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Deliberately Losing Control of C-H Activation Processes in the Design of Small Molecule Fragment Arrays Targeting Peroxisomal Metabolism

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Abstract: combined photochemical arylation, “nuisance effect” (S_NAr) reaction sequences have been employed in the design of small arrays for immediate deployment in medium throughput X-ray protein-ligand structure determination. Reactions have been deliberately let “out of control,” in terms of selectivity; for example the ortho-arylation of 2-phenylpyridine gave five products resulting from mono-, bis-, arylations combined with S_NAr processes. As a result, a number of crystallographic hits against NUDT7, a key peroxisomal CoA ester hydrolase, have been identified.

Introduction

Given their atom and step economy, C-H activation processes are now commonplace in organic synthesis^[1]. Highly decorated bioactive or synthetically relevant molecules can be functionalized via a late stage activation process, enabling the efficient production of derivatives for e.g. structure activity studies or pharmacokinetic evaluation, saving significant time and cost compared to previous cumbersome multistep syntheses^[2–14].

We have recently disclosed our findings on the microwave mediated ortho-C-H activation of benzodiazepines using iodonium salts under Pd catalysis (Figure 1)^[15]. These processes tend to give monoarylated products although, under more forcing conditions, a second ortho-arylation was observed. Recent, complementary, studies on the visible light mediated “Sanford” arylation^[16–18] of benzodiazepines using diazonium salts and dual Ru/Pd catalysis led mainly to mono-functionalized product^[19]. However, in the case of 2- or 4- substituted fluoro-benzene diazonium salt coupling partners, further competing S_NAr

reactions were observed (“nuisance effect”), when a nucleophilic solvent such as methanol or ethanol was used.

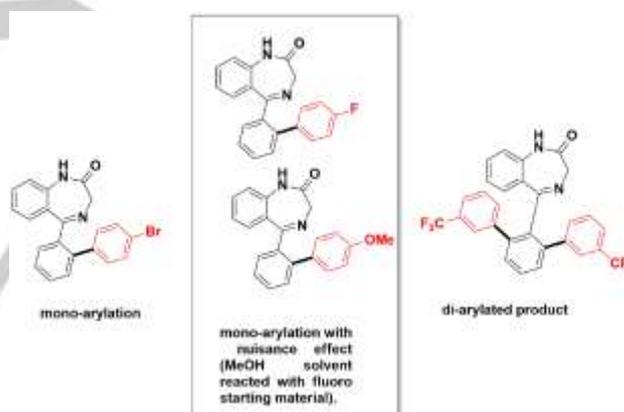
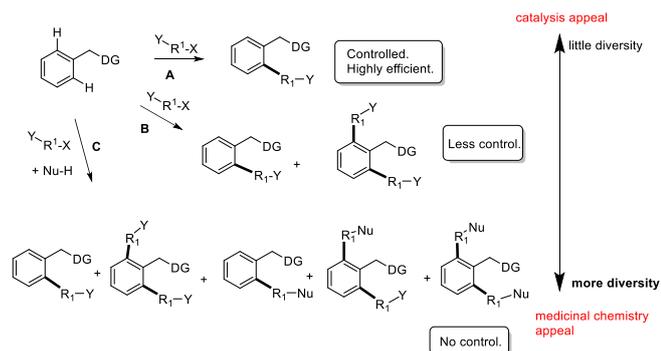


Figure 1. Examples of diverse benzodiazepines formed from ortho C-H activation processes.

Such a spectrum of reactivity opens up scope for performing ortho C-H activations with complete control, driving towards the formation of a single product in a highly efficient manner (see **A**, Scheme 1). Conversely, from the previous example (Figure 1), erosion of selectivity *via* the competing formation of bis-arylated product, as in **B** or even total loss of control, as in **C**, where the coupling partner has a group (Y in Scheme 1) capable of further functionalisation, can also be envisioned. Outcome **A** is irrefutably *catalysis friendly* whereas **C** might be more appropriate in a medicinal chemistry setting, where making small arrays with minimal work-up bottlenecks is desirable, given the high compound attrition and cost of drug discovery.

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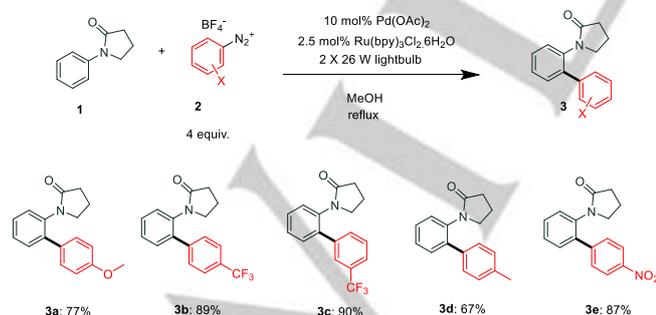


Scheme 1. Extremes of reactivity scenarios in ortho C-H activation chemistry with varying degrees of control. R₁-Y is a coupling partner with a group, Y, capable of further reactivity; X is a halogen or diazonium group.

It was our intention to undertake a proof of principle feasibility study of the development of C-H activation chemistry capable of *losing control*, in the selectivity (not health and safety) context, creating small arrays and diverse mixtures of compounds for immediate deployment in a medicinal chemistry setting with minimal work up or purification^[20–23]. To assist in the process, protein crystallographic screening of the small arrays vs a key peroxisomal protein of current interest was used as a means of validating this approach (*vide infra*).

1. Results and Discussion

We chose 1-phenylpyrrolidin-2-ones as a starting point given their low molecular weight, potential as drug-like fragments as well as their known ability to undergo C-H activation. *Controlled* Sanford arylations of diazonium salts on 1-phenylpyrrolidin-2-one using dual Pd/Ru catalysis and slightly modified standard literature conditions (reflux vs. ambient temperature)^[17], in our hands, led to one major product **3**, in good to excellent yields (Scheme 2).



Scheme 2. Controlled Arylations.

Next, we tested the possibility of *losing control* by performing nuisance effect reactions on the fluorodiazonium salt **2a** (Table 1) where there is a possibility of an S_NAr reaction on **2a** prior to the CH activation. The best conditions (entry 1) gave excellent

conversion and a good 75% combined isolated yield of **3f** and **3a**. In entry 2, higher conversions of **3g** were found but with a lower overall yield of **3f**. Entries 4 and 5 are in line with the earlier work of Sanford *et al.*, who obtained a 62% conversion to **3** in the absence of a Ru catalyst, at ambient temperature, whereas entries 3 and 6 show that low conversions are observed in the absence of light. It was anticipated that the ratio of the products could be influenced by the sequence in which the reactions were performed; for instance, the ratio of the ether to fluoro products, **3a** vs **3f**, was significantly increased when **2a** was heated to reflux in methanol first, to initiate the S_NAr process (entry 7) prior to the addition of the other reagents.

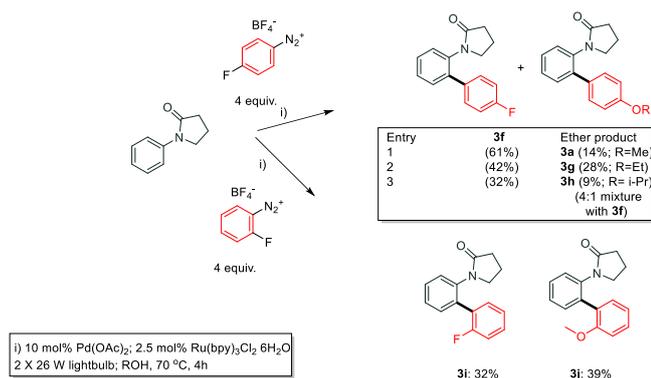
Table 1. Varying C-H activation conditions.

Entry	Light source	Ru(bpy) ₃ Cl ₂ ·6H ₂ O mol%	Temp.	Conversion LC-MS (%) (3f : 3a)
1	a	2.5	reflux	85 (4:1)
2	b	2.5	reflux	60 (2:1)
3	c	2.5	reflux	25 (2:1)
4	a	-	reflux	65 (6:1)
5	a	-	r.t.	58 (20:1)
6	c	-	reflux	20 (99:trace)
7	a	-	reflux	31 (1:4) ^d

^a 26W compact fluorescent light bulb, ^b daylight. ^c in absence of light. ^d **2a** and MeOH were refluxed first (1h) then the other components were added and reacted for 4h.

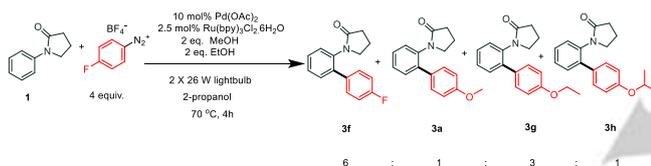
Using the optimized conditions, a small array of arylated products was formed (Scheme 3). Interestingly, under identical conditions, a higher ratio of the ether product from ethanol was achieved in comparison with methanol, i.e. **3g** vs. **3a**. The reaction of *i*-PrOH gave a low yield of **3h**, which was obtained as an inseparable mixture with **3f**. Unsurprisingly, ortho-substituted analogues **3i** and **3j** can also be synthesised.

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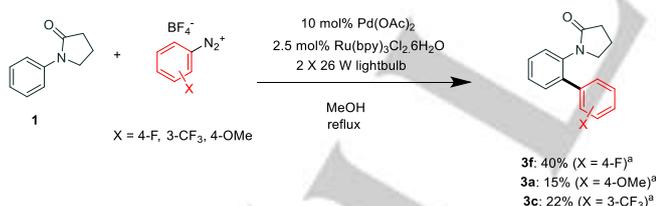
Scheme 3. 1-Phenylpyrrolidin-2-one derivatives (isolated yields) from C-H activation/nuisance effect reactions.

Next, a one-pot reaction, employing a mixture of alcohols, led to a small array of ether products alongside the expected fluorobiphenyl **3f** (Scheme 4). We did not observe any significant bis-arylations in these reactions and the array was subjected, without purification, to an X-ray protein crystallographic analysis.



Scheme 4. *Losing control*: small array of 1-phenyl-2-pyrrolidinone derivatives formed from a mixture of alcohols.

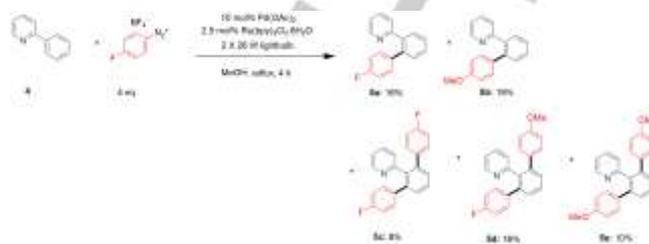
Similarly, a small array of monoarylated compounds can be produced by using a mixture of diazonium salts. The mixture of products was deployed immediately in an X-ray protein crystallographic screen without any further purification (*vide infra*) (Scheme 5).



Scheme 5. *Synthesis of a small array from mixture of diazonium salt precursors.* ^a LC-MS conversion rates.

To test the limits of this chemistry, i.e. scenario **C** in Scheme 1, we attempted *out of control* reactions on a different scaffold, namely 2-phenylpyridine **4**. This was partly driven by the fact that scaffold **1** did not lead to any observed bis-arylations. Interestingly, many literature C-H activations on **4** are carried out on methylated phenylpyridines, presumably to limit reactivity to a single arylation^[17,18].

Reaction of **4** with excess 4-fluorodiazonium salt was carried out under reflux in methanol and gratifyingly led to five products **5a** – **5e**, resulting from a combination of mono, di-arylation and combined “nuisance effects” i.e. “no control” (Scheme 6). The components were separable or were subjected, as a crude mixture/small array, for protein X-ray studies.



Scheme 6. *Out of control* small array of 2-phenylpyridine derivatives from combined C-H arylation and nuisance effects.

This process is somewhat limited i.e. just the three alcohols tried, other nucleophiles e.g. thiols gave mixed results and similar C-H activation attempts with simple benzamides in methanol, such as *N*-phenylacetamide, *N*-methyl-*N*-phenylacetamide, 2,2-dimethyl-*N*-phenylpropanamide and *N*,2,2-trimethyl-*N*-phenylpropanamide, led predominantly to *bis*(4-methoxyphenol)diazene. Solvent screens gave little improvement or any extra S_NAr scope, e.g. DCE, 1,4-dioxane, DME, xylenes, *i*-PrOH, *t*-BuOH, DMSO, MeCN, phenol, and acetone led to little change in yields in these processes.

The above arrays were subjected to X-ray crystallographic evaluation against NUDT7, a member of the superfamily of enzymes, Nudix hydrolases, which, hydrolyse a wide range of pyrophosphates and are thought to act as cellular “housecleaners.”^[24,25] Two isoforms of NUDT7 have been identified: NUDT7 α and NUDT7 β . The former is a peroxisomal CoA ester diphosphatase, whereas NUDT7 β is an inactive splice variant^[26]. NUDT7 \square regulates CoA metabolism by hydrolysing CoA esters to various fatty acids of varying chain lengths of acyl-phosphopantetheines and 3',5'-ADP^[27–29]. Recently, the upregulation of NUDT7 α has been implicated in high risk of inflammatory bowel disease, colorectal cancer and pantothenate kinase-associated neurodegeneration (PKAN)^{[30][31]}. All arrays above were submitted for X-ray analysis; of note, only **3f** was detected from the small array shown with **3a** and **3c** (Scheme 5).^[32] Individually purified, compounds **3a**, **3c**, **3d** and **3f** were found to crystallise in NUDT7 α (Figure 2) involving predominantly van der Waals interactions.

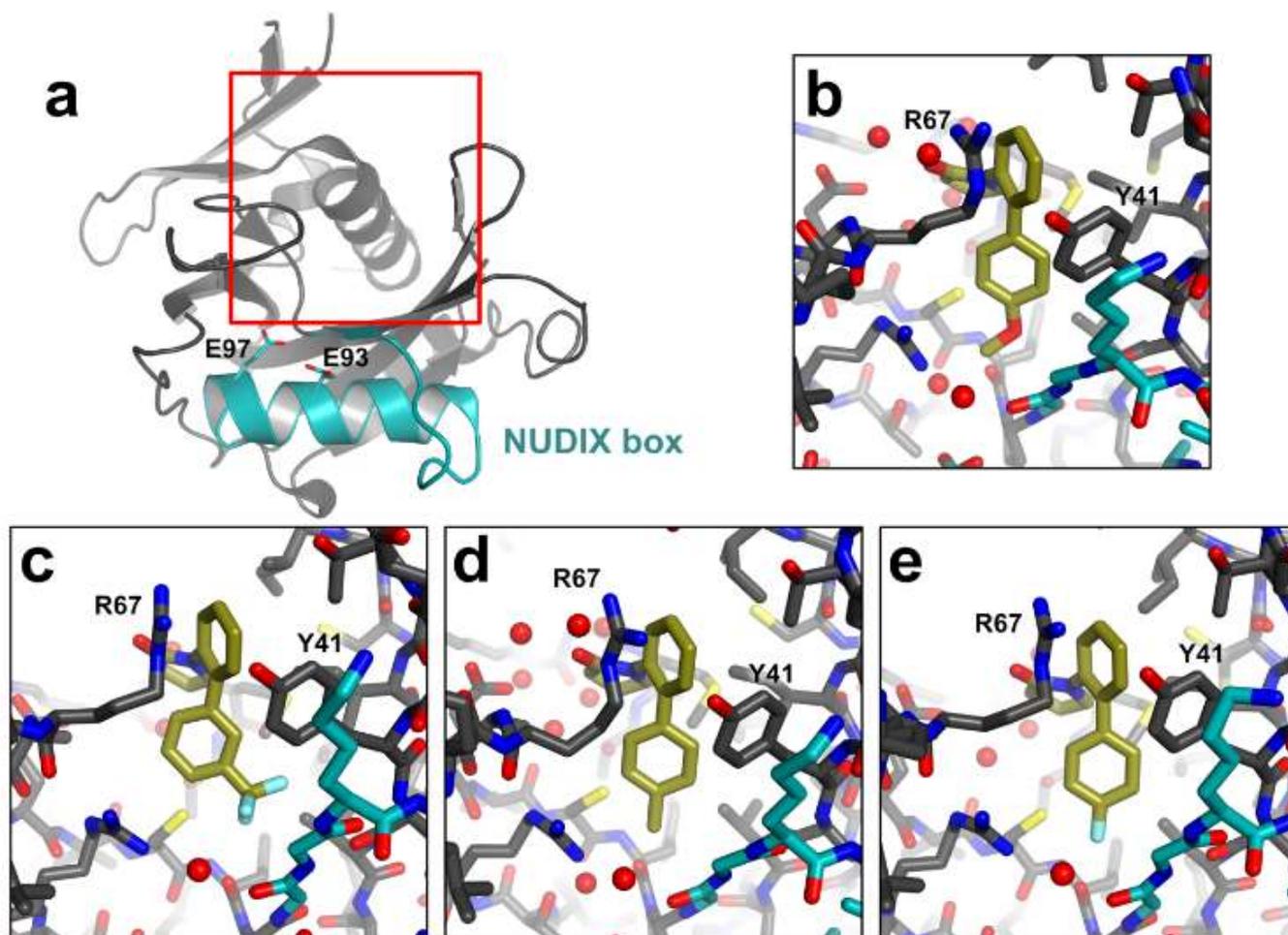


Figure 2. Crystal structures of NUDT7 α in complex with compounds **3a**, **3c**, **3d** and **3f**. (a) Cartoon representation of ligand-free NUDT7 α with the NUDIX box coloured in cyan. The compound binding region is highlighted by with a red square. (b-e) Magnified views of the bound compounds: (b) compound **3a** (PDB iD 5QGM); (c) compound **3c** (PDB ID 5QHC); (d) compound **3d** (PDB ID 5QHB); (e) compound **3f** (PDB ID 5QHE).

An overlay of independent X-ray co-crystals of **3a** and an independent carbamate fragment **NU181** showed their proximity in the binding pocket and a potential fragment merging opportunity (Figure 3).

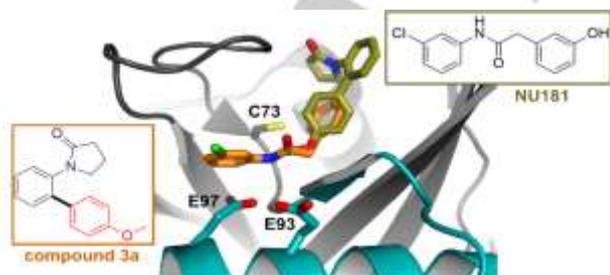
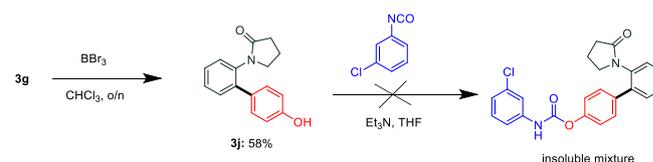


Figure 3. Overlay of NUDT7 α in complex with compound **3a** (PDB ID 5QGM) and in complex with **NU181** (PDB ID 5QH1). The protein structure of 5QH1 is omitted for clarity.

Thereafter, we attempted to merge the two fragments with the aim of improving activity as well as to combine covalent binding due to the presence of a proximal Cys residue (C73) in the protein.^[33] Demethylation of **3a** was achieved using boron tribromide to afford **3k**, which, upon attempted reaction with an isocyanate, led to an insoluble mixture.

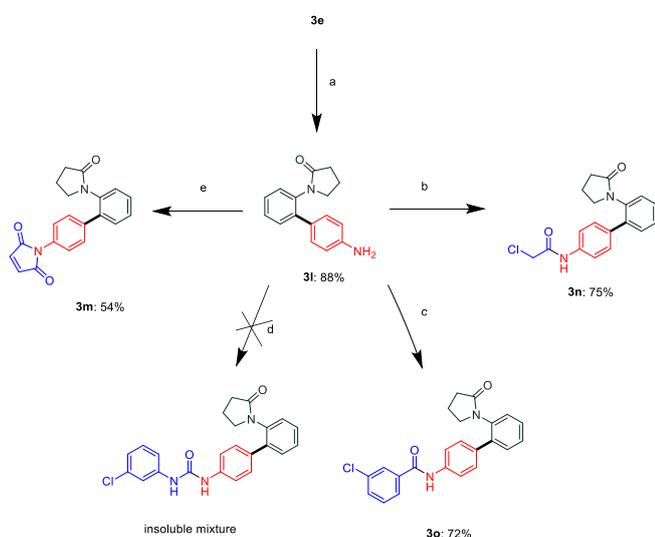


Scheme 7. Demethylation of **3a**.

Next, the 4-nitrobiaryl pyrrolidinone compound **3e** was reduced to aniline **3l** using tin(II) chloride dihydrate and was further functionalized (Scheme 8) to afford the maleimide **3m** and the amides **3n** and **3o** respectively. As with the desired carbamate

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synthesis (Scheme 7), the attempted synthesis of a urea product was hampered by the formation of an inseparable mixture of insoluble products.



Scheme 8. Functionalization of 1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one, **3i**. a) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, EtOAc, 70°C , o/n; b) chloroacetyl chloride, Et_3N , CH_2Cl_2 , o/n; c) chlorobenzoyl chloride, Et_3N , CH_2Cl_2 , o/n; d) 3-chlorophenyl isocyanate, Et_3N , CH_2Cl_2 , o/n; e) i. maleic anhydride, CHCl_3 , 2h ii. Acetic anhydride, sodium acetate, 2h, reflux.

Unfortunately, none of these compounds described, including **3n** - **3o**, above displayed any appreciable binding in a SPR assay towards NUDT7 α or any binding in Xray protein crystallographic analyses.

Conclusion

This proof of principle study has shown that it is indeed possible to get “more bang for your buck” by allowing C-H activations to lose a certain degree of control. By creating small arrays for immediate deployment in biological studies, purification bottlenecks are reduced and direct X-ray analysis vs new protein targets of interest are indeed possible. This study is, nevertheless limited to a narrow range of chemically-similar directing group-containing substrates, a few alcohols as nucleophiles and and also relies on an x-ray screening of impure mixtures since not all techniques are that tolerant. However, it may highlight the need to check for competing “nuisance effect” reactions when using fluorobenzene diazonium salts in alcoholic solutions. It nevertheless gives us the confidence to try larger, more diverse arrays in biological studies. Results of these endeavours are ongoing and will be published in due course.

Experimental Section

General Information

All commercially purchased materials and solvents were used without further purification unless specified otherwise. NMR spectra were recorded on a Varian VNMRS 500 (^1H 500 MHz, ^{13}C 126 MHz) spectrometer and prepared in deuterated solvents such as CDCl_3 and DMSO-d_6 . ^1H and ^{13}C chemical shifts were recorded in parts per million (ppm). Multiplicity of ^1H -NMR peaks are indicated by s – singlet, d – doublet, dd – doublets of doublets, t – triplet, pt – pseudo triplet, q – quartet, m – multiplet and coupling constants are given in Hertz (Hz). Electrospray ionisation – high resolution mass spectra (ESI-HRMS) were obtained using a Bruker Daltonics Apex III where Apollo ESI was used as the ESI source. All analyses were conducted by Dr A. K. Abdul-Sada. The molecular ion peaks $[\text{M}]^+$ were recorded in mass to charge (m/z) ratio. LC-MS spectra were acquired using Shimadzu LC-MS 2020, on a Gemini 5 m C18 110 Å. column. All X-ray analyses were performed at the UK National Crystallography Services, Southampton. Purifications were performed by flash chromatography on silica gel columns or C18 columns using a Combi flash RF 75 PSI, ISCO unit.

1-(4'-Fluorobiphenyl-2-yl)pyrrolidin-2-one (**3f**); 1-(4'-Methoxybiphenyl-2-yl)pyrrolidin-2-one (**3a**) “Standard method.” 1-Phenyl-2-pyrrolidinone (0.065 g, 0.40 mmol), 4-fluorobenzenediazonium tetrafluoroborate (0.35 g, 1.67 mmol), palladium (II) acetate (0.009 g, 0.04 mmol) and $\text{Ru}(\text{bpy})_3\text{Cl}_2 \cdot 6\text{H}_2\text{O}$ (0.007 g, 0.01 mmol) were suspended in degassed, anhydrous methanol (4 mL). Two fluorescent light bulbs (26 W) were placed on either side of the reaction vessel and the reaction mixture was heated at reflux for 4 hours under inert atmosphere. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (50 mL) and washed with water (20 mL) and aqueous sodium sulphite (10%, 35 mL x 2). The combined aqueous layers were extracted with ethyl acetate (50 mL) and thereafter the combined organic layer was washed with brine (50 mL), dried (MgSO_4) and concentrated under reduced pressure. The resulting crude material was purified by reversed phase chromatography (water/acetonitrile with 0.1% formic acid, 5 min at 0%, 30%-90%). The reaction generated two products, **3f** was obtained as a viscous oil (0.062 g, 61%) and **3a** was obtained also as a viscous oil (0.015 g, 14%). The spectral data were concurrent with those reported.¹⁶

1-(4'-Methoxybiphenyl-2-yl)pyrrolidin-2-one (**3a**)

3a was synthesised on a bigger scale by combining 1-phenyl-2-pyrrolidinone (0.50 g, 3.1 mmol), 4-methoxybenzenediazonium tetrafluoroborate (2.75 g, 12.4 mmol), palladium (II) acetate

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(0.069 g, 0.31 mmol) and Ru(bpy)₃Cl₂·6H₂O (0.58 g, 0.078 mmol) were suspended in degassed, anhydrous methanol (30 mL). Two fluorescent light bulbs (26 W) were placed on either side of the reaction vessel and the reaction mixture was heated at reflux for 4 hours under inert atmosphere. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (50 mL) and washed with water (20 mL) and aqueous sodium sulphite (10%, 35 mL x 2). The combined aqueous layers were extracted with ethyl acetate (50 mL) and thereafter the combined organic layer was washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting crude material was purified by reversed phase chromatography (water/acetonitrile with 0.1% formic acid, 5 min at 0%, 30%-90%). Product **3a** was obtained as a viscous oil (0.64 g, 77%).

1-(4'-Ethoxybiphenyl-2-yl)pyrrolidin-2-one (**3g**)

The standard method was used except that ethanol (5 mL) was used as the solvent instead of methanol. Starting material, 1-phenyl-2-pyrrolidinone (0.007 g, 0.043 mmol) was recovered and two products were generated, product **3f** was obtained as an oil (0.038 g, 42%) and product **3g** was obtained also as an oil (0.028 g, 28%). ¹H-NMR (500 MHz) CDCl₃: δ = 7.40 – 7.34 (m, ArH, 3H), 7.33 – 7.28 (m, ArH, 3H), 6.93 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 4.08 (q, ³J_{HH} = 7.0 Hz, O-CH₂CH₃, 2H), 3.23 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.44 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.89 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H), 1.45 (t, ³J_{HH} = 7.0 Hz, O-CH₂CH₃, 3H). ¹³C-NMR (126 MHz) CDCl₃: δ = 175.6 (C=O), 158.6 (ArC), 139.4 (ArC), 136.4 (ArC), 131.4 (ArC), 130.9 (ArC), 129.5 (2 x ArC), 128.4 (ArC), 128.1 (ArC), 127.9 (ArC), 114.4 (2x ArC), 63.5 (O-CH₂CH₃), 50.1 (COCH₂CH₂CH₂N), 31.2 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N), 14.8 (O-CH₂CH₃). HRMS-ESI (m/z) calculated for C₁₈H₁₉NO₂ [+H]⁺: 282.1489, found: 282.1487. LCMS purity (UV) = 97 %, tR 11.85 min.

1-(4'-Isopropoxybiphenyl-2-yl)pyrrolidin-2-one (**3h**)

The usual method was used but 2-propanol (5 mL) was used as the solvent instead of methanol. Starting material, 1-phenyl-2-pyrrolidinone (0.027 g, 0.17 mmol) was recovered and two products were generated, product **3f** was obtained as a white solid (0.019 g, 32%) and a mixture of **3f** and **3h** was obtained an oil (0.0059 g, 9%) in 1:4 ratio as determined by ¹H-NMR and LC-MS.

3f/3h mixture: ¹H-NMR (500 MHz) CDCl₃: δ = 7.62 – 7.52 (m, ArH, 1H), 7.42 – 7.35 (m, ArH, 4H), 7.32 – 7.26 (m, ArH, 3H), 6.91 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 4.62 – 4.55 (m, O-CHCH₃CH₃, 1H), 3.92 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 1H), 3.22 (t, ³J_{HH} = 7.0 Hz,

COCH₂CH₂CH₂N, 2H), 2.64 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N 1H), 2.44 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N x 4, 8H), 2.23 – 2.16 (m, COCH₂CH₂CH₂N, 1H), 1.90 (q, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H), 1.37 (d, ³J_{HH} = 6.0 Hz, O-CHCH₃CH₃, 6H). HRMS-ESI (m/z) calculated for C₁₉H₂₁NO₂ [+H]⁺: 296.1650, found: 296.1647. LCMS ratio (UV) = **3h** 18%, tR 12.37 min, **3f**, 75%, tR 12.29 min.

1-(2'-Fluorobiphenyl-2-yl)pyrrolidin-2-one (**3i**); 1-(2'-Methoxybiphenyl-2-yl)pyrrolidin-2-one (**3j**)

This reaction was performed on a 0.30 mmol scale by the general procedure but with 2-fluorobenzenediazonium tetrafluoroborate (0.25 g, 1.20 mmol). Starting material, 1-phenyl-2-pyrrolidinone was recovered (0.006 g, 0.037 mmol) and two products were generated; product **3i** was obtained as a viscous oil (0.022 g, 32%) and **3j** was obtained as a viscous oil (0.027 g, 39%). **3i**: ¹H-NMR (500 MHz) CDCl₃: δ = 7.46 – 7.42 (m, ArH, 1H), 7.41 – 7.37 (m, ArH, 2H), 7.36 – 7.31 (m, ArH, 3H), 7.20 – 7.16 (m, ArH, 1H), 7.15 – 7.10 (m, ArH, 1H), 3.39 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.35 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.91 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). ¹³C-NMR (126 MHz) CDCl₃: δ = 174.8 (C=O), 165.4 (d, ¹J_{FC} = 246.5 Hz, ArC), 137.8 (ArC), 133.5 (ArC), 131.6 (ArC), 131.5 (ArC), 131.4 (ArC), 129.6 (d, ³J_{FC} = 8.0 Hz, ArC), 129.1 (ArC), 127.6 (d, ³J_{FC} = 8.5 Hz, ArC), 126.7 (d, ²J_{FC} = 16.0 Hz, ArC), 124.1 (d, ⁴J_{FC} = 3.5 Hz, ArC), 115.4 (d, ²J_{FC} = 22.5 Hz, ArC), 50.2 (COCH₂CH₂CH₂N), 31.3 (COCH₂CH₂CH₂N), 19.1 (COCH₂CH₂CH₂N). HRMS-ESI (m/z) calculated for C₁₆H₁₄FNO [+Na]⁺: 278.0952, found: 278.0952. LCMS purity (UV) = 96 %, tR 12.30 min. **3j**: ¹H-NMR (500 MHz) CDCl₃: δ = 7.42 – 7.37 (m, ArH, 1H), 7.37 – 7.31 (m, ArH, 4H), 7.22 (d, ³J_{HH} = 7.5 Hz, ArH, 1H), 7.00 (d, ³J_{HH} = 7.5 Hz, ArH, 1H), 6.98 – 6.94 (m, ArH, 1H), 3.76 (s, O-CH₃, 3H), 3.26 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂CH₂N, 2H), 2.34 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.82 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂CH₂N, 2H). ¹³C-NMR (126 MHz) CDCl₃: δ = 174.7 (C=O), 156.4 (ArC), 137.3 (ArC), 136.0 (ArC), 131.8 (ArC), 130.9 (ArC), 129.1 (ArC), 128.3 (ArC), 128.0 (ArC), 127.8 (ArC), 127.2 (ArC), 120.6 (ArC), 110.7 (ArC), 55.5 (O-CH₃), 49.9 (COCH₂CH₂CH₂N), 31.3 (COCH₂CH₂CH₂N), 19.2 (COCH₂CH₂CH₂N). HRMS-ESI (m/z) calculated for C₁₇H₁₇NO₂ [+Na]⁺: 290.1151, found: 290.1151. LCMS purity (UV) = 94 %, tR 11.65 min.

1-(4'-Trifluoromethylbiphenyl-2-yl)pyrrolidin-2-one (**3b**)

The general method was used on a 0.3 mmol scale with 4-trifluoromethylbenzene diazonium tetrafluoroborate (1.2 mmol, 0.31 g). The spectral data of **3b** – **3e** were concurrent with those reported.^[16]

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1-(3'-Trifluoromethylbiphenyl-2-yl)pyrrolidin-2-one (**3c**)

The general method was used on a 0.3 mmol scale with 3-trifluoromethylbenzene diazonium tetrafluoroborate (1.2 mmol, 0.31 g). The title product was obtained as an oil (0.082 g, 90%).

1-(4'-Methylbiphenyl-2-yl)pyrrolidin-2-one (**3d**)

The general method was used on a 0.3 mmol scale with 4-methylbenzene diazonium tetrafluoroborate (1.21 mmol, 0.25 g). The title product was obtained as an oil (0.051 g, 67%).

1-(4'-Nitrobiphenyl-2-yl)pyrrolidin-2-one (**3e**)

The general method was used on a 3.5 mmol scale with 4-nitrobenzene diazonium tetrafluoroborate (11 mmol, 2.61 g). The title product was obtained as an oil (0.86 g, 87%).

1-(4'-Hydroxybiphenyl-2-yl)pyrrolidin-2-one (**3k**)

To a stirred solution of 1-(4'-methoxybiphenyl-2-yl)pyrrolidin-2-one (1.6 mmol, 0.42 g) in DCM (10 mL) was added 1M BBr₃ (10 mL) in DCM dropwise at 0°C under inert atmosphere. The reaction mixture was allowed to warm to ambient temperature and stirred for additional 16 h. The resulting mixture was carefully quenched with saturated sodium bicarbonate (50 mL) and the mixture was extracted with DCM (40 mL x 2). The combined organic layer was dried (MgSO₄) and concentrated under reduced pressure. The resulting crude product was triturated with diethyl ether overnight. The precipitate was collected by filtration to afford a grey solid (0.24 g, 58%). ¹H-NMR (500 MHz) DMSO-D₆: δ = 7.36 – 7.29 (m, ArH, 3H), 7.26 – 7.22 (m, ArH, 1H), 7.10 (d, ³J_{HH} = 8.7 Hz, 2H), 6.81 – 6.76 (m, ArH, 2H), 3.19 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.23 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.81 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). ¹³C-NMR (126 MHz) DMSO-D₆: δ = 174.7 (C=O), 157.3 (ArC), 137.3 (ArC), 139.5 (ArC), 136.9 (ArC), 130.9 (ArC), 129.8 (ArC), 129.5 (ArC x 2), 129.0 (ArC), 128.1 (ArC), 128.0 (ArC), 115.7 (ArC x 2), 49.9 (COCH₂CH₂CH₂N), 31.1 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N). HRMS-ESI (m/z) calculated for C₁₆H₁₅NO₂ [H]⁺: 267.1259, found: 267.1262 LCMS purity (UV) = 99%, tR 18.51 min.

1-(4'-Aminobiphenyl-2-yl)pyrrolidin-2-one (**3l**)

To a stirred solution of 1-(4'-nitrobiphenyl-2-yl)pyrrolidin-2-one (2.8 mmol, 0.8 g) in ethyl acetate (20 mL) was added tin(II) chloride dihydrate (14 mmol, 3.2 g) and the reaction was stirred at 70 °C overnight. The resulting mixture was neutralised with saturated sodium bicarbonate and extracted with ethyl acetate (40 mL x 2).

The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure to afford the product as a white solid (0.62 g, 88%). ¹H-NMR (500 MHz) DMSO-D₆: δ = 7.34 – 7.24 (m, ArH, 3H), 7.20 (d, ³J_{HH} = 7.5 Hz, ArH, 1H), 6.96 (d, ³J_{HH} = 7.5 Hz, ArH, 2H), 6.61 – 6.52 (m, ArH, 2H), 3.18 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.25 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.82 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). ¹³C-NMR (126 MHz) CDCl₃: δ = 175.7 (C=O), 145.9 (ArC), 139.6 (ArC), 136.2 (ArC), 130.8 (ArC), 130.8 (ArC), 129.3 (ArC x 2), 129.2 (ArC), 128.4 (ArC), 128.0 (ArC), 127.8 (ArC), 115.0 (ArC x 2), 49.9 (COCH₂CH₂CH₂N), 31.1 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N). HRMS-ESI (m/z) calculated for C₁₆H₁₆N₂O [H]⁺: 253.1335, found: 253.1328. LCMS purity (UV) = 95%, tR 13.38 min.

1-[2'-(2-Oxopyrrolidin-1-yl)biphenyl-4-yl]1*H*-pyrrole-2,5-dione (**3m**)

1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one (0.20 mmol, 0.050 g), maleic anhydride (0.24 mmol, 0.024 g) were dissolved in CHCl₃ (3 mL) and stirred for 2 h. The reaction mixture was concentrated under reduced pressure. To a stirred solution of the crude maleic acid in acetic anhydride (19.5 mmol, 2.0 g) was added sodium acetate (0.40 mmol, 0.033 g) and heated at reflux for 2 h. After cooling to ambient temperature, the reaction was quenched with water (20 mL) and extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The crude mixture was purified by column chromatography (hexane/ethyl acetate over 0% - 10% gradient) to afford the title compound as a yellow solid (0.036g, 54%). ¹H-NMR (500 MHz) CDCl₃: δ = 7.48 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 7.44 – 7.41 (m, ArH, 2H), 7.40 – 7.38 (m, ArH, 3H), 7.35 – 7.31 (m, ArH, 1H), 6.88 (s, COCHCHCO, 2H), 3.25 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.45 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.91 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). ¹³C-NMR (126 MHz) CDCl₃: δ = 175.8 (CH₂NC=O), 169.4 (CHCONCOCH), 138.7 (ArC), 136.4 (ArC), 134.3 (ArC x 2), 130.8 (ArC), 130.7 (ArC), 129.1 (ArC x 2), 129.0 (ArC), 128.5 (ArC), 128.2 (ArC), 125.8 (ArC x 2), 50.3 (COCH₂CH₂CH₂N), 31.2 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N). HRMS-ESI (m/z) calculated for C₂₀H₁₆N₂O₃ [H]⁺: 333.1234, found: 333.1225. LCMS purity (UV) = 97 %, tR 18.77 min.

2-Chloro-N-[2'-(2-oxopyrrolidin-1-yl)biphenyl-4-yl]acetamide (**3n**)

To a stirred solution of 1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one (0.38 mmol, 0.095 g) and triethylamine (0.38 mmol, 0.05 mL) in anhydrous DCM (8 mL) was added chloroacetyl chloride (0.46

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mmol, 0.052 g) dropwise at 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure. The residue was washed with washed with water (10 mL x 3) and the resulting precipitate was collected by filtration to afford the final product as a white solid (0.093g, 75%). ¹H-NMR (500 MHz) CDCl₃: δ = 8.55 (s, NH, 1H), 7.59 (d, ³J_{HH} = 8.1 Hz, ArH, 2H), 7.41 – 7.33 (m, ArH, 5H), 7.30 (d, ³J_{HH} = 7.2 Hz, ArH, 1H), 4.17 (s, COCH₂Cl, 2H), 3.27 (t, ³J_{HH} = 7.0 Hz, COCH₂CH₂CH₂N, 2H), 2.42 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.90 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). ¹³C-NMR (126 MHz) CDCl₃: δ = 175.7 (CH₂NC=O), 164.0 (NHC=O), 138.9 (ArC), 136.5 (ArC), 136.2 (ArC), 135.8 (ArC), 130.8 (ArC), 128.7 (ArC x 2), 128.3 (ArC), 128.2 (ArC), 119.9 (ArC x 2), 50.3 (COCH₂CH₂CH₂N), 43.0 (COCH₂Cl), 31.2 (COCH₂CH₂CH₂N), 19.0 (COCH₂CH₂CH₂N). HRMS-ESI (m/z) calculated for C₁₈H₁₇ClN₂O₂ [H]⁺: 329.1051, found: 329.1053. LCMS purity (UV) = 97%, tR 19.77 min.

2-Chloro-N-[2'-(2-oxopyrrolidin-1-yl)biphenyl-4-yl]acetamide (**3o**)

To a stirred solution of 1-(4'-aminobiphenyl-2-yl)pyrrolidin-2-one (0.39 mmol, 0.10 g) and triethylamine (1.98 mmol, 0.20 g) in anhydrous DCM (10 mL) was added 3-chlorobenzoyl chloride (1.2 mmol, 0.21 g) and the reaction mixture was stirred overnight. The reaction mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (DCM/methanol over 0% - 10% gradient) to afford the title product as a white amorphous solid (0.11 g, 72%). ¹H-NMR (500 MHz) CDCl₃: δ = 8.72 (s, NH, 1H), 7.95 – 7.90 (m, ArH, 1H), 7.79 (d, ³J_{HH} = 7.5 Hz, ArH, 1H), 7.72 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 7.50 (dd, ^{3,4}J_{HH} = 8.0, 2.0 Hz, ArH, 1H), 7.40 – 7.34 (m, ArH, 6H), 7.32 – 7.26 (m, 1H), 3.31 (t, ³J_{HH} = 7.0 Hz, ArH, COCH₂CH₂CH₂N, 2H), 2.38 (t, ³J_{HH} = 8.0 Hz, COCH₂CH₂CH₂N, 2H), 1.91 (p, ³J_{HH} = 7.5 Hz, COCH₂CH₂CH₂N, 2H). ¹³C-NMR (126 MHz) CDCl₃: δ = 175.8 (CH₂NC=O), 164.6 (NHC=O), 139.1 (ArC), 137.8 (ArC), 136.6 (ArC), 136.1 (ArC), 135.1 (ArC), 134.7 (ArC), 131.8 (ArC), 130.9 (ArC), 129.9 (ArC), 128.9 (ArC x 2), 128.5 (ArC), 127.6 (ArC), 125.5 (ArC x 2), 50.5 (COCH₂CH₂CH₂N), 31.2 (COCH₂CH₂CH₂N), 18.9 (COCH₂CH₂CH₂N). HRMS-ESI (m/z) calculated for C₂₃H₁₉ClN₂O₂ [H]⁺: 391.1208, found: 391.1199. LCMS purity (UV) = 91 %, tR 18.38 min.

One-pot Reaction Towards **3a**, **3c**, and **3f**

This reaction was performed following the standard procedure by using 1-phenyl-2-pyrrolidinone (0.048 g, 0.3 mmol) and a mixture of 4-fluorobenzene diazonium tetrafluoroborate (84 mg, 0.40 mmol), 4-methoxybenzene diazonium tetrafluoroborate (89 mg, 0.40 mmol) and 3-trifluoromethylbenzene diazonium

tetrafluoroborate (104 mg, 0.40 mmol). The products **3a**, **3c** and **3f** were obtained as a mixture with the ratio of 15%, 22% and 40% respectively (determined by LC-MS).

Reaction with 2-Phenylpyridine

2-Phenylpyridine (0.078 g, 0.50 mmol), 4-fluorodiazonium tetrafluoroborate (0.42 g, 2.0 mmol), palladium (II) acetate (0.011 g, 0.05 mmol) and Ru(bpy)₃Cl₂·6H₂O (0.009 g, 0.013 mmol) were suspended in degassed, anhydrous methanol (4 mL). Two fluorescent light bulbs (26 W) were placed on either side of the reaction vessel and the mixture was heated at reflux for 4 hours. The reaction mixture was allowed to cool to ambient temperature, diluted with ethyl acetate (40 mL) and washed with water (20 mL) and aqueous sodium sulphite (10%, 35 mL x 2). The combined aqueous layers were extracted with ethyl acetate (50 mL) and thereafter the combined organic layers were washed with brine (50 mL), dried (MgSO₄) and concentrated under reduced pressure. The resulting crude material was purified by reversed phase chromatography (water/acetonitrile with 0.1% formic acid, 5 min at 0%, 30%-90%). Starting material, 1-phenyl-2-pyrrolidinone was recovered (0.008 g, 0.052 mmol) and five products were generated from this reaction:

2-(4'-Fluorobiphenyl-2-yl)pyridine (**5a**)

The title compound was obtained as a viscous oil (0.018 g, 16%). The spectral data were concurrent with those reported.^[34]

2-(4'-Methoxybiphenyl-2-yl)pyridine (**5b**)

The title compound was obtained as a green/yellow oil (0.022 g, 19%). The spectral data were concurrent with those reported.^[34]

2-(4,4'-Fluorobiphenyl-2,6-yl)pyridine (**5c**)

The title product was obtained as a viscous oil (0.012 g, 8%). The spectral data were concurrent with those reported.^[34]

2-(4,4'-Fluoromethoxybiphenyl-2,6-yl)pyridine (**5d**)

The title compound was obtained as a viscous oil (0.024 g, 15%). ¹H-NMR (500 MHz) CDCl₃: δ = 8.37 – 8.32 (m, ArH, 1H), 7.49 (pt, ³J_{HH} = 7.5 Hz, ArH, 1H), 7.45 – 7.42 (m, ArH, 1H), 7.38 (d, ³J_{HH} = 7.5 Hz, ArH, 1H), 7.35 – 7.30 (m, ArH, 1H), 7.07 – 7.03 (m, ArH, 2H), 7.01 (d, ³J_{HH} = 8.5 Hz, ArH, 2H), 6.95 – 6.92 (m, ArH, 1H), 6.87 – 6.81 (m, ArH, 3H), 6.69 (d, ArH, ³J_{HH} = 8.5 Hz, 2H), 3.75 (s, O-CH₃, 3H). ¹³C-NMR (126 MHz) CDCl₃: δ = 161.5 (d, ¹J_{FC} = 246.0 Hz, ArC), 158.9 (ArC), 158.2 (ArC), 148.4 (ArC), 141.5 (ArC), 140.8 (ArC), 137.5 (ArC), 135.2 (ArC), 133.7 (ArC), 131.1 (d, ³J_{FC} = 7.8 Hz; 2 x ArC), 130.7 (2 x ArC), 128.6 (ArC), 129.1 (ArC), 128.2 (ArC), 126.9 (ArC), 126.6 (ArC), 121.0 (ArC), 114.5 (d, ²J_{FC} = 21.1 Hz; 2 x ArC), 113.2 (2 x ArC), 55.1 (O-CH₃). HRMS-ESI (m/z) calculated for C₂₄H₁₈FNO [H]⁺: 356.1445, found: 356.1444. LCMS purity (UV) = 93 %, tR 16.35 min.

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2-(4,4'-Methoxybiphenyl-2,6-yl)pyridine (**5e**)

The title compound was obtained as a green/yellow oil (0.016 g, 10%). The spectral data were concurrent with those reported.^[34]

Crystallographic Methods

NUDT7 was expressed and purified as described previously^[32,33] NUDT7 was crystallised in sitting drops at 20 °C by mixing 100 nL of 30 mg/mL protein in 10 mM Na-HEPES pH 7.5, 500 mM NaCl, 5% glycerol with 50 nL of reservoir solution containing 0.1 M BisTris pH 5.5, 0.1 M ammonium acetate, and 6% (w/v) PEG 10000. NUDT7 crystals were soaked with a mixture containing 600 nL of 100 mM of the respective compound in DMSO with 1200 nL of reservoir solution. Crystals were incubated overnight at room temperature and then harvested (without further cryoprotection) and flash-cooled in liquid nitrogen.

All X-ray diffraction data were collected on beamline I04-1 at the Diamond Light Source. Diffraction data were automatically processed by software pipelines at the Diamond Light Source.^[35] Initial refinement and map calculation was carried out with DIMPLe.^[36] Ligand restraints were generated with ACEDRG.^[37] Refinement and model building was performed with REFMAC^[38] and COOT,^[39] respectively. All structure determination steps were performed within the XChemExplorer^[40] data management and workflow tool. Final models and structure factors have been deposited with PDB accession codes 5QGM, 5QHB, 5QHC and 5QHE.

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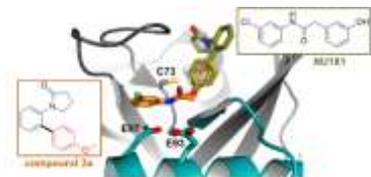
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C-H activation reactions coupled with “nuisance effect” S_NAr processes have been designed to “lose control” in order to make discrete libraries for immediate testing, by x-ray, versus targets of current interest. Although somewhat limited, these reactions may encourage others to try to reduce synthetic/work-up bottlenecks and use crystallography as a more routine analytical format for drug discovery.

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