Abstract

Pd-catalysed C–C bond formation is an essential tool within the pharmaceutical and agrochemical industries. Many of these reactions rely heavily on polar aprotic solvents; however, despite their utility, these solvents are incompatible with the drive towards more sustainable chemical synthesis. Herein, we describe the scope and limitations of an alternative to DMF derived from renewable sources (Cyrene™) in Sonogashira cross-coupling and Cacchi-type annulations.

Introduction

The Sonogashira reaction [1,2] (Scheme 1) is a robust and broadly applicable Pd-catalysed bond-forming process that, alongside the Suzuki–Miyaura reaction [3], has steadily become an indispensable tool for C–C bond formation in the pharmaceutical industry [4]. While the Sonogashira reaction can be effectively carried out in a variety of media [1,2], in the general sense this process clearly relies upon the use of dipolar aprotic solvents, in particular DMF. Indeed, some 41% of all Sonogashira reactions reported using aryl iodides can be linked to the use of DMF as a solvent [5].

In this context, the sustainability movement within pharmaceutical research and development strives to substitute solvents that have regulatory and environmental issues for those with a lower perceived risk. Indeed, solvent replacement has been designated a key research area with numerous pharmaceutical companies detailing their efforts towards a more sustain-
able solvent selection as part of their overall sustainability programmes [6-23].

Based on its associated regulatory issues [24], it is perhaps no surprise that DMF continues to be a priority solvent for replacement. With legislation surrounding the use of DMF becoming increasingly stringent [24], numerous efforts have been made towards the use of alternative media in the Sonogashira reaction [25-30]. However, notwithstanding its issues, DMF is an excellent solvent for the Sonogashira reaction and its replacement frequently occurs at the expense of increased temperature (and therefore potentially substrate compatibility), reaction time, catalyst loading or the requirement for non-commercial/expensive catalysts, and yield [25-30]. Consequently, poor choice of solvent replacement can result in one of industry’s workhorse reactions becoming rather less predictable and robust.

In this regard, dihydrolevoglucosenone (Cyrene, Figure 1), accessed in two steps from cellulose [31,32], has been shown to possess similar physical properties to those of DMF and other dipolar aprotic solvents [31,32]. In addition to its renewability, Cyrene, as yet, has no associated pernicious effects and could potentially represent a direct and functional replacement in many of the fundamental reactions that typically employ DMF [31,32]. The replacement of solvents with regulatory issues with bio-derived alternatives has provided a series of advances within the cross-coupling arena [33], allowing efficient C–C bond formation via cornerstone Pd-based methods including Suzuki–Miyaura [34,35], Mizoroki–Heck [36,37], Sonogashira [38], Stille [39], Hiyama reactions [40], and hydroformylation reactions [41].

In the current study, we present the use of Cyrene as an alternative solvent (direct DMF replacement) for the Sonogashira reaction, as well as related Cacchi-type annihilations [42,43], with an emphasis on scope and limitations of its application.

Results and Discussion

To explore the use of Cyrene in the context of the Sonogashira cross-coupling, we established a simple benchmark reaction using iodobenzene (1a) and phenylacetylene (2a) (Table 1). A typical literature-derived catalyst system was employed (Pd(PPh3)2Cl2 with CuI additive [44,45]) and conversion to diphenylacetylene (3a) was monitored.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction conditions</th>
<th>3a (%)</th>
<th>Ph–I + Ph+</th>
<th>Cacchi-type annihilation</th>
<th>Cyrene, T (°C), t (h)</th>
<th>1a</th>
<th>2a</th>
<th>Ph–I + Ph+</th>
<th>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</th>
<th>base (x equiv)</th>
<th>Cyrene, T (°C), t (h)</th>
<th>3a</th>
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<tr>
<td>1</td>
<td>0.1 M, Et3N (3 equiv), 20 °C, 5 h</td>
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<td>Cyrene, T (°C), t (h)</td>
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<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
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<td>Cyrene, T (°C), t (h)</td>
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<tr>
<td>2</td>
<td>0.3 M, Et3N (3 equiv), 20 °C, 5 h</td>
<td>98</td>
<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
<td>3a</td>
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<tr>
<td>3</td>
<td>0.5 M, Et3N (3 equiv), 20 °C, 5 h</td>
<td>100</td>
<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
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<tr>
<td>4</td>
<td>0.5 M, K3PO4 (3 equiv), 20 °C, 5 h</td>
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<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
<td>3a</td>
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<tr>
<td>5</td>
<td>0.5 M, Cs2CO3 (3 equiv), 20 °C, 5 h</td>
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<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
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<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
<td>3a</td>
</tr>
<tr>
<td>7</td>
<td>0.5 M, Et3N (1.1 equiv), 30 °C, 1 h</td>
<td>96</td>
<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
<td>3a</td>
</tr>
<tr>
<td>8</td>
<td>0.5 M, Et3N (1.1 equiv), 30 °C, 1 h</td>
<td>81</td>
<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
<td>3a</td>
</tr>
<tr>
<td>9</td>
<td>0.5 M, Et3N (1.1 equiv), 30 °C, 1 h</td>
<td>81</td>
<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
<td>3a</td>
</tr>
<tr>
<td>10</td>
<td>0.5 M, Et3N (1.1 equiv), 30 °C, 1 h</td>
<td>87</td>
<td>Ph–I + Ph+</td>
<td>Cacchi-type annihilation</td>
<td>Cyrene, T (°C), t (h)</td>
<td>1a</td>
<td>2a</td>
<td>Ph–I + Ph+</td>
<td>Pd(PPh3)2Cl2 (2 mol %), CuI (4 mol %)</td>
<td>base (x equiv)</td>
<td>Cyrene, T (°C), t (h)</td>
<td>3a</td>
</tr>
</tbody>
</table>

Pleaseingly, high conversion to product was immediately observed at room temperature in 5 h (94%, Table 1, entry 1). This high conversion was consistent across several reaction concentrations (Table 1, entries 2 and 3) allowing for a reduction in solvent volume, commensurate with the principles of green chemistry [46,47].

In attempts to further limit waste, we scanned a series of bases (see Supporting Information File 1); organic bases consistently performed more effectively and alternatives to Et3N provided no significant advantages. However, during this process we identified some potential limitations of this emerging solvent. Specifically, inorganic bases such as K3PO4 and Cs2CO3 (Table 1, entries 4 and 5) resulted in the generation of a solid reaction mixture. Further analysis revealed that the aldol products 4a and 4b (Figure 2) were generated under specific reaction conditions.

The manufacturers note that when using Cyrene, materials to avoid are strong acids, and strong oxidising and reducing agents. Since sensitivity to base was not specified, we surveyed a range of bases at various temperatures to evaluate the limitations of Cyrene under such conditions (Table 2).
Under these specific reaction conditions, with the exception of Et₃N and DIPEA, there was a clear base sensitivity displayed by Cyrene in the presence of all bases when the temperature was elevated above 25 °C. Organic bases such as pyridine (Table 2, entry 2), DIPEA (Table 2, entry 4), and Et₃N (Table 2, entry 6) were tolerated at 25 °C with DIPEA and Et₃N also tolerated at 50 °C. DBU, however, was not tolerated at any temperature (Table 2, entry 8). With the exception of KOAc (Table 2, entry 1), all inorganic bases resulted in reaction with the solvent at room temperature (Table 2, entries 3, 5, 7, and 9–11). The extent of the reaction varied from the generation of additional components, such as 4a and 4b, to gelation or complete solidification of the reaction mixture. However, in a moderately basic reaction mixture (e.g., using Et₃N) at mild reaction temperatures this issue could be entirely avoided. As such, optimisation of the Sonogashira process allowed complete conversion and 96% isolated yield in 1 h at 30 °C (Table 1, entry 8). Importantly, the Cyrene-based system compared very favourably upon comparison with standard solvents (THF and DMF; Table 1, entries 9 and 10, respectively).

Continuing with the primary investigation and with an optimised set of reaction conditions, we sought to explore the generality of Cyrene in the Sonogashira cross-coupling (Scheme 2). Significantly, a broad range of functionalised aryl and heteroaryl iodides were tolerated (Scheme 2a).

In addition, electron-deficient aryl bromides were accommodated, although with some variation in yield (3c, 3I, 3o, 3n). Functionality on the alkyne component was also typically well tolerated (Scheme 2b). While 3i and 3j required an extended reaction time, this was a substrate-specific problem for the use of 2a with these ortho-substituted aryl iodides that was not apparent for other alkyne/ortho-substituted iodoarene combinations (Scheme 2c).

Judicious selection of reacting components also enabled the development of a useful Cacchi-type annulation (Scheme 3).
Specifically, employing ortho-amino (5) or ortho-hydroxyaryl iodides (6) in the Sonogashira process generated an alkyne intermediate that, upon increasing the reaction temperature from 30 °C to 60 °C, could undergo 5-endo-dig cyclisation to forge functionalised and pharmaceutically relevant indole, benzofuran, and aza-indole scaffolds in a single operation (7a–f) [48-52].

Finally, with the viewpoint of generality of DMF substitution by Cyrene, the base/temperature sensitivity issue may have potential implications for further applications of Cyrene within well-used organic transformations. For example, the majority of many other standard cross-coupling processes employ inorganic or organic bases and heat (e.g., Suzuki–Miyaura, Heck). Accordingly, Cyrene may be projected to be incompatible with...
standard conditions for these reactions and its use would necessitate base-free or exceptionally mildly basic reaction conditions. In contrast, amide-bond formation is the most practiced reaction in the pharmaceutical industry [4] and these are routinely performed in DMF at room temperature in the presence of organic bases [53]. As such, Cyrene may offer considerable potential in this area. However, additional work will be required to validate the practicality of Cyrene as a viable DMF replacement in these applications.

Conclusion
In summary, we have developed a mild and robust method for the Sonogashira reaction, employing the bio-derived and sustainable alternative to DMF, Cyrene. In addition, we have shown the capacity for extension of the utility of this new solvent towards enabling the cascade synthesis of functionalised indoles and benzofurans via a Cacchi-type annulation. Perhaps more importantly, we have documented some of the limitations of the use of Cyrene as a solvent, providing guidance emerging in relation to the thermal and chemical (base) stabilities of this promising green solvent.

Supporting Information
Supporting Information File 1
Experimental procedures, analytical data, copies of NMR spectra, and single X-ray crystal diffraction data of 4b. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-187-S1.pdf]

Acknowledgements
“Sigma-Aldrich Company Limited” is a subsidiary of Merck KGaA. We thank the University of Strathclyde for a PhD studentship (KLW), Sigma-Aldrich for financial and material support, Circa for Cyrene, and the EPSRC UK National Mass Spectrometry Facility at Swansea University for analyses.

References
5. A SciFinder search of Sonogashira reaction of aryl iodides revealed that of 341979 reactions, 140997 were performed in DMF. Search conducted 7th June 2016.

Scheme 3: Cacchi-type annulation of o-amino/hydroxy iodoarenes. Isolated yields. *Yield using DMF as solvent.
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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.187
Supporting Information
for
Scope and limitations of a DMF bio-alternative within Sonogashira cross-coupling and Cacchi-type annulation

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Experimental procedures, analytical data, copies of NMR spectra, and single X-ray crystal diffraction data of 4b
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9. NMR evidence for the evaluation of the base sensitivity
1. General
All reagents and solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Purification was carried out according to standard laboratory methods.\(^1\)

1.1 Purification of solvents
Cyrene was supplied directly by Circa and used as obtained. DMF was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N\(_2\) in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. THF was obtained from a PureSolv SPS-400-5 solvent purification system and transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. THF was obtained from a PureSolv SPS-400-5 solvent purification system and transferred to and stored in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves and purged with and stored under N\(_2\). CH\(_2\)Cl\(_2\), Et\(_2\)O, EtOAc, MeCN, and petroleum ether 40–60 °C for purification purposes were used as obtained from suppliers without further purification.

1.2 Purification and drying of bases
Et\(_3\)N was dried by heating to reflux over previously activated 4 Å molecular sieves and distilling under vacuum before being purged with, and stored under N\(_2\) in a septum-sealed oven-dried flask over previously activated 4 Å molecular sieves. Inorganic bases were dried in a Heraeus Vacutherm oven at 60 °C under vacuum for a minimum of 24 h before use.

1.3 Experimental details
Reactions were carried out using conventional glassware (preparation of S1 and S2) or in sealed 5 mL microwave vials (optimization reactions and reactions for Schemes 2 and 3). The glassware was oven-dried (150 °C) and purged with N\(_2\) before use. Purging refers to a vacuum/nitrogen-refilling procedure. Room temperature was generally ca. 18 °C. Reactions were carried out at elevated temperatures using a temperature-regulated hotplate/stirrer.

1.4 Purification of products
Thin layer chromatography was carried out using Merck silica plates coated with fluorescent indicator UV254. These were analyzed under 254 nm UV light or developed using a vanillin solution. Normal phase flash chromatography was carried out using ZEOprep 60 HYD 40-63 µm silica gel. Reverse phase flash chromatography was carried out using IST Isolute C18 cartridges. Strong cation-exchange purification was carried out using an SCX cartridge.

1.5 Analysis of products
Fourier transformed infrared (FTIR) spectra were obtained on a Shimadzu IRAffinity-1 machine. \(^1\)H, \(^{13}\)C, \(^{19}\)F and \(^{11}\)B NMR spectra were obtained on a Bruker DRX 500 spectrometer (Avance III HD console, Ascend 500 MHz magnet, BBO smart probe) at 500 MHz, 126 MHz, 471 MHz and 160 MHz, respectively. \(^1\)H NMR for the evaluation of the base sensitivity were obtained on a Bruker AV 400 at 400 MHz. Chemical shifts are reported in ppm and coupling constants are reported in Hz with CDCl\(_3\) referenced at 7.26 (\(^1\)H) and 77.0 ppm (\(^{13}\)C) and DMSO-\(d_6\) referenced at 2.50 (\(^1\)H) and 39.5 (\(^{13}\)C). High-resolution mass spectra were obtained through analysis at the EPSRC UK National Mass Spectrometry Facility at Swansea University or at Glasgow University’s School of Chemistry Mass Spectrometry Service. Crystal data was obtained at 123(2) K using an Oxford Diffraction Gemini instrument and monochromatic Mo radiation.
2. General experimental procedures

General Procedure A: Optimized conditions

For example, synthesis of 1,2-diphenylethylene, 3a.

To an oven-dried 5 mL microwave vessel was added Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %) and CuI (1.9 mg, 0.01 mmol, 4 mol %). The vessel was then capped and purged with N$_2$ before addition of Cyrene (0.5 mL, 0.5 M), Et$_3$N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). The reaction mixture was heated to 30 °C and maintained at this temperature with stirring for 1 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0–5% EtOAc in petroleum ether) to afford the title compound as a white solid (44.5 mg, quant.).

$\nu_{\text{max}}$ (solid): 3068, 1603, 1495, 1446 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 500 MHz): δ 7.55 (dd, $J = 7.2$, 1.9 Hz, 4H), 7.36 (m, 6H).

$^{13}$C NMR (CDCl$_3$, 126 MHz): δ 131.6, 128.4, 128.3, 123.3, 89.4.

HRMS: exact mass calculated for [M] (C$_8$H$_{16}$N) requires $m/z$ 178.0782, found $m/z$ 178.0784.

Characterisation data is consistent with literature reported values.$^2$

General Procedure B: Synthesis of indoles and benzofuran

For example, synthesis of 2-phenyl-1-tosyl-1H-indole (7a).

To an oven-dried 5 mL microwave vessel was added Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), and N-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv). The vessel was then capped and purged with N$_2$ before addition of Cyrene (0.5 mL, 0.5 M), Et$_3$N (104 µL, 0.75 mmol, 3 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). The reaction mixture was heated to 30 °C and maintained at this temperature with stirring for 1 h. The reaction was subsequently heated to 60 °C and maintained at this temperature for 6 h before the vessel was vented and decapped. The solution was then diluted with EtOAc (10 mL), and washed with water (2 × 20 mL) and brine (2 × 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a white solid (78.4 mg, 90%).

$\nu_{\text{max}}$ (solid): 3073, 1368, 1169 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 500 MHz): δ 8.33 (d, $J = 8.4$ Hz, 1H), 7.54–7.50 (m, 2H), 7.45 (t, $J = 8.2$ Hz, 4H), 7.38 (t, $J = 7.4$ Hz, 1H), 7.31–7.28 (m, 3H), 7.06 (d, $J = 8.1$ Hz, 2H), 6.56 (s, 1H), 2.31 (s, 3H).


HRMS: exact mass calculated for [M+H]$^+$ (C$_{21}$H$_{18}$NO$_3$S) requires $m/z$ 348.1058, found $m/z$ 348.1061.

Characterisation data is consistent with literature reported values.$^3$
3. Reaction optimization data

3.1. Variation of concentration
Reactions were carried out according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (X M), Et₃N (104 µL, 0.75 mmol, 3 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at 20 °C for 5 h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the desired compound as a white solid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Concentration (M)</th>
<th>Volume (mL)</th>
<th>Isolated yield (%)</th>
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<tr>
<td>1</td>
<td>0.3</td>
<td>0.83</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>2.5</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.5</td>
<td>100</td>
</tr>
</tbody>
</table>

3.2. Variation of the base
Reactions were carried out according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Base (X equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at 20 °C for 5 h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the desired compound as a white solid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (mass)</th>
<th>Equiv</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂PO₄ (159 mg)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Cs₂CO₃ (245 mg)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>DIPEA (97 mg)</td>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Pyridine (59 mg)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Et₃N (28 mg)</td>
<td>1.1</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>Et₃N (38 mg)</td>
<td>1.5</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>Et₃N (51 mg)</td>
<td>2</td>
<td>92</td>
</tr>
</tbody>
</table>

*a* Formation of solid Cyrene dimer – product was not isolated

3.3. Variation of time and temperature
Reactions were carried out according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at X °C for X h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the desired compound as a white solid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>1</td>
<td>86</td>
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<tr>
<td>2</td>
<td>20</td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>5</td>
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<tr>
<td>4</td>
<td>25</td>
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<td>91</td>
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<tr>
<td>5</td>
<td>30</td>
<td>1</td>
<td>96</td>
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</table>
3.4. Variation of solvent
Reactions were carried out according to General Procedure A using Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), solvent (0.5 mL, 0.5 M), Et$_3$N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After stirring at 30 °C for 1 h, the reaction was subjected to the purification outlined in the General Procedure (silica gel, 0–5% Et$_2$O in petroleum ether) to afford the desired compound as a white solid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
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<tr>
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<tr>
<td>3</td>
<td>DMF</td>
<td>87</td>
</tr>
</tbody>
</table>

4. Base sensitivity study
Base (0.07 mmol) was added to a test tube and Cyrene (0.5 mL) was added. The tube was then capped and the mixture stirred at X °C. After 24 h the reaction mixture was sampled and analysed by TLC (60% EtOAc in petroleum ether) and $^1$H NMR and the resulting spectrum compared with that of Cyrene.

<table>
<thead>
<tr>
<th>Base</th>
<th>Mass (mg)</th>
<th>Temperature (°C)</th>
<th>Reaction (Y/N)</th>
<th>Solid Formation</th>
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<td>N</td>
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<td></td>
<td></td>
<td>50</td>
<td>N</td>
<td>x</td>
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<tr>
<td></td>
<td></td>
<td>100</td>
<td>N</td>
<td>x</td>
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<td>Pyridine</td>
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<tr>
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</tr>
<tr>
<td>K$_3$PO$_4$</td>
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<tr>
<td>KOH</td>
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<td>√</td>
</tr>
</tbody>
</table>
5. Compound characterisation data

5.1. Preparation of intermediates

**S1: N-(5-Chloro-2-iodophenyl)-4-methylbenzenesulfonamide**

![Structure of S1](image)

To a round-bottomed flask charged with 5-chloro-2-iodoaniline (1 g, 3.95 mmol, 1 equiv) was added a solution of 1:1 pyridine in CH₂Cl₂ (0.7 M, 40 mL) and the reaction mixture was cooled to 0 °C. 4-Methylbenzenesulfonyl chloride (750 mg, 3.95 mmol, 1 equiv) was added portionwise, and the reaction mixture was allowed to slowly warm to room temperature and then stirred for 24 h. Upon completion of the reaction, water (80 mL) and CH₂Cl₂ (80 mL) were added. The reaction mixture was separated and the organics were washed with 1 N NaOH (2 × 40 mL), 1 N HCl (2 × 40 mL), and brine (2 × 40 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography (silica gel, 0–12% EtOAc in petroleum ether) to afford the title compound as an off white solid (890 mg, 52%).

1H NMR (CDCl₃, 500 MHz): δ 7.72–7.65 (m, 3H), 7.57 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 6.88–6.80 (m, 2H), 2.42 (s, 3H).

13C NMR (CDCl₃, 126 MHz): δ 144.1, 139.1, 138.1, 135.1, 135.1, 129.4, 127.0, 126.4, 121.4, 88.3, 21.2.

Characterisation data is consistent with literature reported values.

**S2: N-(3-Iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide**

![Structure of S2](image)

Prepared in two steps from 3-iodo-5-nitropyridin-2-amine:

**Step 1:** To a 25 mL three-necked flask charged with 5-nitropyridin-2-amine (1 g, 7.1 mmol, 1 equiv), was added concentrated sulfuric acid (12 mL, 0.6 M) and potassium iodate (653 mg, 2.8 mmol, 0.4 equiv) portionwise, before subsequent heating to 200 °C. Potassium iodide (1.18 g, 7.1 mmol, 1 equiv) was then added dropwise as an aqueous solution (4 mL), and the reaction mixture was stirred at 200 °C for 1.5 h. Upon completion, the reaction mixture was allowed to cool to room temperature before the slow addition of saturated sodium bicarbonate solution (20 mL) and EtOAc (20 mL). The reaction mixture was separated and the organics were washed with an aqueous solution of saturated Na₂S₂O₃ (2 × 30 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give a yellow solid, 3-iodo-5-nitropyridin-2-amine, which was used without further purification (1.64 g, 87%).

**Step 2:** To a 100 mL round-bottomed flask charged with 3-iodo-5-nitropyridin-2-amine (1.29 g, 4.86 mmol, 1 equiv) was added THF (40 mL, 0.13 M) and the reaction mixture was cooled to 0 °C.
Sodium hydride (224 mg, 9.72 mmol, 2 equiv) was added portionwise and the reaction mixture was stirred at 0 °C for 20 minutes. 4-Methylbenzenesulfonyl chloride (1.09 g, 4.86 mmol, 1 equiv) was added portion wise, and the reaction mixture was allowed to slowly warm to room temperature and was stirred for 18 h. Upon completion of the reaction, water (50 mL) and CH₂Cl₂ (50 mL) were added and the reaction mixture was separated and the organics washed with 1 M NaOH (2 × 50 mL), 1 M HCl (2 × 50 mL), and brine (2 × 50 mL). The organics were passed through a hydrophobic frit and concentrated under reduced pressure to give a crude residue, which was purified by flash chromatography (silica gel, 0–30% EtOAc in petroleum ether) to afford the title compound as a yellow solid (1.43 g, 70%).

υₘₐₓ (solid): 3581, 3268, 3064, 2919, 1571, 1444, 1320 cm⁻¹.

¹H NMR (DMSO-d₆, 500 MHz): δ 8.66 (d, J = 2.6 Hz, 1H), 8.40 (d, J = 2.5 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 3.35 (bs, 1H), 2.32 (s, 3H).

¹³C NMR (DMSO-d₆, 126 MHz): δ 161.9, 145.0, 142.3, 140.9, 140.7, 134.7, 128.9, 127.4, 86.7, 21.4.

HRMS: exact mass calculated for [M+H]⁺ (C₁₂H₁₁N₅O₄S) requires m/z 419.9509, found m/z 419.9510.

Characterisation data is consistent with literature reported values.

5.2. Products from Table 1

3a: 1,2-Diphenylethylne

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as a white solid (44.5 mg, quant.).

υₘₐₓ (solid): 3068, 1603, 1495, 1446 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.55 (dd, J = 7.2, 1.9 Hz, 4H), 7.36 (m, 6H).

¹³C NMR (CDCl₃, 126 MHz): δ 131.6, 128.9, 127.4, 86.7, 21.4.

HRMS: exact mass calculated for [M]⁺ (C₁₄H₁₀) requires m/z 178.0782, found m/z 178.0784.

Characterisation data is consistent with literature reported values.

5.3. Products from Scheme 2a

3b: 1-Fluoro-4-(phenylethynyl)benzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 4-fluoroiodobenzene (28.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as a white solid (48.8 mg, quant.).

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 4-fluoroiodobenzene (28.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv).
After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as a white solid (46.9 mg, 96%).

νmax (solid): 2921, 1595, 1508, 1217 cm⁻¹.

'H NMR (CDCl₃, 500 MHz): δ 7.55–7.50 (m, 4H), 7.38–7.33 (m, 3H), 7.05 (t, J = 8.7 Hz, 2H).

'C NMR (CDCl₃, 126 MHz): δ 162.5 (d, 1J_CF = 249.6 Hz), 133.5 (d, 1J_CF = 8.2 Hz), 131.6, 128.4, 128.4, 123.3, 119.4 (d, J_CF = 3.4 Hz), 115.7 (d, 2J_CF = 22.4 Hz), 89.1, 88.3.

19F NMR (CDCl₃, 471 MHz): δ -110.98.

HRMS: exact mass calculated for [M] (C₁₄H₉F) requires m/z 196.0688, found m/z 196.0689.

Characterisation data is consistent with literature reported values.⁵

3e: 1-Nitro-4-(phenylethynyl)benzene

![Chemical structure of 1-Nitro-4-(phenylethynyl)benzene]

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 4-nitro-iodobenzene (62.3 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as an off white solid (48.8 mg, quant.).

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 4-nitro-bromobenzene (50.5 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as an off white solid (14.6 mg, 28%).

νmax (solid): 3107, 2926, 2217, 1593, 1511 cm⁻¹.

'H NMR (CDCl₃, 500 MHz): δ 8.22 (d, J = 8.9 Hz, 2H), 7.67 (d, J = 8.9 Hz, 2H), 7.58–7.54 (m, 2H), 7.39 (dd, J = 5.3, 1.8 Hz, 3H).

'C NMR (CDCl₃, 126 MHz): δ 147.0, 132.3, 131.9, 130.4, 129.3, 128.6, 123.7, 122.1, 94.7, 87.6.

HRMS: exact mass calculated for [M+H]+ (C₁₄H₁₀NO₂) requires m/z 224.0712, found m/z 224.0714.

Characterisation data is consistent with literature reported values.⁵

3d: 1-Methoxy-4-(phenylethynyl)benzene

![Chemical structure of 1-Methoxy-4-(phenylethynyl)benzene]

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 4-iodoanisole (58.5 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% Et₂O in petroleum ether) to afford the title compound as an off white solid (51.9 mg, quant.).

νmax (solid): 3014, 2841, 2217, 1509 cm⁻¹.

'H NMR (CDCl₃, 500 MHz): δ 7.51 (dt, J = 3.9, 2.1 Hz, 2H), 7.49–7.46 (m, 2H), 7.36–7.29 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H).
13C NMR (CDCl₃, 126 MHz): δ 159.6, 133.1, 131.5, 128.3, 127.9, 123.6, 115.4, 114.0, 89.4, 88.1, 55.3.
HRMS: exact mass calculated for [2M+H]+ (C₃₀H₂₅O₂) requires m/z 417.1855, found m/z 417.1847. Characterisation data is consistent with literature reported values.

3e: 4-(Phenylethynyl)phenol

\[
\text{HO} \quad \equiv \quad \text{C} \quad \equiv \\
\text{Ar} \quad \text{Ar}
\]

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (70 µL, 0.5 mmol, 2 equiv), 4-iodophenol (55 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% Et₂O in petroleum ether) to afford the title compound as an off white solid (32.6 mg, 68%).

νmax (solid): 3412, 3059, 1513, 1254 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.51 (dd, J = 7.7, 1.4 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.33 (m, 3H), 6.81 (d, J = 8.6 Hz, 2H).

13C NMR (CDCl₃, 126 MHz): δ 155.7, 133.3, 131.5, 128.3, 127.9, 123.6, 115.7, 115.5, 89.2, 88.1.

HRMS: exact mass calculated for [M+H]+ (C₁₅H₁₃O) requires m/z 209.0966, found m/z 209.1008. Characterisation data is consistent with literature reported values.

3f: 1-Methoxy-3-(phenylethynyl)benzene

\[
\text{MeO} \\
\text{C} \quad \equiv \\
\text{Ar} \\
\text{Ar}
\]

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 3-iodoanisole (29.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as a yellow oil (51.4 mg, 99%).

νmax (liquid film): 2937, 2838 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.57–7.53 (m, 2H), 7.35 (dd, J = 4.9, 2.4 Hz, 3H), 7.27 (t, J = 7.9 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 7.08 (s, 1H), 6.91 (dd, J = 8.3, 2.0 Hz, 1H), 3.83 (s, 3H).

13C NMR (CDCl₃, 126 MHz): δ 159.4, 131.7, 129.4, 128.4, 128.3, 124.3, 124.2, 123.2, 116.4, 114.9, 89.3, 89.2, 55.3.

HRMS: exact mass calculated for [M+Na]+ (C₁₄H₁₁O) requires m/z 195.0810, found m/z 195.0813. Characterisation data is consistent with literature reported values.

3g: 1-Chloro-3-(phenylethynyl)benzene

\[
\text{Cl} \\
\text{C} \quad \equiv \\
\text{Ar} \\
\text{Ar}
\]

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 3-
chloro-iodobenzene (30.9 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as a yellow oil (53.5 mg, 82%).

νₘₐₓ (liquid film): 3064, 2224, 884 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.55–7.51 (m, 3H), 7.41 (dt, J = 7.3, 1.4 Hz, 1H), 7.36 (dd, J = 4.9, 1.7 Hz, 3H), 7.31 (dt, J = 8.0, 1.5 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H).

¹³C NMR (CDCl₃, 126 MHz): δ 134.4, 131.9, 131.6, 129.9, 129.8, 128.8, 128.7, 128.6, 125.2, 122.9, 90.7, 88.1.

HRMS: exact mass calculated for [M]⁺ (C₁⁴H₉Cl) requires m/z 212.0393, found m/z 212.0395.

Characterisation data is consistent with literature reported values.

3h: 1-Nitro-3-(phenylethynyl)benzene

![Chemical Structure](image)

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 3-nitro-iodobenzene (62.3 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as a white solid (55.2 mg, 99%).

νₘₐₓ (solid): 3083, 2213, 1517, 1349 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 8.40–8.37 (m, 1H), 8.19 (m, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.56 (m, 3H), 7.40 (m, 3H).

¹³C NMR (CDCl₃, 126 MHz): δ 148.2, 137.2, 131.8, 129.4, 129.1, 129.5, 126.4, 125.2, 122.9, 91.9, 86.9.

HRMS: exact mass calculated for [M+H]⁺ (C₁₄H₁₀NO₂) requires m/z 224.0712, found m/z 224.0710.

Characterisation data is consistent with literature reported values.

3i: 1-Methyl-2-(phenylethynyl)benzene

![Chemical Structure](image)

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 24 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20–65% MeCN in water) to afford the title compound as a yellow oil (40 mg, 83%).

νₘₐₓ (liquid film): 3023, 2924, 2855, 2217, 1496 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.56–7.53 (m, 2H), 7.50 (d, J = 7.5 Hz, 1H), 7.35 (m, 3H), 7.24 (d, J = 3.9 Hz, 2H), 7.17 (m, 1H), 2.52 (s, 3H).

¹³C NMR (CDCl₃, 126 MHz): δ 140.3, 131.9, 131.7, 129.6, 128.5, 128.3, 125.7, 123.7, 123.2, 93.5, 88.5, 20.9.

HRMS: exact mass calculated for [M]⁺ (C₁₅H₁₂) requires m/z 192.0939, found m/z 192.0935.

Characterisation data is consistent with literature reported values.
3j: 1-Chloro-2-(phenylethynyl)benzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-chloro-iodobenzene (30.5 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 24 h, the reaction mixture was subjected to purification by reverse phase chromatography (C18 cartridge, 20–65% MeCN in water) to afford the title compound as a yellow oil (54.9 mg, quant.).

ν<sub>max</sub> (liquid film): 3060, 2926, 2224, 1495 cm<sup>-1</sup>.

¹H NMR (DMSO-<sup>d</sup>₆, 500 MHz): δ 7.69 (dd, <i>J</i> = 7.5, 1.7 Hz, 1H), 7.62–7.58 (m, 3H), 7.48–7.41 (m, 5H).

¹³C NMR (DMSO-<sup>d</sup>₆, 126 MHz): δ 135.1, 133.8, 131.9, 130.9, 129.9, 129.8, 129.3, 127.9, 122.4, 122.3, 94.8, 86.4.

HRMS: exact mass calculated for [M]+ (C₁₄H₉Cl) requires m/z 212.0393, found m/z 212.0385.

Characterisation data is consistent with literature reported values.

3k: 2-(Phenylethynyl)thiophene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodothiophene (27.6 µL, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et₂O in petroleum ether) to afford the title compound as an off white solid (41.4 mg, 92%).

ν<sub>max</sub> (liquid film): 3088, 2204 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.54–7.50 (m, 2H), 7.35 (dd, <i>J</i> = 5.2, 1.9 Hz, 3H), 7.31–7.28 (m, 2H), 7.02 (dd, <i>J</i> = 5.0, 3.8 Hz, 1H).

¹³C NMR (CDCl₃, 126 MHz): δ 131.9, 131.4, 128.4, 128.4, 127.3, 127.3, 127.1, 123.4, 122.9, 93.0, 82.6.

HRMS: exact mass calculated for [M]+ (C₁₂H₈S) requires m/z 184.0347, found m/z 184.0348.

Characterisation data is consistent with literature reported values.

3l: 2-Nitro-5-(phenylethynyl)pyridine

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 5-bromo-2-nitropyridine (50.8 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% Et₂O in petroleum ether) to afford the title compound as a white solid (51.4 mg, 92%).

ν<sub>max</sub> (solid): 3058, 2219, 1532, 1348 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 8.73 (d, <i>J</i> = 1.6 Hz, 1H), 8.26 (d, <i>J</i> = 8.4 Hz, 1H), 8.10 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 7.58 (dd, <i>J</i> = 7.7, 1.4 Hz, 2H), 7.44–7.38 (m, 3H).
\[^{13}\text{C}\text{ NMR (CDCl}_3\text{, 126 MHz): }\delta 154.8, 151.1, 141.8, 131.9, 129.8, 128.7, 126.7, 121.4, 117.7, 97.9, 84.2.\]

HRMS: exact mass calculated for \([\text{M+H}]^+\) (C\(_{13}\)H\(_9\)N\(_2\)) requires m/z 225.0664, found m/z 225.0670.

3m: 5-Chloro-2-(phenylethynyl)pyridine

![3m structural formula]

Prepared according to General Procedure A using Pd(PPh\(_3\))\(_2\)Cl\(_2\) (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et\(_3\)N (38 µL, 0.275 mmol, 1.1 equiv), 3-chloro-6-iodopyridine (59.8 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–5% Et\(_2\)O in petroleum ether) to afford the title compound as a white solid (54.5 mg, quant.).

\(\nu\)\(_{\text{max}}\) (solid): 3040, 2221, 1493, 1459 cm\(^{-1}\).

\(\text{H NMR (CDCl}_3\text{, 500 MHz): }\delta 8.58\) (d, \(J = 1.8\) Hz, 1H), 7.67 (dd, \(J = 8.4, 2.4\) Hz, 1H), 7.60 (dd, \(J = 7.5, 1.9\) Hz, 2H), 7.48 (d, \(J = 8.4\) Hz, 1H), 7.40–7.36 (m, 3H).

\(\text{C NMR (CDCl}_3\text{, 126 MHz): }\delta 149.1, 141.5, 136.0, 132.1, 131.3, 129.2, 128.5, 127.7, 121.9, 90.4, 87.6.

HRMS: exact mass calculated for \([\text{M+H}]^+\) (C\(_{13}\)H\(_9\)N\(_2\)) requires m/z 214.0418, found m/z 214.0421.

3n: 2-(Phenylethynyl)-1,8-naphthyridine

![3n structural formula]

Prepared according to General Procedure A using Pd(PPh\(_3\))\(_2\)Cl\(_2\) (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et\(_3\)N (38 µL, 0.275 mmol, 1.1 equiv), 2-bromo-1,8-naphthyridine (52.3 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–65% Et\(_2\)O in petroleum ether) to afford the title compound as a white solid (54.3 mg, 94%).

\(\nu\)\(_{\text{max}}\) (solid): 3049, 3008, 2211, 1601, 1498 cm\(^{-1}\).

\(\text{H NMR (CDCl}_3\text{, 500 MHz): }\delta 9.15\) (s, 1H), 8.17 (d, \(J = 8.2\) Hz, 2H), 7.69–7.64 (m, 3H), 7.48 (dd, \(J = 7.7, 3.9\) Hz, 1H), 7.43–7.37 (m, 3H).

\(\text{C NMR (CDCl}_3\text{, 126 MHz): }\delta 156.1, 154.3, 146.9, 137.2, 136.6, 132.4, 129.5, 128.5, 125.4, 122.3, 121.9, 91.6, 89.3.\) Quaternary carbon at ring junction not observed.

HRMS: exact mass calculated for \([\text{M+H}]^+\) (C\(_{16}\)H\(_{11}\)N\(_2\)) requires m/z 231.0922, found m/z 231.0923.

3o: 2-Chloro-6-(phenylethynyl)pyridine

![3o structural formula]

Prepared according to General Procedure A using Pd(PPh\(_3\))\(_2\)Cl\(_2\) (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et\(_3\)N (38 µL, 0.5 mmol, 1.1 equiv), 2-bromo-6-chloropyridine (48 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the
General Procedure (silica gel, 0–10% Et₂O in petroleum ether) to afford the title compound as an off white solid (52.3 mg, quant.).

$\nu_{\text{max}}$ (solid): 3059, 2960, 2226, 1577, 1435 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.63 (t, $J = 7.8$ Hz, 1H), 7.60–7.56 (m, 2H), 7.44 (d, $J = 7.6$ Hz, 1H), 7.37 (q, $J = 5.7$ Hz, 3H), 7.28 (d, $J = 8.0$ Hz, 1H).

$^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ 151.4, 143.6, 138.7, 132.1, 129.3, 128.5, 125.7, 123.6, 121.8, 90.7, 87.5.

HRMS: exact mass calculated for [M+H]$^+$ (C$_{13}$H$_9$NCl) requires m/z 214.0424, found m/z 214.0427.

$^1$H NMR and HRMS data is consistent with literature reported values.

83p: 1-Methyl-5-(phenylethynyl)-1H-indole

Prepared according to General Procedure A using Pd(PPh$_3$)$_2$Cl$_2$ (2.6 mg, 0.004 mmol, 2 mol %), CuI (1.4 mg, 0.007 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et$_3$N (28 µL, 0.20 mmol, 1.1 equiv), 5-iodo-1-methyl-1H-indole (47 mg, 0.18 mmol, 1 equiv), and phenylacetylene (21 µL, 0.19 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% Et$_2$O in petroleum ether) to afford the title compound as an off white solid (27.7 mg, 67%).

$\nu_{\text{max}}$ (solid): 3051, 2926, 2208, 1597, 1496 cm$^{-1}$.

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.85 (s, 1H), 7.57–7.54 (m, 2H), 7.41 (dd, $J = 8.5$, 1.2 Hz, 1H), 7.35 (t, $J = 7.2$ Hz, 2H), 7.30 (t, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 3.1$ Hz, 1H), 6.49 (d, $J = 2.7$ Hz, 1H), 3.80 (s, 3H).

$^{13}$C NMR (CDCl$_3$, 126 MHz): $\delta$ 136.4, 131.5, 129.8, 128.4, 128.3, 127.7, 125.2, 124.8, 124.1, 113.8, 109.3, 101.3, 91.2, 87.0, 32.9.

HRMS: exact mass calculated for [M] (C$_{17}$H$_{13}$N) requires m/z 231.1048, found m/z 231.1057.

Characterisation data is consistent with literature reported values.

5.4. Products from Scheme 2b

3q: Phenylethynylboronic acid, MIDA ester

Prepared according to General Procedure A using Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et$_3$N (38 µL, 0.275 mmol, 1.1 equiv), iodosobenzene (27.9 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (61.3 mg, 95%).

Prepared according to General Procedure A using Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et$_3$N (38 µL, 0.275 mmol, 1.1 equiv), iodosobenzene (27.9 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined
in the General Procedure (silica gel, 0-60% EtOAc in petroleum ether) to afford the title compound as an off white solid (61.2 mg, 95\%).

\( \nu_{\text{max}} \) (solid): 3025, 2198, 1768, 1493 cm\(^{-1}\).

\(^1\)H NMR (DMSO-\(d_6\), 500 MHz): \( \delta \) 7.51–7.48 (m, 2H), 7.42–7.37 (m, 3H), 4.32 (d, \( J = 17.1 \) Hz, 2H), 4.15 (d, \( J = 17.1 \) Hz, 2H), 3.08 (s, 3H).

\(^{13}\)C NMR (DMSO-\(d_6\), 126 MHz): \( \delta \) 169.1, 132.0, 129.4, 129.1, 122.9, 99.9, 61.9, 48.4. Carbon bearing boron not observed.

\(^{11}\)B NMR (DMSO-\(d_6\), 160 MHz): \( \delta \) 6.24.

HRMS: exact mass calculated for \([M+\text{NH}_4]^+\) (C\(_{13}\)H\(_{16}\)BN\(_2\)O\(_4\)) requires \( m/z \) 275.1202, found \( m/z \) 275.1198.

Characterisation data is consistent with literature reported values.

3r: Trimethyl(phenylethynyl)silane

\[ \text{Prepared according to General Procedure A using Pd(PPh}_3\text{)_2Cl}_2 (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et}_3\text{N (38 \( \mu\)L, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 \( \mu\)L, 0.25 mmol, 1 equiv), and ethynyltrimethylsilane (37 \( \mu\)L, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% EtOAc in petroleum ether) to afford the title compound as a colourless oil (44 mg, quant.).} \]

\( \nu_{\text{max}} \) (liquid film): 2962, 2161, 1491, 1251 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 7.50–7.47 (m, 2H), 7.34–7.29 (m, 3H), 0.27 (s, 9H).

\(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta \) 131.9, 128.5, 128.2, 123.1, 105.1, 94.1, -0.01.

HRMS: exact mass calculated for [M] (C\(_{11}\)H\(_{14}\)Si) requires \( m/z \) 174.0865, found \( m/z \) 174.0866.

Characterisation data is consistent with literature reported values.

3s: 4-Phenylbut-3-yn-1-yl 4-methylbenzenesulfonate

\[ \text{Prepared according to General Procedure A using Pd(PPh}_3\text{)_2Cl}_2 (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et}_3\text{N (38 \( \mu\)L, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 \( \mu\)L, 0.25 mmol, 1 equiv), and 3-butylnyl-p-toluenesulfonate (46.3 \( \mu\)L, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0-30% EtOAc in petroleum ether) to afford the title compound as a colourless oil (60.7 mg, 81\%).} \]

\( \nu_{\text{max}} \) (liquid film): 2924, 2980, 1493, 1261 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 7.79 (d, \( J = 8.3 \) Hz, 2H), 7.32–7.28 (m, 3H), 7.28–7.23 (m, 4H), 4.16 (t, \( J = 7.0 \) Hz, 2H), 2.75 (t, \( J = 7.0 \) Hz, 2H), 2.39 (s, 3H).

\(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta \) 144.9, 132.9, 131.7, 129.9, 128.2, 128.2, 127.9, 122.9, 83.8, 82.7, 67.8, 21.6, 20.4.

HRMS: exact mass calculated for [M+Na\(^{+}\)] (C\(_{17}\)H\(_{16}\)O\(_3\)SNa) requires \( m/z \) 323.0712, found \( m/z \) 323.0702.

Characterisation data is consistent with literature reported values.

3t: N,N-Dimethyl-3-phenylprop-2-yn-1-amine
Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and dimethyl(prop-2-ynyl)amine (28 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to purification by SCX (MeOH in 3M ammonium MeOH) to afford the title compound as a yellow oil (23.6 mg, 60%).

νmax (liquid film): 3058, 2941, 2824, 2775, 1690, 1493 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.46–7.42 (m, 2H), 7.32–7.28 (m, 3H), 3.49 (s, 2H), 2.39 (s, 6H).

¹³C NMR (CDCl₃, 126 MHz): δ 131.7, 128.3, 128.1, 123.2, 85.4, 84.4, 48.6, 44.2.

HRMS: exact mass calculated for [M+H]⁺ (C₁₁H₁₄N) requires m/z 160.1126, found m/z 160.1125.

Characterisation data is consistent with literature reported values.

3u: Pent-1-yn-1-ylbenzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 1-pentyne (25.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et₂O in petroleum ether) to afford the title compound as a yellow oil (34.5 mg, 96%).

νmax (liquid film): 3058, 2963, 2934, 2872, 2237, 1601, 1491 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.32 (dd, J = 7.5, 1.9 Hz, 2H), 7.22–7.17 (m, 3H), 2.31 (t, J = 7.0 Hz, 2H), 1.56 (h, J = 7.3 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H).

¹³C NMR (CDCl₃, 126 MHz): δ 131.6, 128.2, 127.5, 124.1, 90.3, 80.7, 22.2, 21.4, 13.6.

HRMS: exact mass calculated for [M+H]⁺ (C₁₁H₁₂N) requires m/z 144.0939, found m/z 144.0941.

Characterisation data is consistent with literature reported values.

3v: (Cyclopropylethynyl)benzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and ethynylcyclopropane (22 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et₂O in petroleum ether) to afford the title compound as a colourless oil (30.3 mg, 85%).

νmax (liquid film): 3034, 2924, 2219, 1597, 1513 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.42–7.38 (m, 2H), 7.30–7.26 (m, 3H), 1.47 (m, 1H), 0.91–0.87 (m, 2H), 0.83 (m, 2H).

¹³C NMR (CDCl₃, 126 MHz): δ 131.6, 128.1, 127.4, 123.9, 93.4, 75.8, 8.6, 0.1.

Characterisation data is consistent with values reported in the literature.
3w: Prop-1-yne-1,3-diyl dibenzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 3-phenyl-1-propyne (32.6 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et₂O in petroleum ether) to afford the title compound as a colourless oil (38.7 mg, 81%).

υmax (liquid film): 3064, 3032, 2924, 1601, 1493 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.46 (dd, J = 6.5, 3.0 Hz, 2H), 7.35 (d, J = 7.4 Hz, 2H), 7.30–7.26 (m, 3H), 7.13 (t, J = 8.8, 5.8 Hz, 1H), 3.85 (s, 2H).

¹³C NMR (CDCl₃, 126 MHz): δ 136.8, 131.4, 128.2, 127.7, 123.8, 123.7, 87.5, 82.7, 25.8.

HRMS: exact mass calculated for [M⁺] (C₁₅H₁₂) requires m/z 192.0939, found m/z 192.0932.

Characterisation data is consistent with literature reported values.

3x: (Cyclohex-1-en-1-ylethynyl)benzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 1-ethynylcyclohexene (30.8 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et₂O in petroleum ether) to afford the title compound as an off-white solid (46.3 mg, quant.).

υmax (liquid film): 3064, 2935, 2865, 2204, 1716, 1670 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.46 (dd, J = 7.8, 1.6 Hz, 2H), 7.28–7.23 (m, 3H), 6.20–6.16 (m, 1H), 2.20 (dd, J = 8.1, 6.0 Hz, 2H), 2.13–2.09 (m, 2H), 1.68–1.63 (m, 2H), 1.61–1.56 (m, 2H).

¹³C NMR (CDCl₃, 126 MHz): δ 135.2, 131.4, 128.2, 127.7, 123.8, 120.8, 91.3, 86.8, 29.3, 25.8, 22.4, 21.6.

HRMS: exact mass calculated for [M⁺] (C₁₄H₁₅) requires m/z 182.1095, found m/z 182.1102.

Characterisation data is consistent with literature reported values.

3y: 1-Methyl-4-(phenylethynyl)benzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and p-tolylacetylene (33.2 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure...
Procedure (silica gel, 0–1% Et₂O in petroleum ether) to afford the title compound as an off white solid (46.9 mg, 98%).

ν_max (liquid film): 3032, 2921, 2219, 1597, 1511 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.53 (dd, J = 7.7, 1.5 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.3 Hz, 3H), 7.16 (d, J = 7.9 Hz, 2H), 2.38 (s, 3H).

13C NMR (CDCl₃, 126 MHz): δ 138.4, 131.6, 131.5, 129.1, 128.3, 128.1, 123.5, 120.2, 89.6, 88.7, 21.5.

HRMS: exact mass calculated for [M] (C₁₅H₁₂) requires m/z 192.0939, found m/z 192.0942.

Characterisation data is consistent with literature reported values.

23z: 1-(Phenylethynyl)-2-(trifluoromethyl)benzene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 2-ethynyltrifluorotoluene (36.5 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et₂O in petroleum ether) to afford the title compound as a colourless oil (53 mg, 86%).

ν_max (liquid film): 3066, 2224, 1312 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 7.69 (t, J = 8.3 Hz, 2H), 7.57 (dd, J = 6.5, 3.0 Hz, 2H), 7.53 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.40–7.35 (m, 3H).

13C NMR (CDCl₃, 126 MHz): δ 133.7, 131.7, 131.4, 128.8, 128.4, 127.9, 125.9 (q, 3J_CF = 5.2 Hz), 123.6 (q, 1J_CF = 273.5 Hz), 122.8, 121.6, 94.9, 85.4. Carbon bearing trifluoromethyl group not observed.

19F NMR (CDCl₃, 471 MHz): δ -62.35.

HRMS: exact mass calculated for [M]⁺ (C₁₅H₉F₃) requires m/z 246.0656, found m/z 246.0654.

Characterisation data is consistent with literature reported values.

3aa: 2-(Phenylethynyl)pyridine

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 2-ethynylpyridine (26.5 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a yellow oil (43.3 mg, 97%).

ν_max (liquid film): 3053, 2224, 1582, 1493, 1463 cm⁻¹.

1H NMR (CDCl₃, 500 MHz): δ 8.62 (d, J = 4.4 Hz, 1H), 7.67 (td, J = 7.7, 1.7 Hz, 1H), 7.60 (dd, J = 6.5, 3.1 Hz, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.38–7.35 (m, 3H), 7.26–7.22 (m, 1H).

13C NMR (CDCl₃, 126 MHz): δ 150.1, 143.5, 136.2, 132.1, 128.9, 128.4, 127.2, 122.8, 122.3, 89.2, 88.6.

HRMS: exact mass calculated for [M+Na]⁺ (C₂₁H₁₈BF₃N₂O₆SNa) requires m/z 179.0735, found m/z 179.0731.
Characterisation data is consistent with literature reported values.²

3ab: 2-(Phenylethynyl)thiophene

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodobenzene (27.9 µL, 0.25 mmol, 1 equiv), and 2-ethynylthiophene (24.9 µL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et₂O in petroleum ether) to afford the title compound as an off white solid (42.4 mg, 92%).

ν_max (liquid film): 3088, 2204 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.54–7.50 (m, 2H), 7.35 (m, 3H), 7.31–7.28 (m, 2H), 7.02 (t, J = 4.4 Hz, 1H).

¹³C NMR (CDCl₃, 126 MHz): δ 131.9, 131.4, 128.4, 128.4, 127.3, 127.1, 123.4, 122.9, 93.0, 82.6.

HRMS: exact mass calculated for [M⁻] (C₁₂H₈S) requires m/z 184.0347, found m/z 184.0349.

Characterisation data is consistent with literature reported values.²

5.5. Products from Scheme 2c

3ac: 2-Acetyl phenylethynylboronic acid, MIDA ester

Prepared according to General Procedure A using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodoacetophenone (35.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–100% EtOAc in petroleum ether) to afford the title compound as an off white solid (66.5 mg, 89%).

ν_max (solid): 2960, 2193, 1770, 1684 cm⁻¹.

¹H NMR (DMSO-d₆, 500 MHz): δ 7.79 (dd, J = 7.7, 0.9 Hz, 1H), 7.63 (dd, J = 7.6, 0.9 Hz, 1H), 7.57 (td, J = 7.5, 1.3 Hz, 1H), 7.52 (td, J = 7.6, 1.3 Hz, 1H), 4.34 (d, J = 17.1 Hz, 2H), 4.13 (d, J = 17.1 Hz, 2H), 3.11 (s, 3H), 2.63 (s, 3H).

¹³C NMR (DMSO-d₆, 126 MHz): δ 200.1, 169.1, 141.2, 134.6, 131.9, 129.4, 129.2, 120.7, 98.6, 61.9, 48.4, 29.9. Carbon bearing boron not observed.

¹¹B NMR (DMSO-d₆, 160 MHz): δ 6.23.

HRMS: exact mass calculated for [M⁺NH₄⁺]⁺ (C₁₅H₁₆BN₂O₃) requires m/z 317.1305, found m/z 317.1303.

3ad: 2-Methyl-phenylethynylboronic acid, MIDA ester
Prepared according to General Procedure A using Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et$_3$N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (62.9 mg, 93%).

Prepared according to General Procedure A using Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et$_3$N (38 µL, 0.275 mmol, 1.1 equiv), 2-iodotoluene (31.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (62.3 mg, 92%).

$\nu_{\text{max}}$ (solid): 3019, 2911, 1770, 1290, 1247 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$, 500 MHz): δ 7.45 (d, $J = 7.4$ Hz, 1H), 7.31–7.27 (m, 2H), 7.22–7.18 (m, 1H), 4.33 (d, $J = 17.1$ Hz, 2H), 4.15 (d, $J = 17.1$ Hz, 2H), 3.09 (s, 3H), 2.40 (s, 3H).

$^{13}$C NMR (DMSO-$d_6$, 126 MHz): δ 169.2, 140.3, 132.4, 129.9, 129.3, 126.3, 122.7, 98.7, 61.9, 48.4, 20.8. Carbon bearing boron not observed.

$^{11}$B NMR (DMSO-$d_6$, 160 MHz): δ 6.37.

HRMS: exact mass calculated for [M+NH] ($C_{14}H_{18}BN_2O_4$) requires $m/z$ 289.1355, found $m/z$ 289.1354.

Characterisation data is consistent with literature reported values.$^{17}$

3ae: 2-Trifluoromethoxy-phenylethynylboronic acid, MIDA ester

Prepared according to General Procedure A using Pd(PPh$_3$)$_2$Cl$_2$ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et$_3$N (38 µL, 0.275 mmol, 1.1 equiv), 2-(trifluoromethoxy)iodobenzene (38.8 µL, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–60% EtOAc in petroleum ether) to afford the title compound as an off white solid (71.8 mg, 85%).

$\nu_{\text{max}}$ (solid): 3016, 2922, 2965, 2198, 1772, 1217, 1024 cm$^{-1}$.

$^1$H NMR (DMSO-$d_6$, 500 MHz): δ 7.69 (d, $J = 7.5$ Hz, 1H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.45 (dd, $J = 16.7$, 8.6 Hz, 2H), 4.35 (d, $J = 17.2$ Hz, 2H), 4.15 (d, $J = 17.2$ Hz, 2H), 3.09 (s, 3H).

$^{13}$C NMR (DMSO-$d_6$, 126 MHz): δ 169.0, 148.9, 134.5, 131.3, 128.3, 121.9, 120.6 (q, $^1J_{CF} = 257.4$ Hz), 117.3, 93.5, 62.1, 48.3. Carbon bearing boron not observed.

$^{11}$B NMR (DMSO-$d_6$, 160 MHz): δ 6.29.

$^{19}$F NMR (DMSO-$d_6$, 471 MHz): δ -56.54.

HRMS: exact mass calculated for [M+H]$^+$ ($C_{14}H_{12}BF_3NO_4$) requires $m/z$ 342.0763, found $m/z$ 342.0767.
3af: Triisopropyl(2-(trifluoromethoxy)phenyl)ethynyl)silane

\[
\begin{array}{c}
\text{O} \\
\text{CF}_3
\end{array}
\text{Si(Pr)_3}
\]

Prepared according to General Procedure A using Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et\textsubscript{3}N (38 \muL, 0.275 mmol, 1.1 equiv), 2-(trifluoromethoxy)iodobenzene (38.8 \muL, 0.25 mmol, 1 equiv), and (triisopropylsilyl)acetylene (58.9 \muL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% Et\textsubscript{2}O in petroleum ether) to afford the title compound as a colourless oil (58.3 mg, 68%).

\(\nu_{\text{max}}\) (liquid film): 2947, 2868, 2167, 1491, 1258, 1219, 1169 cm\textsuperscript{-1}.

\(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 7.47 (dd, \(J = 7.6, 1.3\) Hz, 1H), 7.28–7.24 (m, 1H), 7.19–7.14 (m, 2H), 1.06 (s, 21H).

\(^{13}\)C NMR (CDCl\textsubscript{3}, 126 MHz): \(\delta\) 149.8, 134.1, 129.4, 126.6, 121.2, 120.6 (q, \(J_{\text{CF}} = 258.1\) Hz), 118.3, 100.4, 97.1, 18.5, 11.2.

\(^{19}\)F NMR (471 MHz, CDCl\textsubscript{3}): \(\delta\) -57.50.

HRMS: exact mass calculated for [M] (C\textsubscript{18}H\textsubscript{25}F\textsubscript{3}SiO) requires \(m/z\) 342.1627, found \(m/z\) 342.1626.

Characterisation data is consistent with literature reported values.\textsuperscript{18}

3ag: 2-((Triisopropylsilyl)ethynyl)aniline

\[
\begin{array}{c}
\text{NH}_2
\end{array}
\text{Si(Pr)_3}
\]

Prepared according to General Procedure A using Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et\textsubscript{3}N (38 \muL, 0.275 mmol, 1.1 equiv), 2-iodoaniline (54.8 mg, 0.25 mmol, 1 equiv), and (triisopropylsilyl)acetylene (58.9 \muL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–10% Et\textsubscript{2}O in petroleum ether) to afford the title compound as a yellow oil (45.3 mg, 66%).

\(\nu_{\text{max}}\) (liquid film): 3487, 3388, 2945, 2867, 2146, 1616, 1318 cm\textsuperscript{-1}.

\(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz): \(\delta\) 7.31 (dd, \(J = 7.7, 1.1\) Hz, 1H), 7.14–7.09 (m, 1H), 6.71–6.64 (m, 2H), 4.25 (s, 2H), 1.14 (s, 21H).

\(^{13}\)C NMR (CDCl\textsubscript{3}, 126 MHz): \(\delta\) 148.3, 132.4, 129.7, 117.7, 114.1, 108.3, 103.7, 95.9, 18.7, 11.3.

HRMS: exact mass calculated for [M+H]\textsuperscript{+} (C\textsubscript{17}H\textsubscript{28}NSi) requires \(m/z\) 274.1986, found \(m/z\) 274.1986.

Characterisation data is consistent with literature reported values.\textsuperscript{18}

3ah: ((2-Chlorophenyl)ethynyl)triisopropysilane

\[
\begin{array}{c}
\text{Cl}
\end{array}
\text{Si(Pr)_3}
\]

Prepared according to General Procedure A using Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et\textsubscript{3}N (38 \muL, 0.275 mmol, 1.1 equiv), 2-chloro-iodobenzene (30.5 \muL, 0.25 mmol, 1 equiv), and (triisopropylsilyl)acetylene (58.9 \muL, 0.263 mmol, 1.05 equiv). After 1 h, the reaction mixture was subjected to purification by reverse phase chromatography (C\textsubscript{18} cartridge, 20–100% MeCN in water) to afford the title compound as a yellow oil (47.7 mg, 65%).
\( \nu_{\text{max}} \) (liquid film): 2945, 2867, 2163, 1472, 1225 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 7.51 (dd, \( J = 7.5, 1.6 \) Hz, 1H), 7.38 (dd, \( J = 7.9, 0.9 \) Hz, 1H), 7.23 (td, \( J = 7.7, 1.8 \) Hz, 1H), 7.19 (td, \( J = 7.5, 1.2 \) Hz, 1H), 1.15 (s, 21H).

\(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta \) 136.5, 133.9, 129.4, 126.4, 123.6, 103.3, 96.9, 18.8, 11.5.

HRMS: exact mass calculated for [M] (C\(_{17}\)H\(_{25}\)ClSi) requires \( m/z \) 292.1414, found \( m/z \) 292.1431.

5.6. Cyrene homo-aldol adducts, 4a and 4b

To a stirred solution of Cyrene (256 mg, 2.0 mmol, 1 equiv) was added DBU (30 mg, 0.2 mmol, 0.1 equiv) and the mixture heated to 100 °C for 10 minutes. The resulting mixture was cooled to 20 °C giving a viscous brown oil and then kept at 20 °C for 72 hours over which time the mixture began to crystallise. The mixture was then purified by flash chromatography (30% EtOAc/hexanes to EtOAc) to give 4a as a colourless oil (40 mg, 16%).

\( \nu_{\text{max}} \) (neat): 3470, 2962, 2895, 1731 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 5.71 (s, 1H), 5.04 (s, 1H), 4.73–4.70 (m, 1H), 4.44–4.41 (m, 1H), 4.01 (br d, \( J = 7.4 \) Hz, 1H), 3.91 (ddd, \( J = 7.4, 4.9, 1.6 \) Hz, 1H), 3.83 (d, \( J = 7.1 \) Hz, 1H), 3.76 (ddd, \( J = 7.1, 5.1, 0.9 \) Hz, 1H), 3.35 (dd, \( J = 12.0, 7.4 \) Hz, 1H), 2.72 (s, 1H), 2.27 (dddd, \( J = 13.3, 12.0, 3.7, 1.8 \) Hz, 1H), 1.96 (ddd, \( J = 13.3, 7.4, 1.6 \) Hz, 1H), 1.64–1.59 (m, 3H), 1.50–1.46 (m, 1H).

\(^{13}\)C NMR (CDCl\(_3\), 126 MHz): \( \delta \) 203.7, 102.9, 101.6, 73.6, 73.2, 72.9, 68.4, 67.9, 42.7, 32.6, 26.7, 25.1.

ESI-MS: \( m/z \) 257 (50, [M+H]+), 279 (100, [M+Na]).

To an oven-dried 5 mL microwave vessel was added K\(_3\)PO\(_4\) (637 mg, 3 mmol, 3 equiv). The vessel was then capped and purged with N\(_2\) before addition of THF (4 mL, 0.25 M), and Cyrene (123 \( \mu \)L, 1 mmol, 1 equiv). The reaction mixture was heated to 70 °C and maintained at this temperature with stirring for 8 h before the vessel was vented, and decapped. The solution was then diluted with EtOAc (20 mL), and washed with water (2 \( \times \) 20 mL) and brine (2 \( \times \) 20 mL). The organics were then passed through a hydrophobic frit and concentrated under reduced pressure to give an off white solid, which was purified by flash chromatography (silica gel, 0–50% EtOAc in petroleum ether) to afford the title compound as a white solid (105 mg, 88%).

\( \nu_{\text{max}} \) (solid): 2898, 1703, 1621, 1098 cm\(^{-1}\).

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 6.76 (s, 1H), 5.18 (s, 1H), 4.79 (t, \( J = 5.1 \) Hz, 1H), 4.60 (t, \( J = 4.0 \) Hz, 1H), 3.94–3.83 (m, 4H), 2.78 (dd, \( J = 16.3, 2.6 \) Hz, 1H), 2.56 (d, \( J = 16.3 \) Hz, 1H), 2.41–2.24 (m, 2H), 2.14–2.07 (m, 1H), 1.75 (dd, \( J = 13.5, 6.5 \) Hz, 1H).
13C NMR (CDCl3, 126 MHz): δ 190.7, 151.0, 123.4, 101.5, 97.2, 72.6, 72.5, 68.7, 67.8, 34.1, 28.8, 20.4. 
HRMS: exact mass calculated for [M] (C12H14) requires m/z 236.0841, found m/z 236.0839.

5.7. Products from Scheme 3
7a: 2-Phenyl-1-tosyl-1H-indole

Prepared according to General Procedure B using Pd(PPh3)2Cl2 (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et3N (104 µL, 0.75 mmol, 3 equiv), N-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a white solid (78.4 mg, 90%).

Prepared according to General Procedure B using Pd(PPh3)2Cl2 (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), DMF (0.5 mL, 0.5 M), Et3N (104 µL, 0.75 mmol, 3 equiv), N-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–15% EtOAc in petroleum ether) to afford the title compound as a white solid (78.6 mg, 91%).

υmax (solid): 3073, 1368, 1169 cm⁻¹.

1H NMR (CDCl3, 500 MHz): δ 8.33 (d, J = 8.4 Hz, 1H), 7.54–7.50 (m, 2H), 7.45 (t, J = 8.2 Hz, 4H), 7.38 (t, J = 7.4 Hz, 1H), 7.31–7.28 (m, 3H), 7.06 (d, J = 8.1 Hz, 2H), 6.56 (s, 1H), 2.31 (s, 3H).


HRMS: exact mass calculated for [M+H]+ (C25H16N2O2S) requires m/z 348.1058, found m/z 348.1061. Characterization data is consistent with literature reported values.3

7b: 5-Nitro-2-phenyl-1-tosyl-1H-pyrrolo[2,3-b]pyridine

Prepared according to General Procedure B using Pd(PPh3)2Cl2 (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et3N (104 µL, 0.75 mmol, 3 equiv), N-(3-iodo-5-nitropyridin-2-yl)-4-methylbenzenesulfonamide (104 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–30% EtOAc in petroleum ether) to afford the title compound as an off white solid (71.4 mg, 73%).

υmax (solid): 3070, 2935, 1593, 1517, 1394, 1346, 1184 cm⁻¹.

1H NMR (CDCl3, 500 MHz): δ 9.32 (d, J = 2.4 Hz, 1H), 8.61 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.3 Hz, 2H), 7.55 – 7.48 (m, 5H), 7.24 (d, J = 8.1 Hz, 2H), 6.63 (s, 1H), 2.37 (s, 3H).

13C NMR (CDCl3, 126 MHz): δ 151.3, 145.8, 145.8, 141.4, 140.3, 135.3, 131.5, 129.9, 129.6, 129.6, 128.2, 127.9, 124.3, 121.4, 108.3, 21.7.

HRMS: exact mass calculated for [M+H]+ (C25H16N2O2S) requires m/z 394.0862, found m/z 394.0869.
7c: 2-Phenylbenzofuran

![2-Phenylbenzofuran](image)

Prepared according to General Procedure B using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (104 µL, 0.75 mmol, 3 equiv), 2-iodophenol (55 mg, 0.25 mmol, 1 equiv), and phenylacetylene (28.8 µL, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–1% EtOAc in petroleum ether) to afford the title compound as a white solid (43.3 mg, 89%).

νmax (solid): 3038, 2924, 2855 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, J = 7.4 Hz, 2H), 7.59 (d, J = 7.5 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.03 (s, 1H).

¹³C NMR (CDCl₃, 126 MHz): δ 155.9, 154.9, 130.5, 129.2, 128.8, 128.6, 124.9, 124.3, 122.9, 120.9, 111.2, 101.3

HRMS: exact mass calculated for [M] (C₁₄H₁₀O) requires m/z 194.0732, found m/z 194.0737.

Characterization data is consistent with literature reported values.

7d: (1-Tosyl-1H-indol-2-yl)boronic acid, MIDA ester

![1-Tosyl-1H-indol-2-yl]boronic acid, MIDA ester](image)

Prepared according to General Procedure B using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (104 µL, 0.75 mmol, 3 equiv), N-(2-iodophenyl)-4-methylbenzenesulfonamide (93 mg, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–80% EtOAc in petroleum ether) to afford the title compound as a white solid (87.4 mg, 82%).

νmax (solid): 2928, 1763, 1450, 1176, 1038 cm⁻¹.

¹H NMR (DMSO-d₆, 500 MHz): δ 8.12 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 7.7 Hz, 1H), 7.37 (dd, J = 13.1, 8.0 Hz, 3H), 7.25 (t, J = 7.4 Hz, 1H), 7.06 (s, 1H), 4.47 (d, J = 17.5 Hz, 2H), 4.23 (d, J = 17.4 Hz, 2H), 2.96 (s, 3H), 2.32 (s, 3H).

¹³C NMR (DMSO-d₆, 126 MHz): δ 169.6, 145.72, 138.9, 135.5, 130.4, 130.1, 127.08, 125.7, 123.9, 122.2, 122.0, 114.7, 64.8, 49.9, 21.5. Carbon bearing boron not observed.

¹¹B NMR (DMSO-d₆, 160 MHz): δ 10.28.

HRMS: exact mass calculated for [M+H]⁺ (C₂₀H₂₀BN₂O₂S) requires m/z 427.1139, found m/z 427.1139.

Characterization data is consistent with literature reported values.

7e: (5-Fluoro-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester

![5-Fluoro-1-tosyl-1H-indol-2-yl]boronic acid, MIDA ester](image)

Prepared according to General Procedure B using Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol, 2 mol %), CuI (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et₃N (104 µL, 0.75 mmol, 3 equiv), N-(4-fluoro-2-iodophenyl)-4-methylbenzenesulfonamide (98 mg, 0.25 mmol, 1 equiv), and ethynyl boronic
acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–80% EtOAc in petroleum ether) to afford the title compound as a white solid (98 mg, 88%).

υ\text{max} \text{(solid):} 2930, 1750, 1305, 1174, 1040 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (DMSO-\textit{d}_6, 500 MHz): \(δ\) 8.13 (dd, \(J = 9.2, 4.3\) Hz, 1H), 7.91 (d, \(J = 8.4\) Hz, 2H), 7.47 (dd, \(J = 8.8, 2.6\) Hz, 1H), 7.40 (d, \(J = 8.2\) Hz, 2H), 7.22 (td, \(J = 9.2, 2.6\) Hz, 1H), 7.06 (s, 1H), 4.48 (d, \(J = 17.5\) Hz, 2H), 4.24 (d, \(J = 17.5\) Hz, 2H), 2.96 (s, 3H), 2.33 (s, 3H).

\textsuperscript{13}C NMR (DMSO-\textit{d}_6, 126 MHz): \(δ\) 169.6, 159.3 (d, \(J_{CF} = 238.2\) Hz), 145.9, 135.4, 135.3, 131.2 (d, \(J_{CF} = 10.4\) Hz), 130.5, 127.1, 121.9, 116.1 (d, \(J_{CF} = 9.4\) Hz), 113.5 (d, \(J_{CF} = 25.5\) Hz), 107.1 (d, \(J_{CF} = 23.5\) Hz), 64.8, 49.9, 21.5. Carbon bearing boron not observed.

\textsuperscript{11}B NMR (DMSO-\textit{d}_6, 160 MHz): \(δ\) 10.09.

\textsuperscript{19}F NMR (DMSO-\textit{d}_6, 471 MHz): \(δ\) -120.04.

HRMS: exact mass calculated for [M] \((C_{21}H_{18}BF_3N_2O_6SNa)\) requires \(m/z\) 444.2966, found \(m/z\) 444.0951.

Characterization data is consistent with literature reported values.\textsuperscript{4}

**7f**: (6-Chloro-1-tosyl-1H-indol-2-yl)boronic acid, MIDA ester

Prepared according to General Procedure B using Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} (3.5 mg, 0.005 mmol, 2 mol %), Cul (1.9 mg, 0.01 mmol, 4 mol %), Cyrene (0.5 mL, 0.5 M), Et\textsubscript{3}N (104 µL, 1 equiv), N-(4-chloro-2-iodophenyl)-4-methylbenzenesulfonamide (102 mg, 0.25 mmol, 1 equiv), and ethynyl boronic acid, MIDA ester (47.5 mg, 0.263 mmol, 1.05 equiv). After 7 h, the reaction mixture was subjected to the purification method outlined in the General Procedure (silica gel, 0–80% EtOAc in petroleum ether) to afford the title compound as a white solid (116 mg, quant.).

υ\text{max} \text{(solid):} 2922, 1763, 1455, 1267, 1173, 1038 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (DMSO-\textit{d}_6, 500 MHz): \(δ\) 8.11 (s, 1H), 7.90 (d, \(J = 8.4\) Hz, 2H), 7.69 (d, \(J = 8.4\) Hz, 1H), 7.42 (d, \(J = 8.2\) Hz, 2H), 7.34 (dd, \(J = 8.4, 1.7\) Hz, 1H), 7.09 (s, 1H), 4.48 (d, \(J = 17.5\) Hz, 2H), 4.23 (d, \(J = 17.4\) Hz, 2H), 2.94 (s, 3H), 2.34 (s, 3H).

\textsuperscript{13}C NMR (DMSO-\textit{d}_6, 126 MHz): \(δ\) 169.6, 146.1, 139.3, 135.2, 130.6, 130.4, 128.9, 127.0, 124.4, 123.4, 121.9, 114.4, 64.7, 49.9, 21.5. Carbon bearing boron not observed.

\textsuperscript{11}B NMR (DMSO-\textit{d}_6, 160 MHz): \(δ\) 10.21.

HRMS: exact mass calculated for [M+Na\textsuperscript{+}] \((C_{20}H_{16}ClN_2O_6SB)\) requires \(m/z\) 460.0671, found \(m/z\) 460.0658.

Characterization data is consistent with literature reported values.\textsuperscript{4}

**6. Crystallographic Data for Compound 4b**

Single crystal diffraction measurements were made with an Oxford Diffraction Gemini S instrument. Refinement was to convergence against \(F^2\) and used all unique reflections. Programs used were from the SHELX suite.\textsuperscript{20} Non-hydrogen atoms were refined anisotropically whereas hydrogen atoms were placed in idealized positions and refined in riding modes. Selected crystallographic and refinement parameters are given in Table 1. CCDC reference number CCDC 1485168 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
Table S1 Selected crystallographic data and refinement parameters for compound 4b.

<table>
<thead>
<tr>
<th>Compound</th>
<th>4</th>
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<tbody>
<tr>
<td>Formula</td>
<td>C_{12}H_{14}O_{5}</td>
</tr>
<tr>
<td>M, (g mol⁻¹)</td>
<td>238.23</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
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<tr>
<td>Space group</td>
<td>P2₁</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>123(2)</td>
</tr>
<tr>
<td>a (Å)</td>
<td>6.4668(2)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>9.8239(3)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>8.5963(2)</td>
</tr>
<tr>
<td>β (°)</td>
<td>96.341(3)</td>
</tr>
<tr>
<td>V/Å³</td>
<td>542.78(3)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Wavelength (Å)</td>
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</tr>
<tr>
<td>Measured reflections</td>
<td>9884</td>
</tr>
<tr>
<td>Unique reflections</td>
<td>3457</td>
</tr>
<tr>
<td>(R_{\text{int}})</td>
<td>0.03024</td>
</tr>
<tr>
<td>Observed rflns [(I &gt; 2\sigma(I))]</td>
<td>3286</td>
</tr>
<tr>
<td>(\mu) (mm⁻¹)</td>
<td>0.114</td>
</tr>
<tr>
<td>No. of parameters</td>
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</tr>
<tr>
<td>(2\theta_{\text{max}}) (°)</td>
<td>63.8</td>
</tr>
<tr>
<td>(R) [on F, obs rflns only]</td>
<td>0.0329</td>
</tr>
<tr>
<td>w(R) [on F², all data]</td>
<td>0.0852</td>
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<tr>
<td>GoF</td>
<td>1.043</td>
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<tr>
<td>Largest diff. peak/hole/e Å⁻³</td>
<td>0.242/−0.191</td>
</tr>
</tbody>
</table>

7. References


8. NMR spectra for intermediates and products

$^1$H NMR of S1
$^{13}$C NMR of S1

$^1$H NMR of S2
$^{13}$C NMR of S2

$^1$H NMR of 3a
$^{13}$C NMR of 3a

$^1$H NMR of 3b
$^{13}$C NMR of 3b

$^{19}$F NMR of 3b
$^{13}$C NMR 3c

$^1$H NMR 3d
$^{13}$C NMR 3d

$^1$H NMR 3e
$^{13}$C NMR 3e

$^1$H NMR 3f
$^{13}$C NMR 3f

$^1$H NMR 3g
$^{13}$C NMR 3g

$^1$H NMR 3h
\( ^{13}\)C NMR 3h

\( ^{1}H\) NMR 3i
$^{13}\text{C NMR 3k}$

$^{1}\text{H NMR 3l}$
$^{13}$C NMR 3l

$^1$H NMR 3m
\[ {^{13}C \text{ NMR} \ 3n} \]

\[
\begin{array}{c}
\text{[Chemical structure diagram]}
\end{array}
\]

\[ {^1H \text{ NMR} \ 3o} \]

\[
\begin{array}{c}
\text{[Chemical structure diagram]}
\end{array}
\]
$^{13}$C NMR 3o

$^1$H NMR 3p
$^{13}\text{C NMR 3p}$

$^{1}\text{H NMR 3q}$
$^{13}$C NMR 3q

$^{11}$B NMR 3q
$^1$H NMR 3s

$^{13}$C NMR 3s
$^1$H NMR 3t

$^{13}$C NMR 3t
$^1$H NMR 3u

$^{13}$C NMR 3u
$^1$H NMR 3z

$^{13}$C NMR 3z
$^{13}\text{C NMR 3aa}$

$^{1}\text{H NMR 3ab}$
$^{13}$C NMR 3ab

$^1$H NMR 3ac
$^{13}$C NMR 3ac

$^{11}$B NMR 3ac
$^{11}$B NMR 3ad

$^1$H NMR 3ae
$^{13}$C NMR 3ae

$^{11}$B NMR 3ae
$^{19}\text{F NMR 3ae}$

$^{1}\text{H NMR 3af}$
$^1$H NMR 3ag

$^{13}$C NMR 3ag
$^1$H NMR 3ah

$^{13}$C NMR 3ah
$^{1}H$ NMR of 4a

$^{13}C$ NMR of 4a
$^1$H NMR 7a

$^{13}$C NMR 7a
$^1$H NMR 7c

$^{13}$C NMR 7c
$^{19}$F NMR 7e

$^{1}$H NMR 7f
9. $^1$H NMR Evidence for the Evaluation of the Base Sensitivity
Cyrene $^1$H NMR

KOAc 25 °C
KOAc 50 °C

KOAc 100 °C
Pyridine 100 °C

\[ \text{Pyridine}_{100\degree C} \]

K\(_2\)CO\(_3\) 25 °C

\[ \text{K}_2\text{CO}_3_{25\degree C} \]
$\text{K}_2\text{CO}_3$ 50 °C

$\text{K}_2\text{CO}_3$ 100 °C
DIPEA 25 °C

DIPEA 50 °C
DIPEA 100 °C

Cs₂CO₃ 25 °C
$\text{Cs}_2\text{CO}_3 50 \, ^\circ\text{C}$

$\text{Cs}_2\text{CO}_3 100 \, ^\circ\text{C}$
$\text{Et}_3\text{N} \ 25 \ ^\circ\text{C}$

$\text{Et}_3\text{N} \ 50 \ ^\circ\text{C}$
$\text{K}_3\text{PO}_4$ $50 \degree \text{C}$

$\text{K}_3\text{PO}_4$ $100 \degree \text{C}$
DBU 100 °C

KOH 25 °C
$t$-BuOK $25^\circ C$

$\delta$-BuOK $25^\circ C$

$t$-BuOK $50^\circ C$

$\delta$-BuOK $50^\circ C$
$t$-BuOK 100 °C

NaH 25 °C
NaH 50 °C

NaH 100 °C