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Synthesis of Imides by Palladium-Catalyzed C–H Functionalization of Aldehydes with Secondary Amides

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Abstract: An efficient palladium-catalyzed C–H functionalization of aldehydes with various N-substituted *N*-heteroarene-2-carboxamides has been developed for the synthesis of secondary imides. The reaction tolerates various functionalities, such as methoxy, fluoro, chloro, and bromo groups. A tentative radical mechanism for a Pd^{II}/Pd^{IV} catalytic cycle is proposed.

Keywords: aldehydes · C–H activation · imides · palladium · picolinamides

Introduction

Imide moieties are present in a wide variety of natural products.[1] There are several strategies for the synthesis of imide derivatives, for example, acylation of amides with carboxylic acid derivatives,[2] direct oxidation of amides,[3] and the Mumm rearrangement of isoimides.[4] Among them, acylation of amides with anhydrides or acyl chlorides is a typical strategy.[2a–d,h] For example, under sulfuric acid catalysis, primary amides could be acylated with anhydrides at 100 °C to give primary imides in 44–64 % yield.[2b] Secondary imides, in which each nitrogen atom bears a substituent, are a main class of imides. Although many secondary imide derivatives possess important biological activities,[5] there are only a few reports on their synthesis.[6] In 2002, Yamada et al. found that some cyclic secondary amides reacted with anhydrides to furnish cyclic secondary imides in the presence of $MgBr_2{\cdot}OEt_2$.[6a] Recently much attention was attracted to activation of the acyl C–H bond in aldehydes as an elegant acylation strategy.[7,8] However, only Zhao et al. reported the synthesis of imides by C–H functionalization of aldehydes with a range of amides (various primary amides, one example of a secondary cyclic amide, and one example of an *N*-methyl amide as an intramolecular acylation) under copper catalysis mediated by *N*-bromo- or *N*-chlorosuccinimide (NBS or NCS, respectively).[8] However, to the best of our knowledge, no successful reports of intermolecular C–H functionalization of aldehydes with secondary acyclic amides has been disclosed. Considering that the pyridin-2-yl group in a secondary picolinamide can promote activation of the nearby N–H moiety by palladium to form a five-membered palladacycle intermediate,[9] which may increase the reactivity of the nitrogen atom, we embarked on an investigation into the acylation of various *N*-heteroarene-2-carboxamides with aldehydes. Herein, we present our recent results on the palladium-catalyzed acyl C–H functionalization of aldehydes with various N-substituted *N*-heteroarene-2-carboxamides for the synthesis of secondary imides.

Results and Discussion

The reaction of *N*-benzylpicolinamide (**1a**) with 4-chlorobenzaldehyde (**2a**) was chosen as a model reaction to explore and optimize the C–H bond functionalization reaction. Gratifyingly, the desired imide **3aa** was obtained in 26 % yield when palladium(II) acetate ($[Pd(OAc)_2]$) and *tert*-butyl hydroperoxide (TBHP) were used as catalyst and oxidant, respectively, in toluene (Table 1, entry 1). Subsequently, various palladium and other transition-metal catalysts were examined in the reaction (see Table 1, entries 2–8 and the Supporting Information, respectively). Among them, $[Pd(PPh_3)_2(OAc)_2]$ proved to be best catalyst and gave **3aa** in 55 % yield (Table 1, entry 8). The effect of the oxidant on the reaction was also examined. It was found that only a trace amount of **3aa** was obtained when either *tert*-butyl peroxide (TBP) or $K_2S_2O_8$ were used as the oxidant instead of TBHP (Table 1, entries 10 and 11). Our experiments also showed that use of oxygen as an oxidant was ineffective for the reaction (Table 1, entry 9). The solvent choice was also crucial for this reaction. Solvation in CH_3CN resulted in a 68 % yield of **3aa** (Table 1, entry 14), whereas the use of THF, 1,2-dichloroethane (DCE), DMF,

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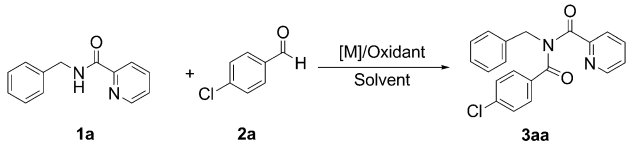
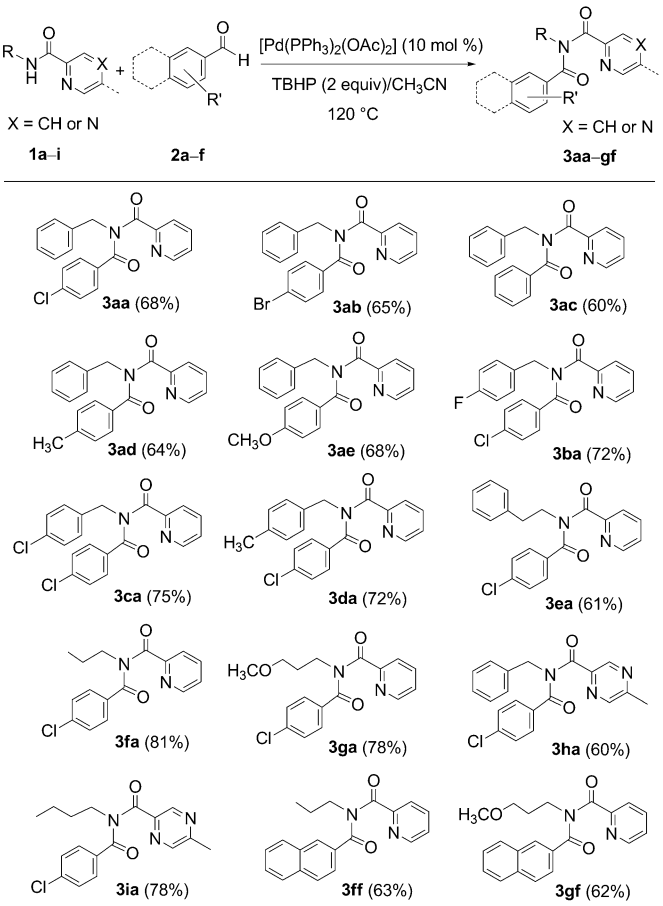
Table 1. Optimization of the C–H functionalization of aldehyde **2a** with picolinamide **1a** to give secondary imide **3aa**.[a]



1a **2a** **3aa**

Entry	[M]	Oxidant	Solvent	Yield [%][b]
1	$[Pd(OAc)_2]$	TBHP	toluene	2
2	$[PdCl_2]$	TBHP	toluene	28
3	$[Pd(PPh_3)_2Cl_2]$	TBHP	toluene	50
4	$[PdCl_2(dppf)]$[c]	TBHP	toluene	<5
5	$[Pd(dba)_2]$[d]	TBHP	toluene	0
6	$[Pd(PPh_3)_4]$	TBHP	toluene	53
7	$[Pd(tfa)_2]$[e]	TBHP	toluene	28
8	$[Pd(PPh_3)_2(OAc)_2]$	TBHP	toluene	55
9	$[Pd(PPh_3)_2(OAc)_2]$	O_2 (1 atm)	toluene	0
10	$[Pd(PPh_3)_2(OAc)_2]$	TBP	toluene	10
11	$[Pd(PPh_3)_2(OAc)_2]$	$K_2S_2O_8$	toluene	<5
12	$[Pd(PPh_3)_2(OAc)_2]$	TBHP	THF	46
13	$[Pd(PPh_3)_2(OAc)_2]$	TBHP	DCE	23
14	$[Pd(PPh_3)_2(OAc)_2]$	TBHP	CH_3CN	68
15	$[Pd(PPh_3)_2(OAc)_2]$	TBHP	benzene	51
16	$[Pd(PPh_3)_2(OAc)_2]$	TBHP	CH_3CN	52[f]

[a] A mixture of **1a** (0.25 mmol), **2a** (0.5 mmol), catalyst (0.025 mmol, 10 mol%), and oxidant (2.0 equiv) in solvent (1 mL) was stirred at 120°C for 24 h. [b] Yield of isolated products. [c] dppf = 1,1′-bis(diphenylphosphino)ferrocene. [d] dba = dibenzylideneacetone. [e] tfa = trifluoroacetate. [f] Reaction temperature was 100°C.



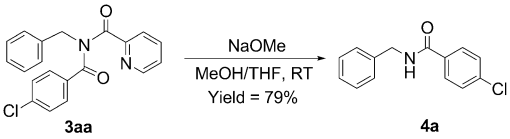
Scheme 1. Palladium-catalyzed C–H functionalization of aldehydes for the synthesis of secondary imides **3**. A mixture of **1** (0.25 mmol), aldehyde **2** (0.5 mmol), $[Pd(PPh_3)_2(OAc)_2]$ (0.025 mmol, 10 mol%), and TBHP (2.0 equiv) in CH_3CN (1 mL) was stirred at 120°C for 24 h; yields of isolated products are given.

or benzene led to lower yields (see Table 1, entries 12, 13, and 15 and the Supporting Information). The yield decreased when the reaction temperature was below 120°C (Table 1, entry 16). Notably, in the absence of a palladium catalyst, **3aa** was not obtained. When the pyridin-2-yl group of **1a** was replaced by a phenyl group, the desired C–H functionalization reaction of **2a** did not occur.

The optimal reaction conditions were $[Pd(PPh_3)_2(OAc)_2]$ (10 mol%) as the catalyst, TBHP as an oxidant, CH_3CN as the solvent, and a reaction temperature of 120°C. Under these conditions it was found that secondary picolinamides **1a–i** and various aryl aldehydes **2a–f** were able to smoothly undergo the coupling reaction to give the desired imides **3aa–gf** in satisfactory yields (Scheme 1). N-Aryl-substituted picolinamides could not perform the coupling reaction with aldehydes, probably due to steric hindrance and electronic effects. Our experiments demonstrated that the reaction tolerates various functionalities, such as methoxy, fluoro, chloro, and bromo groups. Electron-withdrawing or electron-donating substituents on the benzene rings of the aromatic aldehydes led to similar yields of **3** (Scheme 1; **3aa** and **3ab** versus **3ac–ae**). When an aliphatic aldehyde was employed in the reaction none of the desired imide was obtained under the optimal conditions. Similarly to *N*-benzyl picolinamides **1a–d**, *N*-alkyl picolinamides **1f–g** resulted in *N*-alkyl imides **3fa** and **3ga** in good yields. When pyrazine-2-carboxamides **1h** and **1i** were employed, the desired imides **3ha** and **3ia** were obtained in satisfactory yields. This suggests that the pyrazin-2-yl group can play an analogous role to the pyridin-2-yl group. Moreover, our experiments indicated that 2-naphthaldehyde (**2f**) was a suitable partner for the coupling reaction and gave the desired products **3ff** and **3gf** in moderate yields.

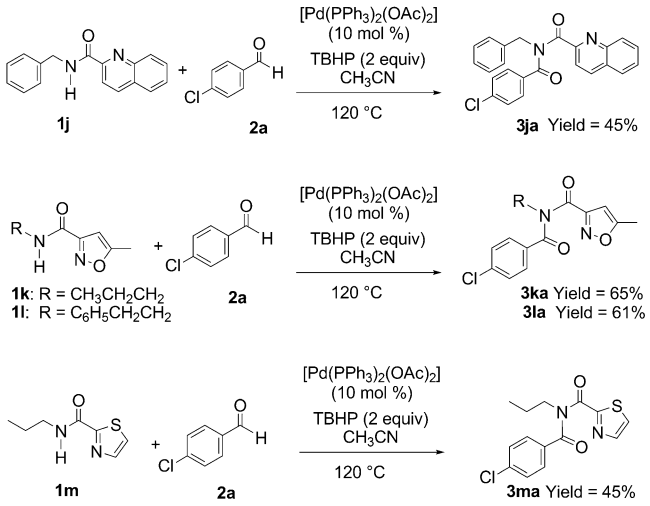
Next, we carried out an experiment to remove one of the acyl groups of imide **3aa**. After treatment of imide **3aa** with NaOMe in a mixture of MeOH and THF at room temperature, the picolinoyl group was selectively cleaved from **3aa** to produce *N*-benzyl-4-chlorobenzamide (**4a**) in good yield (Scheme 2).[10]

In addition, we performed the coupling reaction of quinoline-2-carboxamide (**1j**) with **2a** under the optimized conditions. Although the desired imide **3ja** was obtained, the



Scheme 2. Cleavage of the picolinoyl group from imide **3aa**.

yield was quite low. Five-membered *N*-heteroarene carboxamides, isoxazole-3-carboxamides **1k** and **1l** and thiazole-2-carboxamide **1m**, were also examined in the C–H functionalization of **2a**. It was found that **1k** and **1l** resulted in satisfactory yields of imides **3ka** and **3la**, respectively. Thiazole-2-carboxamide **1m** led to the desired imide **3ma** in a relatively lower yield (45%; Scheme 3).



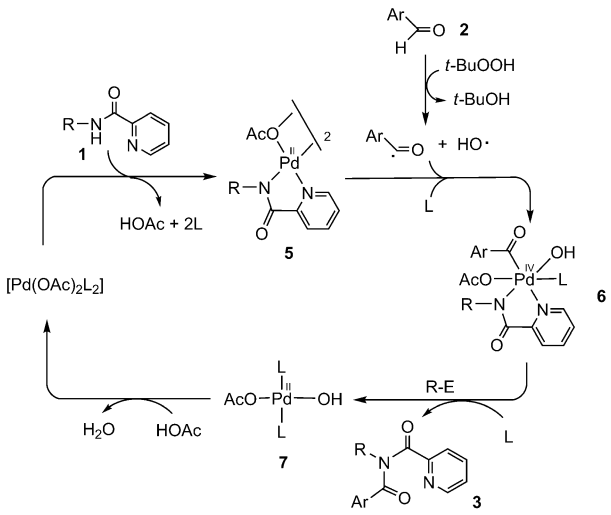
Scheme 3. C–H functionalization of aldehyde **2a** with quinoline-2-carboxamide (**1j**) and five-membered *N*-heteroarene carboxamides **1k–m**.

When 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), a radical scavenger, was added to the reaction of **1a** with **2a** the formation of imide **3aa** was completely suppressed. We captured most of the 4-chlorobenzoyl radical in its ester form with TEMPO (see the Supporting Information).[11]

This result suggests that aldehyde participates in the coupling reaction as an acyl radical species. Thus, a tentative mechanism for this reaction is proposed (Scheme 4). Initially, the picolinamide **1** chelates with $[Pd(OAc)_2L_2]$ to generate a dimeric palladacycle complex (**5**).[9] At the same time, TBHP dissociates into a *tert*-butoxy and a hydroxy radical.[12] Aldehyde **2** is deprived of its hydrogen atom by the *tert*-butoxy radical to form an acyl radical. The acyl radical and the hydroxy radical attach to palladacycle complex **5** to generate Pd^{IV}-complex **6** in the presence of a ligand. Reductive elimination of **6** results in the desired imide **3** and Pd^{II}-complex **7**. Ligand exchange in complex **7** with HOAc regenerates $[Pd(OAc)_2L_2]$ to complete the Pd^{II}/Pd^{IV} catalytic cycle.

Conclusion

We have developed an efficient palladium-catalyzed C–H functionalization of aldehydes with various N-substituted *N*-heteroarene-2-carboxamides for the synthesis of secondary imides. A range of secondary picolinamides and various aryl aldehydes could undergo the coupling reaction smoothly,



Scheme 4. A tentative mechanism for the palladium-catalyzed C–H functionalization of aldehyde **2** with picolinamide **1**.

under mild conditions, to give the corresponding secondary imides in satisfactory yields. The reaction tolerates various functionalities, such as methoxy, fluoro, chloro, and bromo groups. A tentative radical mechanism for a Pd^{II}/Pd^{IV} catalytic cycle was proposed. The reactions of *N*-heteroarene-2-carboxamides with substrates other than aldehydes to form various C–N bonds are currently underway.

Experimental Section

General procedure for the C–H functionalization of aldehydes with *N*-heteroarene-2-carboxamides: A solution of **1** (0.25 mmol), aromatic aldehyde **2** (0.50 mmol), and $[Pd(PPh_3)_2(OAc)_2]$ (19 mg, 0.025 mmol, 10 mol%) in CH_3CN (1.0 mL) was stirred at RT for 2 min in a reaction tube. TBHP (0.50 mmol, 5.5 M in decane) was added dropwise at RT. The reaction mixture was stirred at 120 °C for 24 h. After the reaction, the mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc) to afford the desired imide **3**.

Compound 3aa: White solid; m.p. 119–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (dq, J = 5.0, 0.9 Hz, 1H), 7.74 (dt, J = 7.8, 0.9 Hz, 1H), 7.61 (td, J = 7.8, 1.8 Hz, 1H), 7.54–7.51 (m, 2H), 7.42–7.37 (m, 2H), 7.36–7.29 (m, 2H), 7.28–7.22 (m, 1H), 7.18–7.14 (m, 1H), 7.11–7.07 (m, 2H), 5.25 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 171.5, 152.0, 148.1, 137.8, 137.2, 136.9, 136.0, 129.9, 128.6, 128.5, 128.4, 127.6, 126.1, 125.0, 50.4 ppm; MS (ESI): m/z: 351.00 $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{20}H_{15}ClN_2NaO_2$: 373.0720 $[M+Na]^+$; found: 373.0717.

Compound 3ab: White solid; m.p. 120–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (dq, J = 5.0, 0.9 Hz, 1H), 7.74 (dt, J = 8.1, 0.9 Hz, 1H), 7.62 (td, J = 7.8, 1.8 Hz, 1H), 7.53–7.51 (m, 2H), 7.35–7.29 (m, 4H), 7.27–7.22 (m, 3H), 7.19–7.14 (m, 1H), 5.24 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 171.4, 152.0, 148.1, 137.2, 137.0, 136.5, 131.4, 130.0, 128.6, 128.5, 127.6, 126.4, 126.1, 125.0, 50.4 ppm; MS (ESI): m/z: 394.95 $[M+H]^+$; HRMS (ESI): m/z calcd for $C_{20}H_{16}BrN_2O_2$: 395.0395 $[M+H]^+$; found: 395.0408.

Compound 3ac: White solid; m.p. 83–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, J = 5.1 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.58–7.52 (m, 3H), 7.47–7.43 (m, 2H), 7.35–7.30 (m, 2H), 7.27–7.17 (m, 2H), 7.13–7.08 (m, 3H), 5.27 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 171.8, 152.5, 148.1, 137.5, 137.4, 136.7, 131.6, 128.7, 128.6, 128.5, 128.1, 127.5,

125.7, 124.9, 50.3 ppm; MS (ESI): *m/z*: 317.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}N_2O_2$: 317.1290 $[M+H]^+$; found: 317.1300.

Compound 3ad: White solid; m.p. 108–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, J = 4.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.59–7.52 (m, 3H), 7.37–7.21 (m, 5H), 7.11 (dd, J = 6.9, 5.1 Hz, 1H), 6.91 (d, J = 8.1 Hz, 2H), 5.25 (s, 2H), 2.20 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 171.8, 152.6, 148.1, 142.3, 137.5, 136.6, 134.7, 128.9, 128.8, 128.51, 128.49, 127.5, 125.6, 124.8, 50.3, 21.4 ppm; MS (ESI): *m/z*: 331.00 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}N_2NaO_2$: 353.1266 $[M+Na]^+$; found: 353.1274.

Compound 3ae: White solid; m.p. 81–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 4.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.58–7.51 (m, 3H), 7.46–7.41 (m, 2H), 7.36–7.20 (m, 3H), 7.09 (dd, J = 7.5, 5.1 Hz 1H), 6.62–6.57 (m, 2H), 5.24 (s, 2H), 3.68 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.5, 171.6, 162.3, 152.6, 148.1, 137.5, 136.7, 131.0, 129.8, 128.52, 128.49, 127.5, 125.6, 124.7, 113.4, 55.3, 50.3 ppm; MS (ESI): *m/z*: 347.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}N_2NaO_3$: 369.1215 $[M+Na]^+$; found: 369.1210.

Compound 3ba: White solid; m.p. 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 4.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.61 (td, J = 7.7, 0.9 Hz, 1H), 7.55–7.48 (m, 2H), 7.41–7.35 (m, 2H), 7.16 (dd, J = 6.8, 4.8 Hz, 1H), 7.11–7.07 (m, 2H), 7.03–6.95 (m, 2H), 5.20 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 171.4, 162.3 (d, J(C,F) = 244.1 Hz), 151.9, 148.1, 137.8, 137.0, 136.0, 133.1 (d, J(C,F) = 3.9 Hz), 130.5, 130.4, 129.9, 128.4, 125.6 (d, J(C,F) = 82.1 Hz), 115.4 (d, J(C,F) = 21.3 Hz), 49.6 ppm; MS (ESI): *m/z*: 369.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{15}ClFN_2O_2$: 369.0806 $[M+H]^+$; found: 369.0805.

Compound 3ca: White solid; m.p. 96–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, J = 4.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.59 (td, J = 7.5, 1.2 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.39–7.35 (m, 2H), 7.28–7.26 (m, 2H), 7.15–7.07 (m, 3H), 5.19 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 171.4, 151.8, 148.1, 137.9, 137.0, 135.9, 135.7, 133.5, 130.0, 129.9, 128.7, 128.4, 126.2, 125.1, 49.6 ppm; MS (ESI): *m/z*: 385.00 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{14}C_{l2}N_2NaO_2$: 407.0330 $[M+Na]^+$; found: 407.0360.

Compound 3da: White solid; m.p. 197–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (d, J = 3.9 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 6.9 Hz, 4H), 7.17–7.07 (m, 5H), 5.20 (s, 2H), 2.30 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 171.4, 152.1, 148.1, 137.8, 137.3, 136.9, 136.1, 134.2, 129.9, 129.3, 128.5, 128.4, 126.0, 125.0, 50.2, 21.2 ppm; MS (ESI): *m/z*: 365.10 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{17}ClN_2NaO_2$: 387.0876 $[M+Na]^+$; found: 387.0852.

Compound 3ea: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (dq, J = 4.8, 0.9 Hz, 1H), 7.71 (dt, J = 7.8, 0.9 Hz, 1H), 7.62 (td, J = 7.5, 1.8 Hz, 1H), 7.36 (dt, J = 8.7, 2.1 Hz, 2H), 7.31–7.27 (m, 4H), 7.25–7.14 (m, 2H), 7.11 (dt, J = 9.0, 2.1 Hz, 2H), 4.32–4.27 (m, 2H), 3.18–3.13 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 152.1, 148.0, 138.4, 137.8, 137.0, 135.7, 130.0, 129.2, 128.5, 128.3, 126.6, 126.0, 124.9, 48.5, 35.0 ppm; MS (ESI): *m/z*: 365.00 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}ClN_2O_2$: 365.1057 $[M+H]^+$; found: 365.1080.

Compound 3fa: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, J = 4.5 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.61 (td, J = 7.5, 1.2 Hz, 1H), 7.45 (d, J = 8.7 Hz, 2H), 7.16–7.10 (m, 3H), 4.00 (t, J = 7.5 Hz, 2H), 1.81 (sextet, J = 7.5 Hz, 2H), 0.99 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 171.6, 152.2, 148.0, 137.8, 137.0, 136.0, 130.0, 128.4, 125.9, 124.9, 48.9, 22.2, 11.5 ppm; MS (ESI): *m/z*: 302.95 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{16}ClN_2O_2$: 303.0900 $[M+H]^+$; found: 303.0916.

Compound 3ga: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (d, J = 4.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.62 (td, J = 7.8, 1.5 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.18–7.12 (m, 3H), 4.13 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 6.0 Hz, 2H), 3.26 (s, 3H), 2.08 ppm (quintet, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 171.7, 152.2, 148.0, 137.8, 136.9, 135.8, 130.1, 128.4, 125.9, 124.9, 70.4, 58.5, 44.9, 29.0 ppm; MS (ESI): *m/z*: 333.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{17}ClKN_2O_3$: 371.0565 $[M+K]^+$; found: 371.0568.

Compound 3ha: White solid; m.p. 139–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (d, J = 1.2 Hz, 1H), 8.15 (d, J = 0.9 Hz, 1H), 7.49–7.42 (m, 4H), 7.36–7.26 (m, 3H), 7.18–7.15 (m, 2H), 5.22 (s, 2H), 2.51 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 170.0, 156.6, 145.3, 144.4, 142.2, 138.5, 136.8, 135.2, 130.1, 128.74, 128.67, 128.4, 127.8, 50.4, 21.8 ppm; MS (ESI): *m/z*: 366.00 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{16}ClN_3NaO_2$: 388.0829 $[M+Na]^+$; found: 388.0812.

Compound 3ia: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85 (s, 1H), 8.11 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.7 Hz, 2H), 4.00 (t, J = 7.2 Hz, 2H), 2.48 (s, 3H), 1.74 (quintet, J = 7.8 Hz, 2H), 1.39 (sextet, J = 7.5 Hz, 2H), 0.93 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 170.2, 156.4, 145.2, 144.6, 142.1, 138.5, 135.2, 130.1, 128.8, 47.3, 31.0, 21.8, 20.2, 13.8 ppm; MS (ESI): *m/z*: 332.10 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{19}ClN_3O_2$: 332.1166 $[M+H]^+$; found: 332.1181.

Compound 3ff: White solid; m.p. 88–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, J = 4.5 Hz, 1H), 7.90 (s, 1H), 7.76–7.60 (m, 5H), 7.50–7.37 (m, 3H), 6.97–6.93 (m, 1H), 4.10 (t, J = 7.5 Hz, 2H), 1.91 (sextet, J = 7.5 Hz, 2H), 1.04 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 172.0, 152.6, 148.0, 136.7, 135.1, 134.4, 131.8, 129.0, 128.9, 128.3, 128.0, 127.6, 126.8, 125.5, 125.3, 124.5, 48.9, 22.3, 11.6 ppm; MS (ESI): *m/z*: 319.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{18}N_2NaO_2$: 341.1266 $[M+Na]^+$; found: 341.1234.

Compound 3gf: White solid; m.p. 92–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (dq, J = 4.8, 0.6 Hz, 1H), 7.92 (s, 1H), 7.76–7.60 (m, 5H), 7.51–7.39 (m, 3H), 6.99–6.94 (m, 1H), 4.22 (t, J = 7.2 Hz, 2H), 3.56 (t, J = 6.3 Hz, 2H), 3.30 (s, 3H), 2.16 ppm (quintet, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 172.0, 152.5, 148.0, 136.7, 134.9, 134.4, 131.8, 129.2, 128.9, 128.3, 128.0, 127.6, 126.7, 125.5, 125.3, 124.5, 70.5, 58.5, 44.8, 29.1 ppm; MS (ESI): *m/z*: 349.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{20}N_2NaO_3$: 371.1372 $[M+Na]^+$; found: 371.1355.

Compound 3ja: White solid; m.p. 130–131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.74–7.68 (m, 2H), 7.60–7.54 (m, 3H), 7.38–7.31 (m, 4H), 7.29–7.23 (m, 1H), 6.95–6.90 (m, 2H), 5.33 ppm (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 171.5, 151.5, 145.8, 137.5, 137.32, 137.28, 136.5, 130.4, 129.7, 129.2, 128.7, 128.62, 128.57, 128.4, 128.3, 127.7, 127.6, 120.7, 50.4 ppm; MS (ESI): *m/z*: 401.00 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{24}H_{17}ClN_2NaO_2$: 423.0876 $[M+Na]^+$; found: 423.0887.

Compound 3ka: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.09 (s, 1H), 3.96 (t, J = 7.5 Hz, 2H), 2.31 (s, 3H), 1.78 (sextet, J = 7.5 Hz, 2H), 0.98 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 171.1, 164.4, 159.9, 138.4, 134.9, 130.0, 128.9, 101.7, 48.6, 22.2, 12.1, 11.4 ppm; MS (ESI): *m/z*: 307.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{15}H_{15}ClN_2NaO_3$: 329.0669 $[M+Na]^+$; found: 329.0673.

Compound 3la: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.7 Hz, 2H), 7.31–7.19 (m, 7H), 6.06 (s, 1H), 4.25 (t, J = 7.5 Hz, 2H), 3.11 (t, J = 7.5 Hz, 2H), 2.32 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 171.1, 164.3, 159.7, 138.4, 137.9, 134.5, 130.0, 129.2, 128.8, 128.6, 126.8, 101.8, 48.2, 35.0, 12.1 ppm; MS (ESI): *m/z*: 369.05 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{20}H_{17}ClN_2NaO_3$: 391.0825 $[M+Na]^+$; found: 391.0858.

Compound 3ma: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 3.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 3.0 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 4.03 (t, J = 7.5 Hz, 2H), 1.83 (sextet, J = 7.5 Hz, 2H), 1.00 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 164.8, 163.0, 143.6, 138.2, 135.6, 130.0, 128.7, 125.7, 49.3, 22.3, 11.5 ppm; MS (ESI): *m/z*: 309.00 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $C_{14}H_{14}ClN_2O_2S$: 309.0465 $[M+H]^+$; found: 309.0459.

Cleavage of the picolinoyl group from imide 3aa to give *N*-benzyl-4-chlorobenzamide (4a):[10] NaOMe (2.7 mg, 0.05 mmol) was added to a solution of imide **3aa** (17.5 mg, 0.05 mmol) in MeOH (0.5 mL) and THF (0.2 mL). The reaction mixture was stirred at RT for 5 h. After addition of water (5 mL), the mixture was extracted with ethyl acetate (3× 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by TLC (silica gel,

petroleum ether/EtOAc) to give **4a** (79%). M.p. 162–163 (lit.[13] 163–166 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.73$ (d, $J = 8.4$ Hz, 2H), 7.42–7.28 (m, 7H), 6.42 (br s, 1H), 4.64 ppm (d, $J = 5.7$ Hz, 2H); MS (EI): m/z (%): 245.0 (36) $[M]^+$, 139.0 (100), 111.0 (26), 75.0 (10).

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