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PAPER

# Palladium catalyzed acetoxylation of benzylic C–H bonds using a bidentate picolinamide directing group†

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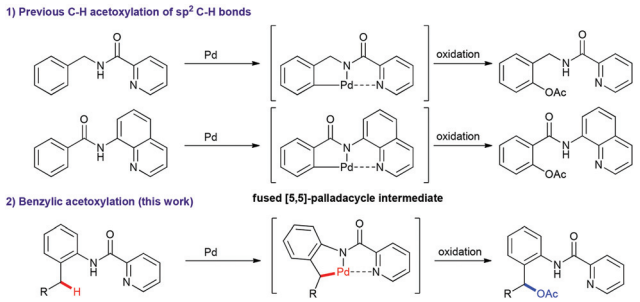
A general palladium catalyzed acetoxylation of benzylic C–H bonds has been developed. Picolinamides serve as an excellent directing group for the C–H activation of benzylic methyls. A wide range of 2-amino benzyl alcohol analogues were synthesized in good yields. The products demonstrated broad synthetic utilities toward various benzo-fused heterocycles. Mechanistic studies revealed the key rate-limiting C–H insertion step, which could be affected by the substitution pattern of the parent arene.

## Introduction

Transition metal catalyzed selective C–H bond activation reactions have mushroomed into one of the most actively studied areas for creating carbon–carbon and carbon–heteroatom bonds in the past decade.[1] While the major effort was devoted to developing novel directing groups and bond formation reactions surrounding $sp^2$ C–H bonds, functionalization of $sp^3$ C–H bonds has also enjoyed impressive progress.[2] In particular, various directing groups have been invented to selectively convert a $sp^3$ C–H to a C–O functionality for a wide spectrum of substrates.[3] However, a general approach for benzylic oxidation remains scarce,[4] despite the tremendous synthetic capability of substituted benzyl alcohols, which are indispensable synthons toward benzo-heterocycles. Herein, we report a general protocol for benzylic acetoxylation *via* palladium catalyzed $sp^3$ C–H activation for the synthesis of various 2-amino benzyl acetates.

Picolinamides were first introduced by Daugulis as a powerful directing group for site selective C–H metallation using palladium.[5] Subsequently, a number of C–H bond functionalization reactions were developed by various research groups.[6] In 2009, Liang *et al.* reported an *ortho*-C–H acetoxylation of benzyl amine derived picolinamides.[7] A fused [5,5]-palladacycle was believed to be the key intermediate for the rate-limiting C–H insertion step. Following a Pd(II)–Pd(IV)–Pd(II) oxidation-reductive elimination cycle, *o*-acetoxy benzyl amine derivatives were synthesized in high yields.[8] Inspired by this result and related [5,5]-palladacycle reports,[9] we decided to move the substrate arene one bond closer to the NH of the picolinamide, hoping that selective benzylic activation would occur in lieu of the *ortho*-aryl C–H functionalization (Scheme 1).




**Scheme 1** Substrate design for benzylic acetoxylation using picolinamides as the bidenate directing group.

## Results and discussion

The substrates were readily available following literature procedures from anilines and picolinic acid.[10] Most commonly used transition-metals for C–H activation failed to yield any product, except palladium. We found that a combination of the substrate (0.1 mmol, 1 equiv.), 10% $Pd(OAc)_2$ and $PhI(OAc)_2$ (0.2 mmol, 2 equiv.) in DCE at 110 °C for 24 h produced the desired benzyl acetate in 40% yield. Encouraged by this result, we surveyed other reaction parameters (Table 1, for the comprehensive investigation of reaction parameters, see ESI†). The highest conversion was observed in toluene among

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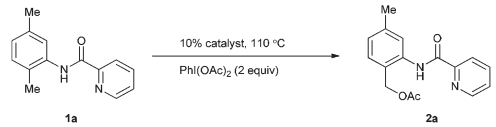
†Electronic supplementary information (ESI) available: Comprehensive reaction condition survey; kinetic experiments and images of $^1H$ and $^{13}C$ NMR of all products. CCDC 969094. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42196a

**Table 1** Reaction condition survey for benzylic acetoxylation of picolinamides[a]




1a 2a

| Entry | Cat. | Solvent | Additive | Conv.[b] (%) |
|---|---|---|---|---|
| 1 | $Fe(acac)_3$ | DCE | — | N.R. |
| 2 | $Ni(acac)_2$ | DCE | — | N.R. |
| 3 | $Cp(Ph_3P)_2RuCl$ | DCE | — | N.R. |
| 4 | $[RhCp^*Cl_2]_2$ | DCE | — | N.R. |
| 5 | $Rh(OAc)_2$ | DCE | — | N.R. |
| 6 | $Pd(OAc)_2$ | DCE | — | 40 |
| 7 | $Pd(OAc)_2$ | Toluene | — | 50 |
| 8 | $Pd(OAc)_2$ | DMF | — | 25 |
| 9 | $Pd(OAc)_2$ | PivOH | — | 30 |
| 10 | $Pd(OAc)_2$ | Toluene/HOAc | — | 50 |
| 11 | $Pd(OAc)_2$ | Toluene | $Li_2CO_3$ | 48 |
| 12 | $Pd(OAc)_2$ | Toluene | KF | 29 |
| 13 | $Pd(OAc)_2$ | Toluene | KOH | N.R. |
| 14 | $Pd(OAc)_2$ | Toluene | $KHCO_3$ | N.R. |
| 15 | $Pd(OAc)_2$ | Toluene | $Na_2CO_3$ | 27 |
| 16 | $Pd(OAc)_2$ | Toluene | AgOAc | 36 |
| 17 | $Pd(OAc)_2$ | Toluene | — | 72[c] |

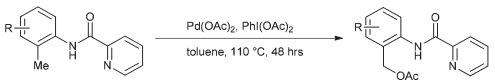
[a] Reaction conditions: **1a** (22.6 mg, 0.1 mmol, 1 equiv.), $PhI(OAc)_2$ (64 mg, 0.2 mmol, 2 equiv.), additive (0.1 mmol, 1 equiv.) and catalyst (0.01 mmol, 0.1 equiv.) in a solvent (1 mL) under argon at 110 °C for 24 h. [b] The conversion was calculated by GC-MS using biphenyl as the internal standard. [c] Isolated yield after 48 h.

the solvents examined. Various bases were tested in an attempt to facilitate the chelation of the metal. No improvement was observed. The reaction was sensitive to the reaction temperature. Decreasing the temperature from 110 °C to 90 °C led to 20% conversion after 24 hours. Further increasing temperature resulted in substrate decomposition and attenuated yields. Fortunately, the active catalyst species was quite robust at 110 °C and prolonging the reaction time to 2 days afforded 72% isolated yield.

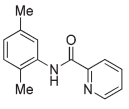
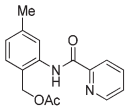
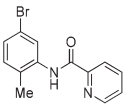
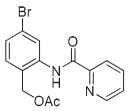
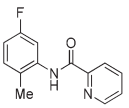
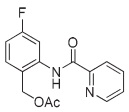
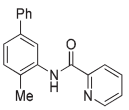
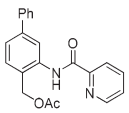
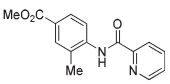
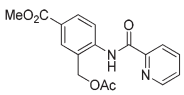
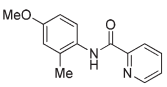
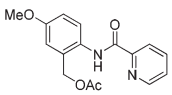
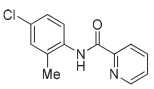
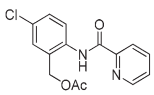
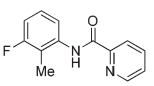
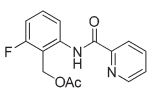
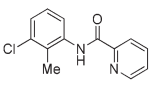
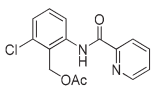
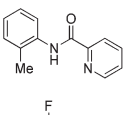
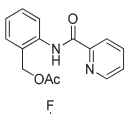
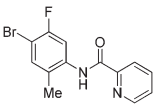
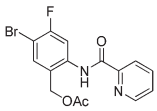
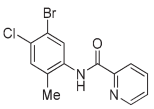
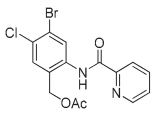
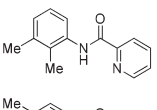
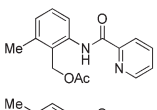
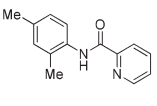
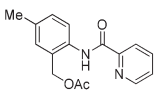
With the optimized conditions in hand, the substrate scope for benzylic oxidation was examined using various aniline derivatives (Table 2). This method was broadly applicable to a variety of aniline derived picolinamides. Aryl substituents of various electronic characteristics had little effect on both reaction rate and yield (entries 1–6, Table 2). When *N*-(*o*-tolyl)picolinamide was used, complete $sp^3$ selectivity was observed and the 2-(picolinamido)benzyl acetate **2j** was isolated as the sole product. Multi-substituted aryl picolinamides were well tolerated, except for aniline derivatives having both *ortho*-positions substituted.

The standard reaction condition was challenged by using difficult substrates (secondary benzylic C–H bonds and aliphatic C–H bonds). The double benzylic substrate **1o** was successfully acetoxylated in 69% yield (entry 1, Table 3). The reaction of the *o*-ethyl aniline derived picolinamide **1p**, on the other hand, was very sluggish and the product was obtained in 45% yield. When the *N*-(2-*tert*-butylphenyl) picolinamide **1q** was used, the dihydroindole product was isolated as a result of C–N bond formation.[11] A similar cyclization was also observed

**Table 2** Palladium-catalyzed acetoxylation of *o*-tolyl picolinamides[a]

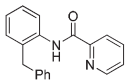
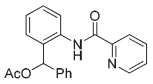
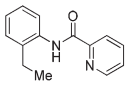
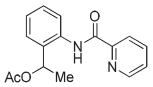
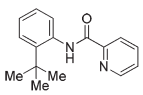
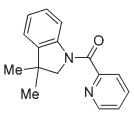
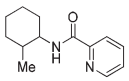
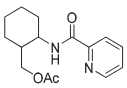
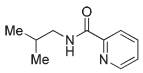
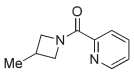



1 2

| Entry | Substrate | Product | | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  | **2a** | 72 |
| 2 |  |  | **2b** | 69 |
| 3 |  |  | **2c** | 70 |
| 4 |  |  | **2d** | 82 |
| 5 |  |  | **2e** | 83 |
| 6 |  |  | **2f** | 84 |
| 7 |  |  | **2g** | 82 |
| 8 |  |  | **2h** | 60 |
| 9 |  |  | **2i** | 67 |
| 10 |  |  | **2j** | 85 |
| 11 |  |  | **2k** | 76 |
| 12 |  |  | **2l** | 67 |
| 13 |  |  | **2m** | 70 |
| 14 |  |  | **2n** | 70 |

[a] Reaction conditions: picolinamide **1** (0.5 mmol, 1.0 equiv.), $PhI(OAc)_2$, (322 mg, 1.0 mmol, 2 equiv.) and $Pd(OAc)_2$ (11.4 mg, 0.1 mmol, 0.1 equiv.) in toluene (5 mL) under argon at 110 °C for 48 hours. [b] Isolated yield.

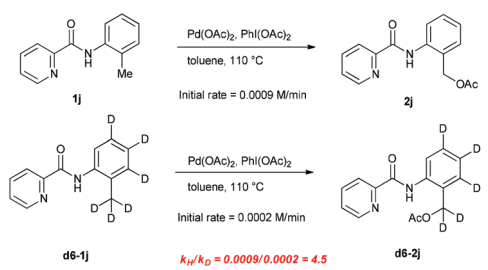
Table 3 Reactions of other substrates[a]

| Entry | Substrate | | Product | | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  | **1o** |  | **2o** | 69 |
| 2 |  | **1p** |  | **2p** | 45[c] |
| 3 |  | **1q** |  | **2q** | 53 |
| 4 |  | **1r** |  | **2r** | 62 |
| 5 |  | **1s** |  | **2s** | 80 |

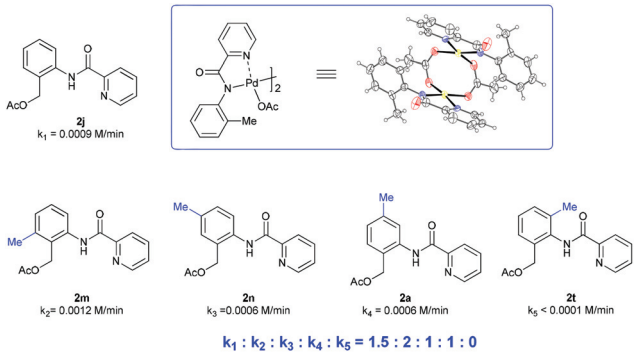
[a] 0.5 mmol scale. [b] Isolated yield. [c] Another portion of $PhI(OAc)_2$ (64 mg, 0.2 mmol, 2 equiv.) was added after 24 h.

for isobutyl picolinamide **1s**. Successful aliphatic $sp^3$ acetoxylation was obtained for *N*-(2-methylcyclohexyl) picolinamide **1r** (62% yield, entry 4, Table 3). Rotational restriction of the substrate forces the methyl group and the directing group in close proximity so that the C–H activation occurs more readily. Interestingly, both the *trans*- and *cis*-isomer of **1s** reacted at similar rates. When a mixture of *trans*- and *cis*-isomers was used, the ratio of *trans*- and *cis*-products was very close to that of the starting material, indicating similar reactivity for both isomers.

The kinetics of the acetoxylation reaction was measured. Interestingly, this reaction required an initial aging period, possibly due to the trace amount of oxygen in the system. When carried out in a glovebox, the acetoxylation for **1a** reached 50% conversion in 4 hours, whereas the same experiment using the traditional degas/refill technique required 12 hours to reach comparable conversion. The reaction is first order to the concentration of the substrate and an initial rate of $9 \times 10^{-4}$ M $min^{-1}$ was determined by GC. The C–H bond cleavage was evidently the rate-limiting step, supported by a large isotope effect ($k_H/k_D$ = 4.5, Scheme 2). The benzylic C–H insertion was irreversible as the deuterated substrate had no isotope scrambling after the reaction.




Scheme 2 Kinetics and isotope effects.




Scheme 3 Substitution effect on initial rate.

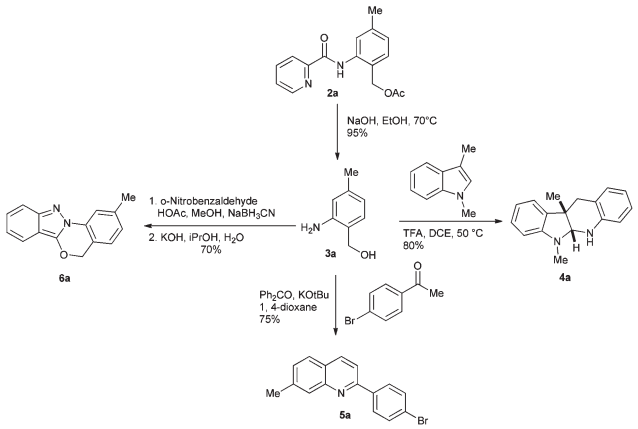
Substrates bearing additional methyl groups exhibited some degree of rate discrepancy, depending on the substitution pattern. The initial rates of those substrates were determined individually and results are summarized in Scheme 3. When a methyl group was introduced next to the reacting methyl, the initial rate of the reaction increased to $k_2$ = 0.0012 M $min^{-1}$; when the methyl group was moved to the 4- and 5-position, the reaction rates decreased to 0.0006 M $min^{-1}$. A 6-methyl group resulted in complete reaction inhibition. In order to better understand the substitution effect, substrate **1j** was heated with $Pd(OAc)_2$ (1 : 1) in toluene at 110 °C. A large amount of yellow solid formed after 5 min. The structure of this solid was determined as a dimeric palladium amide by X-ray. The attempt to intercept the benzyl palladium intermediate was unsuccessful.

We speculated that substitution at 5- and 6-positions would restrict free rotation of the Aryl–N bond so that effective palladium insertion would be more difficult compared to the non-substituted substrate. In contrast, steric repulsion from the 3-methyl substrate forces the reacting 2-methyl group closer to the palladium, facilitating the C–H metallation step. It remains elusive why the dismal 4-methyl substituent also showed diminished reactivity. One explanation could be slow dissociation of the dimer complex. Detailed mechanistic and theoretical investigations are currently underway.

The acetoxylated products could be readily hydrolyzed under basic conditions to generate the 2-amino benzyl alcohols which were transformed to several heterocycles of medicinal chemistry interest (Scheme 4). Condensation of **3a** with acetophenone in the presence of *t*-BuOK resulted in the corresponding quinoline in 75% yield.[12] Acid promoted cycloaddition with 3-methyl indole rendered 5,6-fused indoline aminals, which are widely found in the *Communesin* family natural products.[13] Reductive amination using *o*-nitrobenzaldehyde, followed by base mediated cyclization afforded the 5*H*-benzo[4,5][1,3]oxazino[3,2-*b*]indazole scaffold.[14]

## Conclusions

In summary, we developed a general protocol for Pd catalyzed acetoxylation of benzylic C–H bonds by employing a bidenate




Scheme 4 Synthesis of various heterocycles using the 2-amino benzyl acetate product.

picolinamide as the directing group. This transformation has broad functional group tolerance and interesting mechanistic aspects. The benzyl acetate products demonstrated far-reaching utilization for heterocycle synthesis.

# Experimental

### General methods

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions. All other reagents were purchased and used without further purification unless specified otherwise. Toluene was distilled from $CaH_2$ prior to use. Solvents for chromatography were technical grade and distilled prior to use. Flash chromatography was performed using 200–300 mesh silica gel with the indicated solvent system according to standard techniques. Analytical thin-layer chromatography (TLC) was performed using Huanghai silica gel plates with HSGF 254. Qingdao Haiyang Chemical HG/T2354-92 silica gel was used for silica gel flash chromatography. Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or appropriate stains. $^1$H NMR and $^{13}$C NMR data were recorded on Bruker 400 MHz nuclear resonance spectrometers unless otherwise specified, respectively. Chemical shifts ($\delta$) in ppm are reported as quoted relative to the residual signals of chloroform ($^1$H 7.26 ppm or $^{13}$C 77.16 ppm). Multiplicities are described as: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet); and coupling constants ($J$) are reported in hertz (Hz). $^{13}$C NMR spectra were recorded with total proton decoupling. HRMS (ESI) analysis was performed by The Analytical Instrumentation Center at Peking University, Shenzhen Graduate School and (HRMS) data were reported with ion mass/charge ($m/z$) ratios as values in atomic mass units.

### General procedure for palladium catalysed acetoxylation of benzylic C–H bonds

The picolinamide **1** (0.5 mmol, 1.0 equiv.), $PhI(OAc)_2$, (322 mg, 1.0 mmol, 2 equiv.) and $Pd(OAc)_2$ (11.4 mg, 0.1 mmol, 0.1 equiv.) were placed in a Schlenk tube and capped with a rubber septum. The reaction vessel was degassed and back-filled with argon three times. Toluene (5 mL) was added *via* a syringe. The reaction mixture was stirred at 110 °C for 48 hours, cooled to room temperature and concentrated in vacuum. The residue was purified by silica gel column flash chromatography (eluent: hexane–EtOAc) to give compound **2**.

**4-Methyl-2-(picolinamido)benzyl acetate (2a).** 102 mg, 72%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.58 (s, 1H), 8.67–8.56 (m, 1H), 8.31 (d, $J$ = 7.8 Hz, 1H), 8.15 (s, 1H), 7.93 (m, 1H), 7.50 (m, 1H), 7.26 (d, $J$ = 6.7 Hz, 1H), 6.99 (d, $J$ = 7.7 Hz, 1H), 5.17 (s, 2H), 2.41 (s, 3H), 2.20 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.90, 162.33, 149.99, 148.12, 140.03, 137.68, 136.70, 130.32, 126.52, 125.42, 123.07, 123.01, 122.53, 64.42, 21.54, 20.95; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_2NaO_3$ ([M + $Na^+$]) = 307.1059, found: 307.1053.

**4-Bromo-2-(picolinamido)benzyl acetate (2b).** 120 mg, 69%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.64 (s, 1H), 8.62 (d, $J$ = 4.4 Hz, 1H), 8.59 (s, 1H), 8.30 (d, $J$ = 7.8 Hz, 1H), 7.94 (t, $J$ = 7.6 Hz, 1H), 7.59–7.47 (m, 1H), 7.26 (m, 2H), 5.16 (s, 2H), 2.20 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.51, 162.31, 149.65, 148.13, 138.10, 137.73, 131.46, 127.47, 126.70, 125.13, 124.59, 123.48, 122.63, 63.79, 20.74; HRMS (ESI-TOF) calcd for $C_{15}H_{13}BrN_2NaO_3$ ([M + $Na^+$]) = 371.0007, found: 371.0001.

**4-Fluoro-2-(picolinamido)benzyl acetate (2c).** 101 mg, 70%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.72 (s, 1H), 8.61 (d, $J$ = 4.1 Hz, 1H), 8.30 (d, $J$ = 7.6 Hz, 1H), 8.22 (d, $J$ = 10.9 Hz, 1H), 7.93 (t, $J$ = 7.6 Hz, 1H), 7.55–7.45 (m, 1H), 7.36–7.29 (m, 1H), 6.84 (t, $J$ = 8.0 Hz, 1H), 5.18 (s, 2H), 2.20 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.75, 164.52, 162.21, 149.59, 148.17, 138.56, 137.79, 131.70, 126.78, 122.63, 121.03, 111.02, 109.34, 63.92, 20.87; HRMS (ESI-TOF) calcd for $C_{15}H_{13}FN_2NaO_3$ ([M + $Na^+$]) = 311.0808, found: 311.0801.

**(3-(Picolinamido)-[1,1′-biphenyl]-4-yl)methyl acetate (2d).** 142 mg, 82%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.69 (s, 1H), 8.63 (d, $J$ = 1.5 Hz, 2H), 8.33 (d, $J$ = 7.7 Hz, 1H), 7.93 (td, $J$ = 7.7, 1.4 Hz, 1H), 7.68 (d, $J$ = 7.3 Hz, 2H), 7.50–7.35 (m, 6H), 5.26 (s, 2H), 2.23 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.87, 162.48, 149.93, 148.17, 142.82, 140.31, 137.76, 137.27, 130.80, 128.79, 127.70, 127.31, 126.63, 124.77, 123.23, 122.57, 121.19, 64.32, 20.95; HRMS (ESI-TOF) calcd for $C_{21}H_{18}N_2NaO_3$ ([M + $Na^+$]) = 369.1215, found: 369.1212.

**Methyl 3-(acetoxymethyl)-4-(picolinamido)benzoate (2e).** 136 mg, 83%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.63 (s, 1H), 8.92 (s, 1H), 8.63 (d, $J$ = 4.6 Hz, 1H), 8.33 (d, $J$ = 7.8 Hz, 1H), 7.98–7.90 (m, 1H), 7.89–7.84 (m, 1H), 7.52 (dd, $J$ = 6.9, 5.0 Hz, 1H), 7.46 (d, $J$ = 7.9 Hz, 1H), 5.24 (s, 2H), 3.94 (s, 3H), 2.22 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.54, 166.44, 162.45, 149.64, 148.15, 137.74, 136.82, 131.50, 130.75, 130.08, 126.70, 125.84, 123.58, 122.64, 63.90, 52.24, 20.78; HRMS (ESI-TOF) calcd for $C_{17}H_{16}N_2NaO_5$ ([M + $Na^+$]) = 351.0957, found: 351.0961.

**5-Methoxy-2-(picolinamido)benzyl acetate (2f).** 126 mg, 84%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.40 (s, 1H), 8.62 (d, $J$ = 4.4 Hz, 1H), 8.31 (d, $J$ = 7.8 Hz, 1H), 8.07 (d, $J$ = 8.7 Hz, 1H), 7.92 (t, $J$ = 7.2 Hz, 1H), 7.50 (dd, $J$ = 6.8, 5.2 Hz, 1H), 6.97 (dd,

$J$ = 12.1, 3.2 Hz, 2H), 5.16 (s, 2H), 3.84 (s, 3H), 2.21 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.87, 162.45, 156.68, 149.96, 148.13, 137.64, 129.52, 128.36, 126.45, 124.73, 122.50, 115.73, 114.40, 64.29, 55.56, 20.91; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_2NaO_4$ ([M + $Na^+$]) = 323.1008, found: 323.1013.

**5-Chloro-2-(picolinamido)benzyl acetate (2g).** 125 mg, 82%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.58 (s, 1H), 8.61 (d, $J$ = 4.4 Hz, 1H), 8.27 (dd, $J$ = 12.5, 8.2 Hz, 2H), 7.92 (td, $J$ = 7.7, 1.5 Hz, 1H), 7.54–7.44 (m, 1H), 7.42–7.33 (m, 2H), 5.16 (s, 2H), 2.20 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.65, 162.41, 149.63, 148.17, 137.76, 135.33, 130.04, 129.63, 129.59, 127.72, 126.72, 123.78, 122.62, 63.66, 20.83; HRMS (ESI-TOF) calcd for $C_{15}H_{13}ClN_2NaO_3$ ([M + $Na^+$]) = 327.0512, found: 327.0509.

**2-Fluoro-6-(picolinamido)benzyl acetate (2h).** 60 mg, 60%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.81 (s, 1H), 8.63 (d, $J$ = 4.3 Hz, 1H), 8.30 (d, $J$ = 7.8 Hz, 1H), 8.12 (d, $J$ = 8.3 Hz, 1H), 7.92 (t, $J$ = 7.6 Hz, 1H), 7.54–7.44 (m, 1H), 7.40 (dd, $J$ = 15.0, 7.8 Hz, 1H), 6.92 (t, $J$ = 8.8 Hz, 1H), 5.29 (s, 2H), 2.20 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.08, 162.63, 160.10, 149.76, 148.23, 138.59, 137.70, 130.66, 126.69, 122.66, 118.28, 113.98, 111.43, 56.72, 20.80; HRMS (ESI-TOF) calcd for $C_{15}H_{13}FN_2NaO_3$ ([M + $Na^+$]) = 311.0808, found: 311.0810.

**2-Chloro-6-(picolinamido)benzyl acetate (2i).** 102 mg, 67%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.87 (s, 1H), 8.65 (s, 1H), 8.31 (d, $J$ = 7.1 Hz, 1H), 8.18 (d, $J$ = 7.9 Hz, 1H), 7.93 (s, 1H), 7.52 (s, 1H), 7.36 (d, $J$ = 7.9 Hz, 1H), 7.26 (d, $J$ = 7.6 Hz, 1H), 5.40 (s, 2H), 2.22 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.17, 162.69, 149.75, 148.26, 138.74, 137.70, 135.46, 130.35, 126.70, 125.91, 124.36, 122.69, 121.78, 60.70, 20.81; HRMS (ESI-TOF) calcd for $C_{15}H_{13}ClN_2NaO_3$ ([M + $Na^+$]) = 327.0512, found: 327.0518.

**2-(Picolinamido)benzyl acetate (2j).** 115 mg, 85%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.62 (s, 1H), 8.64 (d, $J$ = 4.1 Hz, 1H), 8.33 (d, $J$ = 7.9 Hz, 2H), 7.94 (m, 1H), 7.51 (m, 1H), 7.46 (m, 1H), 7.40 (d, $J$ = 6.9 Hz, 1H), 7.20 (t, $J$ = 7.5 Hz, 1H), 5.23 (s, 2H), 2.23 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.66, 162.34, 150.08, 148.09, 137.62, 136.91, 130.28, 129.74, 126.46, 126.02, 124.62, 122.55(2C), 64.49, 20.82; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N_2NaO_3$ ([M + $Na^+$]) = 293.0902, found: 293.0910.

**5-Bromo-4-fluoro-2-(picolinamido)benzyl acetate (2k).** 140 mg, 76%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.71 (s, 1H), 8.62 (d, $J$ = 3.8 Hz, 1H), 8.34 (d, $J$ = 10.7, 1H), 8.30 (d, $J$ = 7.6 Hz, 1H), 7.94 (t, $J$ = 7.4 Hz, 1H), 7.53 (m, 2H), 5.15 (s, 2H), 2.20 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.60, 162.36, 160.63, 158.17, 149.35, 148.20, 137.86, 137.67, 134.61, 126.92, 122.70, 110.23, 103.19, 63.11, 20.82; HRMS (ESI-TOF) calcd for $C_{15}H_{12}BrFN_2NaO_3$ ([M + $Na^+$]) = 388.9913, found: 388.9920.

**4-Bromo-5-chloro-2-(picolinamido)benzyl acetate (2l).** 129 mg, 67%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.66 (s, 1H), 8.63 (d, $J$ = 4.4 Hz, 1H), 8.59 (s, 1H), 8.30 (d, $J$ = 7.7 Hz, 1H), 7.95 (m, 1H), 7.62 (s, 1H), 7.54 (m, 1H), 5.16 (s, 2H), 2.22 (s, 3H);$^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.54, 162.34, 149.32, 148.21, 137.85, 136.87, 135.54, 134.68, 126.91, 125.72, 123.55, 122.68, 116.94, 63.02, 20.80; HRMS (ESI-TOF) calcd for $C_{15}H_{12}BrClN_2NaO_3$ ([M + $Na^+$]) = 404.9618, found: 404.9623.

**2-Methyl-6-(picolinamido)benzyl acetate (2m).** 100 mg, 70%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.72 (s, 1H), 8.65 (d, $J$ = 4.6 Hz, 1H), 8.31 (d, $J$ = 7.8 Hz, 1H), 8.00 (d, $J$ = 8.1 Hz, 1H), 7.92 (td, $J$ = 7.7, 1.6 Hz, 1H), 7.50–7.48 (m, 1H), 7.33 (t, $J$ = 7.9 Hz, 1H), 7.06 (d, $J$ = 7.6 Hz, 1H), 5.27 (s, 2H), 2.47 (s, 3H), 2.17 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.31, 162.76, 150.12, 148.25, 138.50, 137.58, 137.18, 129.34, 127.18, 126.46, 125.33, 122.59, 121.47, 60.48, 20.88, 19.74; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_2NaO_3$ ([M + $Na^+$]) = 307.1059, found: 307.1065.

**5-Methyl-2-(picolinamido)benzyl acetate (2n).** 100 mg, 70%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.50 (s, 1H), 8.61 (d, $J$ = 4.3 Hz, 1H), 8.31 (d, $J$ = 7.8 Hz, 1H), 8.14 (d, $J$ = 8.2 Hz, 1H), 7.91 (td, $J$ = 7.7, 1.5 Hz, 1H), 7.49 (dd, $J$ = 6.7, 4.9 Hz, 1H), 7.26–7.22 (m, 1H), 7.18 (s, 1H), 5.17 (s, 2H), 2.36 (s, 3H), 2.20 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.81, 162.32, 150.09, 148.10, 137.62, 134.46, 134.23, 130.89, 130.29, 126.43, 126.06, 122.71, 122.52, 64.53, 20.90, 20.84; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_2NaO_3$ ([M + $Na^+$]) = 307.1059, found: 307.1065.

**Phenyl(2-(picolinamido)phenyl)methyl acetate (2o).** 120 mg, 69%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.59 (s, 1H), 8.61–8.60 (m, 1H), 8.28 (dd, $J$ = 13.2, 8.0 Hz, 2H), 7.87 (td, $J$ = 7.7, 1.7 Hz, 1H), 7.50–7.43 (m, 1H), 7.43–7.35 (m, 4H), 7.33–7.23 (m, 3H), 7.23–7.15 (m, 1H), 7.08 (s, 1H), 2.26 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.97, 162.35, 149.90, 147.96, 138.44, 137.58, 135.71, 130.40, 129.21, 128.94, 128.47, 128.04, 126.87, 126.46, 124.85, 123.38, 122.48, 74.93, 21.19; HRMS (ESI-TOF) calcd for $C_{21}H_{18}N_2NaO_3$ ([M + $Na^+$]) = 369.1215, found: 369.1220.

**1-(2-(Picolinamido)phenyl)ethyl acetate (2p).** 64 mg, 45%; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.86 (s, 1H), 8.65 (d, $J$ = 4.1 Hz, 1H), 8.32 (d, $J$ = 7.8 Hz, 1H), 8.24 (d, $J$ = 7.9 Hz, 1H), 7.92 (td, $J$ = 7.7, 1.7 Hz, 1H), 7.49 (m, 1H), 7.39 (dd, $J$ = 12.1, 4.5 Hz, 2H), 7.24–7.12 (m, 1H), 6.03 (q, $J$ = 6.7 Hz, 1H), 2.17 (s, 3H), 1.62 (d, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.42, 162.57, 150.17, 148.21, 137.61, 135.41, 131.54, 128.97, 127.52, 126.44, 125.02, 123.51, 122.59, 70.97, 21.25, 20.50; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_2NaO_3$ ([M + $Na^+$]) = 307.1059, found: 307.1065.

**(3,3-Dimethylindolin-1-yl)(pyridin-2-yl)methanone (2q).** 67 mg, 53%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.64 (d, $J$ = 4.4 Hz, 1H), 8.29 (d, $J$ = 8.0 Hz, 1H), 7.87 (m, 2H), 7.53–7.33 (m, 1H), 7.33–7.23 (m, 1H), 7.22–7.06 (m, 2H), 4.09 (s, 2H), 1.33 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.08, 154.57, 148.15, 142.05, 141.54, 137.21, 127.71, 125.17, 124.80, 124.42, 121.99, 118.04, 65.15, 40.73, 30.42, 28.30; HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_2NaO$ ([M + $Na^+$]) = 275.1160, found: 275.1165.

**(2-(Picolinamido)cyclohexyl)methyl acetate (2r).** 86 mg, 62%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.60–8.49 (m, 1H), 8.19 (d, $J$ = 7.8 Hz, 1H), 8.01 (d, $J$ = 8.6 Hz, 1H), 7.85 (td, $J$ = 7.7, 1.7 Hz, 1H), 7.42 (m, 1H), 4.11 (m, 1H), 4.00 (dd, $J$ = 11.2, 6.2 Hz, 1H), 3.90 (m, 1H), 2.17–2.06 (m, 1H), 1.98 (s, 3H), 1.95–1.85 (m, 1H), 1.77 (m, 3H), 1.41 (m, 1H), 1.35–1.24 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.18, 163.64, 149.86, 147.93, 137.40, 126.14, 122.34, 66.89, 50.21, 42.54, 33.44, 29.00, 25.15, 25.09, 20.89; HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_2NaO_3$ ([M + $Na^+$]) = 299.1372, found: 299.1380.

**(3-Methylazetidin-1-yl)(pyridin-2-yl)methanone (2s).** 70 mg, 80%; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.56 (d, $J$ = 4.2 Hz, 1H), 8.08

(d, $J$ = 7.8 Hz, 1H), 7.78 (dd, $J$ = 10.9, 4.5 Hz, 1H), 7.34 (m, 1H), 4.79 (t, $J$ = 9.2 Hz, 1H), 4.34 (t, $J$ = 9.3 Hz, 1H), 4.25 (dd, $J$ = 10.2, 5.6 Hz, 1H), 3.79 (dd, $J$ = 10.2, 5.5 Hz, 1H), 2.77 (m, 1H), 1.27 (t, $J$ = 10.6 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 165.34, 152.13, 148.03, 136.75, 125.16, 123.75, 61.65, 55.71, 24.89, 19.67; HRMS (ESI-TOF) calcd for $C_{10}H_{12}N_2NaO$ ([M + $Na^+$]) = 199.0847, found: 199.0853.

### Product derivatization

**(2-Amino-4-methylphenyl)methanol (3a).** Compound **2a** (570 mg, 2.0 mmol, 1 equiv.) and NaOH (320 mg, 8.0 mmol, 4 equiv.) were heated in ethanol (10 mL) for 8 hours at 70 °C. EtOH was removed under vacuum. The residue was dissolved in EtOAc, neutralized with sat. $NH_4Cl$, washed with water and extracted with EtOAc 3 times. The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated under vacuum to give compound **3a** as a yellow solid (260 mg 95%) and used directly in the next step without purification.

**(5*aR**,10*bS**)-6,10*b*-Dimethyl-5*a*,6,10*b*,11-tetrahydro-5*H*-indolo-[2,3-*b*]quinolone (4a).** Compound **3a** (27.4 mg, 0.2 mmol, 1 equiv.) and 3-methyl indole (58.08 mg, 0.4 mmol, 2 equiv.) were dissolved in DCE (1 mL), and TFA (6.8 mg, 0.06 mmol, 0.3 equiv.) was added. The reaction was stirred at 50 °C for 3 hours, cooled to room temperature, and washed with sat. aqueous $NaHCO_3$ solution. The aqueous layer was extracted with DCM three times. The combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated. The residue was purified by silica gel column flash chromatography (EtOAc–hexane = 1 : 20) to give compound **4a** (40 mg, 80%) as a white solid. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.14 (dd, $J$ = 13.8, 7.1 Hz, 2H), 6.89 (d, $J$ = 7.4 Hz, 1H), 6.79 (t, $J$ = 7.4 Hz, 1H), 6.53 (t, $J$ = 8.3 Hz, 2H), 6.48 (s, 1H), 4.60 (s, 1H), 4.13 (d, $J$ = 14.2 Hz, 1H), 2.78 (s, 3H), 2.76 (s, 1H) 2.48 (d, $J$ = 15.1 Hz, 1H), 2.28 (s, 3H), 1.24 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 149.19, 140.86, 137.21, 136.67, 128.95, 127.71, 121.31, 118.77, 118.57, 114.07, 107.95, 83.78, 38.95, 37.13, 32.13, 30.95, 21.39, 21.28; HRMS (ESI-TOF) calcd for $C_{18}H_{20}N_2Na$ ([M + $Na^+$]) = 287.1524, found: 287.1534.

**3-(4-Bromophenyl)-7-methylquinoline (5a).** To a solution of compound **3a** (27 mg, 0.2 mmol, 1 equiv.) in 1,4-dioxane (1 mL) were added 4-bromo benzophenone (40 mg, 0.2 mmol, 1 equiv.) and *t*BuOK (22 mg, 0.2 mmol, 1 equiv.) under argon. The resulting solution was heated at 90 °C for 30 minutes. The reaction mixture was poured into sat. aqueous solution of $NH_4Cl$ (10 mL) and extracted with EtOAc three times. The combined organic layer was back extracted using dilute HCl (2 M, 3 × 10 mL). The combined aqueous phase was treated with NaOH solution until pH = 13, and extracted with EtOAc 3 times. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give compound **5a** (45 mg, 75%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.20 (d, $J$ = 8.6 Hz, 1H), 8.07 (d, $J$ = 8.6 Hz, 2H), 7.97 (s, 1H), 7.80 (d, $J$ = 8.5 Hz, 1H), 7.75 (d, $J$ = 8.3 Hz, 1H), 7.67 (d, $J$ = 8.6 Hz, 2H), 7.43–7.36 (m, 1H), 2.61 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.00, 148.51, 140.15, 138.69, 136.60, 131.91, 129.06, 128.79, 128.72, 127.10, 125.34, 123.78, 117.68, 21.85; HRMS (ESI-TOF) calcd for $C_{16}H_{12}BrNNa$ ([M + $Na^+$]) = 320.0051, found: 320.0060.

**2-Methyl-5*H*-benzo[4,5][1,3]oxazino[3,2-*b*]indazole (6a).** 2-Nitrobenzaldehyde (50 mg, 0.33 mmol, 1 equiv.) and compound **3a** (44 mg, 0.36 mmol, 1.1 equiv.) were dissolved in methanol (1.6 mL). The resulting solution was stirred at room temperature for 5 minutes before HOAc (1.6 mmol, 4.8 equiv.) was added. The mixture was stirred under argon for 3 hours. Then $NaCH_3CN$ (1.32 mmol, 4 equiv.) was added. The reaction was stirred for 3 hours. The solvent was removed under vacuum. The residue was dissolved in iPrOH (3.5 mL). KOH (10% w/w) was added and the basic solution was stirred for 3 hours. The reaction was concentrated and the residue was dissolved in EtOAc and washed with water. The aqueous phase was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography (EtOAc–hexane = 1 : 10) to give compound **6a** (55 mg, 70%). $^1$H NMR (500 MHz, MeOD) $\delta$ 7.72 (s, 1H), 7.54 (d, $J$ = 8.5 Hz, 1H), 7.46 (d, $J$ = 8.9 Hz, 1H), 7.29 (dd, $J$ = 13.2, 7.6 Hz, 2H), 7.20 (d, $J$ = 7.6 Hz, 1H), 7.00–6.89 (m, 1H), 5.50 (s, 2H), 2.46 (s, 3H); $^{13}$C NMR (75 MHz, MeOD) $\delta$ 148.87, 140.07, 132.77, 129.43, 128.50, 127.61, 124.90, 120.16, 118.97, 118.88, 115.93, 115.46, 106.42, 68.17, 20.08; HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_2O$ ([M + $H^+$]) = 237.1028, found: 237.1030.

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