Buchwald–Hartwig Mono-N-arylation with 2,6-Dihaloisonicotinic Acid Derivatives: A Convenient Desymmetrization Method

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Abstract: A method for the Buchwald–Hartwig mono-N-arylation of aniline with methyl 2,6-dichloroisonicotinate using $Pd(OAc)_2$, XPhos, and *t*-BuONa is reported. Use of *m*-anisidine under the same conditions resulted in the amidation of the methyl ester. Mono-N-arylation of *m*-anisidine with 2,6-dichloro-*N*,*N*-diisopropylisonicotinamide and 2,6-dibromo-*N*,*N*-diisopropylisonicotinamide, however, was successfully achieved using $Pd(OAc)_2$/XPhos/*t*-BuONa or $Pd(OAc)_2$/(±)-BINAP/K_2CO_3, respectively. The present study demonstrates the sensitivity of this cross-coupling method to both the steric and electronic nature of the coupling partners.

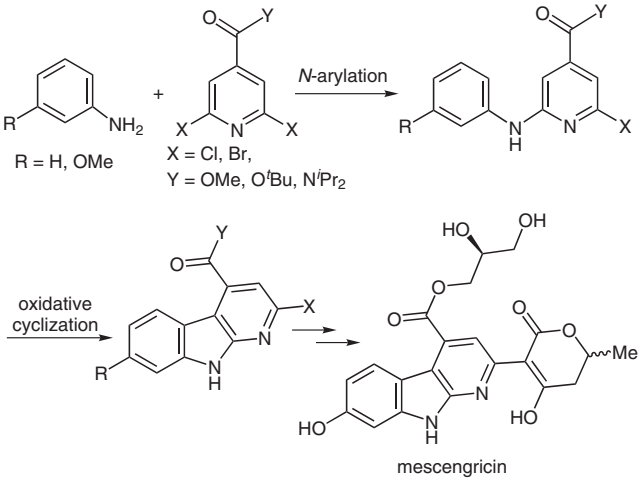
Key words: Buchwald–Hartwig N-arylation, Pd(0) cross-coupling, 2,6-dihaloisonicotinates

The Buchwald–Hartwig amination occupies a prominent position in heterocyclic chemistry and the amenability of the reaction to scale-up is of particular relevance to the pharmaceutical industry.[1–3] Specifically, aminopyridines can be easily prepared using this efficient palladium-catalyzed carbon–nitrogen bond-forming strategy.[4]

As part of a program aimed at preparing substituted α-carbolines[5] (pyrido[2,3-*b*]indoles) via oxidative cyclization of trisubstituted pyridine derivatives, our attention was initially focused on the synthesis of the mono-N-arylated 2-haloisonicotinic acid precursors (Scheme 1). It was envisaged that ready access to a range of aniline-substituted 2-haloisonicotinic acid derivatives would provide valuable trifunctional pyridine scaffolds for further synthetic manipulation.

Initial investigation was focused on the palladium-catalyzed mono-N-arylation of aniline with methyl 2,6-dichloroisonicotinate (**1**) (Table 1). The first choice of reaction conditions was inspired by the work of Maes et al.,[6,7] who reported the palladium-catalyzed coupling of aryl halides with primary amines under microwave conditions. In light of the fact that their reported coupling of 4-bromoanisole with benzylamine to yield *N*-benzyl-4-methoxyaniline was easily reproducible in our hands, these conditions were evaluated for the attempted mono-N-arylation with methyl 2,6-dichloroisonicotinate.

In order to demonstrate proof of principle, Buchwald–Hartwig coupling of methyl 2,6-dichloroisonicotinate (**1**; 1.0 equiv) was first carried out with the more reactive primary amine, benzylamine (3.0 equiv), in toluene using the palladacycle generated from $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos) with excess sodium *tert*-butoxide under microwave conditions (150 °C, 300 W, 10 min) affording the mono-N-arylated product **2** in 44% yield (Table 1, entry 1). Whilst this experiment was encouraging, application of the same reaction conditions using less reactive aniline as the amine coupling partner only resulted in recovered starting material.



Scheme 1 Synthesis of mono-N-arylated 2-haloisonicotinic acid precursors

In light of the fact that there are far more reports of Buchwald–Hartwig reactions using standard thermal conditions in the literature than the use of microwave conditions, the reaction of methyl 2,6-dichloroisonicotinate (**1**) with aniline was attempted under thermal conditions. A number of ligands [XPhos, JohnPhos, (±)-BINAP and DPPF] were investigated and it was found that the use of the ligand XPhos afforded the cleanest reaction with toluene proving it to be a better solvent than *tert*-butyl alcohol or mixtures of toluene–*tert*-butyl alcohol. The optimum reaction time was 4 hours resulting in the formation of the mono-N-arylation product **3** in 53% yield (Table 1, entry 2).

Our attention next focused on the reaction of *m*-anisidine with methyl 2,6-dichloroisonicotinate (**1**) as a possible starting point for the synthesis of the neuroprotective α-carboline, mescengricin (Scheme 1).[8] It was hoped that the presence of the additional methoxy group in the amine coupling partner would improve the reactivity of the cou-

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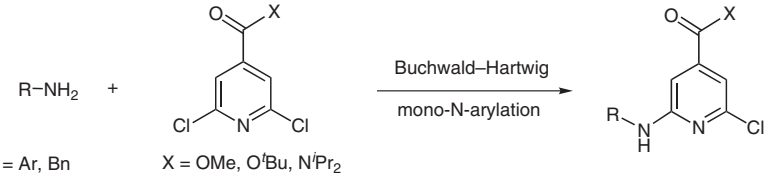
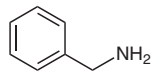
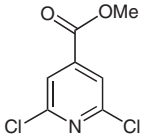
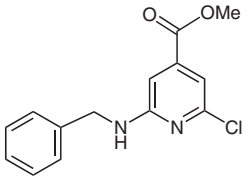
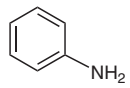
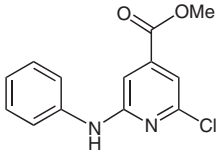
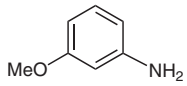
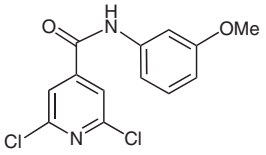
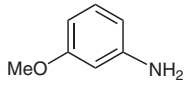
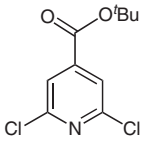
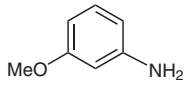
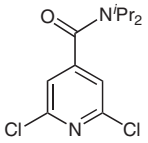
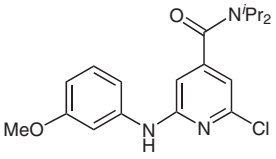
Table 1 N-Arylation of Amines with 2,6-Dichloroisonicotinic Acid Derivatives



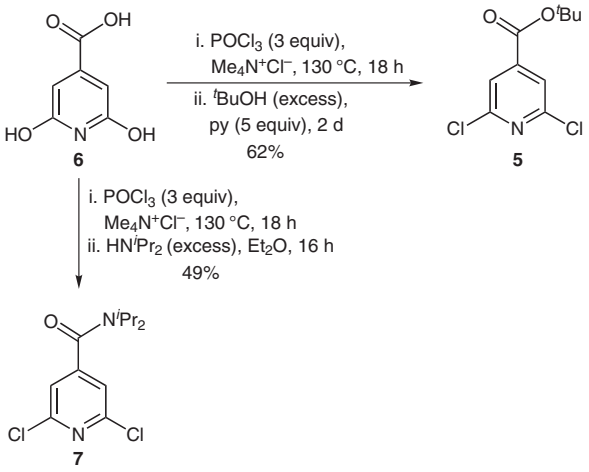
Entry	Amine	Dihalide	Conditions	Product; Yield (%)
1		 **1**	**1** (1 equiv), amine (3 equiv), $Pd(OAc)_2$, (1 mol%), JohnPhos[a] (2 mol%), *t*-BuONa (1.4 equiv), toluene, MW, 10 min, 150 °C, 300 W	 **2**; 44
2		**1**	**1** (1 equiv), amine (1 equiv), $Pd(OAc)_2$, (1 mol%), XPhos[b] (2 mol%), *t*-BuONa (1.4 equiv), Et_3N (0.5 equiv), toluene, 90 °C, 4 h	 **3**; 53
3		**1**	**1** (2 equiv), amine (1 equiv), $Pd(OAc)_2$, (1 mol%), XPhos[b] (2 mol%), *t*-BuONa (1.4 equiv), toluene	 **4**
			110 °C, 18 h	**4**; 28
			90 °C, 22 h	**4**; 36
			25 °C, 3 d	**4**; 34
4		 **5**	**5** (1.5 equiv), amine (1 equiv), $Pd(OAc)_2$, (1 mol%), XPhos[b] (2 mol%), *t*-BuONa (1.4 equiv), toluene	
			25 °C, 4 d	**4**; 67
			80 °C, 2 d	**4**; 66
			130 °C, 3 d	**4**; 34
5		 **7**	**7** (1.5 equiv), amine (1 equiv), $Pd(OAc)_2$, (5 mol%), XPhos[b] (10 mol%), *t*-BuONa (1.4 equiv), toluene, 100 °C, 23 h	 **8**; 14

[a] JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl.
[b] XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

pling reaction. Initial attempts to couple *m*-anisidine with methyl 2,6-dichloroisonicotinate (**1**) using 1 mol% $Pd(OAc)_2$/XPhos in toluene for 18 hours at 110 °C with excess sodium *tert*-butoxide only afforded the amide **4** in 28% yield (Table 1, entry 3). Use of lower reaction temperatures (90 °C for 22 h and r.t. for 3 days) also resulted in the formation of the amide **4** in 36% and 46% yield, respectively (Table 1, entry 3). It was therefore apparent that the increased electron density on the aromatic ring in *m*-anisidine favors displacement of the methoxy group from ester **1** rather than displacement of the chloro substituent.

Use of the more hindered *tert*-butyl 2,6-dichloroisonicotinate (**5**) was examined in order to block the attack of *m*-anisidine at the ester carbonyl group. Compound **5** was prepared by heating citrazinic acid (**6**) with $POCl_3$ at 130

°C for 18 hours in the presence of tetramethylammonium chloride followed by quenching with *tert*-butyl alcohol and pyridine in 62% yield (Scheme 2).



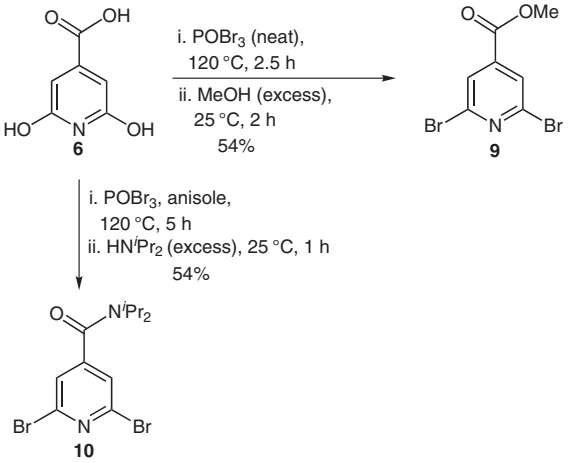
Scheme 2 Synthesis of *tert*-butyl 2,6-dichloroisonicotinate (**5**) and 2,6-dichloro-*N*,*N*-diisopropylisonicotinamide (**7**)

Attempted mono-N-arylation of *m*-anisidine with *tert*-butyl 2,6-dichloroisonicotinate (**5**) under the same conditions as the methyl ester **1** with a range of temperatures and reaction times only afforded amide **4** with no evidence for formation of the desired mono-N-arylation product (Table 1, entry 4). An increased reaction temperature was detrimental to the reaction and the inability to block the reaction at the ester carbonyl prompted adoption of an alternative strategy.

It was hoped that use of a more robust carboxamide group would prevent the undesired acyl substitution from occurring. It was decided to use 2,6-dichloro-*N*,*N*-diisopropylisonicotinamide (**7**) as the substrate for the N-arylation reaction. Reaction of esters **1** and **5** with *m*-anisidine leads to the formation of a stable amide bond, thus providing a driving force for this reaction. Replacement of the ester by an amide group removes this driving force. Amide **7** was therefore prepared by heating citrazinic acid (**6**) with $POCl_3$ at 130 °C for 18 hours followed by dilution with diethyl ether and reaction with diisopropylamine (Scheme 2).

Buchwald–Hartwig coupling of amide **7** with *m*-anisidine using 5 mol% $Pd(OAc)_2$/XPhos in toluene for 23 hours at 110 °C with excess sodium *tert*-butoxide afforded the monoarylation product **8** in only 14% yield together with recovered starting material (Table 1, entry 5). The lack of reactivity of 2,6-dichloro-*N*,*N*-diisopropylisonicotinamide (**7**) as an N-arylation coupling partner prompted the use of more reactive 2,6-dibromoisonicotinic acid derivatives **9** and **10** (Scheme 3) as substrates for this reaction.

Methyl 2,6-dibromoisonicotinate (**9**)[9] was prepared in 54% yield by treatment of citrazinic acid (**6**) with $POBr_3$ at 120 °C for 2.5 hours followed by stirring with methanol for 2 hours. Notably, it was essential to freshly prepare[10] the $POBr_3$ and distill it immediately before use. 2,6-dibromo-*N*,*N*-diisopropylisonicotinamide (**10**) was similarly prepared by treatment of a suspension of citrazinic acid (**6**) in anisole with $POBr_3$ at 120 °C for 5 hours followed by reaction with diisopropylamine at ambient temperature for 1 hour.

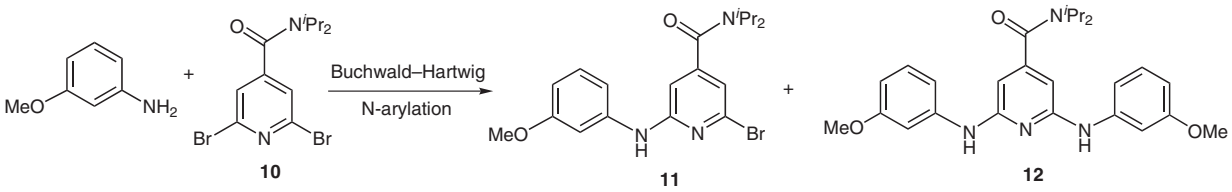


Scheme 3 Synthesis of methyl 2,6-dibromoisonicotinate (**9**) and 2,6-dibromo-*N*,*N*-diisopropylisonicotinamide (**10**)

With the more robust dibromoamide **10** in hand, investigation of its Buchwald–Hartwig reaction with *m*-anisidine was carried out hoping that the increased reactivity of the C–Br bond would facilitate the desired cross coupling (Table 2). Reaction of the dibromoamide **10** with *m*-anisidine in toluene with sodium *tert*-butoxide as base using 10 mol% $Pd(OAc)_2$/XPhos at 90 °C for 24 hours afforded the desired mono-N-arylation product **11** in 19% yield (Table 2, entry 1). Increasing the catalyst loading to 30 mol% did not improve the yield. It also appeared that XPhos was unstable under these conditions; hence, the ligand was changed to (±)-BINAP based on its comparable reactivity to XPhos in our earlier model studies. Use of (±)-BINAP as ligand did not improve the yield of the mono-N-arylation product **11** either, (Table 2, entry 2) and the palladium source was changed to $Pd_2(dba)_3$ based on the observations by the Buchwald group[11] that reactions that were problematic using $Pd(OAc)_2$ often showed better reactivity using $Pd_2(dba)_3$. Changing the palladium source to $Pd_2(dba)_3$ did improve the yield of **11** by 20% (Table 2, entry 4) when using (±)-BINAP as ligand but no improvement was observed when using XPhos (Table 2, entry 3). Focusing on the $Pd_2(dba)_3$/(±)-BINAP system it was next observed that changing the ratio of *m*-anisidine:dibromide **10** to 1:2 offered a further improvement in the yield of **11** (Table 2, entries 5,6).

Surprisingly, there has been little investigation into selective monoamination reactions using Buchwald–Hartwig catalysis. There have been a few reports of aminations that are selective for bromide displacement over chloride,[12] or iodide over bromide,[13] however, monoamination of dichloro or dibromo coupling partners is rare. Maes et al.[14] reported the selective monoamination of simple 2,6-dichloropyridines with amines. In their case, use of a large excess of K_2CO_3 rather than sodium *tert*-butoxide as base

Table 2 N-Arylation of *m*-Anisidine with 2,6-dibromo-*N*,*N*-diisopropylisonicotinamide (**10**)



Entry	Catalyst (mol%)	Ligand (mol %)	Mole ratio *m*-anisidine:**10**	Yield (%) **11**	**12**	Base
1	$Pd(OAc)_2$ (10)	XPhos (20)	1:1	19	23	*t*-BuONa[a]
2	$Pd(OAc)_2$ (10)	(±)-BINAP (20)	1:1	20	26	*t*-BuONa[a]
3	$Pd_2(dba)_3$ (10)	XPhos (20)	1:1	11	30	*t*-BuONa[a]
4	$Pd_2(dba)_3$ (10)	(±)-BINAP (20)	1:1	39	32	*t*-BuONa[a]
5	$Pd_2(dba)_3$ (10)	(±)-BINAP (20)	1:1.5	27	33	*t*-BuONa[a]
6	$Pd_2(dba)_3$ (10)	(±)-BINAP (20)	1:2	53	9	*t*-BuONa[a]
7	$Pd(OAc)_2$[c] (10)	(±)-BINAP (10)	1:1	71	10	K_2CO_3[b]

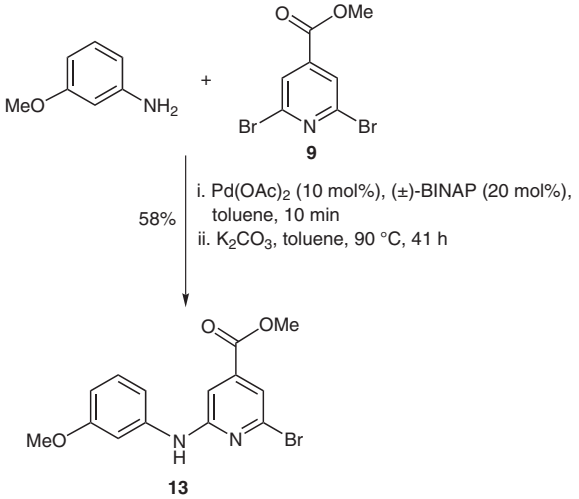
[a] Reactions were carried out in toluene for 24 h at 90 °C using *t*-BuONa (1.4 equiv).
[b] Reaction was carried out in toluene at 90 °C for 41 h.
[c] $Pd(OAc)_2$ and (±)-BINAP were premixed in toluene for 10 min prior to use.

afforded good yields of the monosubstitution product. It was proposed that introduction of an electron-donating amino group increases the electron density of the pyridine ring such that oxidative addition into the second C–Cl bond is rendered less favorable.

The reaction procedure developed by Maes et al.[14] requires preincubation of $Pd(OAc)_2$ and (±)-BINAP in toluene for 10 minutes prior to the addition to the reaction mixture. We were therefore interested to see whether the conditions developed by Maes et al.[14] could be extended to the use of more reactive 2,6-dibromopyridines that also contained a substituent at C-4 for further synthetic manipulation.

Gratifyingly, reaction of dibromo amide **10** with *m*-anisidine using preincubated $Pd(OAc)_2$/(±)-BINAP afforded the mono-N-arylated product **11** in a pleasing 71% yield. Exclusive monoamination of **10** was not observed with all reactions producing some of the diaminated product **12**. This observation can be attributed to two factors. Firstly, bromides are better leaving groups than chlorides, hence the second oxidative addition step could not be prevented upon introduction of the initial *m*-anisidine substituent. Secondly, the amide group at C-4 would withdraw electron density from the pyridine ring counteracting the increased electron density achieved upon amination.

The conditions used to form mono-N-arylated product **11** by reaction of dibromoamide **10** with *m*-anisidine (Table 2, entry 7) were next applied to the use of methyl 2,6-dibromoisonicotinate (**9**) as a substrate (Scheme 4). Use of dibromo ester **9** was considered more synthetically useful in that the tripodal mono-N-arylation product **13** bears an ester group that can be more easily elaborated than a diisopropyl amide group. Dibromo ester **9** also provides a critical substrate on which to evaluate the scope of Buchwald–Hartwig mono-N-arylations in the presence of the C-4 methyl ester group that had previously been observed to undergo reaction with *m*-anisidine (vide supra). Treatment of dibromo ester **9** with *m*-anisidine using preincubated $Pd(OAc)_2$/(±)-BINAP afforded mono-N-arylated product **13** in 58% yield whereas use of the corresponding dichloro ester **1** led to a complex mixture.



Scheme 4 Mono-N-arylation of *m*-anisidine with methyl 2,6-dibromoisonicotinate (**9**)

In conclusion, several 6-anilino-2-haloisonicotinic acid derivatives have been successfully prepared via Buchwald–Hartwig mono-N-arylation of amines with 2,6-

dichloro- or 2,6-dibromoisonicotinic acid derivatives. This methodology has extended the scope of the Buchwald–Hartwig N-arylation reaction to the use of C-4 functionalized dihalopyridines with the usual caveat that the observed outcome of the reaction is highly dependent on the steric and electronic effects of the cross-coupling partners.

All reactions were carried out under N_2 using oven-dried glassware using standard syringe and septum techniques, unless otherwise stated. THF was distilled from Na/benzophenone under N_2. Toluene was distilled from Na under N_2. Flash chromatography was performed using Riedel-de Häen or Merck 0.032–0.063 mm silica gel. Analytical TLC was performed with 0.20 mm silica gel 60 aluminum-backed plates and analyzed using 365 nm ultraviolet irradiation followed by staining with either alkaline $KMnO_4$ or vanillin/H_2SO_4 solution. High-resolution mass spectra were obtained using EI, CI, and FAB techniques on a VG70-SE spectrometer operating at a nominal accelerating voltage of 70 eV and a nominal resolution of 5000 to 10000 as appropriate. NMR spectra were recorded on either a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or on a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. ^{1}H NMR data is reported as chemical shift in d (ppm) from tetramethylsilane as an internal standard. ^{13}C NMR data is reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal indicator ($CDCl_3$ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments).

Methyl 2,6-Dichloroisonicotinate (1)[15]

Citrazinic acid (**6**; 5.1 g, 33.1 mmol) and Me_4NCl (4.1 g, 37.7 mmol) were suspended in $POCl_3$ (9.3 mL, 99.4 mmol) and the mixture was slowly heated to 130 °C (***Caution!*** vigorous release of gaseous HCl). The mixture was heated at 130 ° for 18 h. The reaction was then cooled to 0 °C and anhyd MeOH (100 mL) was added dropwise. (***Caution!*** vigorous release of gaseous HCl). The mixture was warmed to r.t. over 1 h, then neutralized with solid Na_2CO_3 (2 g) and the MeOH was removed in vacuo. The black residue was diluted with H_2O (400 mL) and extracted with EtOAc (100 mL, then 3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The black residue was passed through a plug of silica gel using 10:1 hexane–EtOAc as eluent to afford **1** (3.9 g, 57%) as a pink solid; mp 78–80.5 °C (Lit.[15] mp 80–81 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, OCH_3), 7.81 (s, 2 H, 3-H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): 53.3 (OCH_3), 122.6 (C-3, C-5), 142.4 (C-2, C-6), 151.2 (C-4), 163.2 (C=O).

The ^{1}H and ^{13}C NMR data and melting point were in agreement with that reported in the literature.[15]

Methyl 2-(Benzylamino)-6-chloroisonicotinate (2)

Benzylamine (0.33 mL, 3 mmol), methyl 2,6-dichloroisonicotinate (**1**; 208 mg, 1 mmol), and *t*-BuONa (134 mg, 1.4 mmol) were placed in a 10 mL microwave flask under N_2. A solution of palladacycle (1 mL) prepared from $Pd(OAc)_2$ (2.26 mg, 0.01 mmol) and di-(*tert*-butylphosphino)biphenyl (5.96 mg, 0.02 mmol) in toluene (5 mL) was then added. The mixture was heated to 150 °C with microwave irradiation (300 W) for 10 min, then filtered through Celite that was then washed with CH_2Cl_2 (100 mL) and the solvent removed in vacuo. The residue was purified via flash chromatography using 5:1 hexanes–EtOAc as eluent to afford **2** (120.9 mg, 44%) as a pale green solid; mp 154–155 °C; R_f = 0.3 (hexanes–EtOAc, 5:1).

IR (thin film): 3279, 1647, 1608, 1545, 1389, 1360, 1327, 895 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, OCH_3), 4.60 (d, J = 5.7 Hz, 2 H, CH_2N), 6.49 (br s, 1 H, NH), 6.95 (d, J = 1 Hz, 1 H, 3-H), 7.20 (d, J = 1 Hz, 1 H, 5-H), 7.37 (m, 5 H, H-2′, H-3′, H-4′, H-5′, H-6′).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.3, 54.5, 107.2, 113.9, 127.9, 128.9, 137.2, 146.8, 149.4, 164.3, 164.4.

MS (EI, 70 eV): *m*/*z* (%) = 65 (14), 81 (19), 91 (47), 106 (70), 127 (8), 143 (55), 171 (61), 241 (4), 276 (M^+, 100).

HRMS: *m*/*z* calcd for $C_{14}H_{13}{}^{35}ClN_2O_2$ $[M]^+$: 276.0666; found: 276.0670; $C_{14}H_{13}{}^{37}ClN_2O_2$: 278.0636; found: 278.0632.

Methyl 2-Chloro-6-(aminophenyl)isonicotinate (3)

The ester **1** (103 mg, 0.75 mmol), *t*-BuONa (67 mg, 0.7 mmol), XPhos (5 mg, 0.01 mmol), and $Pd(OAc)_2$ (1.1 mg, 0.005 mmol) were placed in a flask and the flask was flushed with argon. Aniline (70 mg, 0.75 mmol), Et_3N (0.04 mL, 0.25 mmol), and toluene (1 mL) were added via syringe. The mixture was heated under argon before cooling to r.t. The mixture was diluted with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The resultant brown residue was purified by flash column chromatography using hexanes–EtOAc (5:1) as eluent to afford **3** (53%) as an inseparable mixture with aniline as a cream crystalline solid; mp 144–146 °C; R_f = 0.4 (hexanes–EtOAc, 5:1).

IR (thin film): 3295, 1657, 1599, 1539, 1445, 1382, 1360, 1327 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.96 (s, 3 H, OCH_3), 7.00 (d, J = 1.1 Hz, 1 H, H-5), 7.17 (tt, J = 7.4, 1.7 Hz, 1 H, H-4′), 7.25 (d, J = 1.1 Hz, 1 H, H-3), 7.33 (tt, J = 7.9, 2.2 Hz, 2 H, H-3′, H-5′), 7.57 (d, J = 7.6 Hz, 2 H, H-2′, H-6′), 8.09 (s, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.5, 107.2, 113.9, 120.6, 125.4, 129.1, 136.9, 147.2, 149.6, 162.9, 164.4.

MS (EI, 70 eV): *m*/*z* (%) = 39 (17), 51 (10), 65 (27), 81 (19), 85 (15), 94 (21), 146 (29), 174 (100), 262 ($^{35}ClM^+$, 68), 264 ($^{37}ClM^+$, 68).

HRMS: *m*/*z* calcd for $C_{13}H_{11}{}^{35}ClN_2O_2$ $[M]^+$: 262.0509; found: 262.0506; $C_{13}H_{11}{}^{37}ClN_2O_2$: 264.0480; found: 264.0477.

2,6-Dichloro-*N*-(3′-methoxyphenyl)isonicotinamide (4)

The ester **1** (412 mg, 2.0 mmol), *t*-BuONa (135 mg, 1.4 mmol), and XPhos (9.5 mg, 0.02 mmol) were placed in a flask and the flask was flushed with argon. *m*-Anisidine (123 mg, 1.0 mmol) was added followed by $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) dissolved in toluene (3 mL) and the mixture was heated under argon. The mixture was cooled to r.t., diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was removed in vacuo. The resulting brown residue was purified by flash column chromatography using 3:1 hexanes–EtOAc as eluent to afford **4** as fine off-white needles. Recrystallization from Et_2O and hexanes (1:2) afforded **4** (298 mg, 46%) as lilac needles; mp 160–162 °C; R_f = 0.46 (hexanes–EtOAc, 3:1).

IR (thin film): 3433, 2101, 1656, 1538, 1492, 1360, 1278 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H, OCH_3), 6.76 (ddd, J = 8.30, 2.45, 0.78 Hz, 1 H, H-4′), 7.08 (m, J = 8.03, 1.13 Hz, 1 H, H-6′), 7.28 (t, J = 9.35 Hz, 1 H, H-5′), 7.31 (s, 1 H, H-2′), 7.65 (s, 2 H, H-3, H-5), 7.83 (br s, 1 H, NH)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 106.5, 111.4, 112.6, 120.6, 130.6, 137.7, 147.7, 151.7, 160.3.

MS (EI, 70 eV): *m*/*z* (%) = 41 (12.0), 52 (13.0), 64 (8.0), 85 (17.3), 92 (5.3), 95 (16.3), 107 (5.3), 110 (8.0), 124 (22.7), 146 (34.0), 174 (91.4), 233 (2.7), 253 (4.7), 267 (3.7), 281 (1.3), 296 ($^{35}Cl_2M^+$, 100), 298 ($^{35}Cl^{37}ClM^+$, 100), 300 ($^{37}Cl_2M^+$, 100).

HRMS: *m*/*z* calcd for $C_{13}H_{10}{}^{35}Cl_2N_2O_2$ $[M]^+$: 296.0114; found: 296.0119; $C_{13}H_{10}{}^{35}Cl^{37}ClN_2O_2$: 298.0090; found: 298.0101; $C_{13}H_{10}{}^{37}Cl_2N_2O_2$: 300.0060; found: 300.0058.

tert-Butyl 2,6-Dichloroisonicotinate (5)

Citrazinic acid (**6**; 1 g, 6.45 mmol) and Me_4NCl (777 mg, 7.09 mmol) were suspended in $POCl_3$ (20 mL, 19.34 mmol) and the mixture was slowly heated to 130 °C (***Caution!*** vigorous release of gaseous HCl). The mixture was heated at 130 °C for 18 h and then was cooled to 0 °C. Anhyd *tert*-butyl alcohol (10 mL) and pyridine (2.60 mL, 32.25 mmol) were mixed in a flask and then added dropwise to the above mixture. (***Caution!*** vigorous release of gaseous HCl). The mixture was warmed to r.t., stirred for 2 d, neutralized with aq sat. $NaHCO_3$ (100 mL), diluted with H_2O (150 mL), and extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent removed in vacuo. The black residue was purified by flash chromatography using 15:1 hexane–EtOAc as eluent to afford **5** (988 mg, 62%) as pink needles; mp 75–78 °C; R_f = 0.45 (hexanes–EtOAc, 15:1).

IR (thin film): 1730, 1546, 1369, 1354, 1299, 1259, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.60 (s, 9 H, 3 × CH_3), 7.74 (s, 2 H, 3-H and 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.9, 83.9, 122.6, 144.4, 151.2, 161.6.

MS (EI, 70 eV): *m*/*z* (%) = 73 (14), 76 (21), 85 (17), 100 (19), 112 (21), 128 (17), 146 (31), 156 (16), 174 (62), 191 (100), 248 (M^+, 7).

HRMS: *m*/*z* calcd for $C_{10}H_{12}{}^{35}Cl_2NO_2$ $[M]^+$: 248.0245; found: 248.0250; $C_{10}H_{12}{}^{35}Cl^{37}ClNO_2$: 250.0216; found: 250.0211; $C_{10}H_{12}{}^{37}Cl_2NO_2$: 252.0186; found: 252.0181.

2,6-Dichloro-*N*,*N*-diisopropylisonicotinamide (7)

Citrazinic acid (**6**; 1 g, 6.45 mmol) and Me_4NCl (777 mg, 7.1 mmol) were suspended in $POCl_3$ (20 mL, 19.3 mmol) and the mixture was slowly heated to 130 °C (***Caution!*** release of gaseous HCl). The mixture was heated at 130 °C for 18 h, cooled to r.t. and diluted with anhyd Et_2O (15 mL). The mixture was cooled to 0 °C and *i*-Pr_2NH (5.0 mL, 35.5 mmol) was added dropwise. (***Caution!*** release of gaseous HCl). The mixture was warmed to r.t. and stirred overnight. The reaction was quenched with aq sat. NH_4Cl (10 mL) and diluted with H_2O (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (50 mL). The combined organic extracts (65 mL) were washed with aq 1 M HCl (2 × 40 mL), aq 2 M Na_2CO_3 (50 mL), and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography using 10:1 hexanes–EtOAc as eluent to afford **7** (869 mg, 49%) as a colorless solid; mp 143–147 °C; R_f = 0.2 (hexanes–EtOAc, 10:1).

IR (thin film): 1635, 1585, 1537, 1451, 1364, 1340, 1165, 1041 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 and 1.49 (m, 12 H, 4 × CH_3), 3.55 [m, 1 H, C*H*(CH_3)$_2$], 3.65 [m, 1 H, C*H*(CH_3)$_2$], 7.16 (s, 2 H, 3-H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 20.7, 46.4, 51.2, 119.4, 151.0, 151.1, 165.3.

MS (EI, 70 eV): *m*/*z* (%) = 41 (25), 43 (45), 85 (12), 146 (21), 174 (100), 217 (80), 231
(57), 259 (42), 274 (M^+, 35).

HRMS: *m*/*z* calcd for $C_{12}H_{16}{}^{35}Cl_2N_2O$ $[M]^+$: 274.0640; found: 274.0634; $C_{14}H_{13}{}^{35}Cl^{37}ClN_2O_2$: 276.0610; found: 276.0608; $C_{12}H_{16}{}^{37}Cl_2N_2O$: 278.0581; found: 278.0590.

2-Chloro-*N*,*N*-diisopropyl-6-(3′-methoxyphenylamino)isonicotinamide (8)

Compound **7** (200 mg, 0.73 mmol), *m*-anisidine (59.8 mg, 0.49 mmol), X-Phos (23 mg, 0.05 mmol), $Pd(OAc)_2$ (5.5 mg, 0.02 mmol), and *t*-BuONa (65.3 mg, 0.68 mmol) were mixed in toluene (4 mL) under argon. The mixture was heated at 100 °C for 23 h, then cooled to r.t., diluted with H_2O (20 mL), and extracted with EtOAc (3 × 35 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), and concentrated in vacuo to give a brown residue. The residue was purified by flash column chromatography using 3:1 hexanes–EtOAc as eluent. The resulting mixture of *m*-anisidine and the title compound was dissolved in 4% *i*-PrOH in hexanes and purified on a preparative liquid chromatography column [Luna 5μ Silica (2) 100A, 250 × 10.0 mm] using 3% *i*-PrOH in hexanes as eluent to afford **8** (24.6 mg, 14%) as a white solid; mp 155–157 °C; R_f = 0.21 (hexanes–EtOAc, 3:1).

IR (thin film): 3313, 1620, 1524, 1493, 1449, 1372, 1342, 1200, 1180, 1158 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.15–1.49 (m, 12 H, 4 × CH_3), 3.49 [m, 1 H, C*H*(CH_3)$_2$], 3.76 [m, 1 H, C*H*(CH_3)$_2$], 3.81 (s, 3 H, OCH_3), 6.61 (d, *J* = 0.9 Hz, 1 H, 5-H), 6.63 (d, *J* = 0.8 Hz, 1 H, 3-H), 6.67 (m, 1 H, 4′-H), 6.80 (s, 1 H, NH), 6.86 (m, 1 H, 6′-H), 6.93 (t, *J* = 2.2 Hz, 1 H, 2′-H), 7.24 (t, *J* = 8.0 Hz, 1 H, 5′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 20.7, 46.0, 50.1, 55.3, 102.4, 107.1, 109.4, 110.6, 113.4, 130.1, 140.3, 150.1, 150.3, 156.2, 160.6, 167.4.

MS (EI, 70 eV): *m*/*z* (%) = 41 (11), 43 (19), 100 (70), 218 (16), 234 (75), 261 (86), 318 (14), 361 (M^+, 100).

HRMS: *m*/*z* calcd for $C_{19}H_{24}{}^{35}ClN_3O_2$ $[M]^+$: 361.1557; found: 361.1558; $C_{19}H_{24}{}^{37}ClN_3O_2$: 363.1528; found: 363.1521.

Methyl 2,6-Dibromoisonicotinate (9)

Citrazinic acid (**6**; 13 g, 84 mmol) and freshly prepared $POBr_3$ (74.7 g, 261 mmol)[11] were heated slowly under N_2 to 120 °C (***Caution!*** vigorous release of gaseous HBr). The mixture was stirred at 120 °C for 2.5 h, then cooled to 0 °C and methanol (290 mL) was added slowly (***Caution!*** vigorous release of gaseous HBr). The mixture was warmed to r.t. and stirred for 2 h (timing started when the stirring was restarted). The mixture was neutralized with aq sat. $NaHCO_3$ (50 mL) and solid $NaHCO_3$ (3 g). The mixture was diluted with H_2O (150 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed in vacuo. The brown residue was purified via flash column chromatography using 24:1 hexanes–EtOAc as eluent to afford **9** (13.2 g, 54%) as a colorless solid; mp 89–92 °C (Lit.[10] mp 86.8–88.2 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, OCH_3), 7.99 (s, 2 H, 3-H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.3 (OCH_3), 126.6 (C-3, C-5), 141.4 (C-2, C-6), 141.5 (C-4), 162.9 (C=O).

The ^1H and ^{13}C NMR data were in agreement with those reported in the literature.[10]

2,6-Dibromo-*N*,*N*-diisopropylisonicotinamide (10)

Citrazinic acid (**6**; 3.96 g, 25.5 mmol) and freshly prepared $POBr_3$ (22.7 g, 79.2 mmol)[11] were suspended in anhyd anisole (27 mL). The mixture was heated at 120 °C under N_2 for 5 h. The mixture was cooled to 0 °C and then *i*-Pr_2NH (18.1 mL, 127.7 mmol) was added slowly. The mixture was stirred at r.t. for 1 h, then neutralized with aq sat. $NaHCO_3$ (50 mL), diluted with H_2O (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), and the solvent removed in vacuo to give a brown oil, which was purified by flash chromatography using 10:1 hexanes-EtOAc as eluent to afford **10**

(5.0 g, 54%) as cream prisms; mp 145–147 °C; R_f = 0.25 (hexanes–EtOAc, 10:1).

IR (thin film): 1625, 1517, 1462, 1371, 1355, 1341, 1157 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.51 (m, 12 H, 4 × CH_3), 3.54–3.65 [m, 2 H, 2 × C*H*(CH_3)$_2$], 7.35 (s, 2 H, 3-H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 20.6, 46.4, 51.2, 123.4, 141.2, 150.2, 164.9.

MS (EI, 70 eV): *m*/*z* (%) = 43 (73), 76 (22), 129 (10), 234 (21), 262 [M^+ – N(*i*-Pr_2)$_2$, 100], 305 (72), 319 (77), 347 (53), 362 (M^+, 45).

HRMS: *m*/*z* calcd for $C_{12}H_{16}{}^{79}Br_2N_2O_2$ $[M]^+$: 361.9629; found: 361.9635; $C_{12}H_{16}{}^{79}Br^{81}BrN_2O_2$: 363.9609; found: 363.9611; $C_{12}H_{16}{}^{81}Br_2N_2O_2$: 365.9588; found: 365.9595.

2-Bromo-*N*,*N*-diisopropyl-6-(3′-methoxyphenylamino)isonicotinamide (11)

$Pd(OAc)_2$ (154 mg, 0.69 mmol) and (±)-BINAP (428 mg, 0.69 mmol) were placed in a flask and the flask was flushed with N_2. Toluene (120 mL) was added and the mixture was stirred under N_2 for 10 min. *m*-Anisidine (846 mg, 6.87 mmol), **10** (3 g, 8.24 mmol), and K_2CO_3 (18.9 g, 137 mmol) were combined in a N_2-flushed flask. The $Pd(OAc)_2$/(±)-BINAP solution was added and the flask was washed with toluene (2 × 105 mL). The mixture was stirred at 90 °C in an oil bath for 45 h. The mixture was cooled to r.t., the solid was removed by filtration and washed with CH_2Cl_2 (300 mL). The solvent was removed in vacuo to yield a brown-red residue, which was purified by flash column chromatography using 3:1 hexanes–EtOAc as eluent to afford **11** (2.0 g, 71%) as a pale orange solid; mp 93–96 °C; R_f = 0.20 (hexanes–EtOAc, 3:1).

IR (thin film): 3321, 3175, 2974, 2836, 2248, 2080, 1629, 1372, 1342, 1284, 1158 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.50 (m, 12 H, 4 × CH_3), 3.49 [m, 1 H, C*H*(CH_3)$_2$], 3.79 [m, 1 H, C*H*(CH_3)$_2$], 6.62 (m, 1 H, 4′-H), 6.63 (d, *J* = 0.9 Hz, 1 H, 5-H), 6.75 (d, *J* = 0.9 Hz, 1 H, 3-H), 6.85 (m, 1 H, 6′-H), 7.03 (t, *J* = 2.2 Hz, 1 H, 2′-H), 7.20 (t, *J* = 8.1 Hz, 1 H, 5′-H), 7.24 (s, 1 H, NH)).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 20.6, 46.0, 51.0, 55.2, 103.2, 106.4, 109.1, 112.8, 133.9, 129.9, 140.3, 140.5, 149.5, 156.1, 160.3, 167.3.

MS (EI, 70 eV): *m*/*z* (%) = 41 (21), 43 (38), 77 (22), 100 (100), 172 (34), 198 (44), 198 (44), 305 (72), 362 (11), 405 (M^+, 79).

HRMS: *m*/*z* calcd for $C_{19}H_{24}{}^{79}BrN_3O_2$ $[M]^+$: 405.1052; found: 405.1047; $C_{19}H_{24}{}^{81}BrN_3O_2$: 407.1031; found: 407.1033.

Methyl 2-Bromo-6-(3′-methoxyphenylamino)isonicotinate (13)

$Pd(OAc)_2$ (317 mg, 1.41 mmol), and (±)-BINAP (878 mg, 1.41 mmol) were placed in a flask and the flask was flushed with N_2. Toluene (250 mL) was added and the mixture was stirred under N_2 for 10 min. *m*-Anisidine (1.74 g, 14.13 mmol), methyl 2,6-dibromoisonicotinate (**9**; 5 g, 16.95 mmol), and K_2CO_3 (39.06 g, 282.6 mmol) were combined in a N_2-flushed flask. The $Pd(OAc)_2$/(±)-BINAP solution was added and the flask washed with toluene (2 × 100 mL). Toluene (100 mL) was added to the reaction vessel and the mixture was heated at 90 °C in an oil bath for 46 h, until no *m*-anisidine remained as detected by TLC. The mixture was cooled to r.t. and the solid removed by filtration washed with CH_2Cl_2 (300 mL). The solvent was removed in vacuo yielding a brown residue that was purified by flash column chromatography using 3:1 hexanes–EtOAc as eluent to afford **13** (3.4 g, 58%) as fine yellow prisms; mp 146–149 °C; R_f = 0.27 (hexanes–EtOAc, 3:1).

IR (thin film): 3378, 1720, 1624, 1611, 1596, 1568, 1522, 1453, 1380, 1318, 1154 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.65 (m, 1 H, 4′-H), 6.78 (s, 1 H, NH), 6.83 (m, 1H, 6′-H), 6.95 (t, *J* = 2.1 Hz, 1 H, 2′-H), 7.23 (t, *J* = 8.1 Hz, 1 H, 5′-H), 7.30 (d, *J* = 0.8 Hz, 1 H, 5-H), 7.37 (d, *J* = 0.6 Hz, 1 H, 3-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8, 55.3, 106.5, 106.8, 109.7, 113.2, 117.3, 130.2, 140.1, 140.7, 141.2, 156.4, 160.6, 164.6.

MS (EI, 70 eV): *m*/*z* (%) = 64 (19), 77 (25), 92 (21), 107 (12), 197 (27), 214 (12), 229 (20), 257 (19), 336 (M^+, 100).

HRMS: *m*/*z* calcd for $C_{14}H_{13}{}^{79}BrN_2O_3$ $[M]^+$: 336.0110; found: 336.0109; $C_{14}H_{13}{}^{81}BrN_2O_3$: 338.0089; found: 338.0087.

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