Formation of Indoles, Dihydroisoquinolines and Dihydroquinolines by Ruthenium-Catalyzed Heterocyclizations

Alejandro Varela-Fernández, Jesús A. Varela, Carlos Saá*
Departamento de Química Orgánica y Centro Singular de Investigación en Química Biológica y Materiales Moleculares, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain
Fax: (+34)-88-181-5704
E-mail: carlos.saa@usc.es
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Abstract: Indoles, dihydroisoquinolines and dihydroquinolines were efficiently prepared by ruthenium-catalyzed heterocyclizations of aromatic homo- and bis-homopropargyl amines/amides in the presence of an amine/ammonium base-acid pair. These regioselective 5- and 6-endo cyclizations most probably occur by nucleophilic trapping of key Ru vinylidene intermediates.

Key words: heterocyclizations; indoles; isoquinolines; quinolines; ruthenium; vinylidenes.

Introduction

The development of new methods for the synthesis of heterocyclic compounds continues to be a major challenge in modern organic synthesis. During the last few years, many transition metal-catalyzed heterocyclizations have been developed to achieve these goals. Specifically, the nucleophilic trapping of metal vinylidene intermediates derived from terminal acetylenic compounds has been very successful. Oxygenated heterocycles, e.g. dihydrofurans and dihydropyran, were prepared in a pioneer work developed by McDonald and coworkers from heterocyclizations (cycloisomerizations) of homo- and bis-homopropargylic alcohols using catalytic Mo and W vinylidenes. More advances in similar hetero- and oxidative cyclizations were later developed by Trost and Rhee using ruthenium and rhodium catalysts. Seven-membered oxepines were recently synthesized by MacDonald and coworkers from heterocyclizations of preorganized alkynols using catalytic W vinylidenes. The corresponding benzoannulated derivatives, e.g. benzofurans and isochromenes, were synthesized by our own group on having used the regioselective 5-endo and 6-endo ruthenium-catalyzed heterocyclization of aromatic homo- and bis-homopropargylic alcohols. More recently, even the more challenging seven-membered benzoxepines could also be synthesized by regioselective 7-endo heterocyclization of aromatic alkynols using in this case osmium catalysts. In the case of nitrogenated heterocycles, much effort has been devoted mainly to the synthesis of indoles. Since the pioneer work of McDonald using molybdenum catalysts, modern syntheses of indoles by heterocyclization of substituted (2-ethynyl)anilines have been also described in Trost and Grotjahn groups using rhodium and ruthenium catalysts. Herein, we wish to report typical practical procedures, not only for the ruthenium-catalyzed synthesis of indoles, but to the six-membered 1,2-dihydroisoquinolines and 1,4-dihydroquinolines by heterocyclization of aromatic homo- and bis-homopropargyl amines/amides using commercial ruthenium catalysts.
Scope and limitations

The ruthenium-catalyzed 5-endo heterocyclization of 2-(ethynyl)anilines 1 to indoles 2 was accomplished by heating at 90 °C a solution of the corresponding ethynylaniline 1 and 10 mol% of commercial CpRu(PPh3)2Cl in pyridine (Table 1). The cyclization tolerates an unprotected amino group 1a and also electron-withdrawing substituents at the amino function, 1b and 1c, with similar yields being obtained (Table 1, entries 1–3). The tolerance of the cyclization was excellent with the different functional groups tested (nitro 1d, nitrile 1e, ester 1f,g) and gave good-to-excellent yields of the corresponding indoles 2d–g (entries 4–7). Interestingly, cyclization seems more affected with the acid/base properties of the aniline rather than the electrophilicity of the vinylidene intermediates (entries 6 and 7). Internal alkyne such as 2-(hexyn-1-yl)aniline 1h was not suitable for this reaction (entry 8), which seems to indicate that the cyclization does not involve simple alkyne activation with the catalyst.

Table 1 Ru-catalyzed heterocyclization of 2-(ethynyl)anilines 1 into indoles 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Indole</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>25</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>40</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>40</td>
<td>80</td>
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<tr>
<td>4</td>
<td></td>
<td></td>
<td>20</td>
<td>72</td>
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<tr>
<td>5</td>
<td></td>
<td></td>
<td>30</td>
<td>98</td>
</tr>
<tr>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
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<td></td>
</tr>
</tbody>
</table>

* Isolated yields. In all cases, conversion is higher than 97% (GC monitoring).

The same procedure could be applied to the construction of 1,2-dihydroisoquinolines 4 from amide derivatives of 2-alkynylbenzylamines 3 (Table 3). Even though the parent benzylamine 3a and its secondary derivatives N-(methyl) and N-(phenyl)benzylamines failed to undergo heterocyclization, thus showing the important effect of the nature of the coordinating heteroatom, benzamide 3b underwent smooth regioselective 6-endo heterocyclization to give isoquinolone 4b in fairly good isolated yield (entry 2). Furthermore, cyclization of secondary benzamide 3c also gave isoquinolone 4c in quite good yield, although a longer reaction time was required (entry 3). To further highlight the unique synthetic potential of this cycloisomerization, the pharmaceutically active chromophore benzothiazine 1,1-dioxide 4d (benzosultam) was satisfactorily obtained from acyclic sulphonamide 3d (entry 4). By contrast, substituted benzamide 3e was not suitable for this reaction (entry 5), which again seems to indicate that the cyclization is not due to simple alkyne activation with the catalyst. Acetamide 3f and tosylamide 3g were smoothly cyclized to 1,2-dihydroisoquinolines 4f and 4g, thus showing the versatility of the amide nucleophile in the substrates (entries 6 and 7).

Interestingly, the isomeric 2H-1,4-dihydroquinoline 6 could also be prepared by 6-endo heterocyclization of unsubstituted 2-(2-propynyl)tosylanilide 5 in quite reasonable 60% yield (Scheme 2).

Table 2 Ru-catalyzed heterocyclization of aromatic bis-homopropargyl amides 3 into 1,2-dihydroisoquinolines 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>4a</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>4b</td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>4c</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
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<td>4d</td>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>4e</td>
<td>4</td>
<td>82</td>
</tr>
</tbody>
</table>

* Isolated yields. In all cases, conversion is higher than 97% (GC monitoring).

In summary, efficient Ru-catalyzed synthesis of indoles, 1,2-dihydroisoquinolines and 1,4-dihydroquinoline by heterocyclization of aromatic
homo- and bis-homopropargyl amines/amides have been developed. Most probably, these regioselective processes (5- and 6-endo cyclizations) occur by nucleophilic trapping of key Ru vinylidene intermediates. The presence of an amine/ammonium base-acid pair accelerates the cyclization and facilitates the catalytic turnover. The new procedures to synthesize 1,2-dihydroisoquinolines and 1,4-dihydroquinoline by C–N bond formation significantly increase the scope of metal vinylidene intermediates in catalytic processes.

Procedures
All reactions were carried out under an argon atmosphere in flame-dried glassware with magnetic stirring, unless otherwise noted. All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. Solvents were dried by distillation over an appropriate desiccant agent: tetrahydrofuran (THF) and diethyl ether (Et2O) were continuously refluxed and freshly distilled from sodium benzophenone ketyl under Ar; triethylamine (Et3N), pyridine (py) and dichloromethane (CH2Cl2) were continuously refluxed and freshly distilled from calcium hydride. Thin-layer chromatography (TLC) was carried out on silica-coated aluminium plates (silica gel 60 F 254 Merck) using UV light as visualizing agent (256 and 360 nm) and cerium molybdate (Hanessian’s stain, solution of 12 g of ammonium molybdate, 0.5 g of ceric ammonium molybdate and 15 mL of conc. sulfuric acid in 235 mL of water), KMnO4 (solution of 1.5 g of potassium permanganate, 10 g of potassium bicarbonate and 1.25 mL of 10% sodium hydroxide in 200 mL of water) or p-anisaldehyde (solution of 3.7 mL of p-anisaldehyde, 1.5 mL of glacial acetic acid, 5 mL of conc. sulfuric acid in 135 mL of absolute ethanol) with heat as developing agents. Flash chromatography was performed on silica gel using a mixture of EtOAc/Hex as eluent. 1H and 13C NMR were recorded onBruker DPX-250 MHz, AMX-300 MHz, WM-500 MHz and Varian Inova-400 MHz instruments and chemical shifts are reported relative to tetramethylsilane as an internal reference. Coupling constants J are given in Hertz (Hz). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or as a combination of them. Multiplicities of 13C NMR signals were determined by DEPT experiments. Gas chromatography (GC-MS) was recorded on an Agilent HP-6890N with a mass detector HP-5973N using a chemical ionization (CI) technique. High-resolution mass spectra (HRMS) was recorded on a Micromass Autospec spectrometer using CI (Chemical Ionization) or EI (Electron Ionization) techniques. Yields refer to isolated compounds estimated to be > 95% pure as determined by 1H NMR and capillary GC analysis.

Starting materials
General procedure for Sonogashira cross couplings
Procedure 1:
The corresponding alkyne (1.50 equiv) was added to a suspension of aryl iodide (1 equiv), PdCl2(PPh3)2 (0.01 equiv) and CuI (0.03 equiv) in a 3:1 mixture of THF/Et3N (0.1 M). The reaction mixture was stirred at room temperature until disappearance of starting material (TLC and GC-MS monitoring). The mixture was filtered through silica gel and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc and washed twice with brine. The combined organic layers were dried over anhydrous Na2SO4, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a mixture of EtOAc/Hex as eluent to afford the corresponding cross coupling product.

Procedure 2:
The corresponding alkyne (1.50 equiv) was added to a suspension of aryl bromide (1 equiv), Pd(OAc)2 (0.05 equiv), CuI (0.05 equiv) and PPh3 (0.1 equiv) in Et3N (0.1 M). The reaction mixture was heated at 90 °C for 24 h until disappearance of starting material (TLC and GC-MS monitoring). The mixture was filtered through silica gel and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc and washed twice with brine. The combined organic layers were dried over anhydrous Na2SO4, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a mixture of EtOAc/Hex as eluent to afford the corresponding cross coupling product.

General procedure for desilylation of (trimethylsilyl)ethyl derivatives.
A solution of TBAF in THF (1M, 1.5 equiv) was added dropwise to a solution of (trimethylsilyl)ethyl derivative (1 equiv) in THF. The reaction mixture was stirred at room temperature until disappearance of starting material (TLC and GC-MS monitoring). The reaction was quenched by adding brine and extracted three times with EtOAc. The combined organic layers were dried over anhydrous Na2SO4, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a mixture of EtOAc/Hex as eluent to give the corresponding desilylated product.

2-Ethynylaniline (1a)
The general Sonogashira cross coupling procedure 1 was followed using iodoaniline (0.60 g, 2.74 mmol), PdCl2(PPh3)2 (0.019 g, 0.027 mmol), CuI (0.016 g, 0.082 mmol), trimethylsilylacetylene (0.40 g, 0.58 mL, 4.11 mmol), THF (20 mL) and Et3N (7 mL). Upon completion (4 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent.
to give 2-[(trimethylsilyl)ethynyl]aniline (0.52 g, 99%) as a brown oil.

\[ ^{1}H \text{NMR (250 MHz, CDCl}_{3}): \delta = 7.26 (d, J = 7.7 \text{ Hz, 1H}), 7.05 (t, J = 7.7 \text{ Hz, 2H}), 6.61 (t, J = 7.7 \text{ Hz, 2H}), 4.18 (s, 2H), 0.24 (s, 9H). \]

\[ ^{13}C \text{NMR, DEPT (62 MHz, CDCl}_{3}): \delta = 148.1 (C), 132.0 (CH), 129.8 (CH), 117.6 (CH), 114.1 (CH), 107.5 (C), 101.8 (C), 99.5 (C), 0.0 (3 \times \text{CH}_{3}). \]

MS (CI): m/z (%) = 190 (M\textsuperscript{+}
1.0, 97%) as a brown oil.

\[ ^{1}H \text{NMR (250 MHz, CDCl}_{3}): \delta = 7.31 (d, J = 7.7 \text{ Hz, 1H}), 7.13 (t, J = 7.7 \text{ Hz, 1H}), 6.71-6.62 (m, 2H), 4.23 (s, 2H), 3.37 (s, 1H). \]

\[ ^{13}C \text{NMR, DEPT (62 MHz, CDCl}_{3}): \delta = 148.5 (C), 132.5 (CH), 130.1 (CH), 117.7 (CH), 114.2 (C), 106.5 (C), 82.4 (CH), 80.6 (C). \]

MS (EI): m/z (%): 118 (M\textsuperscript{+}, 100), 91 (2).

HRMS-Cl: m/z calc'd for C\textsubscript{11}H\textsubscript{16}NSi [M\textsuperscript{+}]: 190.1052; found: 190.1052.

The general desilylation procedure was followed using 2-[(trimethylsilyl)ethynyl]aniline (0.49 g, 2.59 mmol), a solution of TBAF in THF (1M, 3.89 mL) and THF (25 mL). Upon completion (10 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 1a (0.29 g, 97%) as a brown oil.

\[ ^{1}H \text{NMR (250 MHz, CDCl}_{3}): \delta = 7.82 (d, J = 7.7 \text{ Hz, 1H}), 7.63 (d, J = 7.9 \text{ Hz, 1H}), 7.37 (t, J = 7.4 \text{ Hz, 1H}), 6.93 (t, J = 7.44 \text{ Hz, 1H}), 6.74 (s, \text{br, 1H}), 3.02 (s, 3H). \]

\[ ^{13}C \text{NMR, DEPT (75 MHz, CDCl}_{3}), \text{DEPT (62 MHz, CDCl}_{3}): \delta = 139.3 (CH), 137.5 (C), 129.7 (CH), 127.2 (CH), 122.5 (CH), 92.2 (C), 40.1 (CHs). \]

MS (EI, 70 eV): m/z (%) = 297 (M\textsuperscript{+}, 17), 218 (49), 170 (5), 108 (21), 91 (100).

The general Sonogashira cross coupling procedure was followed using N-(2-iodophenyl)methanesulfonamide (1.20 g, 4.04 mmol), PdCl\textsubscript{2}(PPH\textsubscript{3})\textsubscript{2} (0.028 g, 0.040 mmol), CuI (0.023 g, 0.12 mmol), trimethylsilylacetylene (0.59 g, 0.85 mL, 6.06 mmol), THF (30 mL) and Et\textsubscript{3}N (10 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:5 mixture of EtOAc/Hex as eluent to give N-(2-[(trimethylsilyl)ethynyl]phenyl)methanesulfonamide (1.02 g, 95%) as a colorless solid.

\[ ^{1}H \text{NMR (300 MHz, CDCl}_{3}): \delta = 7.58 (d, J = 7.7 \text{ Hz, 1H}), 7.47 (dd, J = 7.7, 1.4 Hz, 1H), 7.36 (td, J = 7.7, 1.4 Hz, 1H), 7.12 (td, J = 7.7, 1.4 Hz, 1H), 7.00 (s, \text{br, 1H}), 3.00 (s, 3H), 0.29 (s, 9H). \]

HRMS-Cl: m/z calc'd for C\textsubscript{17}H\textsubscript{21}NO\textsubscript{2}SSi [M\textsuperscript{+}]: 267.0750; found: 267.0719.

The general desilylation procedure was followed using N-(2-[(trimethylsilyl)ethynyl]phenyl)methanesulfonamide (1.00 g, 3.74 mmol), a solution of TBAF in THF (1M, 5.61 mL) and THF (30 mL). Upon completion (10 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give 1b (0.62 g, 85%) as a yellow solid.

\[ ^{1}H \text{NMR (300 MHz, CDCl}_{3}): \delta = 8.26 \text{ Hz, 1H), 7.51 (d, J = 7.66 \text{ Hz, 1H}, 7.39 (t, J = 7.84 \text{ Hz, 1H}, 7.14 (t, J = 7.58 Hz, 1H), 7.03 (s, 1H), 3.50 (s, 1H), 3.03 (s, 3H).} \]

\[ ^{13}C \text{NMR, DEPT (75 MHz, CDCl}_{3}), \text{DEPT (62 MHz, CDCl}_{3}): \delta (ppm): 138.6 (C), 132.8 (CH), 130.5 (CH), 124.7 (CH), 119.5 (CH), 112.9 (C), 84.9 (CH), 78.6 (C), 39.7 (CH). \]

HRMS-Cl: m/z calc'd for C\textsubscript{16}H\textsubscript{19}NO\textsubscript{2} [M\textsuperscript{+}]: 195.0354; found: 195.0354.

**4-methyl-N-2-[(trimethylsilyl)ethynyl]phenyl]benzenesulfonamide (1c)**

A solution of 4-methylbenzene-1-sulfonyl chloride (3.97 g, 20.54 mmol) in THF (10 mL) was added dropwise over 2 h to a solution of iodoaniline (4.50 g, 20.54 mmol), pyridine (1.70 g, 1.74 mL, 21.54 mmol) in THF (30 mL) under Ar. The solution was stirred at room temperature for 12 h until disappearance of starting material (TLC, GC-MS monitoring). The resulting mixture was evaporated under vacuum and the residue was purified by flash column chromatography through silica gel using a 1:9 mixture of EtOAc/Hex as eluent to afford N-(2-(iodophenyl)methanesulfonamide (7.50 g, 98%) as a white solid.

\[ ^{1}H \text{NMR (250 MHz, CDCl}_{3}): \delta = 7.60 (m, 4H), 7.28 (td, J = 8.2, 1.3 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.88 (s, 1H), 6.80 (td, J = 7.7, 1.3 Hz, 1H), 2.34 (s, 3H). \]

\[ ^{13}C \text{NMR, DEPT (62 MHz, CDCl}_{3}): \delta = 144.22 (C), 139.09 (CH), 137.40 (CH), 135.79 (C), 129.63 (2xCH), \]
129.45 (CH), 127.39 (2xCH), 126.90 (CH), 122.50 (CH), 92.47 (C), 21.58 (CH3).

MS (CI): m/z (%) = 374 (M+1, 100), 247 (92), 246 (25), 219 (18).

The general Sonogashira cross coupling procedure 1 was followed using N-(2-iodophenyl)-4-methylbenzenesulfonamide (3.00 g, 8.05 mmol), PdCl2(PPh3)2 (0.056 g, 0.080 mmol), CuI (0.045 g, 0.024 mmol), trimethylsilylacetylene (1.18 g, 1.70 mL, 12.06 mmol), THF (60 mL) and Et3N (20 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex a s eluent to give 4-nitro-2-

1H NMR (250 MHz, CDCl3): δ = 8.22 (d, J = 2.6 Hz, 1H), 8.01 (dd, J = 9.0, 2.6 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 4.96 (s, 2H), 0.28 (s, 9H).

13C NMR, DEPT (75 MHz, CDCl3): δ = 153.3 (C), 138.1 (C), 128.9 (CH), 126.1 (CH), 112.7 (CH), 106.9 (C), 102.1 (C), 98.9 (C), -0.1 (3 x CH3).

MS (CI): m/z (%) = 235 (M+1, 100), 219 (69), 205 (83), 189 (52), 73 (35).

HRMS-CI: m/z calcd for C11H16N2O2Si [M+1]: 235.0903; found: 235.0903.

The general desilylation procedure was followed using 4-nitro-2-[[(trimethylsilyl)ethynyl]phenyl]benzenesulfonamide (0.40 g, 1.71 mmol), a solution of TBAF in THF (1M, 2.56 mL) and THF (15 mL). Upon completion (10 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 1d (0.18 g, 63%) as a yellow solid.

1H NMR (300 MHz, CDCl3): δ = 8.25 (s, 1H), 8.04 (d, J = 9.0 Hz, 1H), 6.68 (d, J = 9.0 Hz, 1H), 5.00 (s, 2H), 3.47 (s, 1H).

13C NMR, DEPT (75 MHz, CDCl3): δ = 153.5 (C), 137.3 (C), 129.3 (CH), 126.4 (CH), 112.9 (CH), 105.7 (C), 84.2 (CH), 78.1 (C).

MS (EI, 70 eV): m/z (%) = 162 (M+, 100), 132 (40), 116 (24), 89 (97), 63 (45), 58 (35).

HRMS-EI: m/z calcd for CaH8N2O [M+]: 162.0429; found: 162.0429.

4-Amino-3-ethynylbenzonitrile (1e)

The general Sonogashira cross coupling procedure 1 was followed using 4-amino-3-iodobenzonitrile (1.50 g, 6.15 mmol), PdCl2(PPh3)2 (0.043 g, 0.061 mmol), CuI (0.035 g, 0.18 mmol), trimethylsilylacetylene (0.91 g, 1.30 mL, 9.22 mmol), THF (45 mL) and Et3N (15 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 4-amino-3-

1H NMR (250 MHz, CDCl3): δ = 7.56 (d, J = 1.8 Hz, 1H), 7.33 (dd, J = 8.5, 1.8 Hz, 1H), 6.68 (d, J = 8.5 Hz, 1H), 4.79 (s, 2H), 0.27 (s, 9H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 151.4 (C), 136.4 (CH), 133.3 (CH), 119.3 (C), 113.8 (CH), 107.9 (C), 102.0 (C), 99.7 (C), 98.9 (C), -0.1 (3 x CH3).

MS (CI): m/z (%) = 215 (M+1, 100), 199 (70), 73 (17).

HRMS-CI: m/z calcd for C12H15N2Si [M+1]: 215.1005; found: 215.1005.

The general desilylation procedure was followed using 4-amino-3-[(trimethylsilyl)ethynyl]benzonitrile (0.80 g, 3.74 mmol), a solution of TBAF in THF (1M, 3.60 mL) and THF (35 mL). Upon completion (10 min) and work-up, the residue was purified by flash...
column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give 1e (0.45 g, 84%) as a yellow solid.

1H NMR (300 MHz, CDCl3): δ = 7.57 (s, 1H), 7.36 (d, J = 8.5 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 4.85 (s, 2H), 3.46 (s, 1H).

13C NMR, DEPT (75 MHz, CDCl3): δ = 151.8 (C), 136.8 (CH), 133.5 (CH), 119.2 (C), 114.0 (CH), 106.6 (C), 99.6 (C), 84.2 (CH), 78.1 (C).

MS (EI, 70 eV): m/z (%): 142 (M+, 100), 132 (10), 57 (64).

HRMS-CI: m/z calcd for C12H16N [M++1]: 174 (M++1, 100), 132 (10), 57 (64).

The general Sonogashira cross coupling procedure 1 was followed using methyl 3-iodobenzoate (1.00 g, 3.61 mmol), PdCl2(PPh3)2 (0.025 g, 0.036 mmol), CuI (0.021 g, 0.11 mmol), trimethylsilylacetylene (0.53 g, 0.77 mL, 5.42 mmol), THF (27 mL) and Et3N (9 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give methyl 3-amino-4-((trimethylsilyl)ethynyl)benzoate (0.86 g, 90%) as a colorless solid.

1H NMR (500 MHz, CDCl3): δ = 7.30-7.36 (m, 3H), 4.34 (s, 2H), 3.88 (s, 3H), 0.27 (s, 9H).

13C NMR (125 MHz, CDCl3): δ = 166.8 (C=O), 148.1, 132.2, 131.0, 118.6, 114.9, 112.0, 102.7, 100.9, 52.1, 0.00.

The general desilylation procedure was followed using methyl 3-amino-4-((trimethylsilyl)ethynyl)benzoate (0.49 g, 2.00 mmol), a solution of TBAF in THF (1M, 3.00 mL) and THF (20 mL). Upon completion (10 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 1g (0.33 g, 95%) as a yellow solid.

1H NMR (300 MHz, CDCl3): δ = 7.40-7.29 (m, 3H), 4.41 (s, br, 2H), 3.88 (s, 3H), 0.27 (s, 9H).

HRMS-CI: m/z (%) = 175 (M+, 100), 144 (46), 116 (22), 89 (14).

2-(Hex-1-yn-1-yl)aniline (1h)

The general Sonogashira cross coupling procedure 1 was followed using 2-iodoaniline (0.50 g, 2.28 mmol), PdCl2(PPh3)2 (0.048 g, 0.068 mmol), CuI (0.026 g, 0.14 mmol), hex-1-yne (0.28 g, 0.39 mL, 3.42 mmol), THF (16 mL) and Et3N (6 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 1h (0.34 g, 87%) as a yellowish oil.

1H NMR (250 MHz, CDCl3): δ = 7.23 (dd, J = 7.8, 1.3 Hz, 1H), 7.09-7.00 (m, 1H), 6.69-6.58 (m, 2H), 4.13 (s, 2H), 2.44 (t, J = 6.9 Hz, 2H), 1.64-1.40 (m, 4H), 0.93 (t, J = 7.1 Hz, 3H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 147.5 (C), 131.8 (CH), 128.6 (CH), 117.6 (CH), 114.0 (CH), 108.7 (C), 95.5 (C), 76.9 (C), 30.8 (CH2), 21.9 (CH2), 19.1 (CH2), 13.5 (CH3).

MS (CI): m/z (%) = 174 (M+1, 100), 132 (10), 57 (17).

HRMS-CI: m/z calcd for C13H18N2 [M+1]: 174.1283; found: 174.1283.

2-(Ethynylphenyl)methanamine (3a)

The general Sonogashira cross coupling procedure 1 was followed using 2-iodoaniline (1.50 g, 6.55 mmol), PdCl2(PPh3)2 (0.046 g, 0.066 mmol), CuI (0.021 g, 0.11 mmol), trimethylsilylacetylene (0.53 g, 0.77 mL, 5.42 mmol), THF (27 mL) and Et3N (9 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give methyl 3-amino-4-((trimethylsilyl)ethynyl)benzoate (0.86 g, 90%) as a colorless solid.

HRMS-EI: m/z calcd for C9H6N2 [M+]: 142.0531; found: 142.0531.

Methyl 4-amino-3-ethynylbenzoate (1f)

The general Sonogashira cross coupling procedure 1 was followed using methyl 4-iodobenzoate (1.00 g, 3.61 mmol), PdCl2(PPh3)2 (0.025 g, 0.036 mmol), CuI (0.021 g, 0.11 mmol), trimethylsilylacetylene (0.53 g, 0.77 mL, 5.42 mmol), THF (27 mL) and Et3N (9 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give methyl 4-amino-3-[(trimethylsilyl)ethynyl]benzoate (0.78 g, 87%) as a yellow solid.

HRMS-EI: m/z calcd for C9H6N2 [M+]: 142.0531; found: 142.0531.

Methyl 3-amino-4-ethynylbenzoate (1g)
(0.038 g, 0.20 mmol), trimethylsilylacetylene (0.96 g, 1.39 mL, 9.82 mmol), THF (48 mL) and Et3N (16 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 0.5:9.5 mixture of EtOAc/Hex as eluent to give 2-[(trimethylsilyl)ethynyl]benzonitrile (1.29 g, 99%) as a brown oil.

MS (CID): m/z (%) = 200 (M++1, 100), 184 (56), 128 (00).

The general Sonogashira cross coupling procedure was followed using 2-[(trimethylsilyl)ethynyl]benzonitrile (1.00 g, 5.05 mmol), a solution of TBAF in THF (1M, 4.15 mL) and THF (50 mL). Upon completion (10 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 2-ethylbenzonitrile (0.20 g, 1.57 mmol) in Et2O (0.70 mL) was added dropwise to a suspension of LiAlH4 (0.12 g, 3.15 mmol) in Et2O (2.30 mL) at -10 ºC. The resultant slurry was stirred at -10 ºC for 1 h and then, at room temperature for another 1 h. The reaction was quenched by the careful dropwise addition of H2O (0.2 mL) followed by a solution of NaOH (0.2 mL). The resultant biphasic mixture was stirred vigorously for 2 h at room temperature. The layers were then allowed to separate and the aqueous layer was extracted with additional Et2O (2 mL). The combined organic layers were washed with brine (15 mL), dried (anhydrous Na2SO4), filtered and evaporated under vacuum to afford 3a (0.16 g, 76%) as a brown oil.

1H NMR (250 MHz, CDCl3): δ = 7.35-7.18 (m, 3H), 7.15-7.05 (m, 1H), 0.00 (s, 9H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 132.0 (CH), 131.9 (CH), 131.8 (CH), 128.2 (CH), 126.2 (C), 116.6 (C), 115.2 (C), 101.4 (C), 100.2 (C), -0.8 (3 x CH3).

MS (CI): m/z (%) = 200 (M++1, 100), 184 (56), 128 (00).

A solution of 2-ethylbenzonitrile (0.20 g, 1.57 mmol) in Et2O (0.70 mL) was added dropwise into a suspension of LiAlH4 (0.12 g, 3.15 mmol) in Et2O (2.30 mL) at -10 ºC. The resultant slurry was stirred at -10 ºC for 1 h and then, at room temperature for another 1 h. The reaction was quenched by the careful dropwise addition of H2O (0.2 mL) followed by a saturated solution of NaOH (0.2 mL). The resultant biphasic mixture was stirred vigourously for 2 h at room temperature. The layers were then allowed to separate and the aqueous layer was extracted with additional Et2O (2 mL). The combined organic layers were washed with brine (15 mL), dried (anhydrous Na2SO4), filtered over Celite and concentrated under vacuum. The residue was purified by flash column chromatography through silica gel using a 1:9 mixture of EtOAc/Hex as eluent to afford 3b (0.17 g, 42%) as a yellow solid.

1H NMR (400 MHz, CDCl3): δ = 8.09-8.06 (m, 1H), 7.62-7.58 (m, 1H), 7.48-7.44 (m, 2H), 6.44 (s, 2H), 3.53 (s, 1H).

13C NMR, DEPT (100 MHz, CDCl3): δ = 168.0 (C=O), 135.4 (C), 134.2 (CH), 130.9 (CH), 130.1 (CH), 129.4 (CH), 118.9 (C), 83.9 (CH), 82.3 (C).

MS (EI, 70 eV): m/z (%) = 145 (M+, 91), 129 (40), 117 (35), 101 (80), 75 (56).

HRMS-El: m/z caleed for C9H7NO [M+]: 145.0528; found: 145.0528.

**N-buty1-2-ethylbenzamide (3c)**

In a flame-dried round-bottomed flask under Ar 2-iodobenzoic acid (1.49 g, 6.00 mmol) was introduced and then thionyl chloride (7.14 g, 43.5 mL, 60 mmol) was added dropwise. The mixture was stirred at room temperature for 12 h (NMR monitoring) until no gas emission was observed. Excess SOCl2 was removed in vacuo. The crude 2-iodobenzoyl chloride (1.35 g, 84%) as a white solid was then used without further purification.

A solution of 2-iodobenzoyl chloride (1.30 g, 4.89 mmol) in CH2Cl2 (25 mL) was added dropwise to a mixture of butan-1-amine (0.32 g, 0.44 mL, 4.42 mmol), Et3N (0.54 g, 0.74 mL, 5.33 mmol) in CH2Cl2 (25 mL) under Ar. The solution was stirred at room temperature for 12 h until disappearance of starting material (TLC, GC-MS monitoring). The resulting mixture was filtered by gravity, washed with H2O (2 x 25 mL), dried over anhydrous Na2SO4, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a 1:9 mixture of EtOAc/Hex as eluent to afford 3b (0.17 g, 42%) as a yellow solid.

1H NMR (250 MHz, CDCl3): δ = 7.83 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 4.3 Hz, 2H), 7.13-7.02 (m, 1H), 5.93 (s, 1H), 3.47-3.37 (m, 2H), 1.68-1.54 (m, 2H), 1.51-1.35 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 169.3 (C=O), 142.4 (C), 139.7 (CH), 130.9 (CH), 128.1 (CH), 128.0 (CH), 92.4 (C), 39.7 (CH2), 31.4 (CH2), 20.1 (CH2), 13.7 (CH3).
The general Sonogashira cross coupling procedure 1 was followed using N-butyl-2-iodobenamide (0.70 g, 2.31 mmol), PdCl2(PPh3)2 (0.084 g, 0.12 mmol), CuI (0.023 g, 0.12 mmol), trimethylsilylacetylene (0.49 mL, 3.46 mmol), THF (17 mL) and Et3N (6 mL). Upon completion (4 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give N-butyl-2-[(trimethylsilyl)ethyl]benzamide (0.62 g, 98%) as a yellowish oil.

1H NMR (250 MHz, CDCl3): δ = 8.18-8.06 (m, 1H), 7.69 (s, 1H), 7.59-7.51 (m, 1H), 7.50-7.37 (m, 2H), 3.57-3.43 (m, 2H), 1.69-1.57 (m, 2H), 1.54-1.38 (m, 2H), 0.97 (t, J = 7.2 Hz, 3H), 0.29 (s, 9H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 165.7 (C=O), 139.5 (CH), 133.9 (CH), 130.6 (CH), 129.0 (CH), 119.1 (C), 103.6 (C), 101.4 (C), 39.8 (CH2), 31.6 (CH2), 20.3 (CH3), -0.3 (3 x CH3).

MS (CI): m/z (%) = 274 (M++1, 100), 194 (18), 110 (14), 85 (8).

HRMS (ESI): m/z calcd for C16H24NOSi [M ++1]: 310.1297; found: 310.1298.

The general desilylation procedure was followed using N-butyl-2-[(trimethylsilyl)ethyl]benzamide (0.60 g, 2.20 mmol), a solution of TBAF in THF (1M, 3.30 mL) and THF (22 mL). Upon completion (10 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give 3e (0.27 g, 61%) as a yellow solid.

1H NMR (250 MHz, CDCl3): δ = 7.92-7.87 (m, 1H), 7.56-7.50 (m, 1H), 7.43-7.35 (m, 2H), 7.28 (s, 1H), 3.50 (s, 1H), 3.47-3.42 (m, 2H), 1.67-1.54 (m, 2H), 1.45-1.37 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 166.0 (C=O), 136.8 (C), 133.9 (CH), 130.6 (CH), 129.0 (CH), 118.2 (C), 83.1 (CH), 82.0 (C), 39.6 (CH2), 31.1 (CH2), 20.0 (CH2), 13.6 (CH3).

MS (CI): m/z (%) = 202 (M++1, 100), 146 (11), 126 (18), 110 (14), 85 (8).


N-butyl-2-ethynylbenzenesulfonamide (3d)

Butan-1-amine (0.45 g, 0.61 mL, 6.18 mmol) was added dropwise to a solution of 2-bromobenzene-1-sulfonyl chloride (0.56 g, 2.21 mmol) in CHCl3 (20 mL) cooled at 0 °C. The resulting solution was then stirred at room temperature for 2 h until disappearance of starting material (TLC, GC-MS monitoring). The reaction mixture was evaporated under vacuum and the residue was dissolved in Et2O (10 mL) washed with brine (2 x 10 mL), dried over anhydrous Na2SO4, filtered and evaporated under vacuum. The resulting residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give 2-bromo-N-butylbenzenesulfonamide (0.52 g, 50%) as a white solid.

1H NMR (250 MHz, CDCl3): δ = 8.15 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.53-7.39 (m, 2H), 5.21 (s, 1H), 2.91 (dd, J = 13.3, 6.7 Hz, 2H), 1.52-1.22 (m, 4H), 0.84 (t, J = 7.2 Hz, 3H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 138.6 (C), 134.9 (CH), 133.6 (CH), 131.5 (CH), 127.7 (CH), 119.5 (C), 43.0 (CH2), 31.3 (CH2), 20.0 (CH2), 13.4 (CH3).

MS (CI): m/z (%) = 292 (M++1, 100), 238 (13), 236 (13), 72 (7).

The general Sonogashira cross coupling procedure 2 was followed using 2-bromo-N-butylbenzenesulfonamide (0.50 g, 1.72 mmol), Pd(OAc)2 (0.060 g, 0.086 mmol), CuI (0.016 g, 0.086 mmol), PPh3 (0.045 g, 0.017 mmol), trimethylsilylacetylene (0.253 g, 0.36 mL, 2.58 mmol) and Et3N (17 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give N-butyl-2-[(trimethylsilyl)ethyl]benzenesulfonamide (0.23 g, 43%) as a yellowish oil.

1H NMR (250 MHz, CDCl3): δ = 7.79 (d, J = 7.3 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.34-7.20 (m, 2H), 5.09 (t, J = 6.0 Hz, 1H), 2.67-2.63 (m, 2H), 1.30-1.00 (m, 4H), 0.63 (t, J = 7.3 Hz, 3H), 0.08 (s, 9H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 141.0 (C), 134.3 (CH), 131.9 (CH), 128.8 (CH), 128.7 (CH), 119.8 (C), 103.5 (C), 101.4 (C), 42.8 (CH2), 31.2 (CH2), 19.6 (CH2), 13.3 (CH3), -0.6 (3 x CH3).

MS (CI): m/z (%) = 310 (M++1, 100), 294 (20).

HRMS-CI: m/z calcd for C13H16NO2SSi [M++1]: 310.1297; found: 310.1298.

A solution of TBAF in THF (1M, 5 mL) was added dropwise to a solution of N-butyl-2-[(trimethylsilyl)ethyl]benzenesulfonamide (0.22 g, 0.71 mmol) in THF (5 mL) cooled at -78 °C. The reaction mixture was stirred at -78 °C for 2 h until disappearance of starting material (TLC and GC-MS monitoring). The reaction was quenched by adding a saturated solution of citric acid. The resulting mixture was extracted with Et2O (3 x 5 mL) and washed with H2O (2 x 5 mL) and a saturated solution of NaHCO3 (2 x 5 mL). The combined organic layers were dried over anhydrous Na2SO4, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to afford 3d (0.15 g, 88%) as a brown solid.

1H NMR (250 MHz, CDCl3): δ = 8.08-8.02 (m, 1H), 7.72-7.66 (m, 1H), 7.59-7.47 (m, 2H), 5.21 (t, J = 5.6 Hz, 1H), 3.66 (s, 1H), 2.90 (dd, J = 13.3, 6.6 Hz, 2H), 1.52-1.24 (m, 4H), 0.85 (t, J = 7.2 Hz, 3H).

13C NMR, DEPT (62 MHz, CDCl3): δ = 141.4 (C), 135.1 (CH), 132.0 (CH), 129.2 (CH), 129.1 (CH), 119.2 (C), 85.7 (CH), 80.2 (C), 43.0 (CH2), 31.4 (CH2), 19.6 (CH2), 13.4 (CH3).

SYNTHESIS: PSP

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MS (Cl): m/z (%) = 238 (M^+1, 100), 182 (15).
HRMS-Cl: m/z calcd for C_{12}H_{18}N_{2}O_{2}S [M^+: 1] 238.0902; found: 238.0896.

2-(Hex-1-yn-1-yl)benzamide (3e)
The general Sonogashira cross coupling procedure 2 was followed using 2-bromobenzamide (1.00 g, 5.00 mmol), Pd(OAc)_{2} (0.056 g, 0.25 mmol), Cul (0.048 g, 0.25 mmol), PPh_{3} (0.13 g, 0.50 mmol), 1-hexyne (0.62 g, 0.86 mL, 7.50 mmol) and Et_{3}N (40 mL). Upon completion (24 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:1 mixture of EtOAc/Hex as eluent to afford 3e (0.18 g, 18%) as a brown solid.

1^H NMR (250 MHz, CDCl_{3}): δ = 8.18-8.01 (m, 1H), 7.77-7.31 (m, 5H), 2.46 (t, J = 7.0 Hz, 2H), 1.68-1.40 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H).

13C NMR, DEPT (62 MHz, CDCl_{3}): δ = 168.7 (C=O), 134.1 (C), 133.5 (CH), 130.6 (CH), 129.8 (CH), 127.8 (CH), 120.8 (C), 97.6 (C), 79.3 (C), 30.2 (CH_{2}), 21.8 (CH_{3}), 19.1 (CH_{2}), 13.3 (CH_{3}).

MS (Cl): m/z (%) = 202 (M^+1, 100), 186 (12).

N-(2-ethynylbenzyl)acetamide (3f)
Acetic anhydride (1.15 g, 11.29 mmol) was added dropwise to a solution of 2-(bromophenyl)methanamine (2.00 g, 10.76 mmol) in Et_{3}N (4.50 mL) was cannulated to a solution of (2-bromophenyl)methanamine (2.00 g, 10.76 mmol) in CH_{2}Cl_{2} (22 mL) cooled at 0ºC. The reaction mixture was stirred for 12 h at room temperature until disappearance of starting material (TLC, GC-MS monitoring). Excess of acetic anhydride was quenched with H_{2}O (40 mL) and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_{2}SO_{4}, filtered and evaporated under vacuum to afford quantitatively N-(2-bromobenzyl)acetamide (2.44 g) as a white solid.

mp: 81-82.5 ºC

1^H NMR (250 MHz, CDCl_{3}): δ = 7.51 (d, J = 7.9 Hz, 1H), 7.34-7.21 (m, 2H), 7.11 (t, J = 7.5 Hz, 1H), 6.62 (s, 1H), 4.43 (d, J = 6.0 Hz, 2H), 1.99 (s, 3H).

13C NMR, DEPT (62 MHz, CDCl_{3}): δ = 170.2 (C=O), 137.1 (C), 132.6 (CH), 129.8 (CH), 128.9 (CH), 127.5 (CH), 123.4 (C), 43.6 (CH_{2}), 22.9 (CH_{3}).

MS (Cl): m/z (%) = 174 (M^+1, 71), 160 (11), 132 (100).

N-(2-ethynylbenzyl)-4-methylbenzenesulfonamide (3g)
A solution of p-toluenesulfonyl chloride (2.15 g, 11.30 mL) in Et_{3}N (4.50 mL) was cannulated to a solution of (2-bromophenyl)methanamine (2.00 g, 10.76 mmol) in CH_{2}Cl_{2} (22 mL) cooled at 0ºC. The reaction mixture was stirred for 12 h at room temperature until disappearance of starting material (TLC, GC-MS monitoring). The reaction was quenched adding H_{2}O (20 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous Na_{2}SO_{4}, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give N-(2-ethynylbenzyl)-4-methylbenzenesulfonamide (2.85g, 75%) as a white solid.

MS (Cl): m/z (%) = 340 (M^+1, 8), 260 (68), 184 (100), 155 (23), 139 (19), 91 (77), 77 (25), 65 (22).
HRMS–EI: m/z calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_2\text{SBr}$ $[\text{M}^+]$; found: 338.9914. The general Sonogashira cross coupling procedure 2 was followed using $N$-(2-bromobenzyl)-4-methylbenzenesulfonamide (1.44 g, 4.25 mmol), Pd(OAc)$_2$ (0.029 g, 0.13 mmol), Cul (0.024 g, 0.13 mmol), PPh$_3$ (0.056 g, 0.21 mmol), trimethylsilylelacetylene (0.63 g, 0.90 mL, 3.38 mmol) and Et$_3$N (40 mL). Upon completion (8 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to afford 4-methyl-N-(2-formylphenyl)-4-methylbenzenesulfonamide (0.83 g, 91%) as a brown oil.

1H NMR (250 MHz, CDCl$_3$): $\delta$ = 10.79 (s, 1H), 9.83 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.62-7.57 (m, 1H), 7.55-7.47 (m, 1H), 7.27-7.22 (m, 2H), 7.19-7.11 (m, 1H), 2.37 (s, 3H).

MS (CI): m/z (%) = 276 (M$^+$+1, 50), 248 (20), 155 (26), 125 (100).

A 5 M solution of ethynyl magnesium bromide in THF (5.60 mL, 2.80 mmol) was added dropwise to a solution of $N$-(2-formylphenyl)-4-methylbenzenesulfonamide (0.70 g, 2.54 mmol) in THF (25 mL) cooled at 0 ºC. The reaction mixture was stirred for 7 h at 0 ºC until disappearance of starting material (TLC, GC–MS monitoring). The mixture was evaporated under vacuum and the residue was dissolved in EtOAc (20 mL), washed with brine (2 x 10 mL), dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a 1:1 mixture of EtOAc/Hex as eluent to give 3g (0.28 g, 63%) as a brown solid.

$\text{C NMR, DEPT (125 MHz, CDCl}_3$): $\delta$ = 121.0 (C), 82.4 (CH), 81.0 (C), 46.0 (CH$_2$), 21.3 (CH$_3$).

MS (CI): m/z (%) = 286 (M$^+$+1, 100).

HRMS–EI: m/z calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{S}$ $[\text{M}^+]$; found: 285.0823; 285.0828.

**4-Methyl-N-(2-prop-2-yn-1-yl)phenylbenzenesulfonamide (5)**

To a solution of (2-aminophenyl)methanol (1.00 g, 8.12 mmol) in CH$_2$Cl$_2$ (50 mL) was added MnO$_2$ (0.70 g, 8.12 mmol) at room temperature. The reaction mixture was stirred for 24 h until disappearance of starting material (TLC, GC–MS monitoring). The mixture was filtered through silica gel using EtOAc as eluent. The filtrate was evaporated under vacuum and the residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to give 2-aminobenzaldehyde (0.49 g, 63%) as a yellow oil.

1H NMR (500 MHz, CDCl$_3$): $\delta$ = 7.70 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.3 Hz, 1H), 7.25-7.18 (m, 5H), 5.02 (t, J = 6.2 Hz, 1H), 4.30 (d, J = 6.2 Hz, 2H), 3.20 (s, 1H), 2.40 (s, 3H).

13C NMR, DEPT (62 MHz, CDCl$_3$): $\delta$ = 143.3 (C), 138.6 (C), 137.0 (C), 132.9 (CH), 129.5 (2 x CH), 129.2 (CH), 128.8 (CH), 127.7 (CH), 127.1 (2 x CH), 121.0 (C), 82.4 (CH), 81.0 (C), 46.0 (CH$_2$), 21.3 (CH$_3$).

MS (CI): m/z (%) = 276 (M$^+$+1, 50), 248 (20), 155 (26), 125 (100).

A solution of Et$_3$SiH (0.50 g, 0.69 mL, 4.32 mmol) in THF (5.60 mL) was added to a solution of 4-(2-amino-phenyl)acetic acid (1.00 g, 8.12 mmol) in THF (20 mL). The reaction mixture was stirred for 12 h at room temperature until disappearance of starting material (TLC, GC–MS monitoring). The reaction was quenched by adding a saturated solution of NaHCO$_3$ (15 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to afford 4 (0.32 g, 51%) as a brown oil.

1H NMR (250 MHz, CDCl$_3$): $\delta$ = 7.97 (s, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.33-7.09 (m, 5H), 5.34 (d, J = 2.0 Hz, 1H), 3.69 (s, 1H), 2.64 (d, J = 2.2 Hz, 1H), 2.36 (s, 3H).

13C NMR, DEPT (62 MHz, CDCl$_3$): $\delta$ = 143.9 (C), 136.3 (C), 135.0 (C), 131.2 (C), 129.6 (2 x CH), 129.5 (CH), 128.7 (CH), 127.1 (2 x CH), 125.5 (CH), 123.2 (CH), 81.4 (C), 76.3 (CH), 62.2 (CH), 21.4 (CH$_3$).

A solution of TFA (1 g, 0.67 mL, 8.64 mmol) was slowly added to a solution of 4-(2-hydroxyprop-2-yn-1-yl)phenylbenzenesulfonamide (0.65 g, 2.16 mmol) in THF (20 mL). The reaction mixture was stirred for 12 h at room temperature until disappearance of starting material (TLC, GC–MS monitoring). The reaction was quenched by adding a solution of Na$_2$SO$_4$ and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a 3:7 mixture of EtOAc/Hex as eluent to afford 4 (0.32 g, 51%) as a brown oil.

1H NMR (250 MHz, CDCl$_3$): $\delta$ = 7.61 (d, J = 8.2 Hz, 2H), 7.27-7.15 (m, 6H), 6.99 (s, 1H), 3.24 (d, J = 2.6 Hz, 2H), 2.39 (s, 3H), 2.04 (s, 1H).

13C NMR, DEPT (62 MHz, CDCl$_3$): $\delta$ = 143.8 (C), 136.6 (C), 134.2 (C), 130.7 (C), 129.6 (2 x CH), 129.5...
General procedure for the Ru-catalyzed heterocyclization reactions

Aromatic alkynyl amines/amides (1 equiv) were added to a suspension of the ruthenium catalyst (10 mol%) in pyridine (0.15 M) in a flame-dried sealed tube under Ar and the reaction mixture was heated at 90 °C until the complete consumption of the starting material (GC-MS monitoring). The reaction mixture was then cooled at room temperature, washed with saturated aqueous solution of NH₄Cl and extracted with diethyl ether (3 x). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated under vacuum. The residue was purified by flash column chromatography through silica gel using a mixture of EtOAc/Hex as eluent to afford the corresponding heterocyclization product.

1H-indole (2a)

The general heterocyclization procedure was followed using 1a (0.058 g, 0.50 mmol), CpRuCl(PPh₃)₂ (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (25 min), the reaction was worked-up and the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 2a (0.049 g, 84 %) as a yellow solid.

1H NMR (300 MHz, CDCl₃), δ (ppm): 8.02 (s, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.21-7.09 (m, 3H), 6.54 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H).

13C NMR, DEPT (75 MHz, CDCl₃), δ (ppm): 134.8 (C), 127.8 (C), 124.1 (CH), 120.7 (CH), 119.8 (CH), 110.9 (CH), 102.5 (CH).

MS (CI): m/z (%) = 118 (M⁺+1, 100), 91 (100).

1-Tosyl-1H-indole (2c)

The general heterocyclization procedure was followed using 1c (0.136 g, 0.50 mmol), CpRuCl(PPh₃)₂ (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (40 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 2c (0.108 g, 80 %) as a yellowish oil.

1H NMR (250 MHz, CDCl₃), δ (ppm): 7.99 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.59-7.49 (m, 2H), 7.33-7.18 (m, 4H), 6.65 (d, J = 3.7 Hz, 1H), 2.32 (s, 3H).

13C NMR, DEPT (75 MHz, CDCl₃), δ (ppm): 144.9 (C), 135.3 (C), 134.8 (C), 130.7 (C), 129.8 (2 x CH), 126.8 (2 x CH), 126.4 (CH), 124.5 (CH), 123.2 (CH), 121.3 (CH), 113.6 (CH), 109.0 (CH), 21.5 (CH₃).

MS (CI): m/z (%) = 272 (M⁺+1, 8), 271 (72), 180 (53), 91 (100).

HRMS-CI: m/z calcd for C₁₈H₁₄NO₂S [M⁺+1]: 272.0745; found: 272.0745.

5-Nitro-1H-indole (2d)

The general heterocyclization procedure was followed using 1d (0.081 g, 0.50 mmol), CpRuCl(PPh₃)₂ (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (20 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 2d (0.058 g, 72 %) as a yellow solid.

1H NMR (300 MHz, CDCl₃), δ (ppm): 8.71 (s, 1H), 8.62 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.39 (bs, 1H), 6.74 (s, 1H).

13C NMR, DEPT (75 MHz, CDCl₃), δ (ppm): 141.9 (C), 138.8 (C), 127.4 (CH), 127.2 (C), 118.0 (CH), 117.6 (CH), 111.0 (CH), 105.0 (CH).

MS (EI, 70 eV): m/z (%) = 162 (M⁺, 100), 132 (15), 116 (53), 104 (22), 89 (70), 63 (35).

HRMS-EI: m/z calcd for C₁₃H₁₄N₂O₂ [M⁺]: 272.0429; found: 272.0429.

1H-indole-5-carbonitrile (2e)

The general heterocyclization procedure was followed using 1e (0.071 g, 0.50 mmol), CpRuCl(PPh₃)₂ (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (30 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 2e (0.070 g, 98 %) as a yellow solid.

1H NMR (300 MHz, CDCl₃), δ (ppm): 9.10 (s, 1H), 7.98 (s, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.39 (dd, J = 8.5, 1.4 Hz, 1H), 7.34-7.32 (m, 1H), 6.60 (bs, 1H).

13C NMR, DEPT (75 MHz, CDCl₃), δ (ppm): 137.5 (C), 128.9 (C), 126.8 (CH), 126.2 (CH), 124.6 (CH), 121.0 (CN), 112.1 (CH), 103.1 (CH), 102.3 (C).

MS (EI, 70 eV): m/z (%) = 142 (M⁺, 100), 115 (36), 88 (10).
HRMS-EI: m/z calcd for C_{8}H_{7}NO \ [M^{+}]: 145.0531; found: 142.0531.

**Methyl 1H-indole-5-carboxylate (2f)**

The general heterocyclization procedure was followed using 1f (0.088 g, 0.50 mmol), CpRuCl(PPh_3)_2 (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (30 min) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 2f (0.086 g, 98 %) as a yellow solid.

^1H NMR (300 MHz, CDCl_3), δ (ppm): 8.85 (s, 1H), 8.43 (s, 1H), 7.89 (dd, J = 8.6, 1.5 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.23-7.21 (m, 1H), 6.61 (bs, 1H), 3.92 (s, 3H).

^13C NMR, DEPT (75 MHz, CDCl_3), δ (ppm): 164.4 (C=O), 138.1 (C), 132.5 (CH), 127.6 (CH), 127.3 (CH), 126.8 (CH), 126.2 (CH), 126.1 (C), 106.7 (C=O), 138.1 (C), 132.5 (CH), 127.6 (CH), 127.3 (CH), 126.0 (CH), 125.9 (CH), 124.6 (CH), 109.6 (CH), 44.3 (CH_2), 21.2 (CH_3).

The general heterocyclization procedure was followed using 3c (0.100 g, 0.50 mmol), CpRuCl(PPh_3)_2 (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (6 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 4c (0.074 g, 74 %) as a brown oil.

^1H NMR (500 MHz, CDCl_3), δ (ppm): 8.44 (d, J = 8.1 Hz, 1H), 7.64-7.60 (m, 1H), 7.51-7.46 (m, 2H), 7.06 (d, J = 7.3 Hz, 1H), 6.48 (d, J = 7.3 Hz, 1H), 4.02-3.98 (m, 2H), 1.80-1.74 (m, 2H), 1.40 (td, J = 14.8, 7.4 Hz, 2H), 0.96 (t, J = 7.4 Hz, 3H).

^13C NMR, DEPT (75 MHz, CDCl_3), δ (ppm): 162.1 (C=O), 137.0 (C), 132.0 (CH), 131.7 (CH), 127.8 (CH), 126.7 (CH), 126.3 (C), 125.8 (CH), 105.8 (CH), 49.1 (CH_2), 31.4 (CH_2), 20.0 (CH_2), 13.8 (CH_3).

MS (EI, 70 eV): m/z (%) = 202 (M^+, 100), 149 (8), 123 (16).

HRMS (ESI): m/z calcd for C_{10}H_{12}NO \ [M^{+}+1]: 202.1232; found: 202.1226.

**2-Butyl-2H-1,2-benzothiazine 1,1-dioxide (4d)**

The general heterocyclization procedure was followed using 3d (0.118 g, 0.50 mmol), CpRuCl(PPh_3)_2 (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (6 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 4d (0.072 g, 61 %) as a brown oil.

^1H NMR (400 MHz, CDCl_3), δ (ppm): 7.91 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.47-7.35 (m, 2H), 6.56 (d, J = 7.9 Hz, 1H), 6.24 (d, J = 7.9 Hz, 1H), 3.76-3.71 (m, 2H), 1.75-1.67 (m, 2H), 1.35 (dd, J = 15.1, 7.5 Hz, 2H), 0.92 (t, J = 7.5 Hz, 3H).

^13C NMR, DEPT (75 MHz, CDCl_3), δ (ppm): 133.2 (C), 131.9 (CH), 131.3 (CH), 131.1 (C), 127.3 (CH), 126.5 (CH), 121.6 (CH), 107.1 (CH), 48.0 (CH_2), 32.3 (CH_2), 19.6 (CH_2), 13.6 (CH_3).

MS (CI): m/z (%) = 238 (M^+1, 100), 182 (6), 174 (4).

HRMS (ESI): m/z calcd for C_{12}H_{16}NO_2S \ [M^{+}+1]: 238.0902; found: 238.0896.

**1-(Isoquinolin-2(1H)-yl)ethanone (4f)**

The general heterocyclization procedure was followed using 3f (0.086 g, 0.50 mmol), CpRuCl(PPh_3)_2 (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (5 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 4f (0.086 g, 80 %) as a yellowish oil.

^1H NMR (250 MHz, CDCl_3), δ (ppm): 11.49 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 6.9 Hz, 1H), 7.59-7.51 (m, 2H), 7.20 (d, J = 7.1 Hz, 1H), 6.58 (d, J = 7.1 Hz, 1H).

^13C NMR, DEPT (75 MHz, CDCl_3), δ (ppm): 168.8 (C=O), 130.4 (C), 129.4 (C), 127.6 (CH), 127.3 (CH), 126.0 (CH), 125.9 (CH), 124.6 (CH), 109.6 (CH), 44.3 (CH_2), 21.2 (CH_3).

**SYNTHESIS: PSP**

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MS (Cl): m/z (%) = 174 (M^+ + 1, 100), 132 (30).
HRMS (ESI): m/z calcd for C_{11}H_{12}NO [M^+ + 1]: 174.0919; found: 174.0913.

2-Tosyl-1,2-dihydroisoquinoline (4g)
The general heterocyclization procedure was followed using 3g (0.142 g, 0.50 mmol), CpRuCl(PPh₃)₂ (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (4 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 4g (0.116 g, 82 %) as a brown solid.

1H NMR (250 MHz, CDCl₃), δ (ppm): 7.69 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.15-7.05 (m, 2H), 6.98-6.90 (m, 2H), 6.76 (d, J = 7.8 Hz, 1H), 5.83 (d, J = 7.8 Hz, 1H), 4.56 (s, 2H), 2.37 (s, 3H).

13C NMR, DEPT (75 MHz, CDCl₃), δ (ppm): 144.1 (C), 134.4 (C), 130.4 (C), 129.8 (2 x CH), 128.0 (CH), 127.3 (C), 127.2 (CH), 127.1 (2 x CH), 126.4 (CH), 125.5 (CH), 124.4 (CH), 110.0 (CH), 47.1 (CH₂), 21.5 (CH₃).

HRMS-EI: m/z calcd for C_{16}H_{15}NO₂S [M +]: 285.0823; found: 285.0823.

1-Tosyl-1,4-dihydroquinoline (6)
The general heterocyclization procedure was followed using 5 (0.142 g, 0.50 mmol), CpRuCl(PPh₃)₂ (0.036 g, 0.050 mmol) and pyridine (3.30 mL). Upon completion (12 h) and work-up, the residue was purified by flash column chromatography through silica gel using a 1:4 mixture of EtOAc/Hex as eluent to give 6 (0.085 g, 60 %) as a brown oil.

1H NMR (500 MHz, CDCl₃), δ (ppm): 7.81 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.26-7.22 (m, 1H), 7.15 (d, J = 8.1 Hz, 3H), 6.89 (d, J = 7.5 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 5.54-5.49 (m, 1H), 2.73 (d, J = 3.6 Hz, 2H), 2.37 (s, 3H).

13C NMR, DEPT (75 MHz, CDCl₃), δ (ppm): 143.9 (C), 135.5 (C), 134.5 (C), 129.9 (C), 129.3 (2 x CH), 128.3 (CH), 127.6 (CH), 127.3 (2 x CH), 126.8 (CH), 126.2 (CH), 124.3 (CH), 116.6 (CH), 26.6 (CH₂), 21.6 (CH₃).

MS (Cl): m/z (%) = 286 (M^+ + 1, 85), 160 (30), 132 (100).
HRMS (ESI): m/z calcd for C_{16}H_{15}NO₂SNa [M^+ + Na]: 308.0721; found: 308.0716.

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