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Access to Electron-Rich Dibenzofurans through NBu_4OAc-Mediated Palladium Catalysis

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Dibenzofuran and its derivatives are ubiquitous and important medicinal and natural products. Many contain electron-rich aryl rings. Forming the key intramolecular Ar–Ar bond using traditional cross-coupling is difficult. The C–H functionalisation (C–H activation) approach is, in principle, far more useful. However, we previously found that the well-established conditions, which promote C–H functionalisation through Concerted Metalation-Deprotonation (CMD), proved unsatisfactory. Herein, we report a Pd-catalysed C–H functionalisation protocol that works with electron-rich arenes. We use tetrabutylammonium acetate (NBu_4OAc), which we suspect can act as base, ligand and solvent, rendering this protocol a simple and efficient route to electron-rich dibenzofurans.

Introduction

The dibenzofuran framework **1**, and its analogues, represent a prominent class of natural products and biologically active entities.[1–3] Consequently, synthetic routes toward dibenzofurans have garnered keen interest from synthetic chemists.[4–16] Retrosynthetic analysis of dibenzofuran reveals two separate intramolecular coupling strategies (Figure 1A): C–C bond formation through a diarylether **2** (Pathway A), or C–O bond formation through a biaryl motif **3** (Pathway B). Direct arylation has been applied successfully to form a decent range of dibenzofurans. Fagnou, in particular, demonstrated the power of the strategy to target C–H bonds in this context.[6–8] The mechanism which evolved from the early studies on this work was termed Concerted Metalation-Deprotonation (CMD) or Ambiphilic Metal-Ligand Assistance (AMLA).[17–19] This mechanistic pathway usually relies on the 'acidity' of the aryl C–H bond and thus, is less applicable to electron-rich substrates. As such, the methodology can be less successful, depending on the electronic properties of the diarylether substituent.[4–16] That said, it should be noted that a number of mechanisms can be envisaged here,[20,21] most recently one which relies on the transmetalation step (rather than the C–H cleavage step) to determine regioselectivity.[22] Recently we reported a methodology on the synthesis of substituted dibenzofurans through a palladium-mediated intramolecular direct arylation of a diarylether utilising a quinoline ligand (Figure 1B).[14] This method proved particularly useful for electron-deficient systems,[23] but the scope of the transformation was very limited for more valuable electron-rich examples. Naturally occurring and medicinally relevant dibenzofuran derivatives frequently contain electron-rich aryl rings and electron-donating groups (Figure 1C)[2,24] and thus, there is a need for practical and robust methodologies that access these highly valuable targets.

More broadly, the optimisation of chemical structures by altering the electron donating and withdrawing properties of substituents is a common approach in medicinal chemistry,

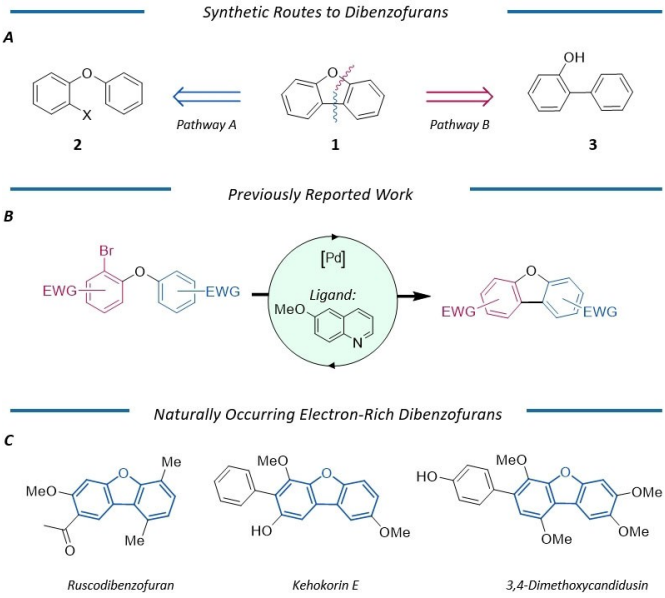

Figure 1. Background to dibenzofurans.

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material sciences and numerous other areas of chemical synthesis.[25] Thus, it is important that new methodologies incorporating electron donating and electron withdrawing substituents are developed, to further access the required chemical space. Therefore, even for the most innovative new methodologies, accessing the full breadth of substrate scope is challenging.[26–30]

Results and Discussion

As mentioned, previous work in our group investigated an intramolecular C–H activation approach to forming dibenzofurans, which faltered when electron-rich substrates were employed.[14] During the evaluation of the substrate scope, we noticed rapid formation of palladium black when electron-rich substrates were used.

We initially considered that the use of a palladium scavenger such as tetrabutylammonium acetate (NBu_4OAc) might prevent palladium aggregation, leading to better conversion. We hoped this reagent could also act as a base, avoiding the need for added inorganic base.[31] Indeed, initial investigations improved the yield for electron-rich substrates over our previous results, and good to excellent yields (up to 96% isolated) were observed (Table, entry 1–3). Lowering the temperature of the reaction gave reduced yields (Table 1 entry, 4). With these conditions to hand, we were able to reduce the Pd loading (2.5 mol%) while maintaining excellent yield (Table 1, entry 5). We also investigated the use of tetramethylammonium acetate (NMe_4OAc), but this gave lower yield (Table 1, entry 6). Finally, the potentially synergistic use of NBu_4Cl and K_2CO_3,[32] was trialled in the system but gave a lower yield of 67% (Table 1, entry 7). Various other conditions were tried but gave inferior results (see Supporting Information for details).

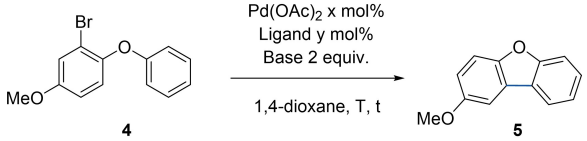
With conditions optimised, we tested this protocol to access a range of dibenzofurans (Scheme 1). It was also important to us that C–H functionalisation could occur on either ring, irrespective of the nature of the substituent, which of course meant that the halogenated aryl ring could also be derivatised. Both these goals were met, and in the case of **5a** and **5b**, C–H functionalisation was enacted on both the halogen-bearing and the halogen-free aryl ring, while also showing tolerance to fluorinated precursors. Another electron-rich substrate was synthesised in **5c** giving an excellent yield and regioselectivity (90% and 96:4). The high yield of **5c** was pleasing to see as this particular substrate was classed as a limitation when investigated using our previously developed methodology. Similarly, the reaction conditions allowed the *m*-methoxy dibenzofuran **5d** to be formed in 94%, with a regioselectivity of 97:3.

Diarylamines were also found to be compatible with the protocol allowing the carbazole motif **5e** to be isolated in 89% yield, in comparison to a moderate yield of 50%, previously reported.[14] Further functionalisation was demonstrated with the acetyl substituted compound **5f** which was furnished in excellent yield (95%). Finally, heterocyclic dibenzofurans were also tolerated and we were delighted to see that benzofuropyridine **5g** was formed, and isolated in 84% yield.

Overall, the methodology successfully handled a range of substrates including electron-deficient, electron-rich and heteroaromatic diarylethers. Importantly, the methodology also functioned well, irrespective of which ring contained the halogen group, providing flexibility as a synthetic tool towards dibenzofuran targets.

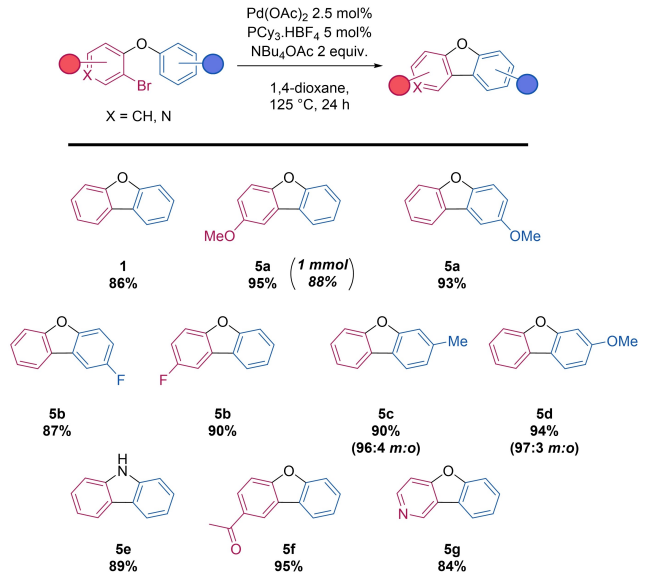
Given that this protocol had clearly surpassed our previously published work and given the ubiquity of the dibenzofurans with multiple methoxy groups, we challenged our methodology with highly electron-rich diarylether precursors, reminiscent of naturally occurring dibenzofuran scaffolds.

Table 1. Reaction optimisation of the electron-rich model substrate.



Entry	Base	$Pd(OAc)_2$ [mol%]	Ligand [mol%]	*t* [h]	Yield[a] [%]
1	NBu_4OAc	5	SPhos (10)	24	81
2	NBu_4OAc	5	$PCy_3.HBF_4$ (10)	24	96[b]
3	NBu_4OAc	5	$PCy_3.HBF_4$ (10)	16	66
4[c]	NBu_4OAc	5	$PCy_3.HBF_4$ (10)	24	41
5	NBu_4OAc	2.5	$PCy_3.HBF_4$ (5)	24	95[b]
6	NMe_4OAc	2.5	$PCy_3.HBF_4$ (5)	24	74
7	NBu_4Cl & K_2CO_3	2.5	$PCy_3.HBF_4$ (5)	24	67

[a] Measured using ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard; [b] compound is isolated after column chromatography; [c] reaction is run at 100 °C instead of 125 °C.



Scheme 1. Substrate scope of the intramolecular ring closure to furnish derivatised dibenzofurans.

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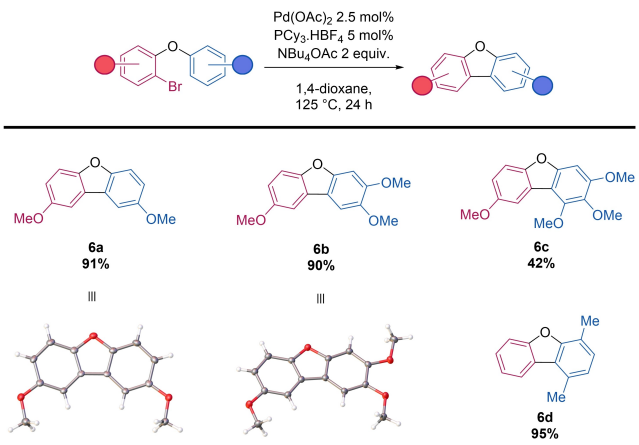
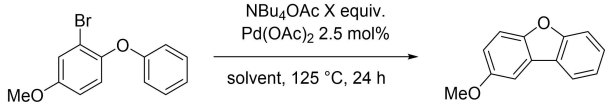
To a methodology relying on a CMD/AMLA mechanism, we suspected these substrates would represent a significant challenge.[19] However, in our case, product **6a** could be formed in a yield of 91% and surprisingly, even the trimethoxy derivative of **6b** could be formed in 90% yield. Crystal structures were obtained for **6a** and **6b** (Scheme 2). A lower yield of 42% was obtained for substrate **6c**, nevertheless, this is a good, usable yield considering the electronic and steric challenges this substrate poses. An excellent yield of 95% was also observed for the dimethyl substrate **6d** using this protocol.

We next investigated the efficiency of the reaction in the absence of phosphine ligand. Pleasingly NBu_4OAc facilitated the ring closure, giving 70% of product formed using 2.5 mol% of palladium acetate in dioxane (Table 2, entry 1). Building on this initial success, we examined the use of excess NBu_4OAc in the absence of phosphine ligand and solvent. Gratifyingly, we were able to remove the need for both added ligand and added solvent using the organic base neat, obtaining a 93% yield (Table 2 entry 3). This interesting result leads us to believe that the NBu_4OAc can potentially play a tripartite role in the reaction: as solvent, base and ligand. It also exhibits potential for performing these reactions in a green fashion with no requirement for solvent (DMF and NMP are commonly used in these type of protocols), added phosphines, or inorganic base.



Scheme 2. Substrate scope of electron-rich arene precursors.

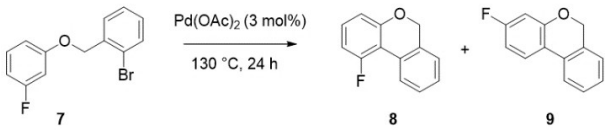
Table 2. Phosphine free and PBu_4OAc investigations.



Entry	Catalyst	Base [equiv.]	Solvent	Yield[a] [%]
1	$Pd(OAc)_2$	NBu_4OAc (2)	1,4-dioxane	70
2	$Pd(OAc)_2$	NBu_4OAc (5)	Neat	81
3	$Pd(OAc)_2$	NBu_4OAc (10)	Neat	93[b]
4[c]	$Pd(OAc)_2$	PBu_4OAc (2)	1,4-dioxane	81
5	$PdCl_4(NBu_4)_2$	NBu_4OAc (2)	1,4-dioxane	20

[a] Measured using ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard; [b] yield is isolated after column chromatography; [c] reaction is run for 2 h.

Table 3. Comparison of our methodology with the literature conditions.



Entry	Ligand (6 mol%)	Solvent	Base (2 equiv.)	Ratio[a] **8:9**
1- Fagnou[7]	$P^tBu_2Me.HBF_4$	DMA	K_2CO_3	6.9:1[b]
2	$PCy_3.HBF_4$	1,4-dioxane	NBu_4OAc	1:1

[a] Ratio is measured by ^{1}H NMR spectroscopy; [b] ratio is as reported in the literature – we performed the same reaction and found the same isomer to predominantly form, but in varying ratios.

Finally, Liu and co-workers have shown that an alternative base, in the form of a phosphonium salt, can reduce reaction time as well as temperature in N-aryl coupling reactions.[33] Thus, tetrabutylphosphonium acetate (PBu_4OAc) was employed in our reaction, and interestingly within 2 hours, gave the desired product in 81% (Table 2, entry 4). Additionally, Hull and co-workers have shown that tetraalkylammonium salts can form active catalytic species with palladium chloride.[34] This palladate species was trialled in our system but proved inferior, giving only 20% yield (Table 2, entry 5).

Fagnou noted that intramolecular C–H bond functionalisation is not significantly influenced by the electronic nature of the arene, and that this is uncharacteristic of an S_EAr pathway.[35] Indeed he noted that under his (CMD) conditions, in an intramolecular competition experiment, it is the H *ortho* to F that is cleaved (Table 3, entry 1). The same substrate using our conditions, gave a *ca.* 1:1 ratio of both constitutional isomers. Overall it is likely that a different mechanism is operative here, most likely involving electrophilic palladation.[36] Further mechanistic investigations are underway and will be reported in due course.

Conclusions

In conclusion, we have developed a robust, efficient methodology to synthesise a range of dibenzofurans. In particular, difficult-to-access, electron-rich scaffolds, in good to excellent yields. Tetraalkylammonium salts, particularly NBu_4OAc, proved the linchpin, and appears to act as solvent, ligand and base in the reaction.

Experimental Section

General Information

Solvents and reagents were used as obtained from commercial sources and without purification. Column chromatography was

carried out using 60 Å (35-70 μm) silica. TLC was carried out on precoated silica gel plates (Merck 60 PF254). The developed plates were visualised under UV light. Melting points were obtained on a uni-melt Thomas Hoover Capillary melting point apparatus. NMR spectra were run in $CDCl_3$ or $(CD_3)_2SO$ using TMS as the internal standard at 25 °C unless otherwise specified. ^{1}H NMR (600 spectra) ^{1}H NMR (500 MHz) spectra, ^{1}H NMR (400 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Burker Avance 400 and Bruker Avance 300 NMR spectrometers respectively. ^{13}C (150 MHz) spectra, ^{13}C (125 MHz) spectra, ^{13}C (100 MHz) spectra and ^{13}C (75.5 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Burker Avance 400 and Bruker Avance 300 NMR spectrometers respectively in proton decoupled mode. ^{19}F NMR (376 MHz) and ^{19}F NMR (282 MHz) spectra were recorded on a Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively in proton decoupled mode. Chemical shifts δ_H and δ_C are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet) and m (multiplet). For ^{13}C NMR spectra, the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes. Nominal mass spectra were recorded on a Waters Quattro Micro triple quadrupole spectrometer (QAA1202) in ESI mode using 50% acetonitrile–water containing 0.1% formic acid as eluent. High resolution mass spectra (HRMS) were recorded on a Waters LCT Premier Time of Flight spectrometer (KD160) or a Waters Vion IMS mass spectrometer (SAA055 K) in ESI mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. Samples (max. 1 mg) were dissolved in acetonitrile, methanol, water or 10% DMSO/acetonitrile. The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.

Experimental Procedure for the synthesis of compounds 1, 5a–g and 6a–d

Diarylether (1 equiv.), $Pd(OAc)_2$ (2.5 mol%), $PCy_3.HBF_4$ (5 mol%), NBu_4OAc (2 equiv.) and 1,4-dioxane (2 mL/mmol) were added to a sealed reaction vial equipped with a magnetic stir bar. The reaction mixture was stirred at 125 °C for 24 hours in a multi-reaction heating mantle. After 24 hours the reaction mixture was cooled to room temperature and diluted with DCM (15 mL), filtered through a pad of Celite® and the solvent was concentrated under reduced pressure. The resulting residue was then purified by column chromatography using hexanes:DCM as eluent on silica gel to elute the title products.

Supporting Information

Additional references cited within the Supporting Information.[37–48]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Dibenzofuran · palladium · catalysis, tetraalkylammonium salt · electron-rich

[1] S. R. Patpi, L. Pulipati, P. Yogeeswari, D. Sriram, N. Jain, B. Sridhar, R. Murthy, A. T. Devi, S. V. Kalivendi, S. Kantevari, *J. Med. Chem.* **2012**, *55*, 3911–3922.
[2] B. E. Love, *Eur. J. Med. Chem.* **2015**, *97*, 377–387.
[3] A. Momotake, N. Lindegger, E. Niggli, R. J. Barsotti, G. C. R. Ellis-Davis, *Nat. Methods* **2006**, *3*, 35–40.
[4] J. Liu, A. E. Fitzgerald, N. S. Mani, *J. Org. Chem.* **2008**, *73*, 2951–2954.
[5] Y. Wei, N. Yoshikai, *Org. Lett.* **2011**, *13*, 5504–5507.
[6] L. C. Campeau, P. Thansandote, K. Fagnou, *Org. Lett.* **2005**, *7*,1857–1860.
[7] L. C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*,581–590.
[8] B. Liégault, D. Lee, M. P. Huestis, D. R. Stuart, K. Fagnou, *J. Org. Chem.* **2008**, *73*, 5022–5028.
[9] H. Zhao, K. Yang, H. Zheng, R. Ding, F. Yin, N. Wang, Y. Li, B. Cheng, H. Wang, H. Zhai, *Org. Lett.* **2015**, *17*, 5744–5747.
[10] N. Panda, I. Mattan, D. K. Nayak, *J. Org. Chem.* **2015**, *80*, 6590–6597.
[11] J. W. Lockner, D. D. Dixon, R. Risgaard, P. S. Baran, *Org. Lett.* **2011**, *13*, 5628–5631.
[12] C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195.
[13] B. Xiao, T. Gong, Z. Liu, D. Luo, J. Xu, L. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 9250–9253.
[14] K. Mackey, D. J. Jones, L. M. Pardo, G. P. McGlacken, *Eur. J. Org. Chem.* **2021**, *2021*, 495–498.
[15] T. Matsuzawa, K. Uchida, S. Yoshida, T. Hosoya, *Org. Lett.* **2017**, *19*, 5521–5524.
[16] S. Prado, V. Toum, B. Saint-Joanis, S. Michel, M. Koch, S. T. Cole, F. Tillequin, Y. L. Janin, *Synthesis* **2007**, *10*, 1566–1570.
[17] P. Gandeepan, T. Muller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, *119*, 2192–2452.
[18] Y. Boutadla, D. L. Davies, S. A. Macgregor, *Dalton Trans.* **2009**, 5820–5831.
[19] M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.
[20] K. M. Engle, D–H. Wang, J–Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137–14151.
[21] S. I. Gorelsky, *Coord. Chem. Rev.* **2013**, *257*, 153–164.
[22] D. Kim, G. Choi, W. Kim, D. Kim, Y. K. Kang, H. H. Soon, *Chem. Sci.* **2021**, *12*, 363–373.
[23] The introduction of electronic withdrawing groups (e.g. F and CF_3) to heterocyclic systems is an important strategy see R. Filler, Y. Kobayashi, L. M. E. Yagupolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, Elsevier, Amsterdam, Netherlands, **1993** and S. L. Clarke, G. P. McGlacken, *Tetrahedron* **2015**, *19*, 2906–2913 and citations therein.
[24] W. Zhang, W. Wei, J. Shi, C. Chen, G. Zhao, R. Jiao, *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2698–2701.
[25] S. Dastmalchi, M. Hamzeh-Mivehroud, B. Sokouti in *Quantitative Structure-Activity Relationship, A Practical Approach*, *1st ed.*, Routledge CRC Press, USA, **2021**.
[26] Y.-H. Zhang, B.-F. Shi, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 5072–5074.
[27] M. Li, M. Shang, H. Xu, X. Wang, H–X. Dai, J–Q. Yu, *Org. Lett.* **2019**, *21*, 540–544.

[28] L–Y. Liu, J. X. Qiao, K–S. Yeung, W. R. Ewing, J–Q. Yu, *J. Am. Chem. Soc.* **2019**, *141*, 14870–14977.
[29] R. E. Tundel, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2006**, *71*, 430–433.
[30] M. A. Mantell, M. R. Lasky, M. Lee, M. Remy, M. S. Sanford, *Org. Lett.* **2021**, *23*, 5213–5217.
[31] F. Bellina, M. Lessi, C. Manzini, *Eur. J. Org. Chem.* **2013**, 5621–5630.
[32] T. Jeffrey, *Tetrahedron* **1996**, *52*, 10113–10130.
[33] C. Yang, Y. Fu, Y. Huang, J. Yi, Q. Guo, L. Liu, *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 7398–7401.
[34] D. G. Kohler, S. N. Gockel, J. L. Kennemur, P. J. Waller, K. L. Hull, *Nat. Chem.* **2018**, *10*, 333–340.
[35] D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126.
[36] For a discussion on the mechanism of Direct Arylation see: a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; b) G. P. McGlacken, L. M. Bateman, *Chem. Soc. Rev.* **2009**, *38*, 2447–2464.

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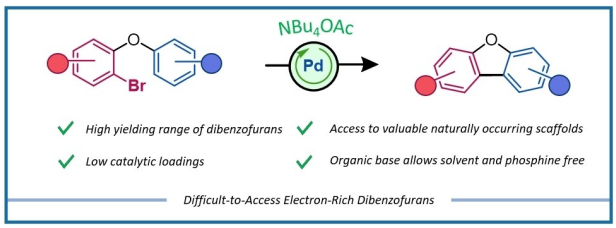

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