

Synthesis of functionalized arylpyridines and -pyrimidines by domino [4+2]/retro [4+2] cycloadditions of electron-rich dienes with alkynylpyridines and -pyrimidines

Obaid-ur-Rahman Abid,^a Muhammad Nawaz,^a Muhammad Farooq Ibad,^a Rasheed Ahmad Khera,^a Viktor Iaroshenko^a and Peter Langer^{*a,b}

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Aryl-substituted pyridines and pyrimidines were prepared by [4+2] cycloadditions of alkynyl-substituted pyridines and -pyrimidines with electron-rich dienes. The reactions proceed by formation of a bridged cycloadduct and subsequent thermal extrusion of ethylene. The pyridine moiety plays a crucial role for the success of the reaction.

Introduction

Biaryls and their heterocyclic analogues are of considerable importance, specifically with respect to their occurrence in bioactive natural products and to their applications in medicinal chemistry and as ligands in metal catalysis.^{1–3} Heterocyclic biaryls have been shown to possess activity in a wide range of therapeutic assays and show, for example, antifungal, anti-inflammatory, antirheumatic, antitumor and antihypertensive activity.³ They have been shown to be useful as antibacterial agents by inhibiting Gram-positive and Gram-negative bacteria⁴ and as anti-inflammatory agents. Owing to their heterocyclic structure, 4-phenylpyridines have been reported as a novel class of selective glucagon antagonists.⁵ Particular 4-aryl-1,4-dihydropyridines are already in use for the treatment of a number of cardiovascular disorders, such as hypertension, cardiac arrhythmias or angina.^{6,7} (Pyrid-2-yl)arenes are also present, hidden in a cyclic framework, in natural 4-azafluorenones (e.g. kinabaline, darienine and onychine) which exhibit a strong antimicrobial activity.⁸

Because of the significant importance of biaryls possessing a heterocyclic aromatic ring in natural products, as well as in molecular recognition phenomena and in asymmetric synthesis,³ the development of new and selective synthetic strategies, which overcome obstacles of known methods, is an important area of research. For the synthesis of arylpyridines a number of palladium-catalyzed reactions have been developed. This includes particularly the use of palladium-mediated strategies, such as the Kharasch, Negishi, Stille and Suzuki reactions.⁹ Homocoupling reactions of heterocyclic aromatic bromides, leading

to symmetric molecules, catalyzed by Pd(OAc)₂, have also been reported.¹⁰ Syntheses of arylpyridines have been achieved by direct cross-coupling of pyridyl halides and boronic acids. This strategy has been effectively applied to the use of both pyridyl halides as well as pyridine boronic acids as coupling partners.¹¹ Despite the great utility of these methods, the synthesis of more complex, highly functionalized derivatives can be difficult by these methods because the starting materials are not readily available.

An alternative strategy for the synthesis of arylpyridines relies on the application of a building block strategy. Recently, we reported the synthesis of 6-(pyridyl)salicylates based on a building block approach. The products were formed by formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 3-pyridyl-3-silyloxy-2-en-1-ones.¹² Diels–Alder reactions constitute a very important method for the assembly of complex molecules.¹³ In recent years, [4+2] cycloaddition reactions of alkynes have been widely used for the synthesis of biaryls.¹⁴ However, the synthesis of arylpyridines by cycloaddition reactions of pyridylacetylenes has, to the best of our knowledge, not been reported to date. Recently, Carter and co-workers have reported the synthesis of nitro-substituted biaryls by Diels–Alder reaction of (nitrophenyl)acetylenes with electron-rich dienes.¹⁵ It is important to note that the presence of the nitro group played an important role for the success of these reactions. The corresponding reactions of phenylacetylene proceeded in low yields or not at all. It occurred to us that the use of pyridyl- and pyrimidyl-substituted acetylenes in [4+2] cycloaddition reactions should be equally successful as the use of (*ortho*-nitrophenyl)acetylenes because pyridines possess a strong electron withdrawing character. Herein, we report the results of our studies related to [4+2] cycloaddition reactions of pyridyl- and pyrimidyl-substituted acetylenes with electron-rich dienes. These transformations provide a convenient approach to various functionalized arylpyridines and -pyrimidines.

^aInstitut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059, Rostock, Germany. E-mail: peter.langer@uni-rostock.de; Fax: +381 4986412

^bLeibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059, Rostock, Germany

Table 1 Synthesis of **2a–c** and **4a–c**

Diene	Acetylene	Conditions	Product	Yield ^a (%)
A	1	140 °C, 4 h	2a	63
B	1	1) 140 °C, 4 h; 2) K ₂ CO ₃ , MeOH, 15 min	2b	57
C	1	1) 140 °C, 4 h; 2) K ₂ CO ₃ , MeOH, 15 min	2c	55
A	3	140 °C, 16 h	4a	52
B	3	1) 140 °C, 6 h; 2) K ₂ CO ₃ , MeOH, 15 min	4b	44
C	3	1) 140 °C, 6 h; 2) K ₂ CO ₃ , MeOH, 15 min	4c	42

^a Yields of isolated products.

Results and discussion

Cyclic dienes **A** and **B** are commercially available (Chart 1), while **C** was prepared by a known procedure.^{15a} Danishefsky's diene (**D**) is commercially available. Brassard's diene (**E**)¹⁶ and Chan's diene (**F**)¹⁷ are available by known methods.

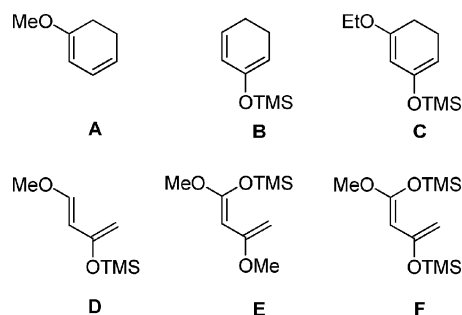
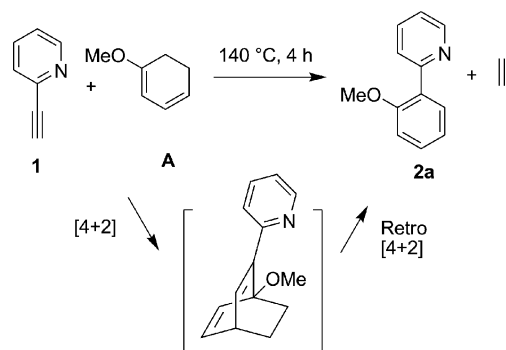
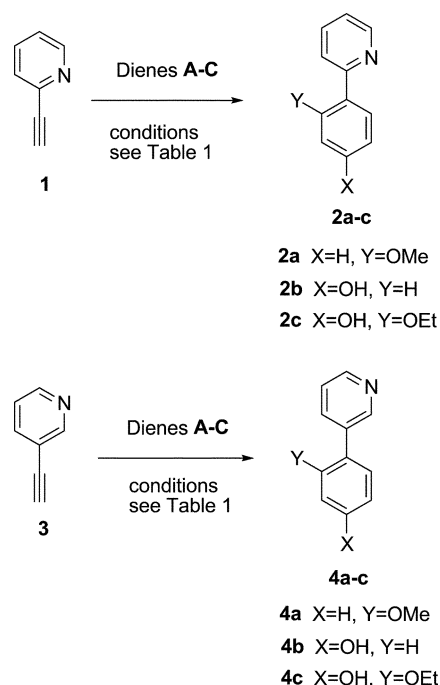


Chart 1 Dienes used in this study.

The [4+2] cycloaddition of (2-pyridyl)acetylene (**1**) with dienes **A–C** afforded the 2-arylpyridines **2a–c** in 55–63% yield (Schemes 1 and 2, Table 1). Likewise, 3-arylpyridines **4a–c** were prepared in 42–52% yield by reaction of (3-pyridyl)acetylene (**3**) with dienes **A–C**. Products **2a–c** and **4a–c** were formed with excellent regioselectivity. Their formation can be explained by formation of a bridged cycloadduct and subsequent thermal extrusion of ethylene by a retro Diels–Alder reaction (Schemes 1). The syntheses of **4a–c** required longer reaction times than the syntheses



Scheme 1 Diels–Alder reactions of **A** with pyridyl acetylene **1**.



Scheme 2 Diels–Alder reactions of **A–C** with pyridyl acetylenes **1** and **3**.

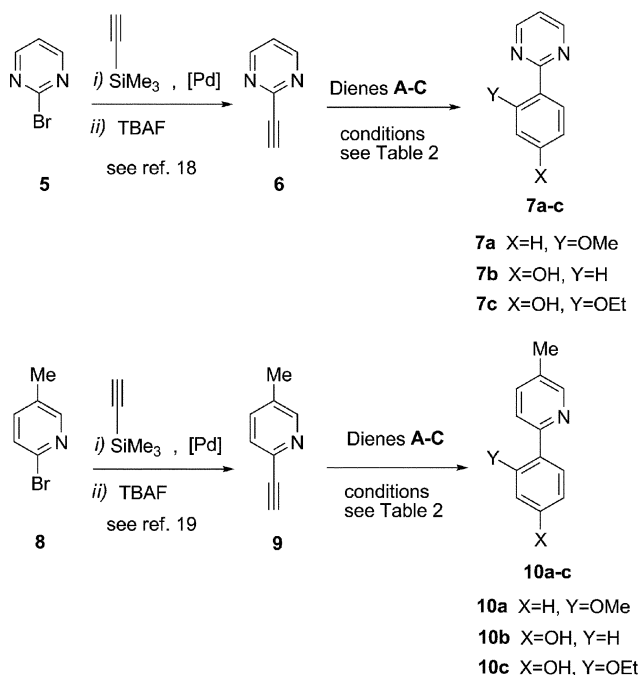
of **2a–c**. In addition, better yields were obtained for **2a–c** as compared to **4a–c**. This can be explained by the higher electron-withdrawing effect of the 2-pyridyl compared to the 3-pyridyl substituent which plays a role because all cycloadditions are of normal electron demand. The reactions were carried out by heating of the neat mixture of the starting materials. The yields decreased when the reactions were carried out in a solution of toluene or xylene. The yields also decreased when the temperature was lowered or when the reaction time was shortened. Products **2a** and **4a** were isolated by directed chromatographic purification of the reaction mixture. In case of **2b,c** and **4b,c** a MeOH suspension of potassium carbonate was added to the mixture to cleave the silyl groups. The reaction of **2** with open-chain dienes **D–F** proved to be unsuccessful. This can be explained by decomposition of the dienes due to the high temperatures required. Carter *et al.* reported that the corresponding reactions of **D–F** with (*ortho*-nitrophenyl)acetylene also failed.

The experiments show that our hypothesis was correct and pyridyl-substituted acetylenes indeed represent useful starting materials for cycloaddition reactions with electron rich dienes. The presence of the electron-withdrawing pyridine moiety plays, as expected, a crucial role for the success of the reaction. The corresponding reaction of **A** and **C** with phenylacetylene has been reported by Carter and co-workers to proceed sluggishly in only 26 and 38% yields.^{15c} The reaction of phenylacetylene with **B** failed. In contrast, the yields of the reactions of (2-nitrophenyl)acetylene with dienes **A–C** (*ca.* 80%)^{15e} are higher than the yields of **2a–c**.

With these promising results in hand, we further studied the preparative scope of the methodology. Alkynes **6**¹⁸ and **9**¹⁹ were prepared, following known procedures, by Sonogashira cross coupling reaction of **5** and **8** with TMS-acetylene and subsequent removal of the TMS group using TBAF, respectively (Scheme 3, Table 2). The reactions of acetylenes **6** and **9** with dienes **A–C** afforded the cycloadducts **7a–c** and **10a–c** in good yields,

Table 2 Synthesis of **7a–c** and **10a–c**

Diene	Acetylene	Conditions	Product	Yield ^a (%)
A	6	140 °C, 2 h	7a	69
B	6	1) 140 °C, 3 h; 2) K ₂ CO ₃ , MeOH, 15 min	7b	62
C	6	1) 140 °C, 3 h; 2) K ₂ CO ₃ , MeOH, 15 min	7c	62
A	9	140 °C, 4 h	10a	55
B	9	1) 140 °C, 6 h; 2) K ₂ CO ₃ , MeOH, 15 min	10b	43
C	9	1) 140 °C, 6 h; 2) K ₂ CO ₃ , MeOH, 15 min	10c	48

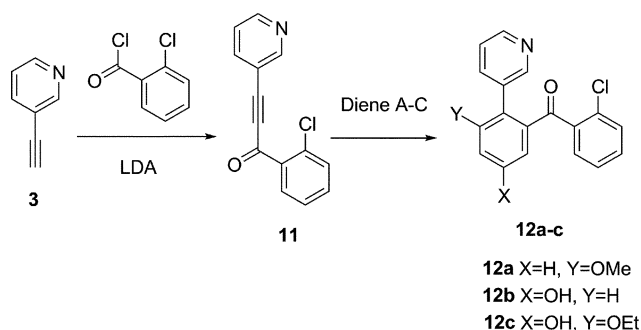
^a Yields of isolated products.**Scheme 3** Diels Alder reactions of **A–C** with acetylenes **6** and **9**.

respectively. The presence of a weak electron-donating group in the pyridyl ring of **9** resulted in a slight decrease of the yields of cycloadducts **10a–c** as compared to **2a–c**.

Acetylene **11** was prepared by deprotonation of acetylene **3** with LDA followed by addition of 2-chlorobenzoyl chloride. The cycloaddition of acetylene **11** with dienes **A–C** resulted in the formation of the highly functionalized products **12a–c** in 55–61% yields (Scheme 4, Table 3). The yields of **12a–c** are higher than those of products **4a–c**. This is remarkable because alkyne **11** is more sterically hindered than alkyne **3**. On the other hand, the 2-chlorobenzoyl group has a strong electron withdrawing character.

Table 3 Synthesis of **12a–c**

Diene	Conditions	Product	Yield ^a (%)
A	140 °C, 2 h	12a	61
B	1) 140 °C, 3 h; 2) K ₂ CO ₃ , MeOH, 15 min	12b	51
C	1) 140 °C, 3 h; 2) K ₂ CO ₃ , MeOH, 15 min	12c	55

^a Yields of isolated products.**Scheme 4** Diels Alder reactions of dienes **A–C** with acetylene **11**.

In conclusion, the [4+2] cycloaddition of pyridyl- and pyrimidyl-substituted acetylenes with electron-rich dienes provide a convenient approach to aryl-substituted pyridines and pyrimidines which are not readily available by other methods. The presence of the electron-withdrawing pyridine moiety plays a crucial role for the success of the reaction. Our present work is directed towards exploring the scope and applications of the reactions reported herein.

Experimental section

General procedure for the synthesis of biaryls

To a pressure tube containing the acetylene (1.0 equiv.) was added the diene (1.5 or 3.0 equiv.). The reaction mixture was stirred at 140 °C for 2–16 h. In the case of diene **A** the reaction mixture was directly then subjected to purification by chromatography over silica gel eluting with EtOAc–heptane to give the product. In case of dienes **B** and **C**, MeOH (5 mL) and K₂CO₃ (5 mmol) was added at 20 °C. After stirring for 15 min, the solution was quenched with a saturated aqueous solution of NH₄Cl (30 mL). The mixture was extracted with dichloromethane (2 × 50 mL). The aqueous and the organic layers were separated and the latter was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel eluting with EtOAc–heptane to give the product.

2-(2-Methoxyphenyl)pyridine (**2a**)

Starting with 2-ethynylpyridine **1** (0.13 mL, 2.0 mmol) and diene **A** (0.35 mL, 3.0 mmol), **2a** was isolated as a colorless viscous liquid (233 mg, 63%); ¹H NMR (300 MHz, CDCl₃): δ 3.77 (s, 3H, OCH₃), 6.93 (d, *J* = 8.3 Hz, 1H, ArH), 7.01 (dt, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.12 (dd, *J* = 7.4, 4.9, Hz, 1H, ArH), 7.27–7.33 (m, 1H, ArH), 7.61 (dt, *J* = 7.9, 1.9 Hz, 1H, ArH), 7.70 (dd, *J* = 7.6, 1.8 Hz, 1H, ArH), 7.74 (td, *J* = 8.0, 1.1 Hz, 1H, ArH), 8.63 (d, *J* = 4.8 Hz, 1H, ArH); ¹³C NMR (75.46 MHz, CDCl₃): δ 55.5 (OCH₃), 111.3 (CH), 120.9 (CH), 121.5 (CH), 125.0 (CH), 129.0 (C), 129.8 (CH), 131.0 (CH), 135.5 (CH), 149.3 (CH), 156.0 (C), 156.8 (C); IR (ATR, cm⁻¹): ν̄ = 3049 (w), 2834 (w), 1599 (m), 1580 (s), 1563 (m), 1492 (s), 1459 (s), 1422 (s), 1300 (m), 1237 (s), 1160 (m), 1021 (s), 987 (m), 852 (w), 791 (m), 745 (s), 611 (m); MS (GC, 70 eV): *m/z* (%): 186 (M⁺ + 1, 9), 185 (M⁺, 76), 184 (81), 156 (41), 155 (53), 154 (100), 141 (14), 128 (12), 127 (13), 115 (11), 89 (8), 80 (24), 78 (12), 51 (9); HRMS (ESI⁺): calc. for C₁₂H₁₂NO [M + H]⁺ 186.0913; found 186.0916.

4-(Pyrid-2-yl)phenol (2b)

Starting with 2-ethynylpyridine **1** (103 mg, 1.0 mmol), diene **B** (505 mg, 3.0 mmol), MeOH (5 mL) and K₂CO₃ (0.69 g, 5 mmol), **2b** was isolated as colorless crystals (97 mg, 57%), mp 151–153 °C; ¹H NMR (300 MHz, *d*₆-DMSO): δ 6.87 (td, *J* = 8.8, 1.9 Hz, 2H, ArH), 7.20–7.24 (m, 1H, ArH), 7.77–7.83 (m, 2H, ArH), 7.93 (td, *J* = 8.8, 1.9 Hz, 2H, ArH), 8.58 (d_(br), *J* = 4.8 Hz, 1H, ArH), 9.73 (s_(br), 1H, OH); ¹³C NMR (75.46 MHz, *d*₆-DMSO): δ 115.4 (2CH), 119.0 (CH), 121.4 (CH), 127.9 (2CH), 129.6 (C), 136.9 (CH), 149.2 (CH), 156.1 (C), 158.5 (C); IR (ATR, cm⁻¹): ν̄ = 3180–2481 (br), 1592 (s), 1561 (m), 1523 (m), 1467 (s), 1422 (s), 1268 (s), 1246 (s), 1181 (s), 1098 (m), 998 (s), 837 (s), 776 (s), 743 (s), 576 (m); MS (GC, 70 eV): *m/z* (%): 172 (M⁺ + 1, 11), 171 (M⁺, 100), 170 (30), 154 (9), 142 (11), 117 (8), 115 (9), 63 (3), 39 (2); HRMS (ESI⁺): calc. for C₁₁H₁₀NO [M + H]⁺ 172.0757; found 172.0756.

3-Ethoxy-4-(pyrid-2-yl)phenol (2c)

Starting with 2-ethynyl pyridine **1** (103 mg, 1.0 mmol), diene **C** (636 mg, 3.0 mmol), MeOH (5 mL) and K₂CO₃ (0.69 g, 5 mmol), **2c** was isolated as colorless crystals (118 mg, 55%), m.p 142–143 °C; ¹H NMR (300 MHz, CDCl₃): δ 1.21 (t, *J* = 7.0 Hz, 3H, CH₃), 3.66 (q, *J* = 7.0 Hz, 2H, OCH₂), 6.22–6.24 (m, 1H, ArH), 6.26 (d, *J* = 2.2 Hz, 1H, ArH), 7.11 (dt, *J* = 6.2, 1.3 Hz, 1H, ArH), 7.37 (d, *J* = 8.1 Hz, 1H, ArH), 7.63 (dt, *J* = 8.0, 1.8 Hz, 1H, ArH), 7.71 (d, *J* = 7.9 Hz, 1H, ArH), 8.51–8.53 (m, 1H, ArH), 10.91 (s_(br), 1H, OH); ¹³C NMR (62.89 MHz, CDCl₃): δ 14.6 (CH₃), 63.5 (OCH₂), 100.3 (CH), 108.2 (CH), 118.9 (C), 121.2 (CH), 125.5 (CH), 131.8 (CH), 136.5 (CH), 147.9 (CH), 156.4 (C), 157.4 (CH), 160.0 (C); IR (ATR, cm⁻¹): IR (ATR, cm⁻¹): ν̄ = 3220–2550 (br), 1613 (w), 1575 (s), 1454 (s), 1295 (m), 1180 (s), 1128 (s), 1035 (m), 991 (m), 774 (s), 632 (m), 563 (m); MS (GC, 70 eV): *m/z* (%): 216 (M⁺ + 1, 9), 215 (M⁺, 63), 214 (55), 201 (13), 200 (92), 187 (12), 186 (55), 172 (23), 171 (100), 170 (23), 130 (31), 117 (12), 80 (11), 63 (7), 51 (5), 29 (4); HRMS (EI): calc. for C₁₃H₁₃NO₂ [M⁺]: 215.09408, found 215.09396.

3-(2-Methoxyphenyl)pyridine (4a)

Starting with 3-ethynylpyridine **3** (206 mg, 2.0 mmol) and diene **A** (0.35 mL, 3.0 mmol), **4a** was isolated as a colorless viscous liquid (192 mg, 52%); ¹H NMR (300 MHz, CDCl₃): δ 3.72 (s, 3H, OCH₃), 6.92 (d, *J* = 8.3 Hz, 1H, ArH), 6.97 (dt, *J* = 7.5, 1.0 Hz, 1H, ArH), 7.21–7.31 (m, 3H, ArH), 7.77 (td, *J* = 8.0, 2.0 Hz, 1H, ArH), 8.47 (d, *J* = 3.7 Hz, 1H, ArH), 8.70 (s_(br), 1H, ArH); ¹³C NMR (62.89 MHz, CDCl₃): δ 55.4 (OCH₃), 111.2 (CH), 120.9 (CH), 122.8 (CH), 126.9 (C), 129.4 (CH), 130.5 (CH), 134.1 (C), 136.6 (CH), 147.8 (CH), 150.2 (CH), 156.5 (C); IR (ATR, cm⁻¹): IR (ATR, cm⁻¹): ν̄ = 3025 (w), 2936 (w), 2833 (w), 1598 (w), 1496 (s), 1462 (s), 1405 (s), 1333 (w), 1264 (s), 1235 (s), 1179 (m), 1121 (m), 1024 (s), 997 (s), 800 (m), 710 (s); MS (GC, 70 eV): *m/z* (%): 186 (M⁺ + 1, 13), 185 (M⁺, 100), 184 (10), 170 (49), 141 (5), 115 (23), 89 (5), 63 (4); HRMS (EI): calc. for C₁₂H₁₁NO [M⁺]: 185.08352, found 185.08289.

4-(Pyrid-3-yl)phenol (4b)

Starting with 3-ethynylpyridine **3** (103 mg, 1.0 mmol), diene **B** (505 mg, 3.0 mmol), MeOH (5 mL) and K₂CO₃ (0.69 g, 5 mmol),

4b was isolated as colorless crystals (75 mg, 44%), mp 198–199 °C; ¹H NMR (300 MHz, *d*₆-DMSO): δ 6.90 (d_(br), *J* = 8.5 Hz, 2H, ArH), 7.39 (dd, *J* = 7.8, 4.8 Hz, 1H, ArH), 7.54 (d_(br), *J* = 8.5 Hz, 2H, ArH), 7.94 (d_(br), *J* = 8.1 Hz, 1H, ArH), 8.48 (d, *J* = 4.0 Hz, 1H, ArH), 8.82 (s, 1H), 9.71 (s_(br), 1H, OH); ¹³C NMR (75.46 MHz, *d*₆-DMSO): δ 116.0 (2CH), 123.7 (CH), 127.7 (C), 128.0 (2CH), 133.2 (CH), 135.6 (C), 147.0 (CH), 147.4 (CH), 157.7 (C); IR (ATR, cm⁻¹): ν̄ = 3170–2480 (br), 1698 (w), 1591 (m), 1580 (m), 1454 (m), 1385 (w), 1271 (m), 1232 (m), 1176 (m), 1062 (m), 1022 (m), 840 (s), 809 (s), 697 (s), 549 (s); MS (GC, 70 eV): *m/z* (%): 172 (M⁺ + 1, 14), 171 (M⁺, 100), 170 (19), 142 (10), 117 (12), 115 (11), 89 (5), 32 (4); HRMS (ESI⁺): calc. for C₁₁H₁₀NO [M + H]⁺ 172.0757, found 172.0756.

3-Ethoxy-4-(pyrid-3-yl)phenol (4c)

Starting with 3-ethynylpyridine **3** (103 mg, 1.0 mmol), diene **C** (636 mg, 3.0 mmol), MeOH (5 mL) and K₂CO₃ (0.69 g, 5 mmol), **4c** was isolated as colorless crystals (90 mg, 42%), mp 168–170 °C; ¹H NMR (300 MHz, *d*₆-DMSO): δ 1.27 (t, *J* = 6.9 Hz, 3H, CH₃), 4.01 (q, *J* = 6.9 Hz, 2H, OCH₂), 6.49 (dd, *J* = 8.2, 2.1 Hz, 1H, ArH), 6.54 (d, *J* = 2.0 Hz, ArH), 7.18 (d, *J* = 8.2 Hz, 1H, ArH), 7.40 (dd, *J* = 7.8, 4.8 Hz, 1H, ArH), 7.87 (d_(br), *J* = 7.9 Hz, 1H, ArH), 8.45 (d, *J* = 3.7 Hz, 1H, ArH), 8.68 (s, 1H, ArH), 9.69 (s_(br), 1H, OH); ¹³C NMR (62.89 MHz, *d*₆-DMSO): δ 14.6 (CH₃), 63.5 (OCH₂), 100.4 (CH), 108.0 (CH), 117.1 (C), 123.3 (CH), 131.1 (CH), 134.3 (C), 136.5 (CH), 146.7 (CH), 149.3 (CH), 156.7 (C), 159.1 (C); IR (ATR, cm⁻¹): IR (ATR, cm⁻¹): ν̄ = 3110–2390 (b), 1598 (m), 1513 (w), 1453 (s), 1385 (m), 1301 (m), 1257 (m), 1198 (s), 1120 (m), 1042 (m), 997 (m), 899 (w), 808 (s), 707 (s), 636 (s); MS (GC, 70 eV): *m/z* (%): 216 (M⁺ + 1, 14), 215 (M⁺, 100), 187 (83), 186 (60), 160 (16), 158 (9), 131 (8), 130 (11), 77 (7), 51 (3); HRMS (ESI⁺): calc. for C₁₃H₁₄NO₂ [M + H]⁺ 216.1019; found 216.1018.

2-(2-Methoxyphenyl)pyrimidine (7a)

Starting with 2-ethynylpyrimidine **6** (208 mg, 2.0 mmol) and diene **A** (0.35 mL, 3.0 mmol), **7a** was isolated as a yellowish viscous liquid (257 mg, 69%); ¹H NMR (300 MHz, CDCl₃): δ 3.79 (s, 3H, OCH₃), 6.96 (d, *J* = 8.3 Hz, 1H, ArH), 6.99 (dt, *J* = 7.5, 0.9 Hz, 1H, ArH), 7.13 (t, *J* = 4.9 Hz, 1H, ArH), 7.32–7.38 (m, 1H, ArH), 7.64 (dd, *J* = 7.5, 1.8 Hz, 1H, ArH), 8.77 (d, *J* = 4.9 Hz, 2H, ArH); ¹³C NMR (62.89 MHz, CDCl₃): δ 56.0 (OCH₃), 111.9 (CH), 118.6 (CH), 120.7 (CH), 128.3 (C), 131.0 (CH), 131.7 (CH), 157.0 (2CH), 157.6 (C), 165.9 (C); IR (ATR, cm⁻¹): ν̄ = 3033 (w), 2937 (w), 2834 (w), 1714 (w), 1600 (m), 1566 (s), 1552 (s), 1494 (m), 1460 (m), 1412 (s), 1275 (m), 1238 (s), 1179 (m), 1127 (m), 1057 (m), 1021 (s), 803 (m), 750 (s), 633 (s); MS (GC, 70 eV): *m/z* (%): 187 (M⁺ + 1, 12), 186 (M⁺, 100), 185 (50), 169 (34), 158 (12), 157 (39), 156 (29), 155 (13), 130 (29), 104 (13), 103 (44), 90 (15); HRMS (ESI⁺): calc. for C₁₁H₁₁N₂O [M + H]⁺ 187.0866, found 187.0866.

4-(Pyrimidin-2-yl)phenol (7b)

Starting with 2-ethynylpyrimidine **6** (104 mg, 1.0 mmol), diene **B** (505 mg, 3.0 mmol), MeOH (5 mL) and K₂CO₃ (0.69 g, 5 mmol), **7b** was isolated as colorless crystals (107 mg, 62%), mp 183–185 °C; ¹H NMR (300 MHz, *d*₆-DMSO): δ 6.89 (td, *J* = 8.8, 2.1 Hz, 2H,

ArH), 7.31 (t, $J = 4.9$ Hz, 1H, ArH), 8.26 (td, $J = 8.8, 2.1$ Hz, 2H, ArH), 8.81 (d, $J = 4.9$ Hz, 2H, ArH), 9.97 (s_{br} , 1H, OH); ^{13}C NMR (62.89 MHz, d_6 -DMSO): δ 115.6 (2CH), 118.8 (CH), 128.3 (C), 129.6 (2CH), 157.6 (2CH), 160.2 (C), 163.6 (C); IR (ATR, cm^{-1}): $\tilde{\nu} = 3129$ – 2354 (b), 1704 (w), 1609 (m), 1550 (s), 1519 (m), 1407 (s), 1317 (m), 1283 (s), 1204 (s), 1166 (s), 1100 (m), 993 (m), 783 (s), 646 (s), 630 (s); MS (GC, 70 eV): m/z (%): 173 ($\text{M}^+ + 1$, 12), 172 (M^+ , 100), 171 (12), 144 (2), 119 (55), 91 (4), 64 (5), 39 (2); HRMS (EI): calc. for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}$ [M^+]: 172.06311, found 172.06280.

3-Ethoxy-4-(pyrimidin-2-yl)phenol (7c)

Starting with 2-ethynylpyrimidine **6** (104 mg, 1.0 mmol), diene **C** (636 mg, 3.0 mmol), MeOH (5 mL) and K_2CO_3 (0.69 g, 5 mmol), **7c** was isolated as colorless crystals (134 mg, 62%), mp 185–186 °C; ^1H NMR (300 MHz, d_6 -DMSO): δ 1.25 (t, $J = 6.9$ Hz, 3H, CH_3), 4.00 (q, $J = 6.9$ Hz, 2H, OCH_2), 6.47 (dd, $J = 8.3, 1.8$ Hz, ArH), 6.51 (d, $J = 1.5$ Hz, ArH), 7.31 (t, $J = 4.8$ Hz, 1H, ArH), 7.49 (d, $J = 8.3$ Hz, 1H, ArH), 8.81 (d, $J = 4.8$ Hz, 2H, ArH), 9.81 (s_{br} , 1H, OH); ^{13}C NMR (62.89 MHz, d_6 -DMSO): δ 14.7 (CH_3), 64.0 (OCH_2), 101.1 (CH), 107.5 (CH), 118.5 (CH), 120.2 (C), 132.6 (CH), 157.0 (2CH), 158.4 (C), 160.1 (C), 165.4 (C); IR (ATR, cm^{-1}): $\tilde{\nu} = 3134$ – 2606 (br), 1599 (m), 1571 (s), 1552 (s), 1468 (w), 1407 (s), 1321 (m), 1277 (s), 1235 (s), 1085 (m), 992 (m), 820 (m), 771 (m), 638 (s); MS (GC, 70 eV): m/z (%): 217 ($\text{M}^+ + 1$, 11), 216 (M^+ , 100), 215 (26), 201 (42), 199 (13), 188 (15), 173 (18), 172 (74), 171 (11), 135 (18), 131 (25), 119 (29), 79 (6), 52 (6); HRMS (EI): calc. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$ [M^+]: 216.08933, found 216.08890.

2-(2-Methoxyphenyl)-5-methylpyridine (10a)

Starting with 2-ethynyl-5-methylpyridine **9** (234 mg, 2.0 mmol) and diene **A** (0.35 mL, 3.0 mmol), **10a** was isolated as colorless greenish viscous liquid (219 mg, 55%); ^1H NMR (300 MHz, CDCl_3): δ 2.28 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.91 (d, $J = 8.3$ Hz, 1H, ArH), 7.00 (dt, $J = 7.5, 1.0$ Hz, 1H, ArH), 7.24–7.30 (m, 1H, ArH), 7.42 (dd, $J = 8.1, 2.2$ Hz, 1H, ArH), 7.63 (d, $J = 8.0$ Hz, 1H, ArH), 7.68 (dd, $J = 7.6, 1.8$ Hz, 1H, ArH), 8.46 (s_{br} , 1H, ArH); ^{13}C NMR (75.46 MHz, CDCl_3): δ 18.0 (CH_3), 55.4 (OCH_3), 111.2 (CH), 120.8 (CH), 124.3 (CH), 129.0 (C), 129.4 (CH), 130.8 (CH), 130.9 (C), 136.0 (CH), 149.6 (CH), 153.2 (C), 156.7 (C); IR (ATR, cm^{-1}): IR (ATR, cm^{-1}): $\tilde{\nu} = 2997$ (w), 2920 (w), 2834 (w), 1599 (m), 1581 (m), 1495 (s), 1462 (s), 1434 (s), 1357 (m), 1240 (s), 1178 (m), 1121 (m), 1056 (m), 1022 (s), 832 (m), 750 (s); MS (GC, 70 eV): m/z (%): 200 ($\text{M}^+ + 1$, 13), 199 (M^+ , 100), 198 (99), 170 (46), 169 (63), 168 (60), 167 (14), 154 (22), 142 (10), 141 (29), 128 (15), 115 (12), 94 (34), 84 (11). HRMS (EI): calc. for $\text{C}_{13}\text{H}_{13}\text{NO}$ [M^+]: 199.09973, found 199.09890.

4-(5-Methylpyrid-2-yl)phenol (10b)

Starting with 2-ethynyl-5-methylpyridine **9** (117 mg, 1.0 mmol), diene **B** (505 mg, 3.0 mmol), MeOH (5 mL) and K_2CO_3 (0.69 g, 5 mmol), **10b** was isolated as colorless crystals (80 mg, 43%), mp 173–175 °C; ^1H NMR (300 MHz, d_6 -DMSO): δ 2.30 (s, 3H, CH_3), 6.85 (td, $J = 8.8, 2.1$ Hz, 2H, ArH), 7.61 (dd, $J = 8.2, 2.2$ Hz, 1H, ArH), 7.72 (d, $J = 8.1$ Hz, 1H, ArH), 7.90 (td, $J = 8.8, 2.1$ Hz, 2H, ArH), 8.42 (s_{br} , 1H, ArH), 9.67 (s_{br} , 1H, OH); ^{13}C NMR (62.89 MHz, d_6 -DMSO): δ 17.7 (CH_3), 115.5 (2CH), 118.6 (CH),

127.7 (2CH), 129.8 (C), 130.5 (C), 137.4 (CH), 149.6 (CH), 153.7 (C), 158.3 (C); IR (ATR, cm^{-1}): $\tilde{\nu} = 3080$ – 2470 (br), 1704 (w), 1672 (w), 1601 (s), 1593 (s), 1522 (w), 1472 (s), 1374 (m), 1266 (s), 1234 (s), 1176 (m), 1111 (m), 1043 (m), 819 (s), 759 (m), 651 (m); MS (GC, 70 eV): m/z (%): 186 ($\text{M}^+ + 1$, 14), 185 (M^+ , 100), 184 (30), 157 (11), 141 (3), 131 (5), 128 (5), 63 (3), 39 (2); HRMS (ESI+): calc. for $\text{C}_{12}\text{H}_{12}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 186.0913; found 186.0913.

3-Ethoxy-4-(5-methylpyrid-2-yl)phenol (10c)

Starting with 2-ethynyl-5-methylpyridine **9** (117 mg, 1.0 mmol), diene **C** (636 mg, 3.0 mmol), MeOH (5 mL) and K_2CO_3 (0.69 g, 5 mmol), **10c** was isolated as colorless crystals (110 mg, 48%), mp 189–191 °C; ^1H NMR (300 MHz, d_6 -DMSO): δ 1.34 (t, $J = 6.9$ Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.04 (q, $J = 6.9$ Hz, 2H, OCH_2), 6.45–6.50 (m, 2H, ArH), 7.55 (dd, $J = 8.2, 1.8$ Hz, 1H, ArH), 7.66 (d, $J = 8.3$ Hz, 1H, ArH), 7.78 (d, $J = 8.2$ Hz, 1H, ArH), 8.42 (s, 1H, ArH), 9.66 (s_{br} , 1H, OH); ^{13}C NMR (62.89 MHz, d_6 -DMSO): δ 14.7 (CH_3), 17.7 (CH_3), 63.6 (OCH_2), 100.1 (CH), 107.8 (CH), 119.5 (C), 123.5 (CH), 130.0 (C), 131.5 (CH), 136.2 (CH), 149.3 (CH), 152.7 (C), 157.3 (C), 159.2 (C); IR (ATR, cm^{-1}): $\tilde{\nu} = 3120$ – 2528 (br), 1613 (w), 1579 (m), 1455 (s), 1362 (w), 1300 (s), 1182 (s), 1124 (m), 1040 (s), 899 (w), 818 (s), 724 (w), 589 (m); MS (GC, 70 eV): m/z (%): 230 ($\text{M}^+ + 1$, 6), 229 (M^+ , 47), 228 (36), 214 (82), 200 (26), 186 (26), 185 (100), 184 (28), 144 (21), 115 (9), 94 (12), 65 (5), 32 (4); HRMS (ESI+): calc. for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ [$\text{M} + \text{H}$] $^+$ 238.1176; found 230.1178.

(2-Chlorophenyl)(3-methoxy-2-(pyrid-3-yl)phenyl)methanone (12a)

Starting with 1-(2-chlorophenyl)-3-(pyrid-3-yl)prop-2-yn-1-one **11** (121 mg, 0.5 mmol) and diene **A** (0.18 mL, 1.5 mmol), **12a** was isolated as brown viscous liquid (98 mg, 61%); ^1H NMR (300 MHz, CDCl_3): δ 3.70 (s, 3H, OCH_3), 6.89 (d, $J = 7.7$ Hz, 1H, ArH), 6.95 (d, $J = 8.2$ Hz, 1H, ArH), 7.04–7.10 (m, 2H, ArH), 7.19–7.21 (m, 2H, ArH), 7.36 (d_{br} , $J = 7.7$ Hz, 1H, ArH), 7.42 (t, $J = 8.1$ Hz, 1H, ArH), 7.52 (td, $J = 7.8, 1.9$ Hz, 1H, ArH), 8.36 (d_{br} , $J = 4.0$ Hz, 1H, ArH), 8.41 (s, 1H, ArH); ^{13}C NMR (75.46 MHz, CDCl_3): δ 56.0 (OCH_3), 111.0 (CH), 122.5 (CH), 122.7 (CH), 126.4 (CH), 129.6 (C), 130.9 (CH), 131.1 (CH), 131.6 (CH), 132.5 (CH), 132.9 (C), 135.4 (C), 136.3 (CH), 137.3 (C), 138.1 (C), 148.5 (CH), 149.3 (CH), 157.5 (C), 194.6 (CO); IR (ATR, cm^{-1}): $\tilde{\nu} = 3049$ (w), 2937 (w), 2834 (w), 1600 (m), 1580 (s), 1492 (s), 1459 (s), 1422 (s), 1300 (m), 1256 (s), 1237 (s), 1179 (m), 1122 (m), 1021 (s), 987 (m), 745 (s), 729 (s), 611 (m); MS (GC, 70 eV): m/z (%): 325 (M^+ , ^{37}Cl , 17), 323 (M^+ , ^{35}Cl , 40), 322 (11), 294 (22), 289 (20), 288 (90), 272 (13), 260 (22), 213 (20), 212 (100), 207 (26), 183 (13), 169 (19), 141 (19), 139 (33), 111 (22), 75 (12); HRMS (ESI+): calc. for $\text{C}_{19}\text{H}_{15}^{35}\text{ClNO}_2$ [$\text{M} + \text{H}$] $^+$ 324.0786; found 324.0786.

(2-Chlorophenyl)-(5-hydroxy-2-(pyrid-3-yl)phenyl)methanone (12b)

Starting with 1-(2-chlorophenyl)-3-(pyrid-3-yl)prop-2-yn-1-one **11** (121 mg, 0.5 mmol), diene **B** (252 mg, 1.5 mmol), MeOH (2.5 mL) and K_2CO_3 (0.34 g, 2.5 mmol), **12b** was isolated as colorless crystals (79 mg, 51%), mp 98–100 °C; ^1H NMR (300 MHz, d_6 -DMSO): δ 6.79 (d, $J = 2.4$ Hz, 1H, ArH), 6.93

(dd, $J = 8.5, 2.4$ Hz, 1H, ArH), 7.28–7.41 (m, 5H, ArH), 7.45 (d, $J = 8.5$ Hz, 1H, ArH), 7.65 (td_(br), $J = 8.0, 1.9$ Hz, 1H, ArH), 8.42–8.44 (m, 2H, ArH), 10.67 (s_(br), 1H, OH); ¹³C NMR (75.46 MHz, *d*₆-DMSO): δ 114.8 (CH), 118.3 (CH), 122.9 (CH), 127.0 (CH), 128.1 (C), 129.9 (CH), 130.1 (CH), 130.3 (C), 131.8 (CH), 134.1 (CH), 135.7 (CH), 136.3 (C), 138.8 (C), 141.5 (C), 148.0 (CH), 148.5 (CH), 161.1 (C), 193.9 (CO); IR (ATR, cm⁻¹): $\tilde{\nu} = 3143$ –2425 (br), 1651 (w), 1587 (m), 1462 (w), 1291 (s), 1218 (s), 1124 (m), 1053 (w), 929 (m), 758 (s), 710 (s), 605 (s); MS (GC, 70 eV): m/z (%): 311 (M⁺, ³⁷Cl, 9), 310 (M⁺ + 1, ³⁵Cl, 13), 309 (M⁺, ³⁵Cl, 29), 308 (26), 280 (23), 274 (52), 246 (15), 207 (18), 199 (66), 198 (100), 139 (18), 115 (14), 111 (13), 44 (6); HRMS (EI): calc. for C₁₈H₁₂NO₂³⁵Cl [M⁺]: 309.05511, found 309.05438.

(2-Chlorophenyl)-(3-ethoxy-5-hydroxy-2-(pyridin-3-yl)phenyl)methanone (12c)

Starting with 1-(2-chlorophenyl)-3-(pyridin-3-yl)prop-2-yn-1-one **11** (121 mg, 0.5 mmol), diene **C** (318 mg, 1.5 mmol), MeOH (2.5 mL) and K₂CO₃ (0.34 g, 2.5 mmol), **12c** was isolated as colorless crystals (97 mg, 55%), mp 154–156 °C; ¹H NMR (300 MHz, *d*₆-DMSO): δ 0.82 (t, $J = 6.9$ Hz, 3H, CH₃), 3.82 (q, $J = 6.9$ Hz, 2H, OCH₂), 6.40 (d, $J = 2.1$ Hz, 1H, ArH), 6.50 (d, $J = 2.0$ Hz, 1H, ArH), 7.32–7.50 (m, 5H, ArH), 7.66 (td_(br), $J = 7.9, 2.0$ Hz, 1H, ArH), 8.45 (d, $J = 1.8$ Hz, 1H, ArH), 8.47 (dd, $J = 4.8, 1.4$ Hz, 1H, ArH), 10.37 (s_(br), 1H, OH); ¹³C NMR (62.89 MHz, *d*₆-DMSO): δ 13.9 (CH₃), 63.9 (OCH₂), 99.7 (CH), 110.4 (CH), 120.0 (C), 123.2 (CH), 127.2 (CH), 130.3 (CH), 130.4 (CH), 131.1 (C), 132.2 (CH), 135.9 (CH), 136.4 (C), 140.0 (C), 140.7 (C), 148.2 (CH), 148.7 (CH), 159.5 (C), 160.9 (C), 193.6 (CO); IR (ATR, cm⁻¹): $\tilde{\nu} = 3151$ –2580 (br), 1667 (m), 1558 (m), 1435 (m), 1291 (m), 1178 (s), 1137 (m), 1035 (s), 928 (m), 762 (s), 742 (s), 623 (s); MS (GC, 70 eV): m/z (%): 355 (M⁺, ³⁷Cl, 5), 354 (M⁺ + 1, ³⁵Cl, 10), 353 (M⁺, ³⁵Cl, 24), 308 (42), 242 (18), 214 (100), 199 (32), 198 (43), 139 (3), 115 (94), 111 (7), 44 (21); HRMS (ESI⁺): calc. for C₂₀H₁₇³⁵ClNO₃ [M + H]⁺ 354.0894; found 354.0891.

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