Synthesis of Benzofuropyridines and Dibenzofurans by a Metalation/Negishi Cross-Coupling/S_NAr Reaction Sequence

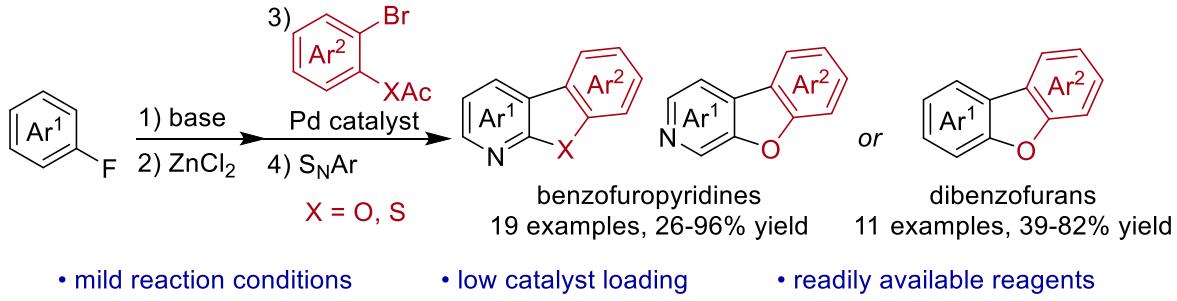
Guy J. Clarkson, Stefan Roesner*

Department of Chemistry, University of Warwick,

Gibbet Hill Road, Coventry, CV4 7AL, UK

E-mail: s.roesner@warwick.ac.uk

An efficient methodology for the synthesis of benzofuropyridines and dibenzofurans from fluoropyridines or fluoroarenes and 2-bromophenyl acetates is reported. This streamlined one-pot procedure consists of a four-step directed ortho-lithiation, zincation, Negishi cross-coupling, and intramolecular nucleophilic substitution, allowing for the facile assembly of a diverse set of fused benzofuro heterocycles.



Nitrogen heterocycles are among the most significant structural motifs of pharmaceuticals with more than half of all FDA approved small-molecule drugs containing at least one N-heterocycle.[1] Among them, benzofuropyridines are tricyclic compounds containing an annulated pyridine, furan and benzene ring. Though, compared to the synthesis and biological evaluation of dibenzofurans,[2,3] benzofuropyridines have been far less explored. This is surprising as this class of compounds shows diverse biological activity and interesting properties for potential applications in material science. Examples include elbfluorene (**I**) and its derivatives that possess high activity as cyclin-dependent kinase (CDK) inhibitors[4] and

benzofuro[2,3-*c*]pyridine **II** with potential applications as an MDR modulator (Figure 1).[5] In addition to their diverse biological activity, benzofuro- and benzothienopyridine derivatives possess interesting fluorescence properties suitable to be applied as green or blue OLED emitters.[6] Moreover, dyes with a benzothieno[2,3-*c*]pyridine (**III**) anchoring group have received considerable attention in the development of dye-sensitized solar cells.[7]

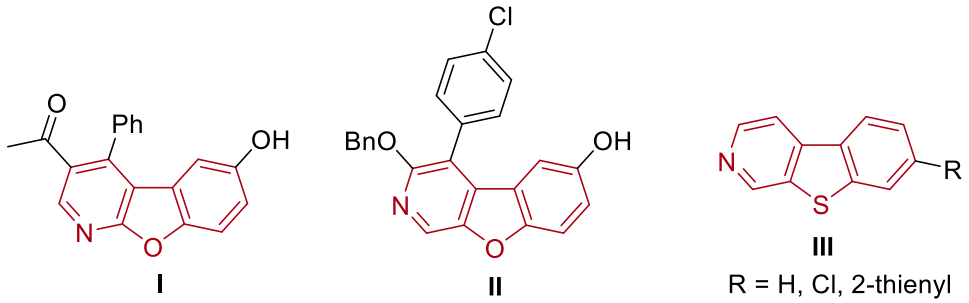
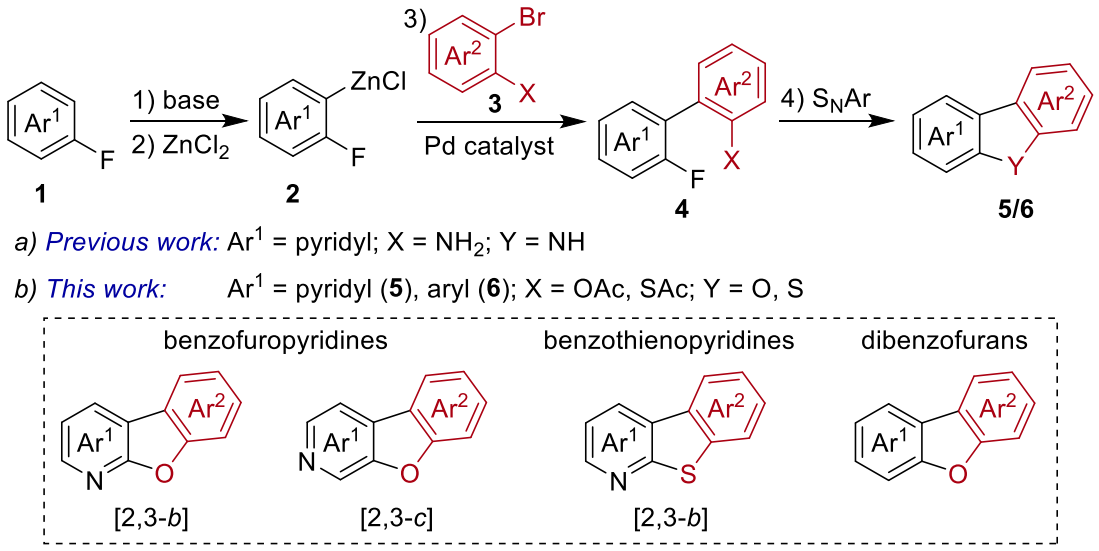


Figure 1. Benzofuropyridines and benzothienopyridines with interesting biological properties and applications in material science.

Several synthetic strategies towards the preparation of benzofuropyridine have been reported. Intramolecular C–C bond formation in diaryl ethers[8,9] and C–O bond formation in 2-biaryl phenols by intramolecular nucleophilic aromatic substitution (S_NAr)[8,10] are the most common strategies. The former approach was successfully applied by Yue and Li, who synthesized all four benzofuropyridine regioisomers.[8] Here, a palladium catalyzed Stille coupling using toxic organotin reagents was a key step. Liu *et al*. reported a more environmental benign strategy generating biaryl phenols from dihalopyridines and 2-hydroxyphenylboronic acids via regioselective Suzuki cross-coupling followed by copper catalyzed intramolecular cyclization.[9b] Alternative strategies for the synthesis of benzofuropyridines include the construction of the pyridine ring from benzofuran derivatives[11] or cascade reactions that generate two annulated rings in the same synthetic operation.[12] However, these approaches often rely on elaborated substrates. Consequently, the development of a concise and general synthesis of benzofuropyridines and its derivatives from readily available starting materials is still of considerable interest.

Recently, we reported an efficient synthesis of tricyclic carbolines employing a four-step *ortho*-lithiation/zincation/Negishi cross-coupling/S_NAr reaction sequence (Scheme 1a).[13] In this methodology a fluorine substituent serves both as directing group for the metalation[14] as well as facile leaving group in the intramolecular cyclisation. As a continuation of our efforts to develop new synthetic procedures for the construction of heterocyclic frameworks, we were curious if we could extend this procedure by using phenols and thiophenols as a route to

tricyclic systems (Scheme 1b). Herein, we describe the first one-pot synthesis of benzofuro[2,3-*b*]- and benzofuro[2,3-*c*]pyridines **5** via a telescoped metalation/cross-coupling/S_NAr reaction sequence from commercially available fluoropyridines and readily accessible 2-bromophenyl acetates.[15] This strategy was expanded to benzothieno[2,3-*b*]pyridines. In addition, directed lithiation of fluoroarenes provided facile access to a range of functionalized dibenzofurans **6**.

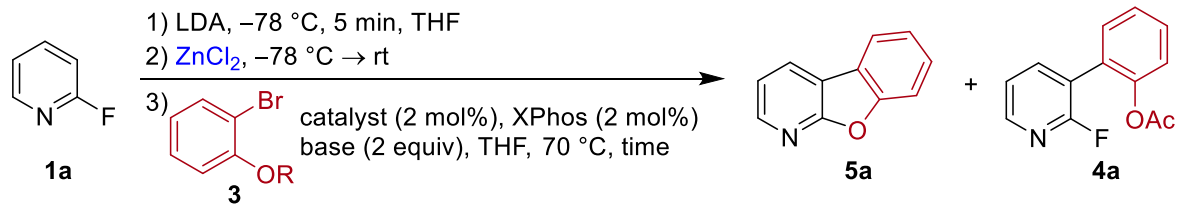


Scheme 1. a) Previously reported synthesis of carbolines by a lithiation/zincation/Negishi cross-coupling/S_NAr reaction sequence and b) extension of this methodology to benzofuro- and benzothienopyridines as well as dibenzofurans.

We initiated our studies by optimizing the reaction conditions for the one-pot Negishi cross-coupling/intramolecular S_NAr reaction sequence (Table 1). Using our previously reported conditions for the formation of organozinc species **2**,[13] 2-fluoropyridine (**1a**) and 2-bromophenyl acetate (**3a**) were converted to benzofuropyridine **5a** in 96% yield for the four-step sequence using 2 mol% of an XPhos-based palladium precatalyst[16] with additional 2 mol% XPhos ligand and 2.0 equiv of KO*t*Bu after heating at 70 °C overnight (entry 1). Reducing either the catalyst loading to 1 mol% or omitting the additional XPhos ligand decreased the yield of **5a** (entry 2-3). Protection of the phenolic oxygen was essential as no product could be detected with 2-bromophenol, even in the presence of excess base (entry 4). This is in stark contrast to 2-bromoanilines, which do not require protection under similar reaction conditions.[13] Employing alternative palladium sources in the presence of 2 mol% XPhos ligand highlights the superior activity of the palladium precatalyst under the applied cross-coupling conditions (entries 5-7). It is worth noting that both the palladium catalyst and the XPhos ligand were essential for the reaction to take place (entries 8-9). In the absence of

additional base, the cross-coupling was complete in 20 min as demonstrated by the isolation of biaryl acetate **4a** in 84% yield (entry 10). Reducing either the amount of base or the reaction time led to incomplete conversion of the intermediate biaryl **4a** (entries 11-13). Finally, while screening other bases to facilitate the deprotection of the acyl group and to promote the S_NAr reaction, we found NaHMDS as valuable alternative to KO*t*Bu (entry 14), whereas Cs_2CO_3 did not fully deprotect the phenolic alcohol under the applied reaction conditions (entry 15).

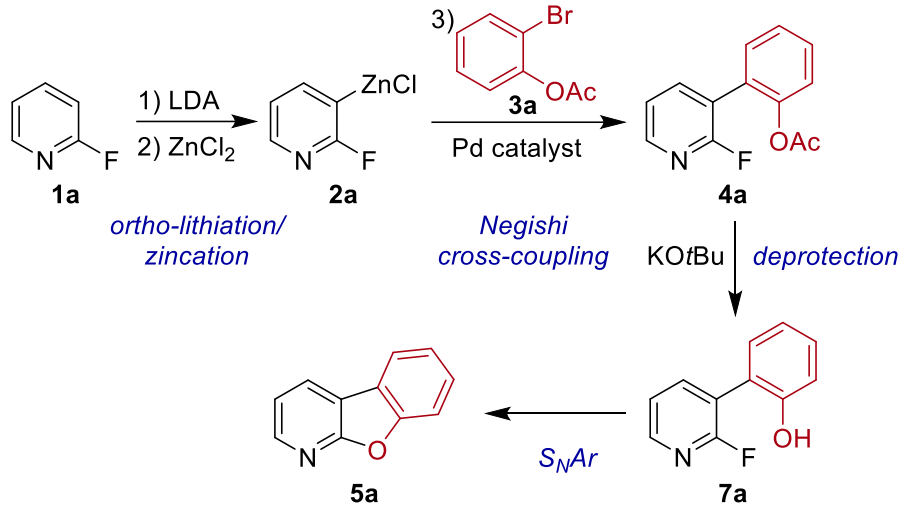
Table 1. Optimization of the reaction conditions.[a]



Entry	R	Catalyst	Base	Time	Yield[b]	
1	Ac	Pd XPhos G3	KO*t*Bu	o/n	96%[c]	–
2[d]	Ac	Pd XPhos G3	KO*t*Bu	o/n	81%	–
3[e]	Ac	Pd XPhos G3	KO*t*Bu	o/n	74%[c]	
4[f]	H	Pd XPhos G3	KO*t*Bu	o/n	0%	–
5	Ac	$Pd(PPh_3)_4$	KO*t*Bu	o/n	50%	–
6	Ac	$Pd(OAc)_2$	KO*t*Bu	o/n	70%	–
7[d]	Ac	$[PdCl(C_3H_5)]_2$	KO*t*Bu	o/n	84%	–
8	Ac	–	KO*t*Bu	o/n	0%	–
9[e]	Ac	$Pd(OAc)_2$	KO*t*Bu	o/n	11%	–
10	Ac	Pd XPhos G3	–	20 min	–	84%[c]
11	Ac	Pd XPhos G3	–	o/n	51%	31%
12[g]	Ac	Pd XPhos G3	KO*t*Bu	o/n	52%	16%
13	Ac	Pd XPhos G3	KO*t*Bu	20 min	11%	28%
14	Ac	Pd XPhos G3	NaHMDS	o/n	86%	–
15	Ac	Pd XPhos G3	Cs_2CO_3	o/n	22%	30%

[a]0.5 mmol scale; reaction conditions: 1) **1a** (1.2 equiv), LDA (1.3 equiv), THF (0.25 M), –25 °C, 5 min; 2) $ZnCl_2$ (1.3 equiv), then –25 °C to rt; 3) 2-bromophenol derivative **3** (1.0 equiv), catalyst (2.0 mol%) and XPhos (2.0 mol%) in THF (0.5 M), base (2.0 equiv), 70 °C. [b]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Isolated yield after column chromatography. [d]1 mol% catalyst loading. [e]No additional XPhos ligand. [f]2.3 equiv of LDA used. [g]1.0 equiv of base.

The results from the optimization studies reveal the reaction order in the formation of **5a** (Scheme 2). After Negishi cross-coupling between organozinc intermediate **2a** and 2-bromophenyl acetate (**3a**) to form biaryl acetate **4a**, deprotection of the acyl group occurs to provide probably biaryl phenol **7a**, which was not observed in the optimization studies, indicating that it must undergo rapid intramolecular cyclisation under the basic conditions to generate the C–O bond and tricyclic **5a** via S_NAr.

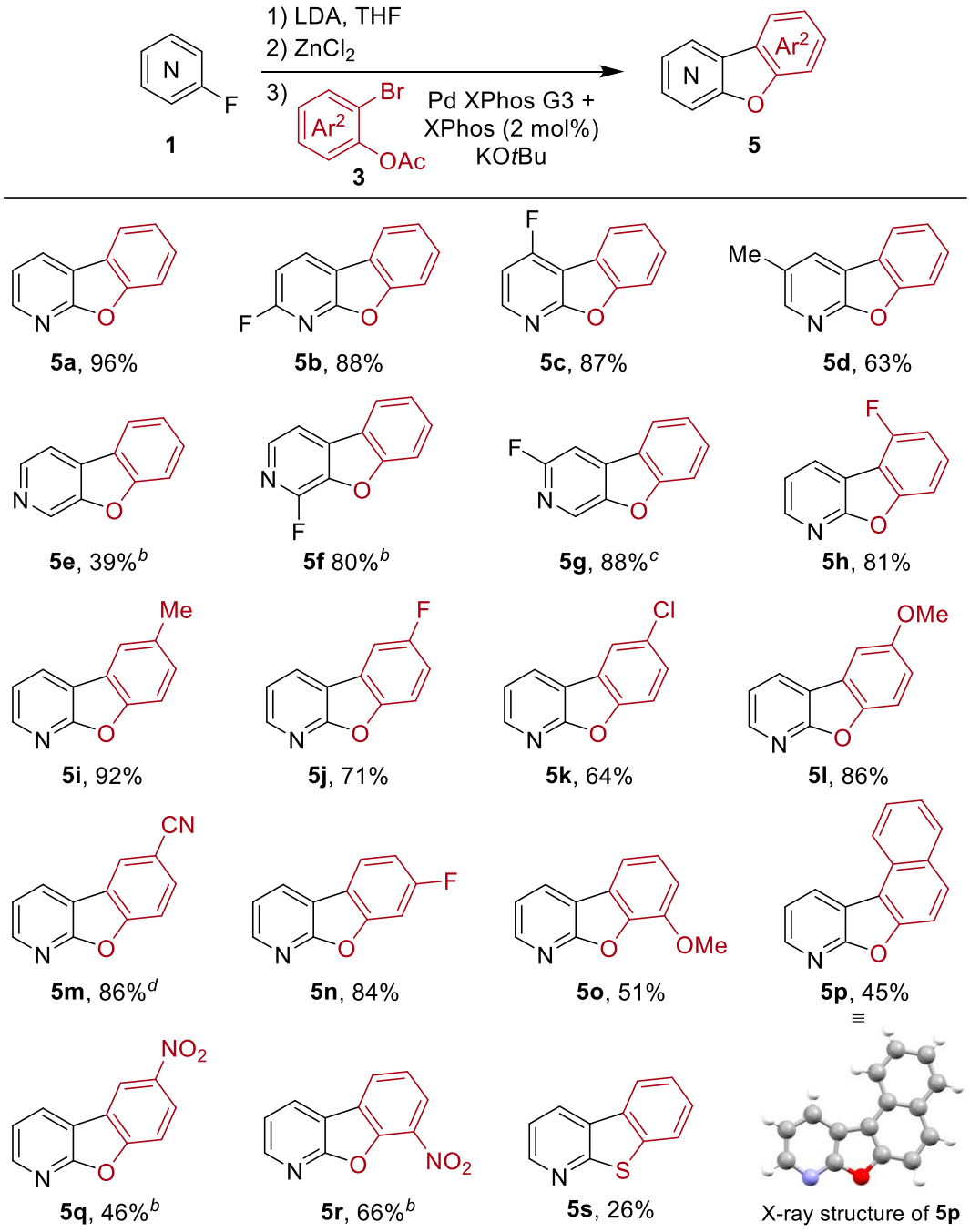


Scheme 2. Reaction sequence and intermediates in the formation of benzofuropyridine **5a**.

With optimized reaction conditions in hand, we next examined the generality of the methodology for a variety of fluoropyridines (Table 2). With 2-fluoro-5-methylpyridine, 2,6- and 2,4-difluoropyridine, the corresponding benzofuro[2,3-*b*]pyridines **5b-d** were obtained as single regioisomer in 63-88% yield. However, for 3-fluoropyridine, 2,3- and 2,5-difluoropyridine no conversion to the corresponding benzofuro[2,3-*c*]pyridines was observed providing biaryl phenols instead. In other words, nucleophilic substitution of the less activated fluorine in 3-position of the pyridyl ring was not achieved. To promote the intramolecular S_NAr reaction, we conducted a solvent exchange from THF to DMF after the cross-coupling step and added additional base (Cs_2CO_3).[10b] After heating to 100 °C for 2 h, **5e-g** could be isolated in 39-88% yield. For **5g** we achieved better results conducting the nucleophilic substitution from the purified biaryl phenol.

We next explored the substrate scope of a variety of 2-bromophenyl acetates **3** (Table 2). Substitution in all positions of **3** with a number of electron-withdrawing and -donating groups was tolerated providing dibenzofuro[2,3-*b*]pyridines **5h-p** in 45-92% yield. The structure of tetracyclic **5p** was verified by single crystal X-ray diffraction.[17] Additionally, we demonstrated the scalability of the procedure by the synthesis of **5m**, which could be

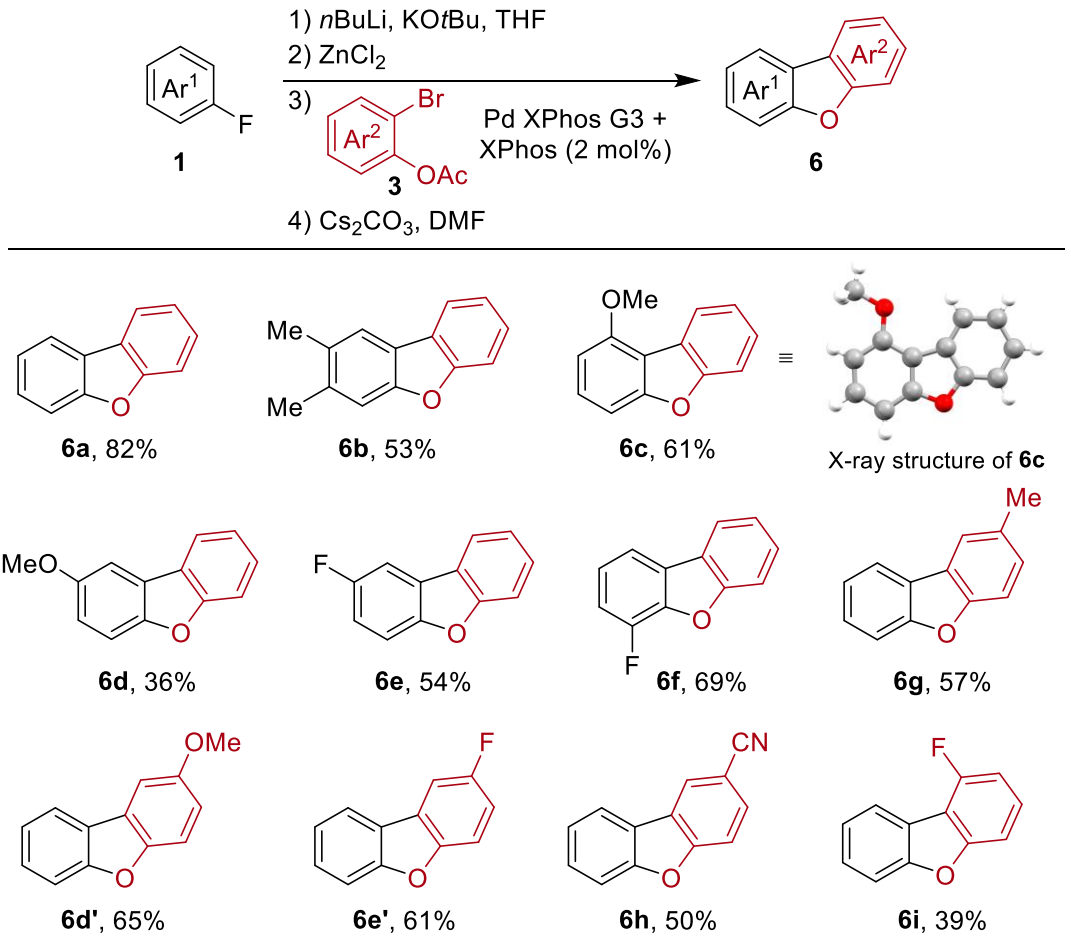
Table 2. Scope of benzofuropyridines.[a]



[a]0.5 mmol scale; reaction conditions: 1) **1** (1.2 equiv), LDA (1.3 equiv), THF (0.25 M), –25 °C, 5 min; 2) $ZnCl_2$ (1.3 equiv), then –25 °C to rt; 3) **3** (1.0 equiv), Pd XPhos G3 (2.0 mol%) and XPhos (2.0 mol%) in THF (0.5 M), then KO*t*Bu (2.0 equiv), 70 °C, o/n. [b]Reaction conditions as shown for *a*, no KO*t*Bu, 70 °C, 20 min, then solvent exchange to DMF (0.1 M), Cs_2CO_3 (5 equiv), 100 °C, 2 h. [c]Reaction conditions as shown for *a*, isolation of **7**, then DMF (0.1 M), Cs_2CO_3 (5 equiv), 100 °C, 2 h. [d]2.5 mmol scale.

obtained in excellent yield after simple recrystallization. Though, for substrates containing a strongly electron-withdrawing nitro group intramolecular nucleophilic substitution was not successful. Under standard conditions the intermediate biaryl phenols were isolated. Here, utilizing the reaction conditions for dibenzofuro[2,3-*c*]pyridines (solvent exchange to DMF, then Cs_2CO_3), **5q** and **5r** could be obtained in 46% and 66% yield, respectively. The procedure also furnished benzothienopyridine **5s**. It is not clear if the low isolated yield is due to poisoning of the palladium catalyst or too rapid deprotection of the acetyl group, which would make 2-bromothiophenol unreactive as coupling partner as previously shown for the related unprotected phenol.

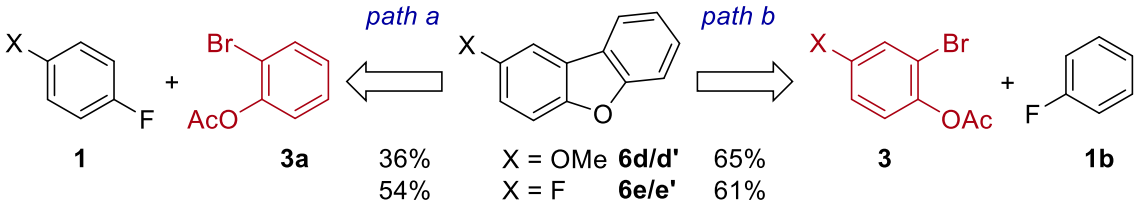
Table 3. Scope of dibenzofurans.[a]



[a]0.5 mmol scale; reaction conditions: 1) **1** (1.2 equiv), KO*t*Bu (1.3 equiv), LDA (1.3 equiv), THF (0.25 M), –78 °C, 5 min; 2) $ZnCl_2$ (1.3 equiv), then –78 °C to rt; 3) **3** (1.0 equiv), Pd XPhos G3 (2.0 mol%) and XPhos (2.0 mol%) in THF (0.5 M), then, 70 °C, 20 min; 4) solvent exchange to DMF (0.1 M), Cs_2CO_3 (5 equiv), 120 °C, o/n.

Next, we extended our methodology to the synthesis of dibenzofurans. In contrast to fluoropyridines, the directed *ortho*-metalation of fluoroarenes requires a stronger base than LDA. Here, the use of the superbasic *n*BuLi/KO*t*Bu system has been well established.[18] Adapting our standard procedure using superbasic metalation conditions, the corresponding biaryl phenols were obtained, i.e., the fluoroarenes were unreactive towards intramolecular S_NAr. Again, solvent exchange to DMF and addition of Cs_2CO_3 followed by heating (120 °C, overnight) provided a solution converting fluoroarenes **1** and 2-bromophenyl acetates **3** to dibenzofuran **6** in a one-pot four-step procedure.

With fluorobenzene and 3,4-dimethylfluorobenzene, the corresponding dibenzofurans **6a** and **6b** were obtained in 82% and 53%, respectively (Table 3). In the case of fluoroanisoles, fluorine proved to be a stronger directing group under superbasic metalation conditions as demonstrated by the formation of **6c** and **6d**.[18b] The structure of **6c** was confirmed by single crystal X-ray diffraction.[17] Furthermore, 1,4- and 1,2-difluorobenzene provided the corresponding fluoro substituted dibenzofurans **6e** and **6f** in reasonable yield. Finally, the 2-bromophenyl acetates **3** coupling partner was varied delivering **6d'-e'** and **6g-i** in 39-64% yield. Here, dibenzofurans **6e/e'** and **6i** have been reported as precursors for the synthesis of host materials for blue phosphorescent OLEDs.[19] With dibenzofurans **6d** and **6d'** as well as **6e** and **6e'** being pairs of identical compounds, our methodology allows flexibility in terms of the choice of starting materials **1** and **3** (Scheme 3). Hereby, slightly higher yields have been achieved utilizing fluorobenzene (**1b**) and substituted 2-bromophenyl acetates **3** via path b.



Scheme 3. Convergent synthesis of dibenzofurans **6d/d'** and **6e/e'**.

Unfortunately, the synthesis of dibenzothiophenes was not successful under these reaction conditions generating 2-bromothiophenol as main product from the corresponding acetate **3**.[20]

In conclusion, we have developed an efficient one-pot procedure for the facile assembly of fused benzofuro heterocycles. Fluoropyridines or fluoroarenes were subjected to a directed *ortho*-lithiation followed by zincation and Negishi cross-coupling with 2-bromophenyl acetates. In situ deprotection of the acyl group and subsequent intramolecular S_NAr facilitates the formation of benzofuropyridines and dibenzofurans. This methodology takes advantage

of readily available starting materials, mild reaction conditions and low catalyst loading to provide a diverse set of benzofuropyridines and dibenzofurans.

Conflicts of interest

The authors declare no competing financial interest.

Author information

Corresponding author: *E-mail: s.roesner@warwick.ac.uk

ORCID

Guy J. Clarkson: 0000-0003-3076-3191

Stefan Roesner: 0000-0003-2143-4708

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References

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57*, 10257–10274.

(2) Ram, V. J.; Sethi, A.; Nath, M.; Pratap, R. *The Chemistry of Heterocycles: Chemistry of Six-to-Eight-Membered N, O, S, P and Se Heterocycles*; Elsevier: Amsterdam, The Netherlands, 2019, pp. 254–259.

(3) Love, B. E. Isolation and synthesis of polyoxygenated dibenzofurans possessing biological activity. *Eur. J. Med. Chem.* **2015**, *97*, 377–387.

(4) (a) Brachwitz, K.; Hilgeroth, A. Synthesis and First Biological Evaluation of 1-Aza-9-oxafluorenes as Novel Lead Structures for the Development of Small-Sized Cytostatics. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 411–413. (b) Voigt, B.; Meijer, L.; Luzach, O.; Schächtele, C.; Totzke, F.; Hilgeroth, A. Novel CDK inhibition profiles of structurally varied 1-aza-9-oxafluorenes. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 823–825.

(5) Krug, M.; Voigt, B.; Baumert, C.; Lüpken, R.; Molnár, J.; Hilgeroth, A. First biological evaluation of developed 3-benzyloxyfluorenses as novel class of MDR modulators. *Eur. J. Med. Chem.* **2010**, *45*, 2683–2688.

(6) (a) Lee, C. W.; Lee, J. Y. Benzo[4,5]thieno[2,3-*b*]pyridine derivatives as host materials for high efficiency green and blue phosphorescent organic light-emitting diodes. *Chem. Commun.* **2013**, *49*, 1446–1448. (b) Kim, H.; Lee, K. Y.; Kim, J. Y.; Noh, H. J.; Yoon, D.-W.; Yang, J. H.; Kim, J.; Kang, I. B.; Lee, S. J. Preparation of Acridine-modified Benzofuropyridine and Benzothienopyridine Derivatives and Their Thermally activated Delayed Fluorescence Properties. *Bull. Korean Chem. Soc.* **2016**, *37*, 1870–1873. (c) Lee, G. H.; Kim, Y. S. Benzofuropyridine-based highly efficient thermally activated delayed fluorescence emitters. *J. Nanosci. Nanotechnol.* **2018**, *18*, 6635–6639.

(7) Ooyama, Y.; Sato, T.; Harima, Y.; Ohshita, J. Development of a D–π–A dye with benzothienopyridine as the electron-withdrawing anchoring group for dye-synthesized solar cells. *J. Mater. Chem. A* **2014**, *2*, 3293–3296.

(8) Yue, W. S.; Li, J. J. A concise synthesis of all four possible benzo[4,5]furopyridines via palladium-mediated reactions. *Org. Lett.* **2002**, *4*, 2201–2203.

(9) (a) Ames, D. E.; Opalko, A. Palladium-catalyzed cyclisation of 2-sustituted halogenoarenes by dehydrohalogenation. *Tetrahedron* **1984**, *40*, 1919–1925. (b) Liu, J.; Fitzgerald, A. E.; Mani, N. S. Facile Assembly of Fused Benzo[4,5]furo Heterocycles. *J. Org. Chem.* **2008**, *73*, 2951–2954. (c) Yoon, W. S.; Lee, S. J.; Kang, S. K.; Ha, D.-C.; Ha, J. D. Facile synthesis of benzo[4,5]furo[3,2-*c*]pyridines via palladium-catalyzed intramolecular Heck reaction. *Tetrahedron Lett.* **2009**, *50*, 4492–4494.

(10) (a) Lai, L.-L.; Lin, P.-Y.; Huang, W.-H.; Shiao, M.-J.; Hwu, J. R. Sodium Trimethylsilanethiolate in Novel Cyclizations for Synthesis of Aromatic Heterocyclic Compounds. *Tetrahedron Lett.* **1994**, *35*, 3545–3546. (b) González, J. P.; Edgar, M.; Elsegood, M. R. J.; Weaver, G. W. Synthesis of fluorinated fused benzofurans and benzothiophenes: Smiles-type rearrangement and cyclisation of perfluoro(het)aryl ethers and sulfides. *Org. Biomol. Chem.* **2011**, *9*, 2294–2305. (c) Zhu, D.; Wu, Z.; Luo, B.; Du, Y.; Liu, P.; Chen, Y.; Hu, Y.; Huang, P.; Wen, S. Heterocyclic Iodoniums for the Assembly of Oxygen-Bridged Polycyclic Heteroarenes with Water as the Oxygen Source. *Org. Lett.* **2018**, *20*, 4815–4818.

(11) (a) Komine, Y.; Kamisawa, A.; Tanaka, K. Flexible Synthesis of Fused Benzofuran Derivatives by Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition with Phenol-Linked 1,6-Diynes. *Org. Lett.* **2009**, *11*, 2361–2364. (b) Rao, Y.; Li, Z.; Yin, G. Clean and efficient

assembly of functionalized benzofuro[2,3-*c*]pyridines *via* metal-free one-pot domino reaction. *Green Chem.* **2014**, *16*, 2213–2218. (c) Hu, J.; Deng, Z.; Zhang, X.; Zhang, F.; Zheng, H. Synthesis of benzofuro[2,3-*c*]pyridines *via* a one-pot three-component reaction. *Org. Biomol. Chem.* **2014**, *12*, 4885–4889. (d) Kumar, S.; Cruz-Hernández, C.; Pal, S.; Saunthwal, R. K.; Patel, M.; Tixari, R. K.; Juaristi, E.; Verma, A. K. Tandem Approach to Benzothieno- and Benzofuropyridines from *o*-Alkynyl Aldehydes via Silver-Catalyzed 6-*endo-dig* Ring Closure. *J. Org. Chem.* **2015**, *80*, 10548–10560. (e) Fu, X.; Yang, J.; Deng, K.; Shao, L.; Xia, C.; Ji, Y. Tandem C–C/C–N Formation via Palladium-Catalyzed C–H Activation/Styrenation and Sequential Annulation of *O*-Methylketoxime with Styrenes. *Org. Lett.* **2019**, *21*, 3505–3509.

(12) Xiong, W.; Hu, K.; Zhen, Q.; Zhao, Z.; Shao, Y.; Li, R.; Zhang, Y.; Chen, J. Palladium-Catalyzed Cascade Reactions of 2-(Cyanomethoxy)chalcones with Arylboronic Acids: Selective Synthesis of Emissive Benzofuro[2,3-*c*]pyridines. *Org. Lett.* **2020**, *22*, 1239–1243.

(13) Sathiyalingam, S.; Roesner, S. Synthesis of α- and β-Carbolines by a Metalation/Negishi Cross-Coupling/S_NAr Reaction Sequence. *Adv. Synth. Catal.* **2022**, *364*, 1769–1774.

(14) Roesner, S.; Buchwald, S. L. Continuous-Flow Synthesis of Biaryls by Negishi Cross-Coupling of Fluoro- and Trifluoromethyl-Substituted (Hetero)arenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 10463–10467.

(15) Pajtás, D.; Patonay, T.; Kónya, K. Synthesis of 8-Bromoflavone and Its Buchwald–Hartwig Reaction with Amines. *Synthesis* **2016**, *48*, 97–102.

(16) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. Design and preparation of new palladium precatalysts for C–C and C–N cross-coupling reactions. *Chem. Sci.* **2013**, *4*, 916–920.

(17) CCDC 2191069 (**5r**) and 2191070 (**6c**) contain the supplementary crystallographic data for this paper.

(18) (a) Schlosser, M.; Takagishi, S. Fluorine- and Trifluoromethyl-Substituted Toluenes: Site Selective Metalation of Aromatic or Benzylic Positions. *Synlett* **1991**, 119–121. (b) Katsoulos, G.; Takagishi, S.; Schlosser, M. The Metalation of Fluoroanisoles: Optional Regioselectivity Due to Metal Mediated Control. *Synlett* **1991**, 731–732. (c) Mongin, F.; Schlosser, M. Regioselective *ortho*-Lithiation of Chloro and Bromo Substituted Fluoroarenes. *Tetrahedron Lett.* **1996**, *37*, 6551–6554.

(19) Yu, J. G.; Byeon, S. Y.; Han, S. H.; Lee, J. Y. Selective F or Br Functionalization of Dibenzofurans for Application as Host Materials of Phosphorescent Organic Light-Emitting Diodes. *Chem. Eur. J.* **2017**, *23*, 16044–16050.

(20) See the Supporting Information for a detailed description.