Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 11513–11520

Palladium-catalysed intramolecular enolate *O*-arylation and thio-enolate *S*-arylation: synthesis of benzo[*b*]furans and benzo[*b*]thiophenes

Michael C. Willis,[a,*] Dawn Taylor[a] and Adam T. Gillmore[b]

[a]*Department of Chemistry, University of Bath, Bath BA2 7AY, UK*
[b]*Chemical Research and Development Department, Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK*

Received 3 March 2006; revised 2 May 2006; accepted 4 May 2006
Available online 2 June 2006

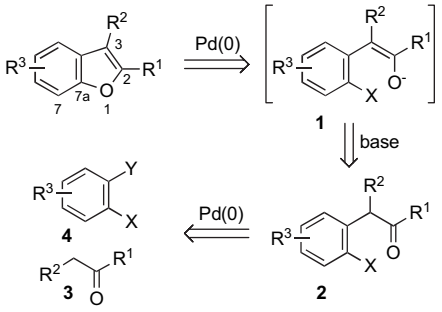
Abstract—Enolates derived from α-(*ortho*-haloaryl)-substituted ketones undergo palladium-catalysed C–O bond formation to deliver benzofuran products in good yield. A catalyst generated from $Pd_2(dba)_3$ and the ligand DPEphos effects the key bond formation to deliver a variety of substituted products from both cyclic and acyclic precursors. The analogous thio-ketones undergo C–S bond formation using identical reaction conditions and are converted to benzothiophene products. A cascade sequence that produces the required α-aryl ketones in situ has also been developed, although the substrate scope is more restricted.

1. Introduction

Benzofurans and benzothiophenes are two of the most common and consequently most studied classes of aromatic heterocycle.[1] The occurrence of these heterocycles in a significant number of medicinal agents, active in a variety of disease areas, has led to an enduring interest in the development of new methods for their synthesis.[2] Methods that utilise new classes of precursor are particularly valuable. Amongst the many syntheses available, transition metal catalysed processes[3] and palladium-mediated methods in particular[4] feature heavily. Syntheses based on palladium-catalysed cyclisations of appropriately substituted alkenyl or alkynyl phenols, or thiophenols, are particularly versatile and have been used on many occasions.[5] Related tandem processes involving catalysed C–C bond formation, usually employing Sonogashira type reactions, before construction of the key C–O or C–S bond have also been developed.[6] The crucial bond-forming event in these processes is intramolecular attack of a nucleophilic oxygen or sulfur atom onto a palladium-activated C–C multiple bond, resulting in formation of the $X–C_2$ bond of the heterocycle. We wished to develop an alternative synthesis involving formation of the $X–C_{7a}$ bond and employing the intramolecular attack of a nucleophilic oxygen or sulfur atom onto a palladium-activated aryl ring; crucially, the nucleophilic heteroatom would be embedded in an enolate or thio-enolate, generated from the corresponding ketone or thio-ketone, respectively. Such a synthesis would open the use of α-(*ortho*-haloaryl)-substituted ketones and thio-ketones as new benzofuran and benzothiophene precursors.[7]

2. Results and discussion

A retrosynthetic scheme representing our proposed route to benzofurans is shown in Scheme 1. The key palladium-catalysed C–O bond formation is represented by the disconnection of $O–C_{7a}$ bond of the benzofuran to generate enolate **1**. In turn, the enolate would be generated from α-aryl ketone **2**. The use of the thio-ketone corresponding to ketone **2** would allow access to the corresponding thio-enolate and ultimately to the benzothiophene. Therefore, α-aryl ketones **2**



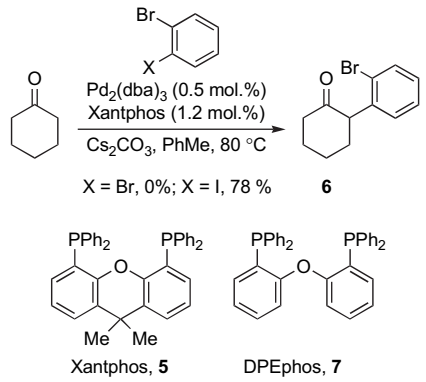
Scheme 1.

Keywords: Benzofuran; Benzothiophene; Palladium catalysis; Enolate.
* Corresponding author. Tel.: +44 1225 386568; fax: +44 1225 386231; e-mail: m.c.willis@bath.ac.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.004

become common intermediates for the synthesis of both classes of heterocycle. Although there are a number of methods for the synthesis of α-arylated ketones,[8] we wished to employ a second palladium-catalysed transformation involving the α-arylation of a simple ketone **3** with a 1,2-dihaloarene **4**.

Over recent years palladium-catalysed intermolecular C-arylation of enolates[9] and similar C-nucleophiles has been developed as a useful synthetic tool.[10] Although the use of 1,2-dihaloarenes to access the required α-(*ortho*-haloaryl)ketones had not been documented, precedent existed for the use of *o*-substituted aryl halides. The preparation of α-(*o*-bromophenyl)cyclohexanone **6** is used as an illustrative example for substrate preparation (Scheme 2). Application of literature conditions,[10a,b] involving combining the substrates with Cs_2CO_3, $Pd_2(dba)_3$ and the ligand Xantphos (**5**),[11] to the coupling of cyclohexanone and 1,2-dibromobenzene, resulted in no reaction. However, the use of 1-bromo-2-iodobenzene under identical reaction conditions delivered the α-arylated ketone **6** in 78% yield. Variations of this protocol were used to prepare all of the α-arylated ketones employed in this study.[12]

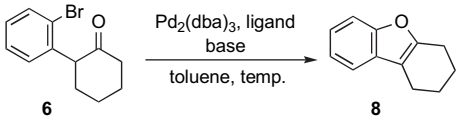


Scheme 2.

With a route to the required 2-(haloaryl)-ketones established, we turned our attention to the key benzofuran-forming transformation. Palladium-catalysed aryl C–X bond formations, and C–N constructions in particular, are now reliable and well established methods, with growing numbers of applications appearing in the literature.[13] Intramolecular versions of these reactions, leading to the formation of a variety of heterocycles, are also well known.[13] Although a diverse range of nucleophiles have been employed in these reactions, the use of *O*- and *S*-enolates as hetero-nucleophiles is rare.[14] Substituted cyclohexanone **6** was selected for initial study (Table 1). Although we had detected trace amounts of benzofuran **8** during the preparation of arylated ketone **6**, when we resubjected ketone **6** to a Xantphos derived catalyst in combination with Cs_2CO_3 we could only isolate small amounts of the benzofuran product (entry 1). The use of the same catalyst system with a stronger base was similarly unsuccessful (entry 2). However, the use of the structurally similar ligand DPEphos[11] **7** with Cs_2CO_3 as base at 100 °C provided benzofuran **8** in 95% yield (entry 3). Lowering the reaction temperature simply resulted in poorer conversions (entries 4 and 5).

With conditions to effect the key intramolecular *O*-enolate aryl-coupling was established using a test system, we next

Table 1. Catalyst optimisation[a]



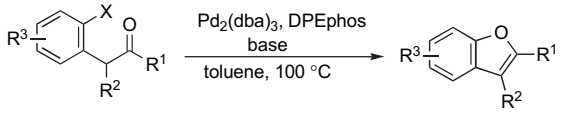
Entry	Ligand	Base	*T* (°C)	Time (h)	Yield (%)[b]
1	Xantphos	Cs_2CO_3	110	20	<5
2	Xantphos	NaO^{t}Bu	110	20	0
3	DPEphos	Cs_2CO_3	110	20	95
4	DPEphos	Cs_2CO_3	80	24	52
5	DPEphos	Cs_2CO_3	50	30	0

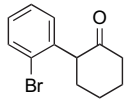
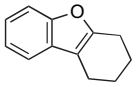
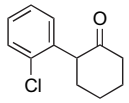
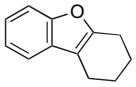
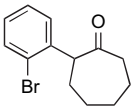
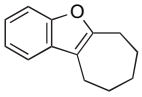
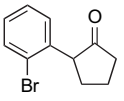
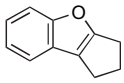
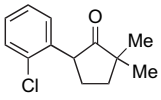
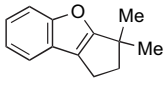
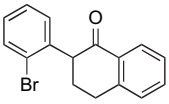
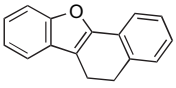
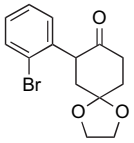
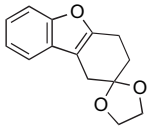
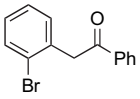
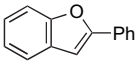
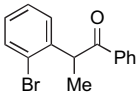
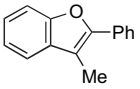
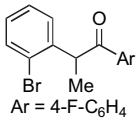
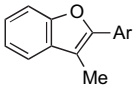
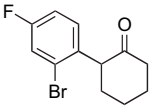
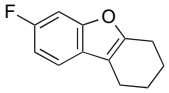
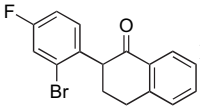
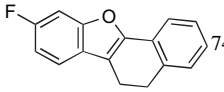
[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), ligand (6 mol %), base (2.2 equiv).
[b] Isolated yields.

explored the scope of the process (Table 2). All of the examples shown below employ the standard catalyst: $Pd_2(dba)_3$ (2.5 mol %), DPEphos (6 mol %). Entries 1–3 provide a comparison between the use of bromo- and chloro-substituents on the aryl ring. With the bromo-substrate, the use of the base Cs_2CO_3 was sufficient to achieve an excellent yield of the benzofuran. Application of these conditions to the chloro-substrate resulted in only a low conversion to product, however, the use of the alternative base NaHMDS delivered the benzofuran in 94% yield. The ability to employ Cl-substituted arenes significantly adds to the appeal of the process given the greater numbers of aryl chlorides that are commercially available.[15] Variation of the base used in the following cyclisations was important in achieving optimal yields. Although the cycloheptanone-derived substrate delivered the corresponding benzofuran as expected (entry 4), the cyclopentanone system was unreactive (entry 5). The use of a variety of base and temperature combinations also failed to deliver the benzofuran. We were concerned that competing aldol processes may have been occurring with the stronger bases, however, the use of the *gem*-dimethyl-substituted variant shown in entry 6 was also unsuccessful. It appears that ring-closure to form a cyclopentane-fused benzofuran is not possible using the current methodology.[16] Entries 7–11 demonstrate that benzo- and ketal substituents are possible on the ketone fragment and that acyclic as well as cyclic substrates can also be employed. The remaining examples show that variation of the arene fragment is also tolerated with F-substituents and a pyridyl ring all delivering the target benzofurans. While ring-closure to the corresponding benzofurans was possible without the use of a palladium catalyst for the pyridyl example, there was a significant reduction in reaction time if a catalyst was employed. Although the same catalyst was employed for all of the examples in Table 2, it can also be seen that some variation in the choice of base is needed.

Having demonstrated that *O*-enolates can perform as competent hetero-nucleophiles with a variety of intramolecular coupling partners we were interested as to whether the process could be extended to *S*-enolates. Although examples of palladium-catalysed C–S bond formation are known,[17,18] they are much less common than the corresponding C–N and C–O examples. To test the ability of *S*-enolates to participate in the desired cyclisation reactions we first needed to convert the α-(*ortho*-haloaryl)-ketone substrates into the corresponding thio-ketones. This was achieved in a straightforward manner using P_2S_5.[19] Pleasingly, treatment of the

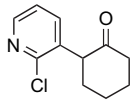
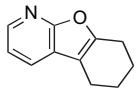
Table 2. Scope of benzofuran formation[a]



Entry	Substrate	Base	Product	Yield (%)[b]
1		Cs_2CO_3		95
2		Cs_2CO_3		54
3		NaHMDS		94
4		NaHMDS		95
5		Cs_2CO_3		0
6		Cs_2CO_3		0
7		NaO^{t}Bu		81
8		NaO^{t}Bu		73
9		NaO^{t}Bu		50
10		NaO^{t}Bu		80
11	 Ar = 4-F-C_6H_4	NaO^{t}Bu		68
12		NaO^{t}Bu		81
13		NaO^{t}Bu		74

(*continued*)

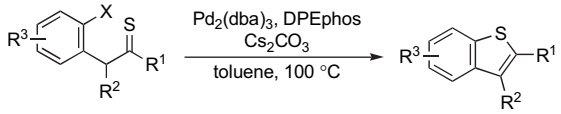
Table 2. (*continued*)

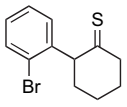
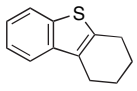
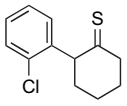
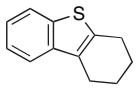
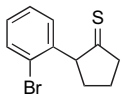
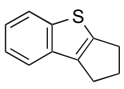
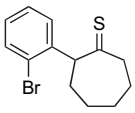
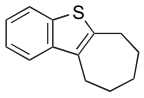
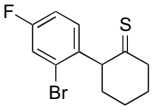
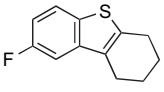
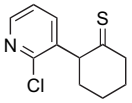
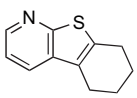
Entry	Substrate	Base	Product	Yield (%)[b]
14		NaO^{t}Bu		86[c]

[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), DPEphos (6 mol %), base (2.2 equiv).
[b] Isolated yields.
[c] In the absence of catalyst a 40% conversion is achieved after 20 h.

cyclohexanone-derived thio-ketone with the standard benzofuran-forming reaction conditions delivered benzothiophene in 74% yield (Table 3, entry 1). The aryl chloride variant also underwent cyclisation, although similar to the corresponding ketone example when using Cs_2CO_3, in a reduced yield (entry 2). In contrast to the equivalent ketone, reaction of the cyclopentanethione derived substrate delivered the expected benzothiophene (entry 3). This difference in reactivity between ketone and thio-ketone may be due to the increased nucleophilicity of the *S*-atom or the longer C–S bond. In line with the ketone examples, entries 4 and 5 demonstrate that further variation in both the ketone and aryl fragments are possible. One class of substrate not amenable to the catalysed

Table 3. Benzothiophene formation[a]

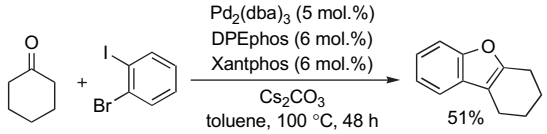


Entry	Thio-ketone	Yield (%) *S*-ketone	Product	Yield (%)[b]
1		71		74
2		40		44
3		38		52
4		40		57
5		53		57
6[c]		0		67

[a] Conditions: $Pd_2(dba)_3$ (2.5 mol %), DPEphos (6 mol %), Cs_2CO_3 (2.2 equiv), toluene, 100 °C.
[b] Isolated yields.
[c] Attempted formation of thio-ketone lead directly to cyclised product.

S-enolate reaction are the pyridyl-substituted variants; attempted conversion of the ketone to the thio-ketone lead directly to the benzothiophene product (entry 6).

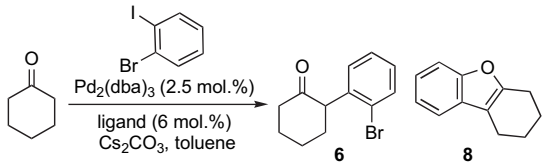
The benzofuran and benzothiophene syntheses as presented consist of two independent palladium-catalysed reactions leading to the efficient preparation of the individual heterocycles. The similarity of the reaction conditions, particularly the ligand choice, for the two independent reactions suggested that a one-pot cascade process might be achievable. Unfortunately, even though there is significant structural homology between the two optimal ligands for each separate reaction (Xantphos for the *C*-arylation, DPEphos for benzofuran/benzothiophene formation), neither ligand would effect the alternate reaction. One solution to this was to combine both ligands in a single reaction:[20] Scheme 3 illustrates the process for the direct preparation of the cyclohexane-fused benzofuran from cyclohexanone and 1-bromo-2-iodobenzene.



Scheme 3.

Although a 51% yield of benzofuran could be obtained from the mixed-ligand reaction we sought a single ligand system capable of achieving the desired cascade sequence. The number of ligands reported to facilitate palladium-catalysed coupling processes is ever increasing and this combined with the number of additional variables (base, Pd source, solvent, temperature) makes a complete evaluation of reaction conditions a prohibitively complex exercise. As a compromise we elected to simply vary the ligand choice while keeping all other variables constant. The coupling of cyclohexanone and 1-bromo-2-iodobenzene was again selected as an appropriate test system. Table 4 documents these studies: as already stated, the ligands Xantphos and DPEphos were not effective for the desired cascade transformation, neither was (*rac*)-BINAP (entries 1–3). The biphenyl-based phosphine ligands developed by Buchwald have been shown to be effective for a number of palladium-mediated transformations, however, the use of ligands **9** or **10** were similarly ineffective (entries 4 and 5).[21] Recently, ferrocene-based ligands have appeared in the literature with more frequency and have shown success in a number of palladium-catalysed *C–O* bond-forming reactions.[22] Unfortunately, application of the bis-chelating isopropyl **11** and phenylphosphino variants **12** gave none of the desired products (entries 6 and 7). However, the *tert*-butyl analogue **13** promoted both steps in the sequence producing 9% of the arylated ketone and 7% of the benzofuran (entry 8). The respective conversions both increased to 25% when the catalyst loading was increased to 5 mol % Pd and 6 mol % ligand (entry 9). Although the bulky tri-isopropyl-substituted dicyclohexylphosphine ligand **14**[23] gave poor conversion to the benzofuran product it gave complete cyclisation of the arylated ketone (entry 10). The *tert*-butyl analogue **15** showed decreased activity (entry 11). Use of the dimethoxy-substituted dicyclohexylphosphine ligand **16**[24] provided the arylated ketone in 9% with 20% conversion to the benzofuran product (entry 12).

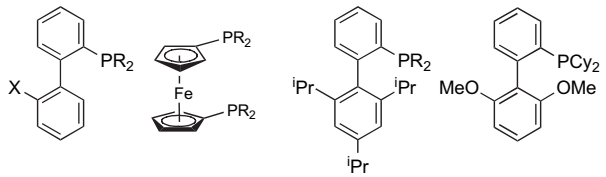
Table 4. Development of a single-ligand cascade reaction[a]



6 **8**

Entry	Ligand	Aryl ketone conv. (%)[b]	Benzofuran conv. (%)[b]
1	Xantphos	78[c]	<5
2	DPEphos	0	0
3	BINAP	0	0
4	**9**	0	0
5	**10**	9	0
6	**11**	0	0
7	**12**	0	0
8	**13**	9	7
9[d]	**13**	25	25
10	**14**	0	9
11	**15**	0	0
12	**16**	9	20
13[d]	**16**	0	91
14[e]	**16**	0	100

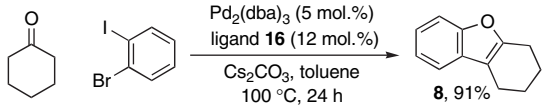
[a] Conditions: 1-bromo-2-iodobenzene (1.0 equiv), cyclohexanone (1.2 equiv), toluene, 80 °C, 24 h.
[b] Determined by ^{1}H NMR.
[c] Isolated yield.
[d] $Pd_2(dba)_3$ (5 mol %), ligand (6 mol %), 100 °C.
[e] $Pd_2(dba)_3$ (5 mol %), ligand (12 mol %), 100 °C.



9, R = ^{t}Bu, X = H
10, R = Cy, X = NMe_2
11, R = Ph
12, R = ^{i}Pr
13, R = ^{t}Bu
14, R = ^{t}Bu
15, R = Cy
16

Increasing the palladium loading to 5 mol % significantly increased the conversion to benzofuran (entry 13), and finally, simultaneously increasing the ligand loading to 12 mol % resulted in complete conversion to benzofuran (entry 14).

A preparative scale reaction using these optimised conditions delivered benzofuran **8** in 91% yield (Scheme 4). Unfortunately, these conditions were not transferable to alternative substrates, with only low yields of mixtures of arylated ketone and benzofuran being obtained in almost all cases. For example, reactions involving the coupling of 2-bromo-iodobenzene with either cycloheptanone or α-tetralone were unsuccessful. It appears that it would be necessary to develop an optimised catalyst system for individual substrates. The effort needed to optimise for individual substrates in cascade processes suggests that the use of multi-ligand systems may offer advantages, in that it is often more convenient to optimise for a single one-step transformation using a single ligand and then apply this information to the cascade sequence.



Scheme 4.

3. Conclusion

We have demonstrated that a simple catalyst comprising $Pd_2(dba)_3$ and the ligand DPEphos effects the cyclisation of α-(*ortho*-haloaryl)-substituted ketones and thio-ketones to benzofurans and benzothiophenes, respectively. The process tolerates variations in both the ketone and aryl fragments to deliver the heterocyclic products in good yields. The key cyclisation reaction involves the coupling of enolate and thio-enolate heteroatoms to palladium-activated aryl halides. Although it is possible to construct a cascade reaction sequence, involving the in situ preparation of the arylated ketones, the process is less general and requires optimsation for individual substrates. Applications of similar enolate-heteroatom cyclisations to the synthesis of alternative heterocycles are underway.

4. Experimental

4.1. General

The preparation of several of the α-arylated ketones and the corresponding benzofuran products has been previously described.[7,12]

4.1.1. General procedure (A) for the preparation of α-arylated ketones. Exemplified by the preparation of 2-(2-bromophenyl)-cyclohexanone 6. Caesium carbonate (4.570 g, 14.00 mmol) was added to a flask charged with $Pd_2(dba)_3$ (0.030 g, 0.033 mmol) and Xantphos (0.040 g, 0.080 mmol) under nitrogen. The reagents were suspended in anhydrous dioxane (6.4 mL) and 1-bromo-2-iodobenzene (1.80 g, 6.370 mmol, 0.82 mL) and cyclohexanone (1.25 g, 12.74 mmol, 1.3 mL) were added under nitrogen and the reaction was heated to 80 °C for 24 h. After cooling, the reaction mixture was diluted with diethyl ether (ca. 10 mL), filtered through Celite and reduced in vacuo. The residue was purified via flash column chromatography (5–10% diethyl ether/petrol) to yield ketone **6** (1.26 g, 78%) as a white solid: mp 57–58 °C (MeOH) (lit. 58–59 °C).[1] ν_{max} (Nujol™)/cm^{-1} 2920, 2855, 1709, 1566 (w), 1462, 1377, 1281, 1196, 1121, 1070, 1027, 977, 940, 769, 746, 722, 674; δ_H (300 MHz, $CDCl_3$) 1.71–2.10 (4H, m, CH_2), 2.15–2.35 (2H, m, ArCHCH_2), 2.51–2.89 (2H, m, CH_2CO), 4.11 (1H, app. dd, *J* 12.4 and 5.3, Ar–C*H*), 7.12 (1H, ddd, *J* 7.9, 7.2 and 1.9, Ar–*H*), 7.21 (1H, dd, *J* 7.9 and 1.9, Ar–*H*), 7.31 (1H, td, *J* 7.9 and 1.1, Ar–*H*), 7.56 (1H, td, *J* 7.9 and 1.5, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 25.1, 27.1, 33.6, 41.8, 56.0, 124.6, 126.8, 127.8, 128.9, 132.1, 137.8, 208.3; *m/z* LRMS (CI^+, NH_3) 270 $[M+NH_4]^+$, 253 $[M+H:^{79}Br]^+$, 173 $[M-^{79}Br]^+$, 145 $[M-^{79}Br-CO]^+$, 115 $[M-^{79}Br-CO-C_2H_4]^+$; HRMS (ES^+) calcd for $C_{12}H_{14}BrO$: 253.0223 $[M+H]^+$, found: 253.0225 $[M+H]^+$.

4.1.1.1. Preparation of 5-(2-chlorophenyl)-2,2-dimethylcyclopentanone (Table 2, entry 6 substrate). General procedure A was followed employing 1-bromo-2-chlorobenzene (159 mg, 0.830 mmol, 0.10 mL), 2,2-dimethylcyclopentanone (112 mg, 0.997 mmol, 0.13 mL) and 2-dicyclohexylphosphino-2′-methylbiphenyl (18 mg, 0.049 mmol) as the ligand, heating at 110 °C for 17 h. The product was purified via flash column chromatography (5–10% diethyl ether/petrol) to yield the *ketone* (90 mg, 50%) as a creamy/white solid: mp 63–64 °C. ν_{max} (KBr)/cm^{-1} 2961, 2867, 1736, 1478, 1460, 1437, 1381, 1360, 1329, 1258, 1190, 1128, 1089, 1062, 1031, 767, 753; δ_H (300 MHz, $CDCl_3$) 1.15 (3H, s, C(CH_3)$_2$), 1.20 (3H, s, C(CH_3)$_2$), 1.81–2.07 (3H, m, CH_2 and ArCHCH_2), 2.42–2.53 (1H, m, ArCHCH_2), 3.85–3.97 (1H, m, Ar–C*H*), 7.03 (1H, dd, *J* 7.5 and 2.1, Ar–*H*), 7.18 (1H, td, *J* 7.5 and 1.9, Ar–*H*), 7.23 (1H, td, *J* 7.5 and 1.9, Ar–*H*), 7.38 (1H, dd, *J* 7.5 and 2.1, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 24.2, 25.5, 28.1, 37.0, 45.8, 53.1, 127.5, 128.6, 129.6, 130.0, 135.0, 137.9, 221.5; *m/z* LRMS (CI^+, NH_3) 242 $[M:^{37}Cl]^+$, 240 $[M:^{35}Cl]^+$, 206 $[M-^{35}Cl]^+$, 204 $[M-^{37}Cl]^+$; HRMS (ES^+) calcd for $C_{13}H_{19}ClNO$: 240.1150 $[M+NH_4]^+$, found: 240.1153 $[M+NH_4]^+$. $C_{13}H_{15}ClO$ requires C 70.11, H 6.79%, found C 69.80, H 6.78%.

4.1.1.2. Preparation of 2-(2-bromophenyl)-1-phenylethanone (Table 2, entry 9 substrate).[25] General procedure A was followed employing 1-bromo-2-iodobenzene (2.000 g, 7.070 mmol, 0.91 mL) and acetophenone (1.020 g, 8.480 mmol, 0.99 mL) using $HP^tBu_3BF_4$ (90 mg, 0.320 mmol) as the ligand and sodium *tert*-butoxide (1.600 g, 16.560 mmol) as the base, heating at 60 °C for 9 h. The product was purified via flash column chromatography (5% diethyl ether/petrol) to yield the *ketone* (1.19 g, 51%) as a white crystalline solid: mp 66–67 °C. ν_{max} (Nujol™)/cm^{-1} 3057, 1691, 1585, 1581, 1567, 1470, 1447, 1427, 1407, 1331, 1277, 1219, 1202, 1174, 1156, 1025, 990, 756, 690, 666, 650, 575; δ_H (300 MHz, $CDCl_3$) 4.46 (2H, s, Ar–CH_2CO), 7.15 (1H, ddd, *J* 7.9, 6.8 and 2.3, Ar–*H*), 7.22–7.32 (2H, m, Ar–*H*), 7.47 (2H, tt, *J* 8.1 and 1.5, Ar–*H*), 7.55–7.62 (2H, m, Ar–*H*), 8.05 (2H, d, *J* 7.2, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 45.8, 125.1, 127.5, 128.3, 128.7, 131.7, 132.8, 133.3, 133.8, 134.9, 136.6, 196.3; *m/z* LRMS (CI^+, NH_3) 294 $[M+NH_4:^{81}Br]^+$, 292 $[M+NH_4:^{79}Br]^+$, 277 $[M+NH_3:^{81}Br]^+$, 275 $[M+NH_3:^{79}Br]^+$; HRMS (ES^+) calcd for $C_{14}H_{15}BrNO$: 292.0332 $[M+NH_4:^{79}Br]^+$, found: 292.0331 $[M+NH_4:^{79}Br]^+$; $C_{14}H_{11}OBr$ requires C 61.11, H 4.03%, found C 61.10, H 4.01%.

4.1.2. General procedure (B) for the preparation of benzofurans from α-arylated ketones. Exemplified by the preparation of 1,2,3,4-tetrahydro-dibenzofuran (Table 2, entry 1). Caesium carbonate (180 mg, 0.560 mmol) was added to a flask charged with $Pd_2(dba)_3$ (9 mg, 0.009 mmol) and DPEphos (13 mg, 0.022 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (1 mL) prior to the addition of ketone **6** (100 mg, 0.40 mmol) and the reaction heated to 100 °C for 20 h. After cooling the reaction mixture was filtered through a plug of Celite and the filtrate reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzofuran* (64 mg, 95%) as a colourless oil. Data consistent with that reported in the literature.[26]

4.1.3. General procedure (C) for the preparation of thioketones. Exemplified by the preparation of 2-(2-bromophenyl)-cyclohexanethione (Table 3, entry 1 substrate). 2-(2-Bromophenyl)-cyclohexanone (500 mg, 1.981 mmol) was added to a flask charged with phosphorus pentasulfide (220 mg, 0.489 mmol) under nitrogen and the reaction

mixture suspended in anhydrous toluene (2.50 mL). The mixture was stirred at room temperature for 10 min prior to the addition of hexamethyldisiloxane (550 mg, 3.360 mmol, 0.71 mL) and heated to 90 °C for 21 h. After cooling, the reaction mixture was filtered through a plug of silica and the filtrate reduced in vacuo to yield the *thio-ketone* (375 mg, 71%) as a colourless oil. The product was used without further purification. ν_{max} (NaCl)/cm^{-1} 3050, 2924, 2855, 1642, 1587, 1559, 1466, 1435, 1334, 1258, 1243, 1136, 1115, 1078, 1050, 1027, 1014, 821, 799, 751, 724, 688; δ_H (300 MHz, $CDCl_3$) 1.63–1.80 (4H, m, CH_2), 1.95–2.12 (1H, m, ArCHCH_2), 2.24–2.38 (3H, m, ArCHCH_2 and CH_2CS), 2.39 (1H, br s, Ar–C*H*), 7.03–7.10 (2H, m, Ar–*H*), 7.24 (1H, td, *J* 7.9 and 1.4, Ar–*H*), 7.53 (1H, dd, *J* 7.9 and 1.4, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.0, 32.0, 34.1, 123.4, 125.9, 128.2, 129.0, 130.6, 133.4, 133.7, 143.8; *m/z* LRMS (EI$^+$) 271 [M:^{81}Br]$^+$ (53%), 270 [M−H:^{81}Br]$^+$ (52%), 269 [M:^{79}Br]$^+$ (100%), 268 [M−H:^{79}Br]$^+$ (48%), 189 [M−Br]$^+$ (40%); (CI$^+$, NH_3) 288 [M+NH_3:^{81}Br]$^+$, 286 [M+NH_3:^{79}Br]$^+$, 272 [M+H:^{81}Br]$^+$, 271 [M:^{81}Br]$^+$, 270 [M+H:^{79}Br]$^+$, 269 [M:^{79}Br]$^+$; HRMS (EI) calcd for $C_{12}H_{13}BrS$: 267.9916 [M]$^+$, found: 267.9917 [M]$^+$.

4.1.3.1. Preparation of 2-(2-chlorophenyl)-cyclohexanethione, (Table 3, entry 2 substrate). General procedure C was followed employing the relevant ketone (180 mg, 1.318 mmol) to yield the *thio-ketone* (119 mg, 40%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3645, 3055, 2925, 2857, 2833, 2661, 2571, 2318, 1799, 1722, 1643, 1590, 1564, 1470, 1428, 1335, 1260, 1174, 1121, 1078, 1059, 1034, 1016, 941, 862, 801, 753, 728, 709, 650; δ_H (300 MHz, $CDCl_3$) 1.69–1.86 (4H, m, CH_2), 2.02–2.19 (2H, m, ArCHCH_2), 2.31–2.44 (2H, m, CH_2CS), 2.46 (1H, br s, Ar–C*H*), 7.15 (1H, dd, *J* 7.2 and 2.3, Ar–*H*), 7.24 (1H, app. qd, *J* 7.2 and 2.3, Ar–*H*), 7.41 (1H, dd, *J* 7.2 and 2.3, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.1, 31.9, 34.2, 126.0, 127.5, 128.9, 130.2, 130.6, 132.2, 133.2, 141.8; *m/z* LRMS (EI$^+$) 224 [M:^{35}Cl]$^+$ (34%), 189 [M−^{35}Cl]$^+$ (100%), 188 [M−H−^{35}Cl]$^+$ (62%), 187 [M−^{37}Cl] (33%); HRMS (ES$^+$) calcd for $C_{12}H_{14}ClS$: 225.0499 [M+H]$^+$, found: 225.0498 [M+H]$^+$.

4.1.3.2. Preparation of 2-(2-bromophenyl)-cyclopentanethione, (Table 3, entry 3 substrate). General procedure C was followed employing relevant ketone (200 mg, 0.837 mmol) to yield the *thio-ketone* (80 mg, 38%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3062, 2923, 2848, 1742 (vs), 1634, 1559, 1467, 1429, 1317, 1262, 1204, 1115, 1057, 1028, 752, 722, 699; δ_H (300 MHz, $CDCl_3$) 1.93–2.05 (2H, m, CH_2), 2.57–2.71 (5H, m, Ar–C*H*, ArCHCH_2 and CH_2CS), 7.04–7.14 (2H, m, Ar–*H*), 7.21–7.27 (1H, m, Ar–*H*), 7.53 (1H, dd, *J* 7.9 and 0.8, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 27.4, 29.0, 30.2, 121.8, 123.5, 123.7, 124.2, 135.7, 141.2, 143.4, 145.5; *m/z* LRMS (EI$^+$) 256 [M+H:^{79}Br]$^+$ (95%), 254 [M−H:^{79}Br]$^+$ (100%); (CI$^+$, NH_3) 272 [M+NH_3:^{79}Br]$^+$, 258 [M+H:^{81}Br]$^+$, 257 [M:^{81}Br]$^+$, 256 [M+H:^{79}Br]$^+$, 255 [M:^{79}Br]$^+$, 254 [M−H:^{79}Br]$^+$; HRMS (EI) calcd for $C_{11}H_{11}BrS$: 253.9759 [M]$^+$, found: 253.9756 [M]$^+$.

4.1.3.3. Preparation of 2-(2-bromophenyl)-cycloheptanethione, (Table 3, entry 4 substrate). General procedure C was followed employing relevant ketone (430 mg, 1.619 mmol) to yield the *thio-ketone* (181 mg, 40%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3049, 2923, 2848, 2569, 1630, 1587, 1558, 1466, 1446, 1432, 1356, 1343, 1269, 1148, 1026, 979, 750, 726, 685; δ_H (300 MHz, $CDCl_3$) 1.61–1.90 (5H, m, CH_2), 2.27–2.69 (5H, m, ArCHCH_2, CH_2CS and CH_2), 2.70 (1H, br s, Ar–C*H*), 7.08–7.17 (2H, m, Ar–*H*), 7.30 (1H, app. td, *J* 7.2 and 1.5, Ar–*H*), 7.61 (1H, app. dd, *J* 7.9 and 1.5, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 26.6, 26.8, 32.1, 35.9, 38.5, 122.9, 128.3, 128.7, 130.4, 131.0, 133.5, 137.3, 146.3; *m/z* LRMS (EI$^+$) 284 [M:^{81}Br]$^+$ (12%), 282 [M:^{79}Br]$^+$ (12%), 203 [M−Br]$^+$ (52%), 202 [M−^{81}Br]$^+$ (54%), 201, 173, 160, 147; (CI$^+$, NH_3) 300 [M+NH_3]$^+$, 286 [M+H_2:^{81}Br]$^+$, 285 [M+H:^{81}Br]$^+$, 284 [M:^{81}Br]$^+$, 283 [M+H:^{79}Br]$^+$, 204 [M−^{79}Br]$^+$, 203 [M+H−^{81}Br]$^+$, 202 [M−^{81}Br]$^+$, 201 [M−H−^{81}Br]$^+$; HRMS (EI) calcd for $C_{13}H_{15}BrS$: 282.0072 [M:^{79}Br]$^+$, found: 282.0072 [M:^{79}Br]$^+$.

4.1.3.4. Preparation of 2-(4-fluoro-2-bromophenyl)-cyclohexanethione, (Table 3, entry 5 substrate). General procedure C was followed employing relevant ketone (200 mg, 0.738 mmol) to yield the *thio-ketone* (113 mg, 53%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 2962, 2932, 2858, 2833, 1715, 1644, 1596, 1577, 1483, 1446, 1384, 1336, 1260, 1198, 1016, 872, 815, 666; δ_H (300 MHz, $CDCl_3$) 1.70–1.88 (4H, m, CH_2), 2.00–2.14 (1H, m, ArCHCH_2), 2.41–2.27 (3H, m, ArCHCH_2 and CH_2CS), 2.43 (1H, s, Ar–C*H*), 7.03 (1H, td, *J* 8.4 and 2.5, Ar–*H*), 7.11 (1H, dd, *J* 8.4 and 6.2, Ar–*H*), 7.35 (1H, dd, *J* 8.4 and 2.5, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 23.2, 24.0, 32.1, 34.2, 115.4 (d, J_{CF} 24.2), 126.9, 120.5 (d, J_{CF} 21.1), 131.5 (d, J_{CF} 8.1), 132.8, 139.8 (d, J_{CF} 3.7), 160.1, 163.5; *m/z* LRMS (EI$^+$) 288 [M:^{81}Br] (87%), 286 [M:^{79}Br] (100%); (CI$^+$, NH_3) 208 [M−^{79}Br]$^+$, 207 [M+H−^{79}Br]$^+$, 206 [M−^{81}Br]$^+$, 205 [M−H−^{81}Br]$^+$; HRMS (EI) calcd for $C_{12}H_{12}BrFS$: 285.9822 [M:^{79}Br]$^+$, found: 285.9826 [M:^{79}Br]$^+$.

4.1.4. General procedure (D) for the preparation of benzothiophenes. Exemplified by the preparation of 1,2,3,4-tetrahydro-dibenzothiophene (Table 3, entry 1). Caesium carbonate (180 mg, 0.557 mmol) was added to a flask charged with $Pd_2(dba)_3$ (9 mg, 0.009 mmol) and DPEphos (13 mg, 0.022 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.5 mL) prior to the addition of 2-(2-bromophenyl)-cyclohexanethione (100 mg, 0.372 mmol) and the reaction heated to 100 °C for 20 h. After cooling, the reaction mixture was filtered through a plug of Celite and the filtrate reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzothiophene* (52 mg, 74%) as a colourless oil.

4.1.4.1. Preparation of 2,3-dihydro-1*H*-benzo(β)cyclopenta(δ)thiophene (Table 3, entry 3). General procedure D was followed employing the relevant thio-ketone (50 mg, 0.196 mmol) to yield the *benzothiophene* (17 mg, 52%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3058, 2923, 2851, 1699, 1571, 1467, 1428, 1378, 1319, 1296, 1258, 1152, 1066, 1017, 800, 750, 728; δ_H (300 MHz, $CDCl_3$) 2.51–2.62 (2H, m, CH_2), 2.86–2.93 (2H, m, CH_2C═CS), 2.98–3.07 (2H, m, CH_2C═CS), 7.24 (1H, td, *J* 7.5 and 1.3, Ar–*H*), 7.32 (1H, td, *J* 7.5 and 1.3, Ar–*H*), 7.56 (1H, d, *J* 7.5, Ar–*H*),

7.76 (1H, dt, *J* 7.5 and 1.3, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 27.4, 29.0, 30.2, 121.8, 123.5, 123.7, 124.2, 135.7, 141.2, 143.4, 145.5; *m/z* LRMS (EI^+) 174 $[M]^+$ (18%), 173 $[M-H]^+$ (39%); (CI^+, NH_3) 173 $[M]^+$; HRMS (EI) calcd for $C_{11}H_9S$: 173.0419 $[M-H]^+$, found: 173.0415 $[M-H]^+$.

4.1.4.2. Preparation of 6,7,8,9-tetrahydro-5*H*-10-oxabenzothiazulene (Table 3, entry 4).[27] General procedure D was followed employing the relevant thio-ketone (100 mg, 0.369 mmol) to yield the *benzothiophene* (42 mg, 57%) as a yellow solid: mp 65–66 °C. ν_{max} (NaCl)/cm^{-1} 3059, 2921, 2838, 1442, 1435, 1359, 1311, 1262, 1223, 1151, 1090, 1019, 823, 800, 750, 725, 667; δ_H (300 MHz, $CDCl_3$) 1.68–1.82 (4H, m, C*H*$_2$), 1.90–1.99 (2H, m, C*H*$_2$), 2.87–2.96 (4H, m, C*H*$_2$C=CS and C*H*$_2$CS=C), 7.25 (1H, td, *J* 7.9 and 1.1, Ar–*H*), 7.34 (1H, td, *J* 7.9 and 1.1, Ar–*H*), 7.62 (1H, d, *J* 7.9, Ar–*H*), 7.75 (1H, dt, *J* 7.9 and 1.1, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 26.0, 26.8, 28.7, 29.3, 31.3, 119.8, 121.1, 122.1, 122.6, 133.2, 137.0, 139.6, 139.9; *m/z* LRMS (EI^+) 202 $[M]^+$ (100%), 173 $[M-C_2H_5]$ (90%), 160 $[M-C_3H_6]$ (45%), 147 $[M-C_4H_7]^+$ (58%); (CI^+, NH_3) 203 $[M+H]^+$, 202 $[M]^+$; HRMS (EI) calcd for $C_{13}H_{14}S$: 202.0811 $[M]^+$, found: 202.0810 $[M]^+$.

4.1.4.3. Preparation of 8-fluoro-1,2,3,4-tetrahydro-dibenzothiophene (Table 3, entry 5). General procedure D was followed employing the relevant thio-ketone (100 mg, 0.369 mmol) to yield the *benzothiophene* (43 mg, 57%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3063, 2932, 2857, 2840, 1603, 1556, 1470, 1446, 1401, 1376, 1349, 1338, 1314, 1298, 1250, 1201, 1150, 1136, 1111, 1069, 1050, 1022, 979, 951, 894, 848, 822, 804, 790, 701, 600, 534; δ_H (300 MHz, $CDCl_3$) 1.85–1.98 (4H, m, C*H*$_2$), 2.69–2.77 (2H, m, C*H*$_2$C=CS), 2.80–2.87 (2H, m, C*H*$_2$CS=C), 7.07 (1H, td, *J* 8.9 and 2.4, Ar–*H*), 7.42–7.51 (2H, m, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 22.6, 23.9, 26.0, 30.1, 108.9 (d, J_{CF} 25.4), 112.8 (d, J_{CF} 23.6), 121.5 (d, J_{CF} 8.7), 129.4, 136.7, 137.0, 159.0, 162.1; *m/z* LRMS (EI^+) 206 $[M]^+$ (73%), 205 $[M-H]^+$ (24%), 178 $[M-C_2H_4]^+$ (100%); (CI^+, NH_3) 207 $[M+H]^+$, 206 $[M]^+$; HRMS (EI) calcd for $C_{12}H_{11}FS$: 206.0560 $[M]^+$, found: 206.0561 $[M]^+$.

4.1.4.4. Preparation of 5,6,7,8-tetrahydrobenzo[4,5]-thieno[2,3,*β*]pyridine (Table 3, entry 6). The starting ketone (Table 3, entry 6 substrate, 200 mg, 0.738 mmol) was added to a flask charged with phosphorus pentasulfide (82 mg, 0.184 mmol) under nitrogen and the reaction mixture suspended in anhydrous toluene (0.74 mL). The mixture was stirred at room temperature for 10 min prior to the addition of hexamethyldisiloxane (204 mg, 1.250 mmol, 0.27 mL) and heated to 90 °C for 18 h. After cooling the reaction mixture was filtered through a plug of silica and the filtrate reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzothiophene* (113 mg, 57%) as a colourless oil. ν_{max} (NaCl)/cm^{-1} 3047, 2924, 2855, 2359, 1728, 1584, 1537, 1456, 1392, 1368, 1350, 1336, 1304, 1261, 1240, 1218, 1156, 1136, 1122, 1094, 1069, 1023, 972, 950, 848, 791, 748, 733, 672; δ_H (300 MHz, $CDCl_3$) 1.87–2.01 (4H, m, C*H*$_2$), 2.69–2.77 (2H, m, C*H*$_2$C=CS), 2.84–2.93 (2H, m, C*H*$_2$CS=C), 7.25 (1H, dd, *J* 7.9 and 4.9, Ar–*H*), 7.81 (1H, dd, *J* 7.9 and 1.5, Ar–*H*), 8.46 (1H, d, *J* 3.8, Ar–*H*); δ_C (75 MHz, $CDCl_3$) 22.6, 23.6, 23.7, 26.1, 30.1, 119.4, 127.7, 128.2, 138.2, 145.6, 161.2; *m/z* LRMS (EI^+) 189 $[M]^+$ (65%), 161 $[M-C_2H_4]$ (100%); (CI^+, NH_3) 190 $[M+H]^+$; HRMS (ES^+) calcd for $C_{11}H_{12}NS$: 190.0685 $[M+H]^+$, found: 190.0686 $[M+H]^+$.

4.1.4.5. Preparation of 1,2,3,4-tetrahydro-dibenzofuran using a one-pot two-ligand cascade reaction (Scheme 3). Caesium carbonate (1.727 g, 5.301 mmol) was added to a flask charged with $Pd_2(dba)_3$ (81 mg, 0.088 mmol), Xantphos (61 mg, 0.106 mmol) and DPEphos (57 mg, 0.106 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (2.00 mL) and 1-bromo-2-iodobenzene (0.500 g, 1.767 mmol, 0.23 mL) and cyclohexanone (0.260 g, 2.651 mmol, 0.28 mL) were added under nitrogen and the reaction heated to 100 °C for 48 h. After cooling, the reaction mixture was diluted with diethyl ether (ca. 10 mL), filtered through Celite and reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzofuran* (0.223 g, 51%) as a colourless oil.

4.1.4.6. Preparation of 1,2,3,4-tetrahydro-dibenzofuran using a one-pot one-ligand cascade reaction (Scheme 4). Caesium carbonate (691 mg, 2.212 mmol) was added to a flask charged with $Pd_2(dba)_3$ (32 mg, 0.035 mmol) and ligand **16** (17 mg, 0.042 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (1.00 mL) and 1-bromo-2-iodobenzene (200 mg, 0.707 mmol, 0.09 mL) and cyclohexanone (80 mg, 0.848 mmol, 0.09 mL) were added under nitrogen and the reaction heated to 100 °C for 48 h. After cooling, the reaction mixture was diluted with diethyl ether (ca. 10 mL), filtered through Celite and reduced in vacuo. The residue was purified via flash column chromatography (petrol) to yield the *benzofuran* (0.111 g, 91%) as a colourless oil.

Acknowledgements

This work was supported by the EPSRC and Pfizer. We thank Mr. Gareth Brace for helpful discussions. The EPSRC Mass Spectrometry Service at the University of Wales Swansea is also thanked for their assistance.

References and notes

1. Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: Chichester, UK, 1997.
2. For reviews dealing with benzofuran and benzothiphene synthesis, see: (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491; (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; (c) Donnelly, D. M. X.; Meegan, M. J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: New York, NY, 1984; Vol. 4, p 657.
3. Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.
4. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000.
5. For reviews, see: (a) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613; (b) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42; (c) Cacchi, S.; Arcadi, A. *Handbook of*

Organopalladium Chemistry for Organic Synthesis; Negishi, E. I., Ed.; Wiley: New York, NY, 2002; Vol. 2, p 2193.
6. For recent examples, see: (a) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2003**, *44*, 8221; (b) Dai, W.-M.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377; (c) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670; (d) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387.
7. A portion of this work has already appeared as a communication; Willis, M. C.; Taylor, D.; Gillmore, A. D. *Org. Lett.* **2004**, *6*, 4755.
8. For examples, see: (a) Katritzky, A. R.; Toader, D.; Xie, L. H. *J. Org. Chem.* **1996**, *61*, 7571; (b) Fraboni, A.; Fagnoni, M.; Albini, A. *J. Org. Chem.* **2003**, *68*, 4886; (c) Ooi, T.; Goto, R.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 10494.
9. (a) Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 953; (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
10. For examples, see: (a) Fox, J. M.; Huang, X. H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360; (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473; (c) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996; (d) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410; (e) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.
11. Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.
12. For details of the preparation of the majority of substrates and the use of similar arylated ketones in the synthesis of indoles, see: Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403.
13. For recent reviews on Pd catalysed C–O and C–N bond formation, see: (a) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, NY, 2002; Vol. 2, p 1051; (b) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., Ed.; Wiley: New York, NY, 2002; Vol. 2, p 1097; (c) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; (d) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041.
14. For examples of this type of cyclisation in the context of tandem reactions, see: (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2345; (b) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez. *Eur. J. Org. Chem.* **2005**, 2481; For a similar Cu-catalysed cyclisation, see: (c) Chen, C.-y.; Dormer, P. G. *J. Org. Chem.* **2005**, *70*, 6964.
15. For a review documenting the use of aryl chlorides in Pd catalysis, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
16. For a synthesis of cyclopentane-fused benzofuran, see: Bachelet, J. P.; Caubere, P. *J. Org. Chem.* **1982**, *47*, 234.
17. Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205.
18. For recent examples, see: (a) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587; (b) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397; (c) Moreau, X.; Campagne, J.-M. *J. Organomet. Chem.* **2003**, *687*, 322; (d) Benedi, C.; Bravo, F.; Uriz, P.; Fernandez, E.; Claver, C.; Castillon, S. *Tetrahedron Lett.* **2003**, *44*, 6073; (e) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069; (f) See also Ref. 16.
19. (a) Curphey, T. J. *Tetrahedron Lett.* **2002**, *43*, 371; (b) Curphey, T. J. *J. Org. Chem.* **2002**, *67*, 6461.
20. For an example of ligand exchange in Pd-cascade, see: Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575.
21. (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722; (b) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
22. Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775.
23. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
24. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.
25. Inaba, S.; Rieke, R. D. *J. Org. Chem.* **1985**, *50*, 1373.
26. (a) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991; (b) Givens, R. S.; Athey, P. S.; Matuszewski, B.; Kueper, L. W.; Xue, J.; Fister, T. *J. Am. Chem. Soc.* **1993**, *115*, 6001.
27. de Groot, A.; Jansen, B. J. M. *Synthesis* **1985**, 434.