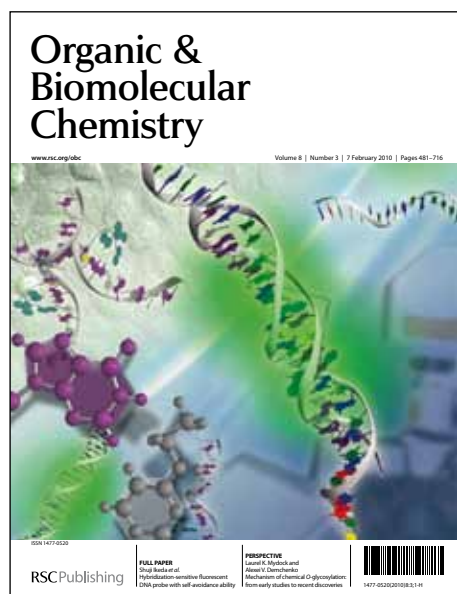


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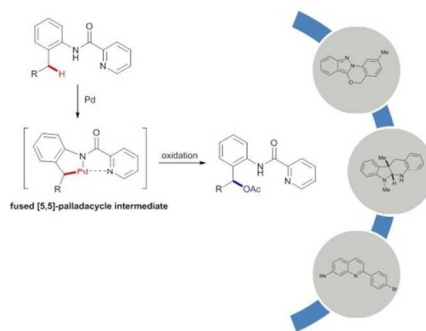
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Palladium catalysed oxygenation of inert benzylic C-H bonds offers a straightforward entry to heterocycle synthesis

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Palladium Catalyzed Acetoxylation of Benzylic C-H Bonds Using a Bidentate Picolinamide Directing Group

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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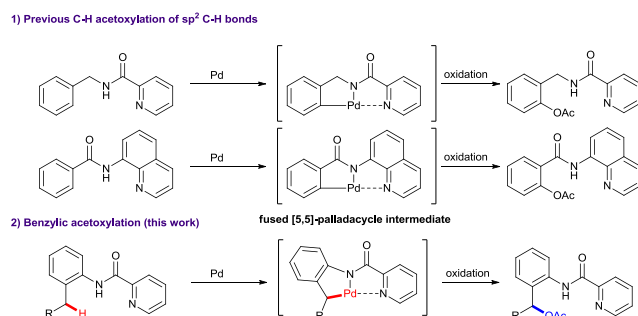
Tao Cheng,^a Weiyu Yin,^a Yi Zhang,^a Yingnan Zhang^b and Yong Huang^{a,*}

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 scope 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 for the past decade.¹ While the major effort was devoted to develop novel directing groups and bond formation reactions surrounding sp² C-H bonds, functionalization of sp³ C-H bonds have also enjoyed impressive progress.² In particular, various directing groups have been invented to selectively convert a sp³ C-H to a C-O functionality for a wide spectrum of substrates.³ However, 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 sp³ 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 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 bidentate directing group

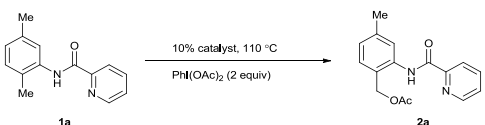
Results and discussion

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 supporting information). The highest conversion was observed in toluene among 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 reaction temperature. Decreasing 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

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°C and prolonging reaction time to 2 days afforded 72% isolated yield.

Table 1 Reaction condition survey for benzylic acetoxylation of picolinamides^a



entry	cat.	solvent	additive	conv. (%) ^b
1	Fe(acac) ₃	DCE	--	N.R.
2	Ni(acac) ₂	DCE	--	N.R.
3	Cp(Ph ₃ P) ₂ RuCl	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 ₂ CO 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 ₂ CO ₃	27
16	Pd(OAc) ₂	Toluene	AgOAc	36
17	Pd(OAc) ₂	Toluene	--	72 ^c

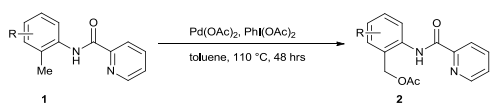
^a Reaction condition: **1a** (22.6 mg, 0.1 mmol, 1 equiv), PhI(OAc)₂ (64 mg, 0.2 mmol, 2 equiv), additive (0.1 mmol, 1 equiv.) and catalyst (0.01 mmol, 0.1 equiv) in a solvent (1 mL) under argon at 110 °C for 24 h. ^b The conversion was calculated by GC-MS using biphenyl as the internal standard. ^c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

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 1-5, Table 2). When N-(*o*-tolyl)picolinamide was used, complete sp³ 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 acetoxylation 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 to C-N bond formation.¹¹ Similar cyclization was also observed for isobutyl picolinamide **1s**. Successful aliphatic sp³ 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 in similar rates. When a mixture of *trans*- and *cis*- isomers was used. The ratio of *trans*- and *cis*- products was very close that of the starting material, indicating similar reactivity for both isomers.

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

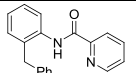
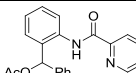
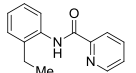
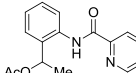
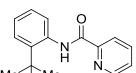
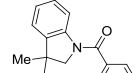
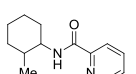
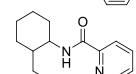
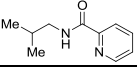
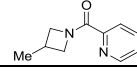


entry	substrate	product	yield (%) ^b
1			72
2			69
3			70
4			82
5			83
6			84
7			82
8			60
9			67
10			85
11			76
12			67
13			70
14			70

^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.

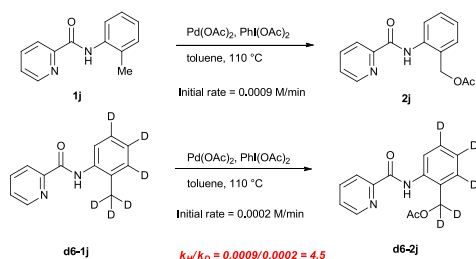
The kinetics of the acetoxylation reaction was measured. Interestingly, this reaction required an initial aging period, possibly due to trace of amount of oxygen in the system. When carried out in a glovebox, the acetoxylation for **1a** reached 50% conversion in 4 hours, whereas the same experiment using 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 9×10^{-4} M/min 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 deuterated substrate had no isotope scrambling after the reaction.

Table 3 Reactions of other substrates^a

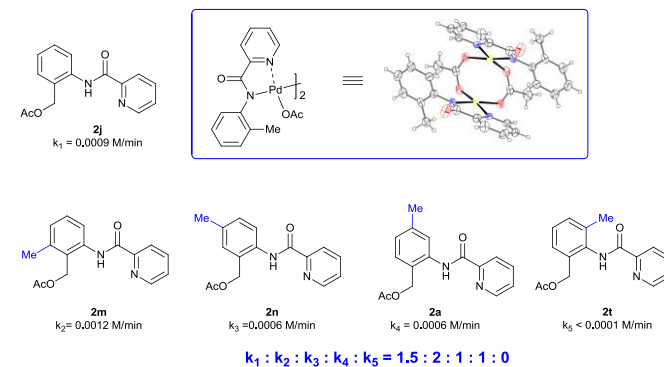
entry	substrate	product	yield (%) ^b
1			69
2			45 ^c
3			53
4			62
5			80

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

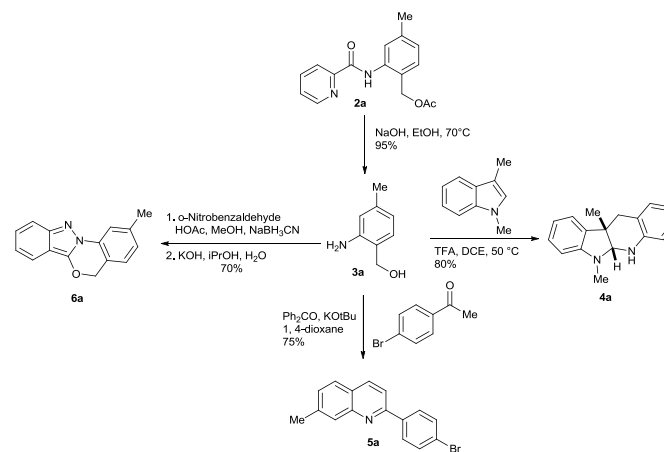
Substrates bearing an additional methyl groups exhibited some degree of rate discrepancy, depending on the substitution pattern. The initial rates of those substrates were determined individually and results are summarized in Scheme 3. When a methyl group was introduced next to the reacting methyl, the initial rate of the reaction increased to $k_2 = 0.0012$ M/min; when the methyl group was moved to the 4- and 5- position, the reaction rates decreased to 0.0006 M/min. A 6-methyl group resulted in complete reaction inhibition. In order to better understand the substitution effect, substrate **1j** was heated with $\text{Pd}(\text{OAc})_2$ (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. Attempt to intercept the benzyl palladium intermediate was unsuccessful.

**Scheme 2** Kinetics and isotope effects

We speculated that substitution at 5- and 6- position 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 undergoing.

**Scheme 3** Substitution effect on initial rate

The acetoxyated products could be readily hydrolyzed under basic conditions to generate the 2-amino benzyl alcohols which were transformed to several heterocycles of medicinal chemistry interests. Condensation of **3a** with acetophenone in the presence of *t*-BuOK resulted 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

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

Conclusions

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

Acknowledgements

This work was financially supported by grants of the National Basic Research Program of China (2010CB833201), National Natural Science Foundation of China (21372013), the Shenzhen Peacock Program (KQTD201103) and Shenzhen innovation funds (GJHZ20120614144733420). Y. H. thanks the MOE for the Program for New Century Excellent Talents in University. The Shenzhen municipal development and reform commission is thanked for a public service platform program.

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 CaH₂ 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. ¹H NMR and ¹³C NMR data were recorded on Bruker 400 Mnuclear resonance spectrometers unless otherwise specified, respectively. Chemical shifts (δ) in ppm are reported as quoted relative to the residual signals of chloroform (¹H 7.26 ppm or ¹³C 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). ¹³C 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 Schlenk tube and capped with a rubber septum. The reaction vessel was degassed and backfilled 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 chromatograph (eluent: Hexane/EtOAc) to give compound **2**.

4-Methyl-2-(picolinamido)benzyl acetate (2a): 102 mg, 72%; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₁₆H₁₆N₂NaO₃ ([M+Na⁺]) = 307.1059, Found 307.1053.

4-Bromo-2-(picolinamido)benzyl acetate (2b): 120 mg, 69%; ¹H NMR (500 MHz, CDCl₃) δ 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) ¹³C NMR (125 MHz, CDCl₃) δ 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 C₁₅H₁₃BrN₂NaO₃ ([M+Na⁺]) = 371.0007, Found 371.0001.

4-Fluoro-2-(picolinamido)benzyl acetate (2c): 101 mg, 70%; ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (100 MHz, CDCl₃) δ 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 C₁₅H₁₃FN₂NaO₃ ([M+Na⁺]) = 311.0808, Found 311.0801.

(3-(Picolinamido)-[1,1'-biphenyl]-4-yl)methyl acetate (2d): 142 mg, 82%; ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (100 MHz, CDCl₃) δ 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 C₂₁H₁₈N₂NaO₃ ([M+Na⁺]) = 369.1215, Found 369.1212.

Methyl 3-(acetoxymethyl)-4-(picolinamido)benzoate (2e): 136 mg, 83%; ¹H NMR (400 MHz, CDCl₃) δ 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); ¹³C NMR (125 MHz, CDCl₃) δ 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 C₁₇H₁₆N₂NaO₅ ([M+Na⁺]) = 351.0957, Found 351.0961.

5-Methoxy-2-(picolinamido)benzyl acetate (2f): 126 mg, 84%; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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%; 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%; 1H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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-Methylazetididin-1-yl)(pyridin-2-yl)methanone (2s): 70 mg, 80%; 1H NMR (500 MHz, $CDCl_3$) δ 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) δ 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 $\text{C}_{10}\text{H}_{12}\text{N}_2\text{NaO}$ ($[\text{M}+\text{Na}^+]$) = 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 for 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 direct in next step without purification.

(5aR*,10bS*)-6,10b-dimethyl-5a,6,10b,11-tetrahydro-5H-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), 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 chromatograph (EtOAc:Hexane = 1:20) to give compound **4a** (40 mg, 80%) as white solid. ^1H NMR (500 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{18}\text{H}_{20}\text{N}_2\text{Na}$ ($[\text{M}+\text{Na}^+]$) = 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 $t\text{BuOK}$ (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, 3x10 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%). ^1H NMR (500 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{16}\text{H}_{12}\text{BrNNa}$ ($[\text{M}+\text{Na}^+]$) = 320.0051, Found 320.0060

2-methyl-5H-benzo[4,5][1,3]oxazino[3,2-b]indazole (6a): 2-Nitrobenzaldehyde (50 mg, 0.33 mmol, 1 equiv), 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. NaCH_3CN (1.32 mmol, 4 equiv) was added. The reaction was stirred for 3 hours. Solvent was removed under vacuum. The residue was dissolved in $i\text{PrOH}$ (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 chromatograph (EtOAc:Hexane = 1:10) to give compound **6a** (55 mg, 70%). ^1H NMR (500 MHz, MeOD) δ 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) δ 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 $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}$ ($[\text{M}+\text{H}^+]$) = 237.1028, Found: 237.1030.

Notes and references

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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. See DOI: 10.1039/b000000x/

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