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Delineating ligand effects in intramolecular aryl amidation reactions: formation of a novel spiro-heterocycle by a tandem cyclisation process

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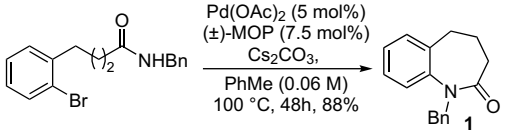
ABSTRACT

Ligand effects for intramolecular Pd-catalysed aryl amidation reaction were examined for the synthesis of seven-membered benzolactam rings. In an attempt to produce an eight-membered ring, tandem C–N/C–O bond forming reactions occurred to give a novel spiro-benzofuran-lactam structure.

1. Introduction

Palladium-catalysed C–N bond forming reactions between *N*-nucleophiles and aryl halides attracted a tremendous amount of attention in the last decade, and are becoming increasingly common in industrial processes.[1]

Compared to amination reactions, arylation substitution reactions with amides, carbamates and ureas are less common as they are generally more challenging. The use of intramolecular Pd-catalysed aryl amidation reaction for the formation of benzolactams was first demonstrated by Buchwald et al., who showed that while 'generic' monodentate phosphine ligands such as P(*o*-tolyl)$_3$ and P(2-furyl)$_3$ are effective for the formation of five- and six-membered heterocycles, they failed to produce larger rings.[2] The synthesis of seven-membered 1-benzazepinone (**1**) was eventually accomplished by using a sterically bulky monophosphine ligand MOP (Scheme 1).[3] Compared to the formation of smaller rings, high dilution and relatively long reaction times were required for the reaction to proceed.

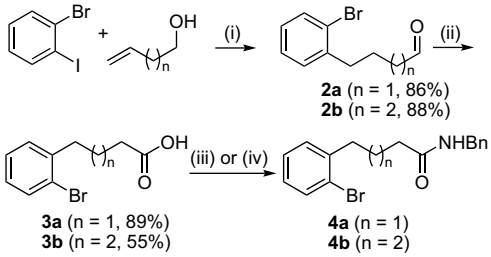


Scheme 1. Original synthesis of 1-benzazepinone **1** by a Pd-catalysed aryl amidation reaction.

As part of our ongoing effort to explore the synthetic utility of metal-catalysed reactions for the synthesis of medium-sized heterocyclic rings,[4] we embarked upon a study to examine the precise role of the phosphine ligand in these challenging C–N bond formations.

2. Result and discussion

Acyclic precursors were constructed using a concise three-step procedure from commercially available reagents (Scheme 2). Tandem Heck-isomerisation coupling between 2-bromoiodobenzene and buten-3-ol or penten-4-ol delivered the corresponding ω-(2-bromophenyl)-aldehydes **2a** and **2b**, respectively, in high yields.[5] These were subjected to Pinnick's oxidation to give carboxylic acids **3a** and **3b**, which were then coupled with benzylamine, either by using DCC/DMAP (**4a**, 85%; **4b**, 40%) or by the direct pyrolysis using microwave irradiation.[6] The latter method was not only cleaner and faster, it also provided analytically pure samples in excellent yields after a simple acid-wash (**4a**, 96%; **4b**, 92%).



Scheme 2. Preparation of acyclic precursors. (i) Pd(OAc)$_2$ (2 mol %), *n*-Bu$_4$NCl, NaHCO$_3$, DMF, 65 °C, 17 h. (ii) NaH$_2$PO$_4$, NaClO$_2$, *t*-BuOH, 2-methyl-2-butene, rt. (iii) BnNH$_2$, DCC, DMAP, CH$_2$Cl$_2$, 17 h. (iv) BnNH$_2$, μwave, 30 min.

Despite a fairly recent ligand modification study,[7] the earlier result reported for the cyclisation of **4a** to **1** (88% yield)[3] remained

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unsurpassed. Given the prohibitive cost of the MOP ligand,[8] we decided to revisit the cyclisation of the amide **4a** using more accessible ligands. The study was performed under previously described conditions, and included diphosphine ligands with large bite angles and sterically bulky monophosphines, both of which are known to be particularly beneficial for C–N bond forming reactions (Fig. 1, Table 1).

As expected, the reaction outcome was highly dependent upon the structure of the ligand employed. DPPF and Xantphos, previously shown to be effective for amination and amidation reactions,[9] furnished only very low yield of the expected product, even after prolonged reaction times (entries 6–8). In contrast, BINAP, with a smaller bite angle, delivered an impressive 89% yield, although the reaction required 10 days (entry 5). This suggests that the catalyst has a slow turnover, but is particularly stable under these conditions. An attempt to facilitate the process by microwave irradiation (100 °C, 30 min)[10] resulted only in catalyst decomposition (Pd black) and recovery of the starting material.

Noting that MOP and BINAP delivered essentially the same TON but with quite different rates (entries 1 and 5), it is reasonable to surmise that the substitution of the PPh_2 donor with OMe promotes the rate-determining step, i.e., weak coordination/hemilability of a second donor group at the 2′-position is critical. With this in mind, other structurally-related biarylphosphines, with or without a second coordinating group at the 2′-position, were subsequently tested: JohnPhos, DavePhos and X-Phos. The results obtained with these ligands showed that while the presence of a 2′-substituent is beneficial (entries 9 and 10), the *absence* of a donor group at the 2′-substituent imparts even greater catalytic activity; demonstrated by the result obtained with X-Phos, which delivered the same yield as MOP in half the time (entry 11).

The result (X-Phos>MOP>BINAP) agrees with a report that the presence of an accessible C–H at the 2′-position in biarylphosphine ligands can lead to the formation of palladacycles; this can affect the catalytic activity in a profound way.[11] Thus, we reasoned that other sterically bulky monophosphine ligands that do not contain such labile C–H bonds should also form active catalysts for this reaction. Gratifyingly, the speculation appears to be correct, when tri-*tert*-butylphosphine was found to deliver a comparable result to X-Phos (entries 11 and 12).

The above study led to the identification of two ligands (X-Phos, t-Bu_3P) that are more active than MOP in the intramolecular amidation reaction for the formation of seven-membered benzolactam ring. The result clearly suggests that steric hindrance and the (in)ability to form a palladacycle during the reaction are critical for good catalytic activity. In contrast, the electronic effect must be largely negligible, given the substantial difference between X-Phos and P(t-Bu)$_3$.

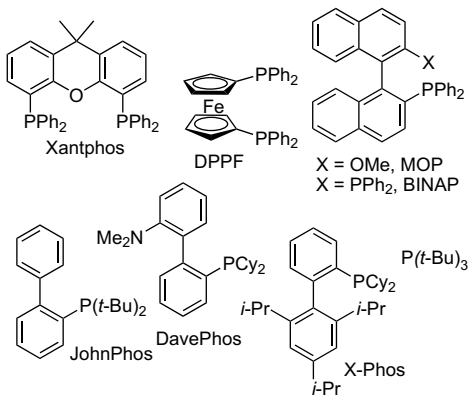


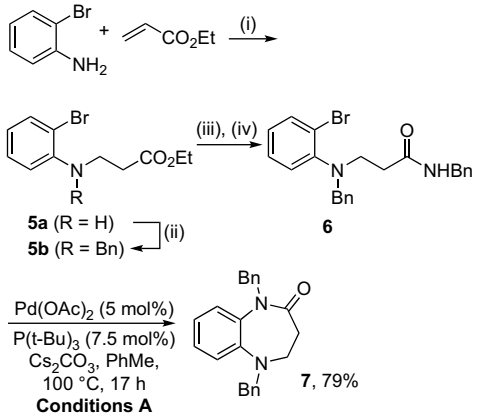
Figure 1. Ligands screened for the intramolecular aryl amidation reaction of **4a**.

Table 1
Cyclisation of acyclic precursor **4a** to **1**[a]

Entry	Ligand	Bite angle[b]/°	Time/h	Yield[c]/%
1	(−)-MOP		48	88[d]
2	(±)-BINAP	92.7	48	26
3	(±)-BINAP		90	56
4	(±)-BINAP		144	67
5	(±)-BINAP		240	89
6	dppf	99.1	48	17
7	dppf		90	18
8	Xantphos	110.0	48	13
9	JohnPhos		48	11
10	DavePhos		48	40
11	X-Phos		24	88
12	P(t-Bu)$_3$		24	84

[a] General reaction conditions: 0.06 M of **4a** in toluene, 5 mol % $Pd(OAc)_2$, 7.5 mol % ligand, Cs_2CO_3 (1.4 equiv), 100 °C.
[b] Obtained from X-ray crystal structures of [(diphosphine)$PdCl_2$] complexes obtained from the Cambridge Crystallographic Database.
[c] Isolated yield after column chromatography.
[d] Ref. 3.

The catalytic protocol was subsequently applied to the synthesis of 1,5-benzodiazepin-2-one, an important core structure known for interesting CNS biological activities[12] (Scheme 3): β-amino ester **5a** was prepared by an aza-Michael reaction between 2-bromoaniline and ethyl acrylate. Following N-benzylation, the ester was transformed into the benzylamide **6** via standard procedures. Under previously described catalytic conditions using P(t-Bu)$_3$ as the ligand (condition A), the Pd-mediated cyclisation afforded the expected product **7** in 76% yield after column chromatography. The result is superior to a reported synthesis of a similar structure by copper-catalysed intramolecular N-arylation reaction (which required 60 h to achieve a moderate yield of 63%).[13] As the two C–N bond forming events occur orthogonally, this should allow for better regiocontrol in the synthesis of unsymmetrical 1,5-diazepinones (with substituted aromatic rings), compared to other methods of synthesis, e.g., ring expansion,[14] or cyclisation with 1,2-diaminobenzene.[15]



Scheme 3. Synthesis of a 1,5-diazepinone by Pd-catalysed intramolecular aryl amidation. (i) H^+, EtOH, reflux, 61%. (ii) $PhCH_2Br$, K_2CO_3, CH_3CN, reflux, 72%. (iii) NaOH, MeOH, 76%. (iv) $BnNH_2$, HOBt, DCC, 73%.

Given there are no known examples of eight-membered ring formation by aryl amidation,[16] it is perhaps unsurprising that the acyclic substrate **4b** defied all our efforts to produce the expected eight-membered heterocycle. Attributing the failure to unfavourable enthalpic and entropic issues associated with the conformational flexibility of the acyclic chain, we investigated the possibility of introducing steric constraints into the precursor. The strategy has previously proven to be successful for the synthesis of

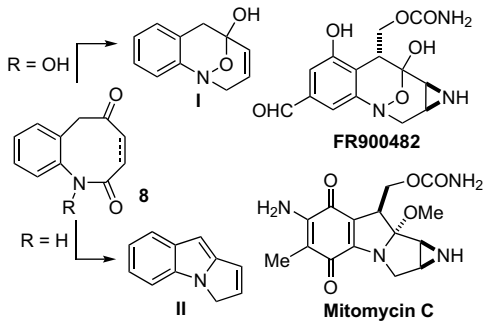
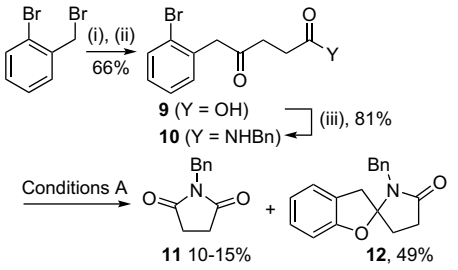


Figure 2. Core structures afforded by 1-benzazocin-5-one **8**.

a novel eight-membered benzazocinone by an intramolecular Heck arylation reaction.[4a]

For this part of the work, 1-benzazocin-5-one **8** (Fig. 2) was chosen as our initial target, as it contains a conformationally restrictive sp^2-hybridised carbon within the cyclising chain. The ketone moiety is also synthetically useful, as it can provide access to important core structures such as bicyclic hemiketal (**I**) and pyrrolindole (**II**), constituents of mitomycin C and FR900482—a family of potent cytotoxic antibodies used in the treatment of solid tumours.[17]

Preparation of the precursor was simply achieved by the reaction of succinic anhydride with the Grignard reagent derived from 2-bromobenzyl bromide. The resultant carboxylic acid **9** was then converted to its corresponding benzylamide in good yield (Scheme 4).



Scheme 4. Preparation and cyclisation of acyclic precursor **10**. (i) Mg, Et_2O, reflux. (ii) succinic anhydride, THF, −78 °C. (iii) $BnNH_2$, DCC, HOBt, CH_2Cl_2, 23 h.

Precursor **10** was promptly subjected to the catalytic conditions described previously (condition A), whereupon the starting material was steadily consumed over the course of the reaction, to yield two distinct products. Following chromatographic separation, the mixture was found to consist of a mixture of *N*-benzylsuccinimide **11** (by comparison with a genuine sample) and an unknown compound **12**, which gave rise to the expected mass ion (m/z=279), but further spectroscopic analyses (infrared and ^{13}C NMR spectra) revealed the absence of a ketone moiety. Identity of compound **12** was eventually established by single crystal X-ray crystallography (Fig. 3), showing the formation of a novel benzo-fused spirocyclic structure, where a benzofuran and a γ-lactam are connected via a stereogenic carbon, at the position adjacent to the heteroatom in each ring. Extensive searches (using CCDC, CAS and Beilstein databases) showed the absence of related structures in the current literature, thus establishing it as a novel structure motif.

The formation of the succinimide **11** prompted us to examine the stability of the acyclic precursor. Under refluxing conditions, a solution of **10** in toluene-d_8 cyclised to form the pyrrolidinone **14** (which can be isolated), presumably the dehydrated form of the keto-amide **13** (Scheme 5). In the presence of Cs_2CO_3, the process was intercepted by an alternate elimination process to generate **11**.

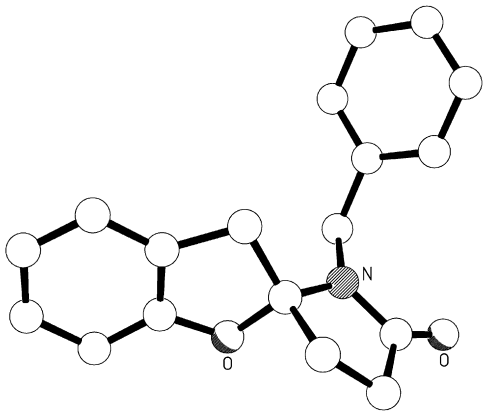
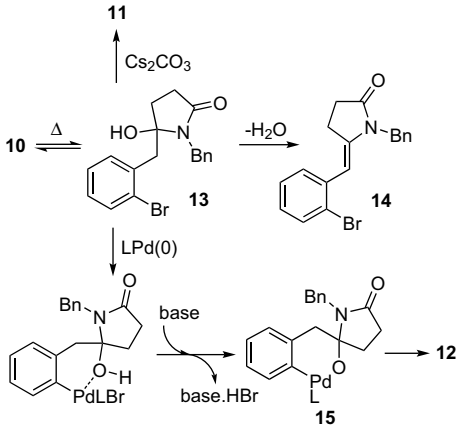


Figure 3. Molecular structure of **12**. Aromatic protons are omitted for the sake of clarity.



Scheme 5. Formation of compounds **11** and **12**.

Thus, the formation of **12** is attributed to a domino C–N/C–O bond forming process, whereby the role of the Pd catalyst is to effect a C–O aryl etheration, initiated by the oxidative addition of keto-amide **13** to a highly active L–Pd(0) precursor. This effectively brings the hydroxyl group within close proximity of the metal centre, and the resultant interaction enables a lowering of pK_a of the O–H moiety, thus facilitating its deprotonation by the weak base to furnish the palladacycle **15**, which generates the spirolactam **12** by reductive elimination.

Within this context, P(*t*-Bu)$_3$ appeared to impart unique utility, as other phosphines (BINAP, X-Phos, JohnPhos and MOP) were far less effective in this reaction, furnishing <15% of **12**.

3. Conclusion

Sterically bulky monophosphines X-Phos and P(*t*-Bu)$_3$ have been found to be particularly effective for the formation of 7-benzolactams using Pd-catalysed aryl amidation reactions. During this work, an unexpected tandem C–N/C–O bond forming process was uncovered, leading to the formation of a novel spiro-benzofuran-γ-lactam ring—a hitherto unknown structural motif.

4. Experimental section

4.1. General

Unless otherwise stated, all starting materials, reagents and anhydrous solvents are procured commercially and used as-received without further purification. Air-sensitive reactions were

conducted in oven-dried glassware under a N_2 atmosphere. Microwave reactions were performed using a CEM Discover Synthesis Unit in 10 mL glass vessels.

^1H and ^{13}C NMR spectra were recorded using Bruker 400 spectrometers. Residual protic solvents were used as an internal standard and ^{13}C resonances were referenced to the deuterated carbon. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are reported in hertz (Hz). Infrared spectra were recorded on a Mattson Instrument Satellite FTIR spectrometer. All liquid samples were recorded as thin films between NaCl plates, whereas solid samples were formulated as KBr discs. Melting points were determined using an Electrothermal Gallenkamp apparatus and are uncorrected. Mass spectra were recorded by the Mass Spectrometry Service at Imperial College London. Elemental analyses were carried out by the Elemental Analysis Service at London Metropolitan University.

X-ray quality crystals of compound **12** were accrued by mixed-solvent recrystallisation, allowing crystal growth at room temperature. *Crystal data for* **12**: $C_{18}H_{17}NO_2$, M=279.33, monoclinic, $P2_1/c$ (no. 14), a=13.378(3), b=11.1011(7), c=9.8519(17) Å, β=106.568(18)°, V=1402.3(4) Å^3, Z=4, D_c=1.323 g cm^{-3}, μ(Mo Kα)=0.086 mm^{-1}, T=173 K, colourless needles, Oxford Diffraction Xcalibur 3 diffractometer; 4487 independent measured reflections, F^2 refinement, R_1=0.039, wR_2=0.111, 3567 independent observed absorption-corrected reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta_{max}$=64°], 190 parameters. This data has been deposited at the Cambridge Crystallographic Database (reference code: CCDC 669098).

4.1.1. Preparation of 1-benzazepinone precursors **4a** and **4b** (Scheme 2)

Compounds **2a** and **2b** were prepared according to a reported procedure.[5]

4.1.1.1. Pinnick oxidation of aldehydes. Sodium chlorite (1.70 g, 15 mmol, 3.4 equiv) was added slowly, in small portions, to a stirred mixture of **2a** (1.0 g, 4.4 mmol, 1.0 equiv), NaH_2PO_4 (0.60 g, 4.4 mmol, 1.0 equiv), 2-methyl-2-butene (3 mL, 28 mmol, 4.4 equiv), *tert*-butanol (22 mL) and H_2O (7 mL). Stirring was continued for 2 h at room temperature, before the mixture was acidified by the addition of 2 M aq HCl, and diluted with CH_2Cl_2 (250 mL). The organic phase was separated, washed with brine (3×50 mL) and dried ($MgSO_4$). Finally, the solvent was evaporated, and the residue was recrystallised from hexane.

*4.1.1.2. 4-(2-Bromophenyl)butanoic acid (**3a**).* Yield: 89% as a white crystalline solid; mp 91–92 °C (lit.[5] 88–89 °C); ν_{max} (KBr)/cm^{-1} 3033 (br s, OH), 1712 (CO); δ_H (360 MHz, $CDCl_3$) 1.96–2.07 (2H, m, $ArCH_2CH_2$), 2.45 (2H, t, J 7.4, CH_2CO_2H), 2.83 (2H, t, J 7.4, $ArCH_2$), 7.06–7.11 (1H, m, ArH), 7.23–7.28 (2H, m, ArH), 7.55 (1H, d, J 8.0, ArH), 10.97 (br s, CO_2H); δ_C (100.6 MHz, $CDCl_3$) 24.7 (1C, $ArCH_2CH_2$), 33.3 (1C, CH_2CO_2H), 35.2 (1C, $ArCH_2$), 124.4 (1C, ArC), 127.5 (1C, ArC), 127.8 (1C, ArC), 130.5 (1C, ArC), 132.9 (1C, ArC), 140.5 (1C, ArC), 179.8 (CO_2H); m/z (EI) 244/242 (M^+, 24/25%), 184/182 (86/90), 163 (100).

*4.1.1.3. 5-(2-Bromophenyl)pentanoic acid (**3b**).* Yield: 55% as a white solid; mp 47–48 °C (lit.[18] 40–42 °C, from CCl_4); ν_{max} (KBr)/cm^{-1} 3037 (br s, OH), 1705 (CO); δ_H (270 MHz, $CDCl_3$) 1.64–1.75 (4H, m, $ArCH_2CH_2$, $CH_2CH_2CO_2H$), 2.41 (2H, t, J 7.2, CH_2CO_2H), 2.75 (2H, t, J 7.2, $ArCH_2$), 7.01–7.07 (1H, m, ArH), 7.18–7.25 (2H, m, ArH), 7.51 (1H, d, J 7.8, ArH), 10.30 (br s, CO_2H); δ_C (100.6 MHz, $CDCl_3$) 24.3 (1C, $ArCH_2CH_2$), 29.2 (1C, $CH_2CH_2CO_2H$), 33.8 (1C, $ArCH_2$), 35.7 (1C, CH_2CO_2H), 124.4 (1C, ArC), 127.4 (1C, ArC), 127.6 (1C, ArC), 130.3 (1C, ArC), 132.8 (1C, ArC), 141.2 (1C, ArC), 179.7 (1C, CO_2H); m/z (EI) 258/256 (M^+, 21/22%), 171/169 (97/96), 159 (100).

4.1.2. Coupling of carboxylic acids **3a** and **3b** with benzylamine

Method A: Benzylamine (1.7 mL, 15.8 mmol, 1.1 equiv), DCC (3.27 g, 15.8 mmol, 1.1 equiv) and DMAP (0.16 g, 1.30 mmol, 9 mol %) were added sequentially to a stirred solution of the carboxylic acid (14.4 mmol, 1.0 equiv) in dry CH_2Cl_2 (90 mL) at 0 °C. Stirring was continued at 0 °C for 1 h, before the reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The white precipitate was removed by filtration and the filtrate was washed with 1 M aq HCl (30 mL), brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The resulting pale yellow solid was purified using column chromatography.

Method B: A microwave vessel was charged with a magnetic stir bar, carboxylic acid (0.82 mmol, 1.0 equiv) and benzylamine (0.13 mL, 1.23 mmol, 1.5 equiv). The contents of the reaction tube were homogenised using a whirlimixer, before it was sealed and irradiated at 150 °C for 30 min with stirring. After cooling to room temperature, the reaction mixture was dissolved in CH_2Cl_2 (10 mL) and washed with 2 M aq HCl (5 mL), 5% aq $NaHCO_3$ (5 mL) and brine (5 mL). The organic layer was dried ($MgSO_4$) and evaporated to yield analytically pure amide.

*4.1.2.1. N-Benzyl-4-(2-bromo-phenyl)-butyramide (**4a**).* Yield: 85% (method A) or 96% (method B) as a white solid; R_f=0.52, CH_2Cl_2/MeOH (20/1); mp 110–111 °C (lit.[2] 111–112 °C); ν_{max} (KBr)/cm^{-1} 3289 (NH), 1638 (CO); δ_H (360 MHz, $CDCl_3$) 1.91–1.98 (2H, m, $ArCH_2CH_2$), 2.21 (2H, t, J 7.6, CH_2CO), 2.73 (2H, t, J 7.8, $ArCH_2CH_2$), 4.38 (2H, close AB, $PhCH_2$), 5.63 (1H, br s, NH), 6.96–7.01 (1H, m, ArH), 7.14–7.29 (7H, m, ArH), 7.45 (1H, d, J 8.0, ArH); δ_C (100.6 MHz, $CDCl_3$) 26.1 (1C, $ArCH_2CH_2$), 35.8 (1C, $ArCH_2CH_2$), 36.3 (1C, CH_2CO), 44.1 ($PhCH_2$), 124.8 (1C, C_2), 127.9 (1C, ArC), 128.0 (1C, ArC), 128.2 (1C, C_4), 128.3 (2C, ArC), 129.2 (2C, ArC), 130.9 (1C, C_6), 133.2 (1C, C_3), 138.7 (1C, C_{ipso}), 141.2 (1C, C_1), 172.2 (1C, CO); m/z (EI) 333/331 (M^+, 37/38%), 252 (47), 149 (100).

*4.1.2.2. 5-(2-Bromophenyl)-pentanoic acid benzylamine (**4b**).* Yield: 40% (method A) or 92% (method B) as a white solid. Found: C, 62.54; H, 5.76; N, 3.94%. Calcd for $C_{18}H_{20}BrNO$: C, 62.44; H, 5.82; N, 4.05%. R_f=0.46, CH_2Cl_2/MeOH (20/1); mp 72–73 °C; ν_{max} (KBr)/cm^{-1} 3289 (NH), 1634 (CO); δ_H (270 MHz, $CDCl_3$) 1.59–1.81 (4H, m, $ArCH_2CH_2$, CH_2CH_2CO), 2.26 (2H, t, J 7.2, CH_2CO), 2.74 (2H, t, J 7.4, $ArCH_2CH_2$), 4.43 (2H, close AB, $PhCH_2$), 5.72 (1H, br s, NH), 7.00–7.07 (1H, m, ArH), 7.17–7.36 (7H, m, ArH), 7.50 (1H, d, J 8.4, ArH); δ_C (100.6 MHz, $CDCl_3$) 25.4 (1C, $ArCH_2CH_2$), 29.5 (CH_2CH_2CO), 35.9 (1C, $ArCH_2CH_2$), 36.5 (1C, CH_2CO), 43.6 ($PhCH_2$), 124.4 (1C, C_2), 127.4 (1C, ArC), 127.5 (1C, ArC), 127.6 (1C, ArC), 127.8 (2C, ArC), 128.7 (2C, ArC), 130.4 (1C, C_6), 132.8 (1C, C_3), 138.3 (1C, C_{ipso}), 141.4 (1C, C_1), 172.6 (1C, CO); m/z (EI) 347/345 (M^+, 14/15%), 266 (47), 149 (59), 91 (100).

4.1.3. Typical procedure for the Pd-catalysed aryl amidation reaction (Table 1, condition A)

A dry Young's tube was charged with $Pd(OAc)_2$ (4.9 mg, 0.022 mmol, 5.0 mol %), **4a** (143 mg, 0.43 mmol, 1.0 equiv), Cs_2CO_3 (196 mg, 0.60 mmol, 1.4 equiv) and the appropriate ligand (0.032 mmol, 7.5 mol %). The reaction vessel was evacuated and filled with N_2, before the addition of dry toluene (6.5 mL, 0.06 M wrt amide) via a syringe. Finally, the reaction vessel was sealed with a Teflon tap and heated at 100 °C in a thermostated oil bath for the appropriate length of time, after which the reaction mixture was filtered through Celite and purified by column chromatography.

*4.1.3.1. 1-Benzyl-1,3,4,5-tetrahydro-1-benzazepin-2-one (**1**)[2].* Pale yellow oil; R_f=0.30, hexane/EtOAc (2/1); ν_{max} (thin film)/cm^{-1} 1660 (CO); δ_H (400 MHz, $CDCl_3$) 2.14–2.16 (2H, br m, $ArCH_2CH_2$), 2.35 (2H, t, J 7.0, CH_2CO), 2.51 (2H, t, J 6.8, $ArCH_2CH_2$), 5.02 (2H, br s, $PhCH_2$), 7.12–7.27 (9H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 29.0 (1C,

$ArCH_2CH_2$), 29.9 (1C, $ArCH_2CH_2$), 33.2 (1C, CH_2CO), 51.2 (1C, $PhCH_2$), 122.7 (1C, ArC), 126.3 (1C, ArC), 127.2 (1C, ArC), 127.4 (1C, ArC), 128.0 (2C, ArC), 128.4 (2C, ArC), 129.3 (1C, ArC), 135.8 (1C, ArC), 137.9 (1C, ArC), 142.5 (1C, ArC), 173.2 (1C, CO); *m*/*z* (EI) 251 (M^+, 87%), 196 (43), 132 (63), 91 (100).

*4.1.3.2. Ethyl 3-(2-bromophenylamino)propionate (**5a**).* A mixture of 2-bromoaniline (2.2 mL, 20 mmol, 1 equiv), ethyl acrylate (2.4 mL, 22 mmol, 1.1 equiv) and concd HCl (2 mL) in ethanol (15 mL) was heated under reflux for 48 h. The solvent was evaporated and the residue was made basic by the addition of 28% aq NH_3. This was then extracted with CH_2Cl_2, and the combined organic fractions were washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography, to give product **5a** as a yellow oil. Yield: 3.3 g, 61%. Found: C, 48.56; H, 5.14; N, 5.04%. Calcd for $C_{11}H_{14}BrNO_2$: C, 48.55; H, 5.19; N, 5.15%. R_f=0.36, petroleum ether 40–60/EtOAc (3/1); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 2.65 (2H, t, *J* 6.5, CH_2CO_2Et), 3.50 (2H, q, *J* 6.5, $CH_2CH_2CO_2Et$), 4.17 (2H, q, *J* 7.2, OCH_2CH_3), 4.70 (1H, br s, NH), 6.58 (1H, td, *J* 2.0, 7.1, ArH), 6.65 (1H, dd, *J* 2.0, 8.0, ArH), 7.18 (1H, t, *J* 7.1, ArH), 7.41 (1H, dd, *J* 2.0, 8.0, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.3 (1C, OCH_2CH_3), 33.9 (1C, CH_2CO_2Et), 39.4 (1C, $CH_2CH_2CO_2Et$), 60.8 (1C, OCH_2CH_3), 110.1 (1C, ArC), 111.2 (1C, ArC), 118.1 (1C, ArC), 128.5 (1C, ArC), 132.6 (1C, ArC), 144.5 (1C, ArC), 172.1 (1C, CO), *m*/*z* (CI) 274/272 (MH^+, 100%).

*4.1.3.3. Ethyl 3-(N-benzyl-N-(2-bromophenyl)amino)propionate (**5b**).* A mixture of **5a** (1.0 g, 3.67 mmol, 1 equiv), benzyl bromide (5 equiv) and K_2CO_3 (1.5 g, 11.0 mmol, 3 equiv) was refluxed in CH_3CN (10 mL) for 48 h. The solvent was evaporated, and the residue extracted with ether. The organic layer was washed with H_2O, dried ($MgSO_4$), concentrated, and purified by column chromatography to give **5b** as a colourless oil. Yield: 960 mg, 72%. Found: C, 59.65; H, 5.54; N, 3.89%. Calcd for $C_{18}H_{20}BrNO_2$: C, 59.68; H, 5.56; N, 3.87%. R_f=0.48, cyclohexane/EtOAc (4/1); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.4, OCH_2CH_3), 2.45 (2H, t, *J* 6.2, CH_2CO_2Et), 3.38 (2H, t, *J* 6.2, $CH_2CH_2CO_2Et$), 4.06 (2H, q, *J* 7.4, OCH_2CH_3), 4.22 (2H, s, CH_2Ph), 6.96 (1H, td, *J* 2.4, 6.3, ArH), 7.09 (1H, dd, *J* 2.0, 8.0, ArH), 7.22–7.38 (6H, m, ArH), 7.61 (1H, dd, *J* 1.5, 8.0, ArH); δ_C (100.6 MHz, $CDCl_3$) 14.1 (1C, OCH_2CH_3), 32.4 (1C, CH_2CO_2Et), 47.4 (1C, $CH_2CH_2CO_2Et$), 58.4 (1C, CH_2Ph), 60.4 (1C, OCH_2CH_3), 122.3 (1C, ArC), 124.6 (1C, ArC), 125.3 (1C, ArC), 127.2 (2C, ArC), 127.8 (2C, ArC), 128.2 (1C, ArC), 128.6 (1C, ArC), 133.9 (1C, ArC), 137.9 (1C, ArC), 148.4 (1C, ArC), 172.3 (1C, CO); *m*/*z* (CI) 364/362 (MH^+, 100%).

*4.1.3.4. 3-(N-Benzyl-N-(2-bromophenyl)amino)-N-benzyl-propanamide (**6**).* The ester **5b** was hydrolysed by refluxing in methanol (20 mL) with NaOH (5 equiv) for 12 h. After cooling to ambient temperature, methanol was evaporated and the residue was acidified by the addition of 1 M aq HCl, before it was extracted with Et_2O, washed (H_2O), dried ($MgSO_4$) and evaporated to yield the carboxylic acid as a colourless oil (76%). It was used directly in the next step without further purification. R_f=0.45, EtOAc/petroleum ether (1/1); δ_H (400 MHz, $CDCl_3$) 2.49 (2H, t, *J* 6.4, CH_2CO_2H), 3.35 (2H, t, *J* 6.5, $CH_2CH_2CO_2H$), 4.22 (2H, s, CH_2Ph), 7.00–7.08 (2H, m, ArH), 7.25–7.34 (6H, m, ArH), 7.65 (1H, dd, *J* 1.5, 8.0, ArH); δ_C (100.6 MHz, $CDCl_3$) 31.8 (1C, CH_2CO_2H), 46.8 (1C, $CH_2CH_2CO_2H$), 59.0 (1C, CH_2Ph), 122.2 (1C, ArC), 124.5 (1C, ArC), 126.1 (1C, ArC), 127.6 (1C, ArC), 128.0 (2C, ArC), 128.3 (2C, ArC), 129.0 (1C, ArC), 134.2 (1C, ArC), 136.8 (1C, ArC), 147.2 (1C, ArC), 176.8 (1C, CO); *m*/*z* (CI) 336/334 (MH^+, 100%).

The carboxylic acid (2.05 g, 6.12 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C, whereupon benzylamine (0.67 mL, 6.12 mmol, 1 equiv), 1-hydroxybenzotriazole monohydrate (0.83 g, 6.12 mmol, 1 equiv), and DCC (1.26 g, 6.12 mmol, 1 equiv) were added sequentially. After 1 h, the reaction mixture was warmed up to room temperature and stirred overnight. The resultant white precipitate was removed by filtration, and the filtrate was washed with 1 M aq HCl (15 mL), brine (15 mL), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography, to furnish **6** as a white solid. Yield: 1.66 g, 64%. Found: C, 65.21; H, 5.43; N, 6.60%. Calcd for $C_{23}H_{23}BrN_2O$: C, 65.25; H, 5.48; N, 6.62%. ν_{max} (thin film)/cm^{-1} 3374 (NH); δ_H (400 MHz, $CDCl_3$) 2.55 (2H, t, *J* 6.5, CH_2CO), 3.58 (2H, t, *J* 6.5, CH_2CH_2CO), 4.74 (1H, br s, NH), 5.97 (1H, br s, NH), 6.59–6.61 (1H, t, *J* 7.6, ArH), 6.68–6.71 (1H, d, *J* 8.0, ArH), 7.18–7.22 (1H, m, ArH), 7.27–7.37 (7H, m, ArH), 7.45 (1H, d, *J* 7.6, ArH); δ_C (400 MHz, $CDCl_3$) 35.8 (1C, CH_2CO), 39.983 (1C, $NHCH_2Ph$), 43.7 (1C, CH_2CH_2CO), 110.2 (1C, ArC), 111.4 (1C, ArC), 118.2 (1C, ArC), 127.6 (1C, ArC), 127.8 (1C, ArC), 128.5 (2C, ArC), 128.8 (2C, ArC), 132.6 (1C, ArC), 137.9 (1C, ArC), 144.5 (1C, ArC), 170.9 (1C, CO); *m*/*z* (CI) 335/333 (MH^+, 100%).

*4.1.3.5. 1,5-Dibenzyl-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (**7**).* This was obtained from **6** (150 mg, 0.35 mmol) by employing the catalytic procedure described before (condition A), using P(*t*-Bu)$_3$ as ligand. The heterocycle was obtained as a viscous colourless oil. Yield: 95 mg, 79%. Found: C, 80.65; H, 6.45; N, 8.15%. Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18%. R_f=0.34, cyclohexane/EtOAc (4/1); ν_{max} (KBr)/cm^{-1} 1665 (CO); δ_H (400 MHz, $CDCl_3$, 298 K) 2.49 (2H, br s, NCH_2CH_2), 3.32 (2H, br s, NCH_2), 4.14 (2H, br s, CH_2Ph), 5.08 (2H, br s, CH_2Ph), 7.02–7.33 (14H, m, ArH); δ_C (100.6 MHz, $CDCl_3$, 298 K) 34.2 (1C, NCH_2CH_2), 51.3 (1C, NCH_2), 56.3 (1C, CH_2Ph), 57.7 (1C, CH_2Ph), 120.8 (1C, ArC), 123.1 (1C, ArC), 123.3 (1C, ArC), 126.9 (1C, ArC), 127.2 (1C, ArC), 127.9 (1C, ArC), 128.3 (1C, ArC), 128.4 (1C, ArC), 137.7 (2C, ArC), 143.8 (1C, ArC), 172.4 (1C, CO); *m*/*z* (CI) 343 (MH^+, 100%).

*4.1.3.6. 5-(2-Bromophenyl)-4-oxo-pentanoic acid (**9**).* A three-necked round-bottomed flask equipped with a reflux condenser and dropping funnel was charged with dried Mg turnings (1.0 g, 41.1 mmol, 1.5 equiv), which were activated by stirring overnight under a dry N_2 atmosphere. 2-Bromobenzyl bromide (10.3 g, 41.1 mmol, 1.5 equiv) was added dropwise as a solution in anhydrous Et_2O (90 mL) over 1 h, during which a gentle reflux was established and maintained. Following the addition, the reaction mixture was heated at reflux for 3 h then allowed to cool to ambient temperature. In a separate flask, a solution of succinic anhydride (2.74 g, 27 mmol, 1.0 equiv) was dissolved in anhydrous THF (160 mL) and cooled to −78 °C, before the addition of the Grignard reagent slowly via cannula. The reaction mixture was stirred at −78 °C for 3.5 h, then quenched by the addition of H_2O (30 mL) and 2 M aq HCl (70 mL). The layers were separated, and the aqueous layer was extracted with EtOAc. Finally, the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a yellow solid, which was then subjected to column chromatography to give **9** as a white solid. Yield: 4.9 g, 66%. Found: C, 48.66; H, 4.06%. Calcd for $C_{11}H_{11}BrO_3$: C, 48.74; H, 4.09%. R_f=0.23, CH_2Cl_2/EtOAc (4/1); mp 88–89 °C; ν_{max} (KBr)/cm^{-1} 2854 (OH), 1713 (CO), 1693 (CO_2H); δ_H (270 MHz, $CDCl_3$) 2.68 (2H, t, *J* 6.0, CH_2CO_2H), 2.83 (2H, t, *J* 6.0, $CH_2CH_2CO_2H$), 3.93 (2H, s, $ArCH_2$), 7.17 (1H, t, *J* 8.0, ArH), 7.24–7.33 (2H, m, ArH), 7.59 (1H, dd, *J* 1.0, 8.0, ArH); δ_C (100.6 MHz, $CDCl_3$) 27.7 (1C, CH_2CO_2H), 36.7 (1C, $CH_2CH_2CO_2H$), 49.9 (1C, $ArCH_2$), 125.0 (1C, ArC), 127.7 (1C, ArC), 129.0 (1C, ArC), 131.8 (1C, ArC), 132.9 (1C, ArC), 134.4 (1C, ArC), 177.9 (1C, CO_2H), 205.0 (1C, CO); *m*/*z* (CI) 290/288 ($[M+NH_4]^+$, 97/100).

*4.1.3.7. 5-(2-Bromophenyl)-4-oxo-pentanoic acid benzylamide (**10**).* A solution of **9** (2.0 g, 6.92 mmol, 1.0 equiv) and 1-hydroxybenzotriazole monohydrate (1.14 g, 6.92 mmol, 1.0 equiv) in dry CH_2Cl_2 (35 mL) was cooled to 0 °C. Benzylamine (7.61 mmol, 1.1 equiv) and DCC (1.43 g, 6.92 mmol, 1.0 equiv) were added sequentially as solutions in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for a further

23 h. The white precipitate was removed by filtration and the filtrate washed with 2 M aq HCl (20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography, furnishing **10** as a white solid. Yield: 2.0 g, 81%. Found: C, 59.96; H, 4.95; N, 3.90%. Calcd for $C_{18}H_{18}NO_2Br$: C, 60.01; H, 5.04; N, 3.89%. R_f=0.39, CH_2Cl_2/EtOAc (4/1); mp 126–127 °C; ν_{max} (KBr)/cm^{-1} 3301 (NH), 1714 (CO), 1640 (NCO); δ_H (270 MHz, $CDCl_3$) 2.47 (2H, t, *J* 6.4, CH_2CONH), 2.90 (2H, t, *J* 6.4, CH_2CH$_2$CONH), 3.90 (2H, s, ArCH_2), 4.41 (2H, close AB, PhCH_2), 5.96 (1H, br s, NH), 7.11–7.35 (8H, m, ArH), 7.56 (1H, dd, *J* 1.0, 8.0, ArH); δ_C (100.6 MHz, $CDCl_3$) 29.9 (1C, *C*H$_2$CONH), 37.7 (1C, *C*H$_2$CH$_2$CONH), 43.6 (1C, PhCH$_2$), 50.0 (1C, ArCH$_2$), 124.9 (1C, ArC), 127.4 (1C, ArC), 127.6 (1C, ArC), 127.7 (2C, ArC), 128.6 (2C, ArC), 128.9 (1C, ArC), 131.8 (1C, ArC), 132.8 (1C, ArC), 134.5 (1C, ArC), 138.2 (1C, ArC), 171.6 (1C, NCO), 206.2 (1C, CO); *m*/*z* (EI) 359/361 (M^+, 50/47%), 252/254 (29/30), 190 (50), 91 (100).

*4.1.3.8. Spiro[benzofuran-2,5′-(1-benzylpyrrolidin-2-one)] (**12**).* A Young's tube was charged with **10** (200 mg, 0.56 mmol, 1.0 equiv), Cs_2CO_3 (253 mg, 0.78 mmol, 1.4 equiv) and $Pd(OAc)_2$ (6 mg, 0.026 mmol, 5 mol %). To this was added P(*t*-Bu)$_3$ (10 wt % in hexane, 0.11 mL, 10 mol %) and anhydrous toluene (9.25 mL, 0.06 M wrt substrate). The tube was sealed with a PTFE tap and stirred at room temperature for 10 min, followed by heating at 100 °C for 16 h. After this time, the reaction mixture was cooled, filtered through a short plug of Celite and concentrated in vacuo. The crude mixture was purified by column chromatography, to give **12** as a colourless oil, which solidified on standing to give a white solid. Yield: 76 mg, 49%. R_f=0.31, CH_2Cl_2/EtOAc (7/1, visualised using a vanillin dip); mp 110–110 °C; ν_{max} (KBr)/cm^{-1} 1709 (CO); δ_H (400 MHz, $CDCl_3$) 2.21–2.35 (1H, m, CH_2), 2.50–2.63 (2H, m, CH_2), 2.70–2.83 (1H, m, CH_2), 3.18 (2H, close AB, ArCH_2), 4.01 (1H, d, *J* 15.6, PhCH_2), 4.69 (1H, d, *J* 15.6, PhCH_2), 6.66 (1H, d, *J* 8.2, ArH), 6.88 (1H, t, *J* 7.7, ArH), 7.05–7.31 (7H, m, ArH); δ_C (100.6 MHz, $CDCl_3$) 28.9 (1C, CH_2), 33.9 (1C, CH_2), 38.7 (1C, CH_2), 43.1 (1C, PhCH_2), 104.1 (1C, O*C*N), 109.0 (1C, ArC), 120.9 (1C, ArC), 124.5 (1C, ArC), 127.2 (1C, C1), 127.4 (2C, ArC), 127.8 (1C, ArC), 128.3 (2C, ArC), 128.5 (1C, ArC), 137.8 (1C, ArC), 158.1 (1C, ArC), 175.5 (1C, CO); *m*/*z* (EI) 279 (M^+, 91%), 188 (87), 91 (100), 55 (67); HRMS (EI) 279.1262, $C_{18}H_{17}NO_2$ requires 279.1259.

*4.1.3.9. 1-Benzyl-5-(2-bromo-benzyl)-5-hydroxy-pyrrolidin-2-one (**13**).* A clean sample could not be isolated, but its presence in the reaction mixture can be detected by ^{1}H NMR and by LC–MS: δ_H (400 MHz, $CDCl_3$) 1.73–1.80 (1H, m, CH_2), 2.28–2.61 (3H, m, CH_2), 3.01 (1H, d, *J* 14.0, ArCH_2), 3.36 (1H, d, *J* 14.0, ArCH_2), 4.53 (1H, d, *J* 15.2, PhCH_2), 4.73 (1H, d, *J* 15.2, PhCH_2); *m*/*z* (ESI) 362/360 ($[M+H]^+$, 96/100%).

*4.1.3.10. 1-Benzyl-5-[1-(2-bromo-phenyl)-methylidene]-pyrrolidin-2-one (**14**).* Isolated as a white solid. Found: C, 63.32; H, 4.59; N, 4.01%. Calcd for $C_{20}H_{22}INO$: C, 63.17; H, 4.71; N, 4.09%. R_f=0.52, hexane/EtOAc (1/2); mp 105–106 °C; ν_{max} (KBr)/cm^{-1} 1702 (CO), 1638 (C=C); δ_H (400 MHz, $CDCl_3$) 2.68 (2H, t, *J* 7.8, CH_2), 2.95 (2H, td, *J* 2.0, 7.8, CH_2), 4.87 (2H, s, PhCH_2), 5.97 (1H, s, CH=C), 7.03 (1H, td, *J* 2.0, 7.2, ArH), 7.23–7.37 (7H, m, ArH), 7.56 (1H, d, *J* 7.2, ArH); δ_C (100.6 MHz, $CDCl_3$) 23.3 (1C, CH_2), 29.0 (1C, CH_2), 44.2 (1C, PhCH_2), 103.6 (1C, *C*H=C), 124.5 (1C, C_2), 127.1 (1C, ArC), 127.3 (1C, ArC), 127.6 (3C, ArC), 128.6 (1C, ArC), 128.7 (2C, ArC), 132.9 (1C, ArC), 135.8 (1C, ArC), 136.2 (1C, ArC), 142.8 (1C, C_{ipso}), 175.6 (1C, CO); *m*/*z* (EI) 343/341 (24/25%), 91 (100).

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