H\}$NMR (100 MHz, $CDCl_3$, ppm) δ 163.7, 157.1, 150.5, 148.3, 137.3, 128.8, 128.5, 127.9, 126.1, 122.4, 120.6, 110.7, 64.9, 55.6, 51.4, 25.9, 18.4, -5.47, -5.48. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{21}H_{31}N_2O_3Si$ 387.2104; found: 387.2108. FT-IR (thin film, cm^{-1}) υ 3394, 2930, 2856, 1694, 1508, 1256, 1110.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(2-fluorophenyl) ethyl)picolinamide (1h).** Synthesized according to procedure B. **Step 1**: Methyl 2-(2-fluorophenyl)-2-(picolinamido)acetate (1.40 g, 4.86 mmol, 1 equiv), $LiBH_4$ (4 M in THF 1.58 mL, 6.32 mmol, 1.3 equiv), THF (24 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (430 mg, 6.32 mmol, 1.3 equiv), TBSCl (952 mg, 6.32 mmol, 1.3 equiv), DMF (10 mL). After column chromatography (hexanes/EtOAc 6:1) 1.30 g (71%) of product was obtained as a colorless oil. R_f = 0.38 (petroleum ether/EtOAc 4:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.91 (d, *J* = 8.2 Hz, 1H), 8.59 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.83 (td, *J* = 7.6, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.7 Hz, 1H), 7.26 – 7.18 (m, 1H), 7.11 – 7.01 (m, 2H), 5.52 (dt, *J* = 8.9, 4.8 Hz, 1H), 4.01 (dd, *J* = 10.1, 4.8 Hz, 1H), 3.95 (dd, *J* = 10.1, 4.8 Hz, 1H), 0.84 (s, 9H), -0.03 (s, 3H), -0.09 (s, 3H). $^{13}C\{1H\}$NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 160.7 (d, J_{C-F} = 245.5 Hz), 150.0, 148.3, 137.4, 129.1 (d, J_{C-F} = 4.5 Hz), 129.0 (d, J_{C-F} = 8.3 Hz), 127.1 (d, J_{C-F} = 13.4 Hz), 126.3, 124.0 (d, J_{C-F} = 3.4 Hz), 122.4, 115.5 (d, J_{C-F} = 21.8 Hz), 65.2 (d, J_{C-F} = 1.2 Hz), 50.0 (d, J_{C-F} = 1.4 Hz), 25.9, 18.3, -5.5, -5.6. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -118.54. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{20}H_{28}N_2O_2SiF$ 375.1904; found: 375.1916. FT-IR (thin film, cm^{-1}) υ 3388, 2955, 2928, 1685, 1514, 1107.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(3-methylphenyl) ethyl)picolinamide (1i).** Synthesized according to procedure B. **Step 1**: Methyl 2-(3-methylphenyl)-2-(picolinamido)acetate (1.00 g, 3.52 mmol, 1 equiv), $LiBH_4$ (4 M in THF 1.07 mL, 4.26 mmol, 1.2 equiv), THF (17 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (312 mg, 4.58 mmol, 1.3 equiv), TBSCl (690 mg, 4.58 mmol, 1.3 equiv), DMF (15 mL). After column chromatography (petroleum ether/EtOAc 6:1) 441 mg (34%) of product was obtained as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.82 (d, *J* = 7.7 Hz, 1H), 8.58 (ddd, *J* = 4.7, 1.5, 0.8 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.24 – 7.16 (m, 3H), 7.10 – 7.01 (m, 1H), 5.22 – 5.10 (m, 1H), 3.99 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.92 (dd, *J* = 10.2, 4.6 Hz, 1H), 2.33 (s, 3H), 0.88 (s, 9H), 0.00 (s, 3H), -0.04 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 164.0, 150.2, 148.3, 140.3, 138.0, 137.3, 128.4, 128.2, 128.0, 126.2, 124.2, 122.3, 66.4, 54.9, 25.9, 21.6, 18.4, -5.4. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{21}H_{31}N_2O_2Si$ 371.2155; found: 371.2159. FT-IR (thin film, cm^{-1}) υ 3397, 2954, 2927, 2857, 1684, 1512, 1101.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(3-trifluoromethyl-phenyl)ethyl)picolinamide (1j).** Synthesized according to procedure B. **Step 1**: Methyl 2-(3-trifluoromethylphenyl)-2-(picolinamido)acetate (1.12 g, 3.30 mmol, 1 equiv), $LiBH_4$ (4 M in THF 1.07 mL, 4.29 mmol, 1.3 equiv), THF (30 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (292 mg, 4.29 mmol, 1.3 equiv), TBSCl (647 mg, 4.29 mmol, 1.3 equiv), DMF (12 mL). After column chromatography (hexanes/EtOAc 6:1) 1.40 g (60%) of product was obtained as a colorless oil. R_f = 0.37 (petroleum ether/EtOAc 3:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.94 (d, *J* = 7.9 Hz, 1H), 8.59 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.69 (s, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.32 (m, 2H), 5.26 (dt, *J* = 8.2, 4.1 Hz, 1H), 4.04 (dd, *J* = 10.2, 4.4 Hz, 1H), 3.94 (dd, *J* = 10.2, 3.8 Hz, 1H), 0.88 (s, 9H), 0.01 (s, 3H), -0.05 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 164.1, 149.8, 148.4, 141.7, 138.5, 130.8, 130.8 (q, J_{C-F} = 32.1 Hz), 128.9, 126.4, 124.4 (q, J_{C-F} = 3.8 Hz), 124.1 (q, J_{C-F} = 3.8 Hz), 124.3 (q, J_{C-F} = 272.4 Hz), 122.4, 66.2, 54.4, 25.8, 18.3, -5.5, -5.6. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -62.54. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{21}H_{28}N_2O_2SiF_3$ 425.1872; found: 425.1881. FT-IR (thin film, cm^{-1}) υ 3386, 2955, 2930, 2859, 1683, 1508, 1329, 1126.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-methylphenyl)-ethyl)picolinamide (1k).** Synthesized according to procedure B. **Step 1**: Methyl 2-(4-methylphenyl)-2-(picolinamido)acetate (668 mg, 2.35 mmol, 1 equiv), $LiBH_4$ (4 M in THF 0.76 mL, 3.05 mmol, 1.3 equiv), THF (15 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (208 mg, 3.05 mmol, 1.3 equiv), TBSCl (460 mg, 3.05 mmol, 1.3 equiv), DMF (8 mL). After column chromatography (hexanes/EtOAc 6:1) 514 mg (59%) of product was obtained as a colorless oil. R_f = 0.46 (petroleum ether/EtOAc 4:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.79 (d, *J* = 7.8 Hz, 1H), 8.56 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 5.17 (dt, *J* = 8.7, 4.7 Hz, 1H), 3.99 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.92 (dd, *J* = 10.2, 4.9 Hz, 1H), 2.32 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 150.2, 148.2, 137.4, 137.3, 137.0, 129.2, 127.1, 126.2, 122.3, 66.4, 54.7, 25.9, 21.2, 18.4, -5.38, -5.42. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{21}H_{31}N_2O_2Si$ 371.2155; found: 371.2164. FT-IR (thin film, cm^{-1}) υ 3389, 2952, 2859, 1679, 1518, 1257, 1115.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-methoxphenyl)-ethyl)picolinamide (1l).** Synthesized according to procedure B. **Step 1**: Methyl 2-(4-methoxyphenyl)-2-(picolinamido)acetate (260 mg, 0.87 mmol, 1 equiv), $LiBH_4$ (4 M in THF 0.28 mL, 1.12 mmol, 1.3 equiv), THF (5 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (77 mg, 1.12 mmol, 1.3 equiv), TBSCl (170 mg, 1.12 mmol, 1.3 equiv), DMF (4 mL). After column chromatography (hexanes/EtOAc 6:1) 180 mg (54%) of product was obtained as a colorless oil. R_f = 0.33 (petroleum ether/EtOAc 4:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.79 (d, *J* = 7.8 Hz, 1H), 8.56 (d, *J* = 4.1 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.82 (td, *J* = 7.7, 1.6 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.37 – 7.29 (m, 2H), 6.94 – 6.80 (m, 2H), 5.16 (dt, *J* = 8.7, 4.6 Hz, 1H), 3.98 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.91 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.78 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 159.0, 150.1, 148.2, 137.4, 132.6, 128.3, 126.2, 122.3, 113.9, 66.4, 55.4, 54.3, 25.9, 18.3, -5.4. HR-MS (ESI-TOF) m/z: Calcd. for $[M+Na]^+$: $C_{21}H_{30}N_2O_3NaSi$ 409.1923; found: 409.1926. FT-IR (thin film, cm^{-1}) υ 3389, 3058, 2952, 2929, 2857, 1688, 1505, 1249, 1109.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-methoxymethoxyphenyl)ethyl)picolinamide (1m).** Synthesized according to procedure B. **Step 1**: Methyl 2-(4-methoxymethoxyphenyl)-2-(picolinamido)-acetate (514 mg, 1.56 mmol, 1 equiv), $LiBH_4$ (4 M in THF 0.51 mL, 2.02 mmol, 1.3 equiv), THF (10 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (138 mg, 2.02 mmol, 1.3 equiv), TBSCl (305 mg, 2.02 mmol, 1.3 equiv), DMF (5 mL). After column chromatography (hexanes/EtOAc 6:1) 370 mg (57%) of product was obtained as a colorless oil. R_f = 0.20 (petroleum ether/EtOAc 4:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.78 (d, *J* = 7.9 Hz, 1H), 8.56 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.41 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.03 – 6.95 (m, 2H), 5.23 – 5.08 (m, 3H), 3.98 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.91 (dd, *J* = 10.2, 4.7 Hz, 1H), 3.46 (s, 3H), 0.88 (s, 9H), 0.01 (s, 3H), -0.02 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 156.3, 150.2, 148.3, 137.4, 133.9, 128.4, 126.2, 122.3, 116.3, 94.6, 66.4, 56.1, 54.3, 25.9, 18.4, -5.37, -5.41. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{22}H_{33}N_2O_4Si$ 417.2210; found: 417.2206. FT-IR (thin film, cm^{-1}) υ 3388, 2930, 1512, 1153, 1108, 1080, 1006.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-trifluoromethoxyphenyl)ethyl)picolinamide (1n).** Synthesized according to procedure B. **Step 1**: Methyl 2-(4-trifluoromethoxyphenyl)-2-(picolinamido)-acetate (1.16 g, 3.27 mmol, 1 equiv), $LiBH_4$ (4 M in THF 1.06 mL, 4.26 mmol, 1.3 equiv), THF (24 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (290 mg, 4.26 mmol, 1.3 equiv), TBSCl (642 mg, 4.26 mmol, 1.3 equiv), DMF (10 mL). After column chromatography (hexanes/EtOAc 6:1) 1.00 g (69%) of product was obtained as a colorless oil. R_f = 0.34 (petroleum ether/EtOAc 4:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.88 (d, *J* = 7.9 Hz, 1H), 8.58 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.21 – 7.12 (m, 2H), 5.21 (dt, *J* = 8.3, 4.3 Hz, 1H), 4.01 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.92 (dd, *J* = 10.2, 4.2 Hz, 1H), 0.87 (s, 9H), 0.01 (s, 3H), -0.05 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 164.1, 149.9, 148.6 (q, J_{C-F} = 1.8 Hz), 148.3,

139.3, 137.5, 128.6, 126.4, 122.4, 121.0, 120.6 (q, J_{C-F} = 256.8 Hz), 66.3, 54.2, 25.9, 18.3, -5.47, -5.48. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -57.19. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{21}H_{28}N_2O_3SiF_3$ 441.1821; found: 441.1828. FT-IR (thin film, cm^{-1}) υ 3386, 2955, 2931, 2858, 1686, 1507, 1260, 1224, 1165, 1109.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethyl)picolinamide (1o).** Synthesized according to procedure B. **Step 1**: Methyl 2-(4-fluorophenyl)-2-(picolinamido)-acetate (742 mg, 2.57 mmol, 1 equiv), $LiBH_4$ (4 M in THF 0.84 mL, 3.34 mmol, 1.3 equiv), THF (20 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (228 mg, 3.34 mmol, 1.3 equiv), TBSCl (504 mg, 3.34 mmol, 1.3 equiv), DMF (10 mL). After column chromatography (petroleum ether/EtOAc 6:1) 590 g (61%) of product was obtained as a colorless oil. R_f = 0.32 (petroleum ether/EtOAc 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.85 (d, *J* = 7.7 Hz, 1H), 8.57 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.46 – 7.33 (m, 3H), 7.05 – 6.94 (m, 2H), 5.18 (dt, *J* = 8.4, 4.4 Hz, 1H), 3.99 (dd, *J* = 10.1, 4.6 Hz, 1H), 3.91 (dd, *J* = 10.1, 4.3 Hz, 1H), 0.88 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 164.0, 162.2 (d, J_{C-F} = 245.0 Hz), 150.0, 148.3, 137.4, 136.3 (d, J_{C-F} = 3.1 Hz), 128.8 (d, J_{C-F} = 8.1 Hz), 126.3, 122.4, 115.3 (d, J_{C-F} = 21.4 Hz), 66.3, 54.2, 25.9, 18.4, -5.4, -5.5. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -115.67. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{20}FH_{28}N_2O_2Si$ 375.1904; found: 375.1910. FT-IR (thin film, cm^{-1}) υ 3388, 2954, 2929, 2858, 1687, 1514, 1258, 1223, 1103.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-bromophenyl)ethyl)picolinamide (1p).** Synthesized according to procedure B. **Step 1**: Methyl 2-(4-bromophenyl)-2-(picolinamido)-acetate (335 mg, 0.96 mmol, 1 equiv), $LiBH_4$ (4 M in THF 0.31 mL, 1.24 mmol, 1.3 equiv), THF (20 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (85 mg, 1.24 mmol, 1.3 equiv), TBSCl (188 mg, 1.24 mmol, 1.3 equiv), DMF (10 mL). After column chromatography (hexanes/EtOAc 6:1) 222 g (53%) of product was obtained as a colorless oil. R_f = 0.33 (petroleum ether/EtOAc 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.85 (d, *J* = 7.7 Hz, 1H), 8.61 – 8.49 (m, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.51 – 7.40 (m, 3H), 7.33 – 7.27 (m, 2H), 5.15 (dt, *J* = 8.3, 4.3 Hz, 1H), 3.99 (dd, *J* = 10.2, 4.5 Hz, 1H), 3.90 (dd, *J* = 10.2, 4.2 Hz, 1H), 0.88 (s, 9H), 0.01 (s, 3H), -0.03 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 164.0, 150.0, 148.3, 136.6, 137.4, 131.5, 129.0, 126.4, 122.4, 121.3, 66.1, 54.3, 25.9, 18.4, -5.4, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{20}BrH_{28}N_2O_2Si$ 435.1103; found: 435.1102. FT-IR (thin film, cm^{-1}) υ 2954, 2928, 2856, 1684, 1515, 1255, 1107.

***N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(thiophen-3-yl)ethyl)picolinamide (1q).** Synthesized according to procedure B. **Step 1**: Methyl 2-(picolinamido)-2-(thiophen-3-yl)acetate (280 mg, 1.01 mmol, 1 equiv), $LiBH_4$ (4 M in THF 0.33 mL, 1.31 mmol, 1.3 equiv), THF (10 mL). **Step 2**: Crude reaction mixture from Step 1, imidazole (89 mg, 1.31 mmol, 1.3 equiv), TBSCl (197 mg, 1.31 mmol, 1.3 equiv), DMF (5 mL). After column chromatography (petroleum ether/EtOAc 6:1) 233 g (64%) of product was obtained as a colorless oil. R_f = 0.36 (petroleum ether/EtOAc 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.72 (d, *J* = 8.4 Hz, 1H), 8.55 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.20 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.16 (dd, *J* = 4.9, 1.4 Hz, 1H), 5.36 (dt, *J* = 8.5, 4.2 Hz, 1H), 4.07 – 3.93 (m, 2H), 0.89 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.8, 150.1, 148.3, 141.3, 137.4, 127.1, 126.3, 125.7, 122.4, 122.0, 65.8, 50.7, 25.9, 18.4, -5.4. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{18}H_{27}N_2O_2SiS$ 363.1563; found: 363.1573. FT-IR (thin film, cm^{-1}) υ 2954, 2928, 1676, 1513, 1510, 1255, 1114.

***N*-(3-((*Tert*-butyldimethylsilyl)oxy)-1-phenylpropyl)picolinamide (1r).** Procedure C. **Step 1**: Under an argon atmosphere 3-amino-3-phenylpropan-1-ol (700 mg, 4.62 mmol, 1 equiv), picolinic acid (570 mg, 4.62 mmol, 1 equiv) and *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (3.51 g, 9.24 mmol, 2 equiv) were dissolved in DMF (15 mL). Pyridine (0.75 mL, 9.24 mmol, 2 equiv) was added to the solution directly. Reaction mixture was stirred at room temperature overnight. Reaction was monitored by TLC to achieve full conversion, and then was diluted with EtOAc (30 mL) and H_2O (30 mL), filtered. Organic phase was separated and aqueous phase was extracted with EtOAc (30 mL), combined organic phase was washed with dist. H_2O (20 mL), brine (20 mL) and dried over Na_2SO_4, filtered. Solvent was evaporated under reduced pressure to afford the crude product, which was used in next step without further purification. **Step 2**: To the solution of crude reaction mixture from previous step in DMF (12 mL) under an argon atmosphere imidazole (471 mg, 6.93 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl chloride (1.04 g, 6.93 mmol, 1.5 equiv) were added. The reaction mixture was stirred at room temperature to achieve full conversion, then was diluted with EtOAc (30 mL) and H_2O (20 mL). Organic phase was separated and water phase was extracted with EtOAc (20 mL), combined organic phase was washed with dist. H_2O (20 mL) and brine (20 mL). Combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether/EtOAc (5/1) as an eluent to give corresponding product 776 mg (68%) as colorless oil. R_f = 0.40 (petroleum ether/EtOAc 3:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.90 (d, *J* = 7.6 Hz, 1H), 8.56 – 8.42 (m, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.35 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.35 – 7.28 (m, 2H), 7.30 – 7.21 (m, 2H), 7.20 – 7.14 (m, 1H), 5.37 – 5.25 (m, 1H), 3.67 – 3.52 (m, 2H), 2.23 – 2.07 (m, 1H), 2.10 – 1.96 (m, 1H), 0.86 (s, 9H), -0.00 (s, 3H), -0.01 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.8, 150.3, 148.1, 142.1, 137.3, 128.6, 127.2, 126.7, 126.1, 122.4, 60.4, 51.9, 38.6, 26.1, 18.5, -5.30, -5.32. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{21}H_{31}N_2O_2Si$ 371.2155; found: 371.2155. FT-IR (thin film, cm^{-1}) υ 3379, 2952, 2928, 2856, 1682, 1519, 1257, 1093.

(*S*)-*N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (*S*-1a). Synthesized according to procedure C. **Step 1**: (*S*)-2-Amino-2-phenylethanol (1.00 g, 7.29 mmol, 1 equiv), picolinic acid (942 mg, 7.65 mmol, 1.05 equiv), *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(1H-benzotriazol-1-yl)uronium hexafluoro-phosphate (5.53 g, 14.58 mmol, 2 equiv), DMF (20 mL), pyridine (1.18 mL, 14.58 mmol, 2 equiv). Reaction mixture was filtered through short silicagel column. **Step 2**: Reaction mixture from previous step, imidazole (645 mg, 9.48 mmol, 1.3 equiv), TBSCl (1.43 g, 9.48 mmol, 1.3 equiv), DMF (25 mL). After column chromatography (petroleum ether/EtOAc 6:1) 1.87 g (72%) of product was obtained as a colorless oil. R_f = 0.34 (petroleum ether/EtOAc 4:1). *ee* = 99.9% (see attached HPLC data). The

NMR data matched to racemate. $[\alpha]_D^{20}$ -27.2 (*c* = 0.993, $CHCl_3$).

(*E*)-*N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(2-styrylphenyl)ethyl)picolinamide (1s). Step 1: Methyl (*E*)-2-(picolinamido)-2-(2-styrylphenyl)acetate (918 mg, 2.47 mmol, 1 equiv) was dissolved in THF (20 mL) under an argon atmosphere. The solution was cooled in water/ice bath to 0 °C and lithium borohydride (4 M in THF, 0.8 mL, 3.21 mmol, 1.3 equiv.) was added slowly dropwise, then reaction mixture was stirred at room temperature for 3 h. The reaction was monitored by TLC to achieve full conversion, then cooled in water/ice bath and quenched by 15% citric acid solution in water. Organic solvent was evaporated in vacuum and water phase was extracted by 2 x DCM (30 mL). Combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product, which was used in next step without further purification. **Step 2**: To the solution of crude product from Step 1 in DMF (7 mL) under an argon atmosphere imidazole (218 mg, 3.21 mmol, 1.3 equiv) and *tert*-butyldimethylsilyl chloride (483 mg, 3.21 mmol, 1.3 equiv) were added. The reaction mixture was stirred at room temperature to achieve full conversion, then was diluted with EtOAc (30 mL) and H_2O (20 mL). Organic phase was separated and water phase was extracted with EtOAc (20 mL), combined organic phase was washed with dist. H_2O (20 mL) and brine (20 mL). Combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product, which was further purified by flash chromatography on silica gel using petroleum ether/EtOAc (6/1) as an eluent to give corresponding product 520 mg (46%) as colorless oil. R_f = 0.37 (petroleum ether/EtOAc 5:1). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.93 (d, *J* = 7.8 Hz, 1H), 8.60 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.22 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H), 7.68 (d, *J* = 16.0 Hz, 1H), 7.65 – 7.56 (m, 3H), 7.52 – 7.38 (m, 4H), 7.37 – 7.25 (m, 3H), 7.02 (d, *J* = 16.0 Hz, 1H), 5.70 (dt, *J* = 8.3, 4.7 Hz, 1H), 4.05 (dd, *J* = 10.3, 4.7 Hz, 1H), 3.95 (dd, *J* = 10.3, 4.9 Hz, 1H), 0.89 (s, 9H), 0.00 (s, 3H), -0.05 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 150.1, 148.3, 137.7, 137.6, 137.4, 136.4, 131.7, 128.8, 127.8, 127.7, 127.6, 126.9, 126.8, 126.7, 126.23, 126.21, 122.3, 65.6, 51.4, 25.9, 18.3, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{28}H_{35}N_2O_2Si$ 459.2468; found: 459.2476. FT-IR (thin film, cm^{-1}) υ 3390, 2953, 2928, 2856, 1682, 1519, 1254, 1105.

Synthesis and characterization of reaction products 2.

General procedure for cobalt-catalyzed sp^2 C-H alkenylation/cyclization. A 30 mL vial equipped with a magnetic stir bar was charged with picolinamide (0.5 mmol), $Co(dpm)_2$ (42.5 mg, 0.10 mmol, 20 mol%), NaOPiv (74.5 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL). The reaction mixture was purged with O_2 for 30 sec and then alkyne (0.75 – 1.50 mmol, 1.5 – 3 equiv) was added and mixture was heated at 80 °C for for indicated time (16 h – 24 h). Reaction was monitored by TLC after 16 h, 20 h and 24 h to determine the completion time. The reaction mixture was cooled to room temperature and solvent was evaporated. To the residue potassium sodium tartrate (10 mL of 1M aqueous solution) was added and mixture was extracted with EtOAc (3 x 15 mL). Combined organic phase was dried over Na_2SO_4, filtered, and solvent was evaporated. Product was purified by column chromatography on silica gel using appropriate eluent. After purification product was dried under reduced pressure. *Note! It was observed that the reaction is sensitive to $Mn(OAc)_3{\cdot}2\,H_2O$. Reproducible results were obtained using $Mn(OAc)_3{\cdot}2\,H_2O$ purchased from Acros Organics and self-made $Mn(OAc)_3{\cdot}2\,H_2O$.*

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)me-thanone (2aa). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 183 mg (84%) of a yellowish oil was obtained. R_f = 0.45 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.71 (d, *J* = 4.7 Hz, 1H), 7.86 – 7.72 (m, 2H), 7.43 – 7.36 (m, 1H), 7.23 – 7.17 (m, 1H), 7.13 (d, *J* = 6.6 Hz, 1H), 7.05 (td, *J* = 7.4, 1.3 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.57 (s, 1H), 5.01 (t, *J* = 6.3 Hz, 1H), 3.97 (dd, *J* = 9.8, 7.3 Hz, 1H), 3.62 (dd, *J* = 9.8, 7.7 Hz, 1H), 1.38 (s, 9H), 0.85 (s, 9H), -0.08 (s, 3H), -0.09 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 153.7, 149.5, 149.3, 136.9, 132.7, 131.7, 128.0, 126.7, 126.5, 125.7, 125.3, 124.8, 118.1, 62.3, 60.7, 36.7, 31.0, 26.0, 18.4, -5.4, -5.6. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{26}H_{37}N_2O_2Si$ 437.2624; found: 437.2624. FT-IR (thin film, cm^{-1}) υ 2955, 2930, 2858, 1653, 1117.

(*S*)-(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)isoquinolin-2(1H)-yl)(pyridin-2-yl) methanone ((*S*)-2aa). (*S*)-*N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 167 mg (77%) of a yellowish oil was obtained. R_f = 0.45 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. *ee* = > 99% (see attached HPLC data). The NMR data matched to racemate. $[\alpha]_D^{20}$ -225.0 (*c* = 0.970, $CHCl_3$).

(3-(*Tert*-butyl)-1-(((4-methoxybenzyl)oxy)methyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)metha-none (2ca). *N*-(2-((4-Methoxybenzyl)oxy)-1-phenylethyl)picolinamide (181 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1, then 2:1), 166 mg (75%) of a yellowish oil was obtained. R_f = 0.16 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.68 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.80 – 7.67 (m, 2H), 7.41 – 7.35 (m, 1H), 7.29 – 7.16 (m, 3H), 7.14 (d, *J* = 6.7 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 6.91 – 6.81 (m, 3H), 6.57 (s, 1H), 5.33 – 5.13 (m, 1H), 4.44 (s, 2H), 3.88 – 3.74 (m, 4H), 3.44 (dd, *J* = 9.8, 6.7 Hz, 1H), 1.35 (s, 9H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 159.3, 153.7, 149.5, 149.4, 136.9, 132.8, 131.8, 130.4, 129.4, 128.1, 126.8, 126.0, 125.9, 125.3, 124.8, 118.2, 113.9, 72.9, 69.2, 58.6, 55.4, 36.8, 31.0. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{28}H_{31}N_2O_3$ 443.2335; found: 443.2341. FT-IR (thin film, cm^{-1}) υ 2959, 2864, 1658, 1607, 1512, 1255, 1169.

(3-(*Tert*-butyl)-1-((methoxymethoxy)methyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2da). *N*-(2-(Methoxymethoxy)-1-phenylethyl)picolinamide (143 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 24 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 2:1 to 1:1), 128 mg (70%) of a yellowish oil was obtained. R_f = 0.40 (petroleum ether/EtOAc 2:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.69 (ddd, *J* = 4.8, 1.6, 1.0 Hz, 1H), 7.81 – 7.67 (m, 2H), 7.39 (ddd, *J* = 7.4, 4.8, 1.4 Hz, 1H), 7.20 (td, *J* = 7.5, 1.2 Hz, 1H), 7.14 (d, *J* = 6.5 Hz, 1H), 7.06 (td, *J* = 7.4, 1.4 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 6.58 (s, 1H), 5.34 – 5.06 (m, 1H), 4.63 – 4.54 (m, 2H), 3.91 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.59 (dd, *J* = 9.8, 7.6 Hz, 1H), 3.24 (s, 3H), 1.37 (s, 9H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 153.6, 149.5, 149.0, 137.0, 132.8, 131.6, 128.0, 126.7, 126.1, 125.8, 125.4, 124.8, 118.1, 96.3, 66.7, 58.5, 55.3, 36.7, 31.0. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{22}H_{27}N_2O_3$ 367.2022; found: 367.2033. FT-IR (thin film, cm^{-1}) υ 2956, 1662, 1653, 1365, 1149, 1116, 1038.

(3-(*Tert*-butyl)-1-methylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ea). *N*-(1-Phenylethyl)picolinamide (113 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 126 mg (82%) of a yellowish oil was obtained. R_f = 0.33 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.72 (d, *J* = 5.4 Hz, 1H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.20 – 7.11 (m, 2H), 7.05 (td, *J* = 7.2, 1.8 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.61 (s, 1H), 5.23 – 5.03 (m, 1H), 1.43 (d, *J* = 6.8 Hz, 3H), 1.38 (s, 9H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 154.2, 148.9, 148.7, 137.21, 137.19, 131.1, 127.5, 127.0, 126.0, 125.4, 124.8, 124.1, 118.2, 55.7, 36.6, 30.9, 19.6. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{20}H_{23}N_2O$ 307.1810; found: 307.1823. FT-IR (thin film, cm^{-1}) υ 2966, 1653, 1395, 1341, 1164.

(3-(*Tert*-butyl)-1-phenylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2fa). *N*-Benzhydrylpicolinamide (144 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 162 mg (88%) of a yellowish oil was obtained. R_f = 0.40 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.77 (d, *J* = 4.3 Hz, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.55 – 7.34 (m, 3H), 7.32 – 7.24 (m, 5H), 7.14 (t, *J* = 6.7 Hz, 1H), 6.99 – 6.77 (m, 1H), 6.69 – 6.24 (m, 2H), 1.02 (s, 9H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 170.5, 153.9, 150.1, 148.6, 139.3, 137.3, 133.4, 132.9, 128.9, 128.1, 127.8, 127.7, 127.0, 126.1, 125.8, 125.5, 125.1, 119.1, 60.7, 36.3, 30.6. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{25}H_{25}N_2O$ 369.1967; found: 369.1973. FT-IR (thin film, cm^{-1}) υ 2967, 2905, 1653, 1648, 1375, 1364, 1334.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-methoxyisoquinolin-2(1H)-yl)(pyri-din-2-yl)methanone (2ga). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(2-methoxyphenyl)ethyl)picolinamide (193 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 20 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 8:1 to 6:1, then 4:1), 127 mg (55%) of a yellowish oil was obtained. R_f = 0.48 (petroleum ether/EtOAc 3:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.72 – 8.64 (m, 1H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H), 7.36 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.1 Hz, 1H), 6.54 (s, 1H), 5.53 – 5.33 (m, 1H), 3.70 (dd, *J* = 10.5, 9.2 Hz, 1H), 3.63 (s, 3H), 3.52 (dd, *J* = 10.6, 4.7 Hz, 1H), 1.38 (s, 9H), 0.91 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.6, 154.8, 154.0, 149.9, 149.7, 136.3, 133.5, 128.5, 124.8, 124.5, 120.7, 118.5, 118.1, 109.5, 61.1, 55.5, 55.2, 36.8, 30.9, 26.1, 18.5, -5.39, -5.40. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{27}H_{39}N_2O_3Si$ 467.2730; found: 467.2747. FT-IR (thin film, cm^{-1}) υ 2952, 2858, 1674, 1474, 1259, 1104.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-8-fluoroisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ha). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(2-fluorophenyl)ethyl)picolinamide (187 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 24 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 169 mg (74%) of a yellowish oil was obtained. R_f = 0.52 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.79 – 8.60 (m, 1H), 7.86 – 7.73 (m, 2H), 7.40 (ddd, *J* = 7.4, 4.8, 1.4 Hz, 1H), 7.16 (td, *J* = 8.0, 5.6 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.79 (t, *J* = 9.1 Hz, 1H), 6.59 (d, *J* = 1.7 Hz, 1H), 5.47 (t, *J* = 7.2 Hz, 1H), 3.92 (dd, *J* = 10.0, 7.7 Hz, 1H), 3.65 (dd, *J* = 10.1, 6.8 Hz, 1H), 1.38 (s, 9H), 0.85 (s, 9H), -0.04 (s, 3H), -0.06 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.4, 158.4 (d, $J_{C\text{-}F}$ = 245.8 Hz), 153.4, 150.9, 149.5, 136.8, 134.2, (d, $J_{C\text{-}F}$ = 4.9 Hz), 129.0 (d, $J_{C\text{-}F}$ = 8.4 Hz), 125.4, 124.7, 121.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 119.5 (d, $J_{C\text{-}F}$ = 17.5 Hz), 117.6 (d, $J_{C\text{-}F}$ = 3.4 Hz), 113.8 (d, $J_{C\text{-}F}$ = 21.9 Hz), 61.5, 54.5, 36.9, 30.9, 26.0, 18.4, -5.49, -5.52. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -121.12. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{26}H_{36}N_2O_2SiF$ 455.2530; found: 455.2543. FT-IR (thin film, cm^{-1}) υ 2957, 2930, 2858, 1653, 1465, 1250, 1111, 1082.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-methylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ia). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(3-methylphenyl)ethyl)picolinamide (185 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 24 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from

6:1 to 3:1), 176 mg (78%) of a yellowish oil was obtained. R_f = 0.71 (petroleum ether/EtOAc 3:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.70 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.84 – 7.71 (m, 2H), 7.42 – 7.34 (m, 1H), 7.07 – 6.97 (m, 2H), 6.68 (s, 1H), 6.53 (s, 1H), 5.08 – 4.82 (m, 1H), 3.95 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.59 (dd, *J* = 9.8, 7.6 Hz, 1H), 2.23 (s, 3H), 1.37 (s, 9H), 0.85 (s, 9H), -0.08 (s, 3H), -0.09 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 153.9, 149.4, 148.4, 136.8, 136.3, 132.7, 129.0, 128.6, 127.4, 125.6, 125.2, 124.7, 118.0, 62.3, 60.8, 36.6, 31.0, 25.9, 21.3, 18.4, -5.48, -5.53. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{27}H_{39}N_2O_2Si$ 451.2781; found: 451.2794. FT-IR (thin film, cm^{-1}) υ 2956, 2928, 2858, 1660, 1388, 1364, 1258, 1113.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-7-trifluoromethylisoquinolin-2(1H)-yl) (pyridin-2-yl)methanone (2ja). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(3-trifluoromethylphenyl)ethyl)picolinamide (212 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 24 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 165 mg (65%) of a yellowish oil was obtained. R_f = 0.77 (petroleum ether/EtOAc 3:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.71 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.87 – 7.74 (m, 2H), 7.51 – 7.38 (m, 2H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.13 (s, 1H), 6.60 (s, 1H), 5.11 (dd, *J* = 8.6, 6.5 Hz, 1H), 4.08 (dd, *J* = 9.4, 6.4 Hz, 1H), 3.69 – 3.58 (m, 1H), 1.37 (s, 9H), 0.82 (s, 9H), -0.10 (s, 3H), -0.12 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 153.1, 152.6, 149.2, 137.2, 134.8, 133.3, 128.2 (q, $J_{C\text{-}F}$ = 32.4 Hz), 125.8, 125.7, 125.2, 124.9 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.3 (q, $J_{C\text{-}F}$ = 272.0 Hz), 124.0 (q, $J_{C\text{-}F}$ = 3.7 Hz), 117.1, 61.9, 60.3, 37.1, 31.0, 25.9, 18.3, -5.5, -5.6. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -62.29. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{27}H_{36}N_2O_2SiF_3$ 505.2498; found: 505.2511. FT-IR (thin film, cm^{-1}) υ 2958, 2930, 2859, 1661, 1331, 1164, 1131, 1125, 1070.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-methylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ka). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-methylphenyl)ethyl)picolinamide (185 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 202 mg (90%) of a yellowish oil was obtained. R_f = 0.44 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.69 (dd, *J* = 5.4, 1.9 Hz, 1H), 7.84 – 7.70 (m, 2H), 7.42 – 7.35 (m, 1H), 6.96 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.52 (s, 1H), 5.09 – 4.87 (m, 1H), 3.93 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.57 (dd, *J* = 9.8, 7.4 Hz, 1H), 2.29 (s, 3H), 1.36 (s, 9H), 0.86 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 153.9, 149.5, 149.4, 137.6, 136.7, 131.6, 130.0, 127.2, 126.5, 126.4, 125.2, 124.7, 118.2, 62.5, 60.6, 36.7, 31.0, 26.0, 21.3, 18.5, -5.4, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{27}H_{39}N_2O_2Si$ 451.2781; found: 451.2786. FT-IR (thin film, cm^{-1}) υ 2956, 2928, 2858, 1661, 1653, 1364, 1111.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-methoxyisoquinolin-2(1H)-yl)(pyri-din-2-yl)methanone (2la). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-methoxyphenyl)ethyl)picolinamide (161 mg, 0.41 mmol), 3,3-dimethyl-1-butyne (150 µL, 1.23 mmol, 3 equiv), $Co(dpm)_2$ (34 mg, 0.08 mmol, 20 mol%), NaOPiv (62 mg, 0.5 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (220 mg, 0.82 mmol, 2 equiv), and MeOH (4 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 143 mg (75%) of a yellowish oil was obtained. R_f = 0.33 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.74 – 8.65 (m, 1H), 7.82 – 7.72 (m, 2H), 7.42 – 7.37 (m, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.61 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.53 (s, 1H), 4.95 (t, *J* = 6.9 Hz, 1H), 3.94 (dd, *J* = 9.8, 7.3 Hz, 1H), 3.77 (s, 3H), 3.57 (dd, *J* = 9.8, 7.6 Hz, 1H), 1.37 (s, 9H), 0.85 (s, 9H), -0.07 (s, 3H), -0.08 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 159.4, 153.8, 150.1, 149.4, 136.8, 132.9, 127.6, 125.3, 125.2, 124.8, 118.2, 112.4, 110.7, 62.5, 60.3, 55.5, 36.8, 31.0, 26.0, 18.4, -5.4, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{27}H_{39}N_2O_3Si$ 467.2730; found: 467.2736. FT-IR (thin film, cm^{-1}) υ 2955, 2930, 2858, 1653, 1246, 1154, 1110.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-(methoxymethoxy)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ma). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-methoxymethoxyphenyl)ethyl)pico-linamide (208 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 20 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 209 mg (84%) of a yellowish oil was obtained. R_f = 0.31 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.73 – 8.64 (m, 1H), 7.85 – 7.63 (m, 2H), 7.43 – 7.35 (m, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.81 – 6.69 (m, 2H), 6.53 (s, 1H), 5.17 – 5.09 (m, 2H), 4.96 (t, *J* = 6.8 Hz, 1H), 3.93 (dd, *J* = 9.8, 7.3 Hz, 1H), 3.57 (dd, *J* = 9.8, 7.5 Hz, 1H), 3.45 (s, 3H), 1.36 (s, 9H), 0.86 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 157.0, 153.8, 150.1, 149.4, 136.8, 132.9, 127.5, 126.5, 125.3, 124.8, 118.2, 114.6, 113.3, 94.6, 62.4, 60.3, 56.0, 36.8, 31.0, 26.0, 18.4, -5.4, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{28}H_{41}N_2O_4Si$ 497.2836; found: 497.2840. FT-IR (thin film, cm^{-1}) υ 2955, 2929, 2857, 1653, 1241, 1152, 1112.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-trifluoromethoxyisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2na). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-trifluoromethoxyphenyl)ethyl)picolin-amide (260 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 17 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 194 mg (75%) of a yellowish oil was obtained. R_f = 0.52 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.70 (dd, *J* = 3.7, 2.4 Hz, 1H), 7.88 – 7.74 (m, 2H), 7.47 – 7.37 (m, 1H), 7.00 (s, 1H), 6.94 – 6.84 (m, 2H), 6.54 (s, 1H),

5.06 (t, J = 7.4 Hz, 1H), 4.01 (dd, J = 9.6, 6.8 Hz, 1H), 3.62 (dd, J = 9.6, 8.3 Hz, 1H), 1.37 (s, 9H), 0.83 (s, 9H), -0.09 (s, 3H), -0.10 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 153.3, 151.6, 149.3, 149.0 (q, J_{C-F} = 1.8 Hz), 137.1, 133.4, 131.3, 128.2, 125.6, 125.0, 120.6 (q, J_{C-F} = 257.0 Hz), 118.8, 118.0, 117.2, 62.0, 60.1, 36.9, 31.0, 25.9, 18.4, -5.47, -5.54. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -57.84. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{27}H_{36}N_2O_3F_3Si$ 521.2447; found: 521.2458. FT-IR (thin film, cm^{-1}) υ 2957, 2930, 2859, 1662, 1260, 1168, 1118.

(3-(*Tert*-butyl)-1-(((*tert*-butyldimethylsilyl)oxy)methyl)-6-fluoroisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2oa). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethyl)picolinamide (187 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 24 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 151 mg (66%) of a yellowish oil was obtained. R_f = 0.76 (petroleum ether/EtOAc 2:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.70 (dt, J = 4.8, 1.3 Hz, 1H), 7.83 – 7.74 (m, 2H), 7.44 – 7.37 (m, 1H), 6.87 – 6.78 (m, 2H), 6.75 (td, J = 8.5, 2.5 Hz, 1H), 6.51 (s, 1H), 5.02 (t, J = 7.3 Hz, 1H), 3.98 (dd, J = 9.6, 6.9 Hz, 1H), 3.59 (dd, J = 9.6, 8.1 Hz, 1H), 1.36 (s, 9H), 0.84 (s, 9H), -0.08 (s, 3H), -0.09 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.3, 162.6 (d, J_{C-F} = 244.7 Hz), 153.5, 151.1, 149.3, 137.0, 133.5 (d, J_{C-F} = 8.6 Hz), 128.6 (d, J_{C-F} = 2.8 Hz), 128.2 (d, J_{C-F} = 8.5 Hz), 125.5, 124.9, 117.5 (d, J_{C-F} = 2.3 Hz), 113.0 (d, J_{C-F} = 21.9 Hz), 112.2 (d, J_{C-F} = 22.3 Hz), 62.2, 60.1, 36.9, 31.0, 26.0, 18.4, -5.4, -5.5. ^{19}F-NMR (376 MHz, $CDCl_3$, ppm) δ -114.98. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{26}H_{36}N_2O_2SiF$ 455.2530; found: 455.2540. FT-IR (thin film, cm^{-1}) υ 2956, 2929, 2858, 1662, 1652, 1365, 1240, 1146, 1109.

(3-(*Tert*-butyl)-1-(((tert-butyldimethylsilyl)oxy)methyl)-6-bromoisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2pa). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(4-bromophenyl)ethyl)picolinamide (202 mg, 0.46 mmol), 3,3-dimethyl-1-butyne (170 µL, 1.38 mmol, 3 equiv), $Co(dpm)_2$ (39 mg, 0.092 mmol, 20 mol%), NaOPiv (69 mg, 0.55 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (247 mg, 0.92 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 165 mg (70%) of a yellowish oil was obtained. R_f = 0.50 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.76 – 8.61 (m, 1H), 7.83 – 7.71 (m, 2H), 7.45 – 7.35 (m, 1H), 7.28 (d, J = 1.9 Hz, 1H), 7.18 (dd, J = 8.0, 1.9 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.50 (s, 1H), 5.01 (t, J = 7.1 Hz, 1H), 3.98 (dd, J = 9.6, 6.8 Hz, 1H), 3.62 – 3.56 (m, 1H), 1.35 (s, 9H), 0.83 (s, 9H), -0.07 (s, 3H), -0.08 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 153.3, 151.3, 149.2, 137.0, 133.6, 131.6, 129.2, 128.4, 128.3, 125.5, 124.9, 121.6, 117.0, 62.0, 60.2, 36.9, 30.9, 26.0, 18.4, -5.4, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{26}H_{36}N_2O_2BrSi$ 515.1729; found: 515.1742. FT-IR (thin film, cm^{-1}) υ 2957, 2929, 2858, 1662, 1653, 1365, 1111.

(6-(*Tert*-butyl)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)thieno[3,2-c]pyridin-5(4H)-yl)(pyridin-2-yl)methanone (2qa). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-(thiophen-3-yl)ethyl)picolinamide (181 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 185 mg (84%) of a yellowish oil was obtained.Unseperable mixture of regioisomers (3.1:1). R_f = 0.54 (petroleum ether/EtOAc 3:1). *Note! In NMR signals for major regioisomer are given.* ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.74 – 8.67 (m, 1H), 7.84 – 7.73 (m, 2H), 7.42 – 7.38 (m, 1H), 7.02 (d, J = 5.0 Hz, 1H), 6.65 (d, J = 5.0 Hz, 1H), 6.58 (s, 1H), 5.19 – 5.06 (m, 1H), 3.93 (dd, J = 9.6, 7.0 Hz, 1H), 3.61 (dd, J = 9.6, 7.9 Hz, 1H), 1.34 (s, 9H), 0.86 (s, 9H), -0.05 (s, 3H), -0.07 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.8, 153.6, 149.4, 147.1, 136.9, 133.8, 133.6, 125.8, 125.4, 125.0, 123.0, 112.6, 62.0, 58.1, 36.9, 31.1, 26.0, 18.4, -5.4, -5.6. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{24}H_{35}N_2O_2SSi$ 443.2189; found: 443.2199. FT-IR (thin film, cm^{-1}) υ 2956, 2928, 2858, 1655, 1364, 1257, 1113.

(3-(*Tert*-butyl)-1-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)isoquinolin-2(1H)-yl)(pyridin-2-yl) methanone (2ra). *N*-(3-((*Tert*-butyldimethylsilyl)oxy)-1-phenylpropyl)picolinamide (185 mg, 0.5 mmol), 3,3-dimethyl-1-butyne (185 µL, 1.5 mmol, 3 equiv; additional 93 µL, 0.75 mmol, 1.5 equiv after 16 h), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 40 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 160 mg (71%) of a yellowish oil was obtained. R_f = 0.51 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.69 (dd, J = 6.0, 1.2 Hz, 1H), 7.75 (td, J = 7.7, 1.7 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.37 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.21 – 7.11 (m, 2H), 7.05 (td, J = 7.3, 1.6 Hz, 1H), 6.81 (d, J = 7.4 Hz, 1H), 6.59 (s, 1H), 5.20 – 5.02 (m, 1H), 3.66 (ddd, J = 10.3, 6.3, 3.8 Hz, 1H), 3.40 (dd, J = 20.2, 4.9 Hz, 1H), 2.28 – 2.18 (m, 1H), 1.80 – 1.72 (m, 1H), 1.39 (s, 9H), 0.84 (s, 9H), 0.02 (s, 3H), -0.00 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 154.2, 149.6, 149.0, 137.0, 134.6, 131.3, 127.6, 126.5, 126.0, 125.4, 125.1, 124.2, 118.2, 59.5, 56.5, 36.6, 35.1, 31.0, 26.1, 18.3, -5.2, -5.3. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{27}H_{39}N_2O_2Si$ 451.2781; found: 451.2786. FT-IR (thin film, cm^{-1}) υ 2955, 2857, 1653, 1098.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-cyclopropylisoquinolin-2(1H)-yl)(pyridin-2-yl) methanone (2ab). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), cyclopropylacetylene (127 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 20 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 154 mg (73%) of a yellowish oil was obtained. R_f = 0.40 (petroleum ether/EtOAc 3:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.61 (d, J = 4.3 Hz, 1H), 7.75 (td, J = 7.7, 1.7 Hz, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.33 (ddd, J = 7.4, 4.9, 1.1 Hz, 1H), 7.25 – 7.16 (m, 1H), 7.17 – 7.08 (m, 2H), 7.06 (d, J = 7.4 Hz, 1H), 5.98 (s, 1H), 5.85 – 5.35 (m, 1H), 3.85 – 3.67 (m, 1H), 3.61

(dd, *J* = 9.8, 7.1 Hz, 1H), 0.92 – 0.79 (m, 10H), 0.65 – 0.48 (m, 3H), 0.48 – 0.31 (m, 1H), -0.10 (s, 6H). $^{13}C\{1H\}$NMR (100 MHz, $CDCl_3$, ppm) δ 168.1, 155.3, 148.8, 140.7, 136.7, 132.0, 131.4, 127.9, 127.3, 126.5, 124.9, 124.8, 124.4, 112.7, 62.8, 57.7, 25.9, 18.3, 16.3, 10.3, 7.8, -5.5, -5.6. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{25}H_{33}N_2O_2Si$ 421.2311; found: 421.2315. FT-IR (thin film, cm^{-1}) υ 2953, 2928, 2857, 1655, 1251, 1108.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3,4-dimethylisoquinolin-2(1H)-yl)(pyridin-2-yl) methanone (2ac). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 2-butyne (60 µL, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 142 mg (70%) of a yellowish oil was obtained. R_f = 0.25 (petroleum ether/EtOAc 4:1). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see comparison of ^{1}H-NMR spectra at RT and 65 °C). Better quality ^{1}H-NMR spectra was obtained at 65 °C temperature (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 65 °C, ppm) δ 8.65 (d, *J* = 4.5 Hz, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.47 – 7.29 (m, 3H), 7.24 – 7.15 (m, 1H), 7.16 – 6.95 (m, 1H), 5.68 – 5.02 (m, 1H), 4.00 – 3.78 (m, 1H), 3.69 (dd, J = 9.7, 7.3 Hz, 1H), 2.12 (s, 3H), 1.96 (bs, 3H), 0.88 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H). $^{13}C\{1H\}$NMR (100 MHz, $C_2D_2Cl_4$, list of peaks given due to the splitted carbon signals caused by rotamers, ppm) δ 168.1, 166.4, 154.2, 153.5, 148.8, 136.8, 132.9, 132.6, 130.2, 128.5, 127.7, 126.9, 126.3, 124.8, 124.0, 122.7, 121.6, 120.2, 118.2, 62.3, 59.9, 56.1, 25.7, 21.0, 18.1, 17.7, 13.8, -5.6, -5.8. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{24}H_{33}N_2O_2Si$ 409.2311; found: 409.2315. FT-IR (thin film, cm^{-1}) υ 2952, 2929, 2857, 1653, 1394, 1250, 1112.

(*S*)-(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3,4-dimethylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone ((*S*)-2ac). (*S*)-*N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 2-butyne (118 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 142 mg (70%) of a yellowish oil was obtained. R_f = 0.25 (petroleum ether/EtOAc 4:1). *ee* = > 99% (see attached HPLC data). The NMR data matched to racemate. $[\alpha]_D^{20}$ -429.2 (*c* = 0.917, $CHCl_3$).

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3,4-diethylisoquinolin-2(1H)-yl)(pyridin-2-yl)metha-none (2ad). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), hex-3-yne (169 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 167 mg (76%) of a yellowish oil was obtained. R_f = 0.33 (petroleum ether/EtOAc 4:1). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see comparison of ^{1}H-NMR spectra at RT and 65 °C). Better quality ^{1}H-NMR spectra was obtained at 65 °C temperature (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 65 °C, ppm) δ 8.65 (d, *J* = 4.4 Hz, 1H), 7.78 (td, *J* = 7.7, 1.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.42 – 7.29 (m, 3H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.15 – 6.87 (m, 1H), 5.55 – 4.77 (m, 1H), 4.03 – 3.79 (m, 1H), 3.66 (dd, *J* = 9.5, 7.9 Hz, 1H), 3.19 – 1.73 (m, 4H), 1.19 (t, *J* = 7.5 Hz, 3H), 1.17 – 1.04 (m, 3H), 0.87 (s, 9H), 0.02 – -0.28 (m, 6H). $^{13}C\{1H\}$NMR (100 MHz, $C_2D_2Cl_4$, list of peaks given due to the splitted carbon signals caused by rotamers, ppm) δ 168.5, 166.9, 153.7, 148.9, 136.6, 135.7, 134.8, 133.3, 131.6, 127.7, 127.3, 127.2, 126.9, 126.2, 124.8, 124.1, 123.6, 122.7, 62.1, 59.6, 55.9, 25.7, 22.1, 20.6, 18.1, 14.0, 13.1, -5.6, -5.8. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{26}H_{37}N_2O_2Si$ 437.2624; found: 437.2629. FT-IR (thin film, cm^{-1}) υ 2959, 2928, 2856, 1649, 1391, 1112.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3,4-dipropylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ae). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), oct-4-yne (110 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 185 mg (80%) of a yellowish oil was obtained. R_f = 0.36 (petroleum ether/EtOAc 4:1). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see comparison of ^{1}H-NMR spectra at RT and 65 °C). Better quality ^{1}H-NMR spectra was obtained at 65 °C temperature (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 65 °C, ppm) δ 8.65 (d, *J* = 4.4 Hz, 1H), 7.78 (td, *J* = 7.7, 1.6 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.42 – 7.28 (m, 3H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.14 – 6.88 (m, 1H), 5.46 – 4.85 (m, 1H), 4.04 – 3.85 (m, 1H), 3.70 – 3.57 (m, 1H), 2.68 –2.46 (m, 3H), 1.75 – 1.39 (m, 5H), 1.06 (t, *J* = 7.3 Hz, 3H), 1.00 – 0.91 (m, 3H), 0.87 (s, 9H), 0.11 – -0.23 (m, 6H). $^{13}C\{1H\}$NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 168.5, 153.7, 148.9, 136.6, 135.1, 133.2, 131.9, 127.7, 127.2, 126.2, 124.9, 124.1, 123.4, 122.9, 62.1, 59.7, 56.0, 31.3, 29.6, 25.7, 22.6, 21.7, 18.1, 14.4, -5.7, -5.8. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{28}H_{41}N_2O_2Si$ 465.2937; found: 465.2946. FT-IR (thin film, cm^{-1}) υ 2957, 2929, 2871, 1653, 1391, 1112.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-phenylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2af). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), phenylacetylene (82 µL, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 167 mg (73%) of a yellowish oil was obtained. R_f = 0.27 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data).*Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see 2D-NOESY NMR for crosspeaks). ^{1}H-NMR spectra at 65 °C temperature did not improve coupling resolution quality (due to the hardware limitations 65 °C is the maximum temperature).*

^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.39 – 8.16 (m, 1H), 7.46 – 7.15 (m, 8H), 7.07 – 6.88 (m, 4H), 6.36 – 6.22 (m, 1H), 6.16 – 5.87 (m, 1H), 3.99 – 3.83 (m, 1H), 3.77 (dd, *J* = 10.1, 6.4 Hz, 1H), 0.89 (s, 9H), 0.08 – -0.10 (m, 6H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 168.2, 154.3, 147.7, 138.9, 138.3, 136.0, 132.3, 131.3, 128.1, 127.9, 127.5, 127.3, 127.2, 126.8, 125.6, 124.2, 124.0, 114.5, 62.3, 56.7, 25.7, 18.0, -5.6, -5.7. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{28}H_{33}N_2O_2Si$ 457.2311; found: 457.2318. FT-IR (thin film, cm^{-1}) υ 2957, 2928, 2856, 1661, 1653, 1363, 1111.

(*S*)-(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-phenylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone ((*S*)-2af). (*S*)-*N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), phenylacetylene (82 µL, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 160 mg (70%) of a yellowish oil was obtained. R_f = 0.27 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. *ee* = > 99% (see attached HPLC data). The NMR data matched to racemate. $[\alpha]_D^{20}$ -264.6 (*c* = 0.923, $CHCl_3$).

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(4-methoxyphenyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ag). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 4-methoxyphenylacetylene (97 µL, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 17 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1, then 2:1), 215 mg (88%) of a yellowish oil was obtained. R_f = 0.66 (petroleum ether/EtOAc 1:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see see comparison of ^{1}H-NMR spectra at RT and 65 °C and 2D-NOESY NMR for crosspeaks). ^{1}H-NMR spectra at 65 °C temperature did not improve coupling resolution quality (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, ppm) δ 8.40 – 8.15 (m, 1H), 7.43 – 7.26 (m, 5H), 7.24 – 7.09 (m, 3H), 7.04 – 6.95 (m, 1H), 6.69 – 6.50 (m, 2H), 6.21 (s, 1H), 6.03 – 5.91 (m, 1H, overlapped with $C_2D_2Cl_4$), 3.94 – 3.83 (m, 1H), 3.78 – 3.62 (m, 4H), 0.92 (s, 9H), 0.03 (s, 3H), -0.03 (s, 3H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 168.3, 158.7, 154.5, 149.8, 137.9, 135.9, 135.5, 132.3, 131.8, 131.5, 130.6, 128.2, 128.0, 127.3, 126.9, 125.4, 123.9, 113.2, 62.2, 56.7, 55.3, 25.8, 18.0, -5.6, -5.7. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{29}H_{34}N_2O_3Si$ 487.2417; found: 487.2415. FT-IR (thin film, cm^{-1}) υ 2954, 2929, 2856, 1653, 1507, 1249, 1180, 1111.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(4-nitrophenyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ah). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 4-nitrophenylacetylene (110 mg, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1, then 2:1), 125 mg (50%) of a yellow oil was obtained. R_f = 0.30 (petroleum ether/EtOAc 3:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see 2D-NOESY NMR for crosspeaks and comparison of ^{1}H-NMR spectra at RT and 65 °C). ^{1}H-NMR spectra at 65 °C temperature did not improve coupling resolution quality (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 65 °C, ppm) δ 8.63 – 8.19 (m, 1H), 8.17 – 6.72 (m, 11H), 6.72 – 6.27 (m, 1H), 6.18 – 5.69 (m, 1H, overlapped with $C_2D_2Cl_4$), 4.24 – 3.86 (m, 1H), 3.89 – 3.72 (m, 1H), 0.92 (s, 9H), 0.25 – -0.25 (m, 6H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 167.4, 153.6, 147.9, 146.1, 145.7, 136.5, 136.4, 132.5, 130.8, 129.3, 127.3, 127.0, 126.2, 126.1, 124.6, 123.8, 123.1, 117.5, 62.8, 56.7, 25.8, 18.0, -5.6, -5.7. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{28}H_{32}N_3O_4Si$ 502.2162; found: 502.2166. FT-IR (thin film, cm^{-1}) υ 2954, 2929, 2856, 1662, 1595, 1520, 1343, 1108.

(*E*)-(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(4-nitrophenyl)-8-(4-nitrostyryl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ah'). In addition to the major product described above, 52 mg (16%) of a minor product as a yellow oil was obtained. R_f = 0.20 (petroleum ether/EtOAc 3:1). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see 2D-NOESY NMR for crosspeaks).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, ppm) δ 8.32 – 8.22 (m, 3H), 8.00 – 7.84 (m, 2H), 7.82 – 7.62 (m, 4H), 7.60 – 7.50 (m, 2H), 7.51 – 7.40 (m, 2H), 7.41 – 7.28 (m, 2H), 7.17 (d, *J* = 16.0 Hz, 1H), 7.11 – 6.99 (m, 1H), 6.58 (dd, *J* = 8.7, 5.1 Hz, 1H), 6.50 (s, 1H), 3.86 (t, *J* = 10.1 Hz, 1H), 3.74 (dd, *J* = 10.9, 4.9 Hz, 1H), 0.92 (s, 9H), 0.18 – -0.22 (m, 6H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 167.4, 153.5, 147.8, 146.8, 146.2, 145.5, 143.3, 142.0, 136.6, 133.9, 131.6, 130.7, 130.0, 128.7, 128.5, 127.4, 127.2, 126.8, 126.1, 124.8, 124.7, 124.1, 123.2, 117.5, 61.2, 53.1, 25.7, 18.0, -5.4, -5.6. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{36}H_{37}N_4O_6Si$ 649.2482; found: 649.2490. FT-IR (thin film, cm^{-1}) υ 2965, 2828, 2847, 1595, 1519, 1341, 1109.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(4-ethynylphenyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ai). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 1,4-diethynylbenzene (95 mg, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 130 mg (54%) of a yellowish oil was obtained. R_f = 0.40 (petroleum ether/EtOAc 3:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted. ^{1}H-NMR spectra at 65 °C temperature did not improve coupling resolution quality (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 65 °C, ppm) δ 8.52 – 8.19 (m, 1H), 8.14 – 6.89 (m, 11H), 6.70 – 6.22 (m, 1H), 6.17 – 5.67 (m, 1H, overlapped with $C_2D_2Cl_4$), 4.25 – 3.85 (m, 1H), 3.79 (dd, J = 10.1, 6.2 Hz, 1H), 3.12 (s, 1H), 0.92 (s, 9H), 0.22 – -0.31 (m, 6H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 167.9, 154.1, 147.8,

139.5, 137.5, 136.2, 132.4, 131.6, 131.2, 128.1, 127.5, 127.1, 126.6, 125.8, 124.3, 124.2, 120.7, 115.3, 83.5, 78.1, 62.5, 56.7, 25.7, 18.0, -5.6, -5.7. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{30}H_{33}N_2O_2Si$ 481.2311; found: 481.2319. FT-IR (thin film, cm^{-1}) υ 2955, 2930, 2857, 1653, 1363, 1111.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(thiophen-3-yl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2aj). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 3-ethynylthiophene (149 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 150 mg (65%) of a yellowish oil was obtained. R_f = 0.55 (petroleum ether/EtOAc 2:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). *Note! Due to restricted rotation about the amide bond, the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted. ^{1}H-NMR spectra at 65 °C temperature did not improve coupling resolution quality (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, 65 °C, ppm) 8.55 – 8.26 (m, 1H), 7.62 – 7.49 (m, 1H), 7.45 – 7.22 (m, 5H), 7.23 – 6.84 (m, 4H), 6.54 – 6.25 (m, 1H), 6.05 – 5.62 (m, 1H, overlapped with $C_2D_2Cl_4$), 4.06 – 3.86 (m, 1H), 3.80 (dd, *J* = 10.0, 6.8 Hz, 1H), 0.91 (s, 9H), 0.19 – -0.18 (m, 6H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 168.0, 154.2, 147.9, 140.5, 136.0, 133.5, 132.5, 131.2, 128.0, 127.4, 127.1, 126.4, 125.5, 124.1, 123.8, 122.8, 113.4, 62.3, 56.8, 25.8, 18.1, -5.6, -5.7. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{26}H_{31}N_2O_2SiS$ 463.1876; found: 463.1877. FT-IR (thin film, cm^{-1}) υ 2957, 2927, 2856, 1653, 1507, 1111.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3,4-diphenylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2ak). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), diphenylacetylene (134 mg, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 205 mg (77%) of a yellowish oil was obtained. R_f = 0.25 (petroleum ether/EtOAc 4:1). *Note! Due to restricted rotation about the amide bond, [3,5] some of the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see 2D-NOESY NMR for crosspeaks).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, ppm) δ 8.34 (d, *J* = 4.0 Hz, 1H), 7.44 – 7.07 (m, 11H), 7.03 – 6.95 (m, 1H), 6.87 – 6.69 (m, 5H), 6.06 – 5.98 (m, 1H, overlapped with $C_2D_2Cl_4$), 4.23 – 4.05 (m, 1H), 3.93 (dd, *J* = 10.2, 6.3 Hz, 1H), 0.98 (s, 9H), 0.13 (s, 3H), 0.08 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 163.3, 155.4, 147.9, 138.8, 137.0, 136.1, 134.3, 133.2, 132.3, 131.2, 130.2, 128.2, 127.9, 127.3, 127.2, 127.0, 126.7, 126.6, 125.8, 123.9, 123.7, 63.2, 56.7, 26.1, 18.5, -5.2, -5.4. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{34}H_{37}N_2O_2Si$ 533.2624; found: 533.2632. FT-IR (thin film, cm^{-1}) υ 2957, 2930, 2857, 1663, 1112.

(*S*)-(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3,4-diphenylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone ((*S*)-2ak). (*S*)-*N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), diphenylacetylene (134 mg, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 177 mg (67%) of a yellowish oil was obtained. R_f = 0.25 (petroleum ether/EtOAc 4:1). *ee* = > 99% (see attached HPLC data). The NMR data matched to racemate. $[\alpha]_D^{20}$ -385.4 (*c* = 0.773, $CHCl_3$).

(3,4-Bis(4-bromophenyl)-1-(((tert-butyldimethylsilyl)oxy)methyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2al). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), bis(4-bromophenyl)acetylene (252 mg, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 261 mg (76%) of a white powder was obtained. R_f = 0.33 (petroleum ether/EtOAc 3:1). *Note! Due to restricted rotation about the amide bond, [3,5] some of the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted. ^{1}H-NMR spectra at 65 °C temperature did not improved coupling resolution quality (due to the hardware limitations 65 °C is the maximum temperature).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, ppm) δ δ 8.65 – 8.14 (m, 1H), 7.50 – 7.19 (m, 7H), 7.12 – 7.00 (m, 3H), 6.95 – 6.87 (m, 2H), 6.76 – 6.70 (m, 1H), 6.11 – 5.94 (m, 1H, overlapped with $C_2D_2Cl_4$), 4.17 – 3.96 (m, 1H), 3.93 – 3.82 (m, 1H), 0.97 (s, 9H), 0.17 (s, 3H), 0.10 (s, 3H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 168.6, 154.6, 147.6, 137.1, 136.3, 135.0, 133.5, 132.4, 132.1, 131.9, 131.5, 131.3, 130.1, 128.0, 127.7, 127.0, 125.4, 125.2, 124.1, 123.8, 121.1, 120.8, 62.9, 56.3, 25.8, 18.1, -5.4, -5.6. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{34}H_{35}N_2O_2SiBr_2$ 689.0828; found: 689.0835. FT-IR (thin film, cm^{-1}) υ 2955, 2929, 2857, 1668, 1389, 1108.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-4-methyl-3-phenylisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2am). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol), 1-phenyl-1-propyne (94 µL, 0.75 mmol, 1.5 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3{\cdot}2\,H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 171 mg (73%) of a yellowish oil was obtained. R_f = 0.22 (petroleum ether/EtOAc 4:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data). *Note! Due to restricted rotation about the amide bond, [3,5] some of the signals observed in ^{1}NMR are broad and coupling resolution is low, some proton signals are splitted (see 2D-NOESY NMR for crosspeaks).* ^{1}H-NMR (400 MHz, $C_2D_2Cl_4$, ppm) δ 8.30 (d, *J* = 4.4 Hz, 1H), 7.48 – 7.17 (m, 6H), 7.08 – 6.98 (m, 5H), 6.81 (d, *J* = 7.7 Hz, 1H), 5.91 (t, *J* = 7.0 Hz, 1H), 4.01 – 3.89 (m, 1H), 3.81 (dd, *J* = 10.3, 6.1 Hz, 1H), 2.06 (s, 3H), 0.93 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H). ^{13}C{1H}NMR (100 MHz, $C_2D_2Cl_4$, ppm) δ 168.7, 155.1, 147.5, 138.4, 136.0, 133.8, 132.9, 132.6, 129.9, 128.0, 127.3, 127.2, 127.0, 126.8, 123.9, 123.6, 123.5, 118.7, 62.6, 56.0, 25.8, 18.0, 15.2, -5.6, -5.7. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{29}H_{35}N_2O_2Si$ 471.2468; found: 471.2469. FT-IR (thin film, cm^{-1}) υ 3060, 2954, 2929, 2857, 1653, 1388, 1363, 1117.

(1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(trimethylsilyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (2an). *N*-(2-((*Tert*-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (178 mg, 0.5 mmol),

trimethylsilylacetylene (213 µL, 1.5 mmol, 3 equiv), $Co(dpm)_2$ (42.5 mg, 0.1 mmol, 20 mol%), NaOPiv (75 mg, 0.6 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (268 mg, 1.0 mmol, 2 equiv), and MeOH (5 mL), 16 h, 80 °C, O_2 atmosphere. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 160 mg (71%) of a yellowish oil was obtained. R_f = 0.80 (petroleum ether/EtOAc 2:1). Isolated as single regioisomer. Structure confirmed by 2D-NMR (COSY, NOESY, see attached NMR data).

Procedure for gram-scale synthesis: A 100 mL pressure tube equipped with a magnetic stir bar was charged with *N*-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide (1.00 g, 2.79 mmol), $Co(dpm)_2$ (238 mg, 0.56 mmol, 20 mol%), NaOPiv (415 mg, 3.35 mmol, 1.2 equiv), $Mn(OAc)_3 \cdot 2\ H_2O$ (1.50 g, 5.58 mmol, 2 equiv), and MeOH (28 mL). The reaction mixture was purged with O2 for 30 sec and then trimethylsilylacetylene (1.2 mL, 8.37 mmol, 3 equiv) was added and mixture was heated at 80 °C for for 18 h. The reaction mixture was cooled to room temperature and solvent was evaporated. To the residue potassium sodium tartrate (50 mL of 1M aqueous solution) was added and mixture was extracted with EtOAc (3 x 50 mL). Combined organic phase was dried over Na2SO4, filtered, and solvent was evaporated. After column chromatography (gradient petroleum ether/EtOAc from 6:1 to 4:1), 1.00 g (80%) of a yellowish oil was obtained. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.64 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.84 – 7.71 (m, 2H), 7.42 – 7.33 (m, 1H), 7.25 (td, *J* = 7.5, 1.3 Hz, 1H), 7.20 – 7.12 (m, 2H), 7.00 (d, J = 7.3 Hz, 1H), 6.61 (s, 1H), 5.37 (t, *J* = 7.1 Hz, 1H), 3.89 (dd, *J* = 9.7, 7.9 Hz, 1H), 3.47 (dd, *J* = 9.7, 6.6 Hz, 1H), 0.78 (s, 9H), 0.33 (s, 9H), -0.11 (s, 3H), -0.16 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 168.2, 154.2, 148.5, 142.0, 136.9, 132.2, 130.8, 128.2, 127.3, 128.1, 125.9, 125.2, 125.0, 124.8, 62.8, 59.5, 26.0, 18.4, 0.9, -5.49, -5.50. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{25}H_{37}N_2O_2Si_2$ 453.2394; found: 453.2397. FT-IR (thin film, cm^{-1}) υ 2952, 2929, 2857, 1647, 1405, 1246, 1118.

Synthesis of tetrahydroisoquinolines (*S,S*)-3an and (*S,S*)-4an.

((*1S,3S*)-1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(trimethylsilyl)-3,4-dihydroisoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (*S,S*)-3an. Approximately 15 - 20 mL of ammonia was condensed in 50 mL flask equipped with a magnetic stirbar and cooled to -78 °C temperature using acetone/dry ice bath. Under an argon atmosphere, at -78 °C temperature (1-(((*tert*-butyldimeth-ylsilyl)oxy)methyl)-3-(trimethyl-silyl)isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (255 mg, 0.56 mmol) solution in THF (6 mL) was added followed by sodium (61 mg, 2.52 mmol, 4.5 equiv). The resulting mixture (dark blue) was stirred at -78 °C temperature until complete conversion (TLC control). The resulting mixture was diluted with dist. H_2O (10 mL) and EtOAc (15 mL), allowed to warm to room temperature and stirred with open cap until all liquid ammonia evaporated. Organic phase was separated, aqueous phase was extracted with EtOAc (2 x 15 mL), dried over Na_2SO_4, filtered, evaporated under reduced pressure. After column chromatography (petroleum ether/EtOAc 4:1), 175 mg (69%) of a yellowish oil was obtained. R_f = 0.50 (petroleum ether/EtOAc 4:1). *Note! ^{1}H-NMR analysis of crude reaction mixture showed d.r. >20/1. Only major diastereomer was collected. Structure of major diastereomer was confirmed by 2D-NMR after directing group removal.* ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 8.61 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H), 7.58 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.33 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.23 – 7.09 (m, 3H), 6.94 (d, *J* = 7.3 Hz, 1H), 5.04 (dd, *J* = 8.4, 6.1 Hz, 1H), 4.19 (dd, *J* = 9.5, 6.1 Hz, 1H), 3.96 (dd, *J* = 12.3, 7.2 Hz, 1H), 3.73 (dd, *J* = 9.4, 8.6 Hz, 1H), 3.08 (dd, *J* = 15.7, 12.4 Hz, 1H), 2.96 (dd, *J* = 15.9, 7.2 Hz, 1H), 0.75 (s, 9H), 0.20 (s, 9H), -0.14 (s, 3H), -0.18 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 169.3, 155.5, 148.5, 136.9, 135.8, 135.6, 128.2, 127.8, 127.3, 126.0, 124.3, 124.1, 65.4, 60.8, 43.4, 29.5, 26.0, 18.4, -1.4, -5.5. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{25}H_{39}N_2O_2Si_2$ 455.2550; found: 455.2564. FT-IR (thin film, cm^{-1}) υ 2952, 2928, 2857, 1628, 1405, 1248, 1109. $[\alpha]_D^{20}$ 66.5 (*c* = 1.140, $CHCl_3$).

(*1S,3S*)-1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(trimethylsilyl)-1,2,3,4-tetrahydroisoqui-noline (*S,S*)-4an. ((*1S,3S*)-1-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-(trimethylsilyl)-3,4-dihydro-isoquinolin-2(1H)-yl)(pyridin-2-yl)methanone (147 mg, 0.32 mmol) was dissolved in THF (4 mL) under an argon atmosphere. The solution was cooled in water/ice bath to 0 °C temperature and $LiAlH_4$ (18.4 mg, 0.48 mmol, 1.5 equiv.) was added, then reaction mixture was stirred at 0 °C temperature for 10 min (until complete conversion by TLC). The reaction was quenched with water (10 mL) and extracted with EtOAc (3 x 10 mL). Combined organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford the crude product. After column chromatography (petroleum ether/EtOAc 10:1), 96 mg (86%) of a yellowish oil was obtained. R_f = 0.50 (petroleum ether/EtOAc 10:1). *ee* = > 99% (see attached HPLC data; for *ee* determination compound was derivatized to *N*-benzoylderivative and TBS group was cleaved). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) δ 7.19 – 7.01 (m, 4H), 4.18 (dd, *J* = 9.6, 3.6 Hz, 1H), 4.13 – 3.99 (m, 1H), 3.66 (dd, *J* = 9.4, 8.1 Hz, 1H), 2.86 – 2.76 (m, 1H), 2.62 (dd, *J* = 15.9, 2.8 Hz, 1H), 2.38 (dd, *J* = 12.6, 3.0 Hz, 1H), 1.80 (bs, 1H, overlapped with water), 0.88 (s, 9H), 0.10 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H). ^{13}C{1H}NMR (100 MHz, $CDCl_3$, ppm) δ 137.5, 136.5, 129.1, 126.1, 125.6, 125.1, 67.5, 59.1, 43.6, 31.8, 26.0, 18.4, -3.8, -5.1, -5.2. HR-MS (ESI-TOF) m/z: Calcd. for $[M+H]^+$: $C_{19}H_{36}NOSi_2$ 350.2335; found: 350.2347. FT-IR (thin film, cm^{-1}) υ 2954, 2929, 2857, 1472, 1249, 1100. $[\alpha]_D^{20}$ 58.3 (*c* = 1.080, $CHCl_3$).

ASSOCIATED CONTENT

The Supporting Information is available free of charge at http://pubs.acs.org.
Optimization studies along with copies of the NMR spectra and HPLC chromatograms.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This research was financially supported by ERDF project Nr.1.1.1.5/17/A/004. We thank Prof. Aigars Jirgensons for scientific discussions and LIOS analytical service.

REFERENCES

(1) Selected reviews on TM-catalyzed C-H functionatization: a) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C–H Functionalization Reactions. *Chem. Rev.* **2010**, 110, 1147-1169; b) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C–H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, 111, 1315-1345; c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C-H Activation/C-C Cross-coupling Reactions: Versatility and Practicality. *Angew. Chem. Int. Ed.* **2009**, 48, 5094-5115; d) Baudoin, O. Transition Metal-Catalyzed Arylation of Unactivated C(sp^3)-H Bonds. *Chem. Soc. Rev.* **2011**, 40, 4902-4911; e) He, J.; Wasa, M.; Chan, K. S. L.; Shiao, Q.; Yu, J.-Q. Palladium-Catalyzed Transformations of Alkyl C-H Bonds. *Chem. Rev.* **2017**, 117, 8754-8786; f) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations. *Acc. Chem. Res.* **2014**, 47, 281-295; g) Baudoin, O. Ring Construction by Palladium(0)-Catalyzed C(sp^3)–H Activation. *Acc. Chem. Res.* **2017**, 50, 1114-1123; h) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Rhodium Catalyzed Chelation-Assisted C-H Bond Functionalization Reactions. *Acc. Chem. Res.* **2012**, 45, 814-825; i) Gao, K.; Yoshikai, N. Low-Valent Cobalt Catalysis: New Opportunities for C–H Functionalization. *Acc. Chem. Res.* **2014**, 47, 1208-1219; j) Dwivedi, V.; Kalsi D.; Sundararaju, B. Electrochemical-/ Photoredox Aspects of Transition Metal-Catalyzed Directed C-H Bond Activations. *Chem. Cat. Chem.* **2019**, *11*, 5160-5187.

(2) Selected reviews on Co-catalyzed C-H functionatization: a) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C–H Activation. *Chem. Rev.* **2019**, *119*, 2192-2452; b) Ujwaldev, S. M.; Harry, N. A.; Divakar, M. A.; Anilkumar, G. Cobalt-Catalyzed C–H Activation: Recent Progress in Heterocyclic Chemistry *Catal. Sci. Technol.* **2018**, *8*, 5983-6018; c) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C–H Activation. *ACS Catal.* **2016**, *6*, 498-525; d) Hyster, T. K. High-Valent Co(III)- and Ni(II)-Catalyzed C–H Activation. *Catal. Lett.* **2015**, *145*, 458-467; e) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc. Chem. Res.* **2015**, *48*, 1053–1064; f) Kommagalla, Y.; Chatani, N. Cobalt(II)-Catalyzed C-H Functionalization Using an *N*,*N*′-Bidentate Directing Group. *Coord. Chem. Rev.* **2017**, 350, 117-135.

(3) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed C(sp^2)-H Bond Alkenylation by Alkynes. *Angew. Chem. Int. Ed.* **2014**, 53, 10209-10212.

(4) Selected examples using Co(II) salts as pre-catalysts with bidentate directing group assistance: C-H functionalization with alkynes a) Kalsi, D.; Dutta, S.; Barsu, N.; Rueping, M.; Sundararaju, B. Room-Temperature C–H Bond Functionalization by Merging Cobalt and Photoredox Catalysis. *ACS Catal.* **2018**, *8*, 8115-8120; b) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed Functionalization of Phosphinic Amide sp^2 C–H Bonds. *ACS Catal.* **2016**, *6*, 551–554; c) Landge, V. G.; Midya, S. P.; Rana, J.; Shinde, D. R.; Balaraman, E. Expedient Cobalt-Catalyzed C–H Alkynylation of (Enantiopure) Benzylamines. *Org. Lett*. **2016**, *18*, 5252–5255; C-H functionalization with alkenes d) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed Coupling of sp^2 C–H Bonds with Alkenes. *Org. Lett.* **2014**, *16*, 4684-4687; e) Kalsi, D.; Barsu, N.; Chakrabarti, S.; Dahiya, P.; Rueping, M.; Sundararaju, B. C–H and N–H bond annulation of aryl amides with unactivated olefins by merging cobalt(iii) and photoredox catalysis. *Chem. Commun.* **2019**, *55*, 11626– 11629; f) Gandeepan, P.; Rajamalli, P.; Cheng, C.-H. Diastereoselective [3+2] Annulation of Aromatic/Vinylic Amides with Bicyclic Alkenes through Cobalt-Catalyzed C-H Activation and Intramolecular Nucleophilic Addition. *Angew. Chem. Int. Ed.* **2016**, *55*, 4308-4311; C-H functionalization with allenes g) Thrimurtulu, N.; Dey, A.; Maiti, D.; Volla, M. R. C. Cobalt-Catalyzed sp^2-C-H Activation: Intermolecular Heterocyclization with Allenes at Room Temperature. *Angew. Chem. Int. Ed.* **2016**, *55*, 12361-12365 h) Thrimurtulu, N.; Nallagonda, R.; Volla, C. M. R. Cobalt-Catalyzed Aryl C–H Activation and Highly Regioselective Intermolecular Annulation of Sulfonamides with Allenes. *Chem. Commun.* **2017**, *53*, 1872-1875; C-H functionalization with isonitriles i) Kalsi, D.; Barsu, N.; Sundararaju, B. CoIII-Catalyzed Isonitrile Insertion/Acyl Group Migration Between C-H and N-H bonds of Arylamides. *Chem. Eur. J.* **2018**, *24*, 2360 – 2364. C-H functionalization CO or CO-surrogates j) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed Direct Carbonylation of Aminoquinoline Benzamides. *Org. Lett.* **2014**, *16*, 4688-4690; k) Ni, J.; Li, J.; Fan, Z.; Zhang, A. Cobalt-Catalyzed Carbonylation of C(sp^2)–H Bonds with Azodicarboxylate as the Carbonyl Source. *Org. Lett.* **2016,** *18*, 5960-5963; l) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. Aminoquinoline-Directed, Cobalt-Catalyzed Carbonylation of Sulfonamide sp^2 C–H Bonds. *Chem. Commun.* **2017,** *53*, 5136-5138;

(5) Cobalt-catalyzed, picolinamide directed benzamide reactions with alkynes: a) Martínez, M.; Rodríguez, N.; Gjmez-Arrayás, R.; Carretero, J. C. Cobalt-Catalyzed *ortho*-C−H Functionalization/Alkyne Annulation of Benzylamine Derivatives: Access to Dihydroisoquinolines. *Chem. Eur. J.* **2017**, 23, 11669-11676; b) Kuai, C.; Wang, L.; Li, B.; Yang, Z.; Cui, X. Cobalt-Catalyzed Selective Synthesis of Isoquinolines Using Picolinamide as a Traceless Directing Group. *Org. Lett.* **2017**, 19, 2102-2105; c) Yao, Y.; Lin, Q.; Yang, W.; Yang, W.; Gu, F.; Guo, W. Yang D. Cobalt(II)-Catalyzed [4 + 2] Annulation of Picolinamides with Alkynes via C−H Bond Activation. *Chem. Eur. J.* 10.1002/chem.202000411.

(6) We tested the reported reaction conditions (Ref. 3, 5a,b) for cobalt catalyzed benzamide sp^2 C-H alkenylation with alkynes using our model substrate – *N*-(2-((tert-butyldimethylsilyl)oxy)-1-phenylethyl)picolinamide. Low reaction conversion was observed. See the Supporting Information for details.

(7) Scott, J. D.; Williams, R. M. Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev.* **2002**, 102, 1669-1730.

(8) Selected reviews on asymmetric synthesis of isoquinoline alkaloids: a) Chrzanowska, M.; Rozwadowska, M. D. Asymmetric Synthesis of Isoquinoline Alkaloids. *Chem. Rev.* **2004**, 104, 3341-3370; b) Liu, W.; Liu, S.; Jin, R.; Guo, H.; Zhao, J. Novel Strategies for Catalytic Asymmetric Synthesis of C1-Chiral 1,2,3,4-Tetrahydroisoquinolines and 3,4-Dihydrotetrahydroisoquinolines. *Org. Chem. Front.* **2015**, 2, 288-299; c) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. Asymmetric Synthesis of Isoquinoline Alkaloids: 2004–2015.*Chem. Rev.* **2016**, 116, 12369-12465.

(9) See the Supporting Information for details.

(10) Planas, O.; Whiteoak, C. J.; Martin-Diaconescu, V.; Gamba, I.; Luis, J. M.; Parella, T.; Company, A.; Ribas, X. Isolation of Key Organometallic Aryl-Co(III) Intermediates in Cobalt-Catalyzed C(sp2)–H Functionalizations and New Insights into Alkyne Annulation Reaction Mechanisms. *J. Am. Chem. Soc.* **2016**, *138*, 14388-14397.

(11) Zeng, W.; Nukeyeva, M.; Wang, Q.; Jiang, C. Synthesis of Unnatural α-Amino Acid Derivatives *via* Selective *o*-C–H Functionalization. *Org. Biomol. Chem.*, **2018**, *16*, 598-608.

(12) Yuan, J.; Liu, C.; Chen, Y.; Zhang, Z.; Yan, D.; Zhang, W. Rhodium-Catalyzed Intramolecular Hydroacylation of 1,2-Disubstituted Alkenes for the Synthesis of 2-Substituted Indanones. *Tetrahedron* **2019**, *75*, 269-277.

(13) Malkov, A. V.; Gouriou, L.; Lloyd-Jones, G. C.; Starý, I.; Langer, V.; Sapoor, P.; Vinader, V.; Kočovskỳ, P. Asymmetric Allylic Substitution Catalyzed by C1-Symmetrical Complexes of Molybdenum: Structural Requirements of the Ligand and the Stereochemical Course of the Reaction. *Chem. Eur. J.* **2006**, *12*, 6910-6929.

(14) Xu, Q.; Xie, H.; Zhang, E.-L.; Ma, X.; Chen, J.; Yu, X.-C.; Li, H. Selective Catalytic Hofmann *N*-Alkylation of Poor Nucleophilic Amines and Amides with Catalytic Amounts of Alkyl Halides. *Green Chem.*, **2016**, 18, 3940-3944.