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Palladium-catalyzed Tsuji–Trost-type reaction of benzofuran-2-ylmethyl acetates with nucleophiles†

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The palladium-catalyzed benzylic-like nucleophilic substitution of benzofuran-2-ylmethyl acetate with N, S, O and C soft nucleophiles has been investigated. The success of the reaction is dramatically influenced by the choice of catalytic system: with nitrogen based nucleophiles the reaction works well with Pd₂(dba)₃/dppf, while with sulfur, oxygen and carbo-nucleophiles [Pd(η³-C₃H₅)Cl]₂/XPhos is more efficient. The regiochemical outcome shows that the nucleophilic substitution occurs only on the benzylic position of the η³-(benzofuryl)methyl complex. The high to excellent yields and the simplicity of the experimental procedure make this protocol a versatile synthetic tool for the preparation of 2-substituted benzo[b]furans.

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The benzo[b]furan core is a key structural feature present in several natural and unnatural pharmacologically active compounds. Members of this class of compound exhibit various biological properties including anti-inflammatory, anti-oxidant, anti-arrhythmic, hemostatic, antimicrobial, anti-viral, anti-fungal, and anti-tumor activities and are antagonists for the H3 receptor and angiotensin II.¹ Some of them are promising drugs against Parkinson's² and Alzheimer's disease.³

Because of this, benzo[b]furans are an attractive synthetic target, and, in this context, transition metal catalysis has played a remarkable role. Particularly, palladium catalyzed reactions have been widely employed in the *de novo* construction of benzo[b]furan ring and in the selective functionalization of the pre-formed benzo[b]furan system providing functional group tolerance, simplified procedures, and improved yields.^{4–9}

Since 1-(benzofuran-2-ylmethyl)-4-benzylpiperazine has been selected as lead compound for σ₁ receptor affinity and selectivity over the σ₂ receptor,¹⁰ we decided to study a new and efficient protocol for the preparation of 2-(aminomethyl)benzo[b]furans.

As part of our continuing interest in the reactivity of propargyl carbonates,¹¹ and in the development of new approaches for the

synthesis of heterocycles, we previously reported the palladium and/or copper catalyzed construction of 2-(aminomethyl)indoles starting from ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargylic carbonates¹² or 3-(*o*-trifluoroacetamidoaryl)-1-propargylic alcohols¹³ and amines (Scheme 1a).

Furthermore, Yoshida showed that benzo[b]furan system could be synthesized through the palladium-catalyzed reaction of phenols bearing an *ortho* propargyl carbonate or acetate and carbon nucleophiles (Scheme 1b); other nucleophiles such as phenols failed because the reactive phenolic hydroxy group would also act as an additional nucleophile leading to complex mixtures.¹⁴

Based on this background, we hypothesized that the palladium catalyzed reaction of 2-(3-hydroxyprop-1-yn-1-yl)phenyl acetate **1** with nitrogen nucleophiles, could be a good strategy for producing a variety of 2-(aminomethyl)benzo[b]furans (Scheme 1c).

However, in our initial attempts, the reactions of **1** with various amines led to the formation of only traces of the desired products together with benzofuran-2-ylmethanol **4a** and polymerized byproducts. These results prompt us to explore the use of the benzofuran-2-ylmethyl acetate **2a** as a more suitable building block to afford our target derivatives through the palladium-catalyzed benzylic-like nucleophilic substitutions with amines and, more generally, with soft nucleophiles (Scheme 1d).

It is well-known that this type of substrate could generate the intermediate η³-heterocyclic complex **A** (Fig. 1).

Although the Tsuji–Trost-type reactions of benzylic derivatives with C, N, O, S soft nucleophiles have been widely studied,¹⁵ only few examples of the related functionalization of

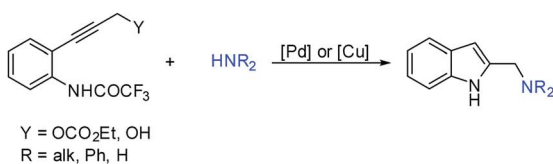
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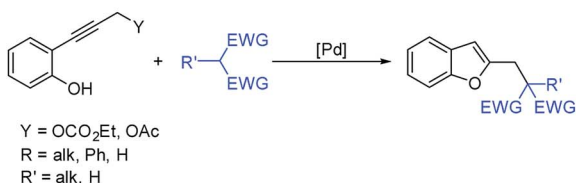
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 † Electronic supplementary information (ESI) available: Experimental details, characterization data of all compounds, and copies of ¹H and ¹³C NMR spectra (PDF). See DOI: 10.1039/d0ra09601f

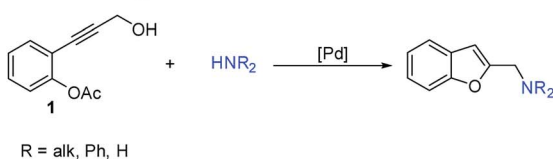

1a. Our previous work



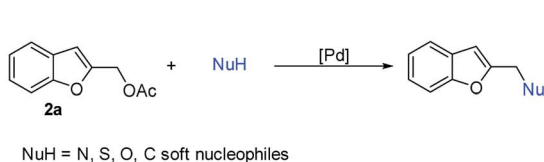
1b. Yoshida's work



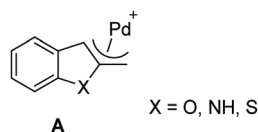
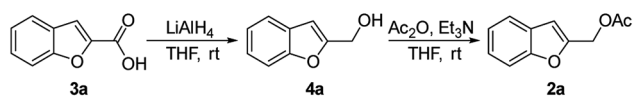
1c. Our initial hypothesis



1d. This work



Scheme 1 (a and b) Previous works; (c and d) work hypotheses.

Fig. 1 Structure of the η³-heterocyclic complex.

Scheme 2 Preparation of 2a.

(heteroaryl)methyl acetates, carbonates and pivalates have been reported and with benzofuran based substrates the reactions are limited to dimethyl malonate anions.¹⁶

Hereafter we report the results of our investigation.

Results and discussion

The starting benzofuran-2-ylmethyl acetate **2a** was prepared in excellent overall yield from commercially available benzofuran-

2-carboxylic acid according to the two-step sequence outlined in Scheme 2.

The reaction of **2a** with 1-ethylpiperazine **5a** was initially examined as the model system. Part of our optimization work using different ligands and solvents is shown in Table 1.

No evidence of the product **6aa** was observed performing the reaction without any catalyst (Table 1, entries 1 and 2), or with palladium complexes containing a monodentate phosphine ligand (Table 1, entry 3). Instead, the product **6aa** was isolated in 60% and 87% yield, switching to bidentate bisphosphine ligands bearing an appropriate bite angle such as dppe and dppf¹⁷ and performing the reaction in MeCN at 120 °C in presence of K₂CO₃ (Table 1, entries 5 and 6).^{15a,d}

We next examined the reaction using various benzofuran-2-ylmethyl acetates **2** and nitrogen-based nucleophiles under the optimized conditions [Pd₂(dba)₃, dppf, K₂CO₃, MeCN, 120 °C] in order to determine the scope and limitations of this process. The results are listed in Table 2. Usually, the reaction gave 2-(aminomethyl)benzofurans **6** in good to excellent yields with a variety of 1-alkyl, aryl and benzyl piperazine (Table 2, entries 1–6, 11 and 12) as well as mono and dialkyl amines (Table 2, entries 7–9) and *N*-alkylanilines (Table 2, entry 10).

Encouraged by these results, we decided to investigate the reactivity of **2a** with other *soft* nucleophiles. Because of the presence of the aryl sulfone fragment in a number of compounds exhibiting important biological activities,¹⁸ a great deal of attention has been devoted to their synthesis.¹⁹

We therefore selected as member of the sulfur nucleophilic class the commercially available sodium *p*-toluenesulfinate **7a**.

When the sulfonylation of **2a** with **7a** was attempted under the reaction conditions that were successfully employed with nitrogen nucleophiles [Pd₂(dba)₃, dppf, K₂CO₃, MeCN, 120

Table 1 Optimization studies for the reaction of **2a** with **5a**^a

Entry	Catalyst system	Solvent	Time (h)	Yield ^b (%)
1	—	MeCN	24	— ^c
2	—	DMSO	24	— ^{d,e}
3	Pd ₂ (dba) ₃ /P(<i>o</i> -fur) ₃ ^f	MeCN	24	—
4	Pd ₂ (dba) ₃ /dppe	DMF	18	34
5	Pd ₂ (dba) ₃ /dppe	MeCN	24	60
6	Pd ₂ (dba) ₃ /dppf	MeCN	20	87

^a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 °C using 0.025 equiv. of Pd₂(dba)₃, 0.05 equiv. of phosphine ligand, 2 equiv. of **5a**, 2 equiv. of K₂CO₃ in 2.0 mL of solvent. ^b Yields are given for isolated products. ^c **2a** was recovered in 91% yield. ^d **2a** was recovered in 50% yield. ^e **4a** was isolated in 39% yield. ^f 0.10 equiv. of phosphine ligand.



Table 2 Palladium-catalyzed synthesis of 2-aminomethylindoles **6** from benzofuran-2-ylmethyl acetates **2** and amines **5**^a

Entry	1	Amine 5	Time (h)	Yield ^b (%)
1			20	87 (6aa)
2			16	78 (6ab)
3			24	76 (6ac)
4			8	88 (6ad)
5			24	94 (6ae)
6			20	91 (6af)
7			5	75 (6ag)
8			27	75 (6ah)
9			24	92 (6ai)
10			48	48 (6aj)
11			3	84 (6ba)
12			3	84 (6bk)

^a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 °C using 0.025 equiv. of Pd₂(dba)₃, 0.05 equiv. of dppf, 2 equiv. of **5**, 2 equiv. of K₂CO₃ in 2.0 mL of MeCN. ^b Yields are given for isolated products.

°C] for 48 h, a dramatic decrease in efficiency was observed and benzofuran **8aa** was obtained only in 30% yield (Table 3, entry 3).

Reexamining the influence of some variables, such as ligands, palladium precatalyst, temperature and equivalents of sulfinate salt on the reaction outcome (Table 3), we found that the employment of Buchwald dialkylmonophosphine ligands²⁰ led to a significant improvement. For example, when the model reaction was carried out with Pd₂(dba)₃ and DavePhos or SPhos in presence of K₂CO₃ in MeCN at 120 °C, **8aa** was isolated in 63% and 82% yield, respectively (Table 3, entry 7 and 8).

The employment of [Pd(η³-C₃H₅)Cl]₂ as a precatalyst, previously used in sulfonylation^{15d,e} and phosphorylation¹⁵ⁱ of benzylic carbonates with bidentate bisphosphine ligands such as DPPF and DPEphos, was also attempted.

Because recently Colacot²¹ and O'Connor²² described the preparation and characterization of neutral Pd(allyl)LCl complexes containing Buchwald-type ligands that are high reactive precatalyst for coupling reactions, we thought that the *in situ* formation of this type of precatalyst could deserve advantages.

Indeed, compound **8aa** was isolated in excellent 92% yield after 2 h along with the desulfination product²³ 2-(4-methylbenzyl)benzofuran **8'aa** by generating the active palladium complex Pd(allyl)(Sphos)Cl in THF and performing the reaction in MeCN (Table 3, entry 11). Interestingly, employing XPhos under the same conditions afforded the desired sulfone in 98% yield after 1.5 h (Table 3, entry 13).

To verify the greater effectiveness of our procedure, we carried out a comparative experiment with the isolated complex Pd(allyl)(XPhos)Cl; the result demonstrated the greater efficiency of the *in situ* generated complex (compare entries 13 and 14, Table 3).

The best result in terms of yield, reaction time, and excess of sulfinate was therefore obtained when the reaction was carried out using [Pd(η³-C₃H₅)Cl]₂/XPhos, 2 equiv. of **7a** at 120 °C in a mixture of MeCN/THF solvents. Consequently, these conditions were employed when the procedure was extended to include functionalized benzofurans and benzene sulfinate **7b** (Table 4). No benzofuran-2-ylmethyl arylsulfinate resulting from the competitive *O*-attack of the ambident sulfinate anion was observed in all experiments,²⁴ while little amount of **8'** was usually isolated.

The potential of this strategy for the preparation of 2-poly-substituted benzo[*b*]furans is further demonstrated by the formation of 2-(aryloxymethyl)benzofuran **10** in good to excellent yields by reaction of **2** with many neutral, electron-rich, and electron-poor phenols **9** (Table 5). The experimental conditions tolerate a variety of functional groups including ether, keto, ester, and cyano, groups.

With phenol **9d**, *C*-alkylated compounds **11a** and **11b** were isolated together with the expected *O*-alkylated main product **10d**. Since with bidentate anions *C/O*-alkylated ratio is affected by the degree of aggregation, we briefly investigated the influence of the cation in the M₂CO₃ bases (Table 6, entries 1–5). As expected, the *O/C*-alkylation ratio correlates with the M⁺ size: larger is the cation, higher *O/C* resulted.

Subsequent studies were directed toward soft carbon nucleophiles derived from compounds with activated methylene group, a target of obvious interest for academic and industrial applications. We also observed very high yields with this class of pro-nucleophiles (Table 7); furthermore, to the best of our knowledge, we are reporting the first example of the Tsuji–Trost-type reaction of heterobenzylic compounds with Meldrum's acid derivatives, whose reactivity in palladium-catalyzed nucleophilic substitution of propargylic carbonates we previously reported.²⁵



Table 3 Optimization studies for the reaction of 2a with 7a^a

Entry	Catalyst system	Solvent	Time (h)	Yield ^b 8aa (%)	Yield ^b 8'aa (%)
1	—	MeCN	24	— ^c	—
2	Pd ₂ (dba) ₃ /dppf	MeCN	24	5 ^d	—
3	Pd ₂ (dba) ₃ /dppf	MeCN	48	30 ^e	—
4	Pd ₂ (dba) ₃ /dppf	DMSO	48	— ^{f,g}	—
5	Pd(PPh ₃) ₄	MeCN	24	— ^h	—
6	Pd ₂ (dba) ₃ /P(<i>o</i> -fur) ₃	MeCN	48	30 ^{i,j}	—
7	Pd ₂ (dba) ₃ /DavePhos	MeCN	2	63	—
8	Pd ₂ (dba) ₃ /SPhos	MeCN	7	82	—
9	[Pd(η ³ -C ₃ H ₅)Cl] ₂ /SPhos	MeCN	2	86	12
10	[Pd(η ³ -C ₃ H ₅)Cl] ₂ /SPhos	THF	20	58	8
11	[Pd(η ³ -C ₃ H ₅)Cl] ₂ /SPhos	MeCN/THF	2	92 ^k	5
12	[Pd(η ³ -C ₃ H ₅)Cl] ₂ /RuPhos	MeCN/THF	3	70 ^k	23
13	[Pd(η ³ -C ₃ H ₅)Cl] ₂ /XPhos	MeCN/THF	1.5	98 ^k	Traces
14	[Pd(η ³ -C ₃ H ₅)Cl] ₂ /XPhos	MeCN/THF	1	72 ^k	5

^a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 °C using 0.05 equiv. of Pd, 0.05 equiv. of phosphine ligand, 2 equiv. of 7a, 2 equiv. of K₂CO₃ in 2.0 mL of anhydrous solvent. ^b Yields are given for isolated products. ^c 2a was recovered in almost quantitative yield. ^d 2a was recovered in 70% yield. ^e 2a was recovered in 60% yield. ^f 2a was recovered in 33% yield. ^g 4a was isolated in 17% yield. ^h 2a was recovered in almost quantitative yield. ⁱ 2a was recovered in 38% yield. ^j 0.10 equiv. of phosphine ligand. ^k Carried out in 2.0 mL of anhydrous MeCN and 0.5 mL of anhydrous THF.

Table 4 Palladium-catalyzed synthesis of 2-((arylsulfonyl)methyl)benzofuran 8 from benzofuran-2-ylmethyl acetates 2 and sodium sulfonates 7^a

Entry	2	Ar	Time (h)	Yield ^b 8 (%)	Yield ^b 8' (%)
1		4-MeC ₆ H ₄ 7a	1.5	98 (8aa)	Traces
2		C ₆ H ₅ 7b	1.5	89 (8ab)	5 (8'ab)
3		4-MeC ₆ H ₄ 7a	3	84 (8ba)	—
4		C ₆ H ₅ 7b	3	84 (8bb)	9 (8'bb)
5		4-MeC ₆ H ₄ 7a	1.5	84 (8ca)	—
6		C ₆ H ₅ 7b	1	91 (8cb)	6 (8'cb)

^a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 °C using 0.025 equiv. of [Pd(η³-C₃H₅)Cl]₂, 0.05 equiv. of XPhos, 2 equiv. of 7, 2 equiv. of K₂CO₃ in 2 mL anhydrous MeCN and 0.5 mL of anhydrous THF. ^b Yields are given for isolated products.

According to literature,^{18a-d} the key intermediate of the functionalization of 2-benzofuranyl methyl acetates was suggested to be the η³-benzofurylmethyl complexes **A**, which

undergoes the nucleophilic attack of the added nucleophile. In our experiments, regardless of the nature of the nucleophiles, the nucleophilic attack was found to occur exclusively at the

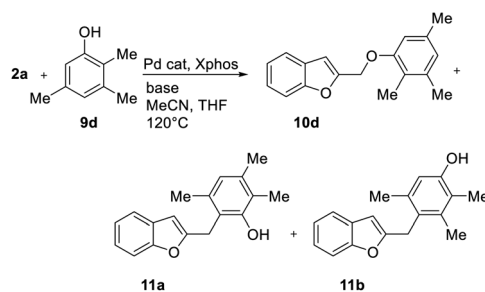


Table 5 Palladium-catalyzed synthesis of 2-(aryloxymethyl)benzofuran **10** from benzofuran-2-ylmethyl acetates **2** and phenols **9**^a

Entry	2	9	Time (h)	Yield ^b (%)
1		4-OMeC ₆ H ₄ 9a	1	90 (10aa)
2		3-CO ₂ MeC ₆ H ₄ 9b	1	92 (10ab)
3		4-FC ₆ H ₄ 9c	1	98 (10ac)
4		2,3,5-Me ₃ C ₆ H ₂ 9d	3	75 (10ad) ^c
5		4-CNC ₆ H ₄ 9e	1.5	84 (10ae)
6		4-PhC ₆ H ₄ 9f	1.5	87 (10af)
7		3-(C ₁₅ H ₃₁) C ₆ H ₄ 9g	0.75	82 (10ag)
8		4-OMeC ₆ H ₄ 9a	0.75	87 (10ba)
9		4- ^t BuC ₆ H ₄ 9h	1	93 (10bh)
10		4-OMeC ₆ H ₄ 9a	2	90 (10ca)
11		3-COMeC ₆ H ₄ 9i	1.5	85 (10ci)

^a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 °C using 0.025 equiv. of [Pd(η³-C₃H₅)Cl]₂, 0.05 equiv. of XPhos, 2 equiv. of **9**, 2 equiv. of K₂CO₃ in 2 mL anhydrous MeCN and 0.5 mL of anhydrous THF. ^b Yields are given for isolated products. ^c **11a** and **11b** were isolated respectively in 6 and 8% yield.

benzylic carbon, the less sterically hindered position; no evidence was ever obtained of products derived from nucleophilic attack at the C3-position of the benzofuran ring.

Table 6 Cation effect in palladium-catalyzed reaction of **2a** with **9d**^a

Entry	Base	Atomic radius (Å)	Yield ^b 10d (%)	Yield ^b 11a (%)	Yield ^b 11b (%)	10d /(11a + 11b)
1	Li ₂ CO ₃	0.76	—	—	—	—
2	Na ₂ CO ₃	1.02	22	13	16	44/56
3	K ₂ CO ₃	1.38	75	6	8	84/16
4	Rb ₂ CO ₃	1.52	86	8	4	87/13
5	Cs ₂ CO ₃	1.67	98	Traces	Traces	≅99/1

^a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 °C using 0.025 equiv. of [Pd(η³-C₃H₅)Cl]₂, 0.05 equiv. of XPhos, 2 equiv. of **9**, 2 equiv. of base in 2 mL anhydrous MeCN and 0.5 mL of anhydrous THF. ^b Yields are given for isolated products.

Conclusions

In conclusion, we have developed a regioselective palladium-catalyzed benzylic-like nucleophilic substitution of benzofuran-2-ylmethyl acetates with N, S, O and C-nucleophiles to afford 2-substituted benzofurans.

The usually high to excellent yields and the simplicity of the experimental procedure make this method particularly convenient for the preparation of this class of compounds.

Experimental

A list of chemicals and instrumentation is provided in the ESI.†

Typical procedure for the preparation of benzofuran-2-ylmethanol **4a**

In a flame dried two-necked round bottom flask charged with a stir bar, LiAlH₄ (2 M, 3.4 mL, 6.787 mmol, 1.1 equiv.) was added drop to drop to a solution of benzofuran-2-carboxylic acid **3a** (1.0 g, 6.170 mmol, 1 equiv.) at 0 °C in anhydrous THF (20 mL) under Ar. The mixture was allowed to warm to room temperature and stirred for 2 hours. After the complete consumption of the starting material (TLC, hexane/EtOAc 90/10 v/v), the reaction was cooled down to 0 °C and quenched by slow addition of an 80 percent aqueous MeOH solution. The mixture was extracted with AcOEt, washed with brine and the combined organic phase was dried over MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, *n*-hexane/EtOAc 85/15 v/v, *R_f* = 0.24) to afford 0.713 g of benzofuran-2-ylmethanol **4a** as a white solid (80% yield).

4a. Pale yellow oil; 80% yield (6.170 mmol scale, 0.713 g); IR (neat): 3347, 2921, 1605, 1454, 1254, 1010; cm⁻¹; ¹H NMR



Table 7 Palladium-catalyzed benzylic alkylation of methylene active compounds **12** with benzofuran-2-ylmethyl acetates **2^a**

Entry	2	12	Time (h)	Yield ^b (%)
1			0.25	87 (13aa)
2			2	86 (13ab)
3			2	70 (13ac)
4			1	97 (13ad)
5			1	57 (13ae) ^c
6			1	98 (13bf)

^a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 °C using 0.025 equiv. of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$, 0.05 equiv. of XPhos, 2 equiv. of **12**, 2 equiv. of K_2CO_3 in 2 mL anhydrous MeCN and 0.5 mL of anhydrous THF. ^b Yields are given for isolated products. ^c Diethyl 2,2-bis(benzofuran-2-ylmethyl)malonate **13'ae** was isolated in 15% yield.

(400.13 MHz) (CDCl_3): $\delta = 7.58$ (dd, $J_1 = 7.6$ Hz, $J_2 = 0.6$ Hz, 1H), 7.49 (dd, $J_1 = 8.2$ Hz, $J_2 = 0.6$ Hz, 1H), 7.31 (td, $J_1 = 7.4$ Hz, $J_2 = 1.3$ Hz, 1H), 7.24 (td, $J_1 = 7.4$ Hz, $J_2 = 1.1$ Hz, 1H), 6.69 (d, $J = 0.6$ Hz, 1H), 4.80 (s, 2H), 1.96 (bs, 1H); ^{13}C NMR (100.6 MHz) (CDCl_3): $\delta = 156.5$ (q), 155.1 (q), 128.1 (q), 124.4 (CH), 122.8 (CH), 121.1 (CH), 111.3 (CH), 104.1 (CH), 58.1. HRMS: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_9\text{H}_8\text{O}_2\text{Na}$: 171.0417; found: 171.0418.

Typical procedure for the preparation of benzofuran-2-ylmethyl acetate **2a**

To a stirred solution of benzofuran-2-ylmethanol **4a** (0.700 g, 4.7 mmol) in THF (10 mL) was successively added acetic anhydride (280 μL , 5.170 mmol, 1.1 equiv.) and triethylamine (350 μL , 5.640 mmol, 1.2 equiv.) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 h. After fully consumption of substrate **4a**, the reaction was quenched with a solution of KHSO_4 (10% w/w), diluted with AcOEt and washed with a saturated NaHCO_3 solution and with brine. The

combined organic layer was dried over Na_2SO_4 , filtered and concentrated under vacuum. The crude product **2a** was pure enough to be used directly in the next step (quantitative yield).

2a. Colorless oil; quantitative yield (4.7 mmol scale, 0.892 g); IR (neat): 2914, 1698, 1420, 1223, 1045 cm^{-1} ; ^1H NMR (400.13 MHz) (CDCl_3): $\delta = 7.59$ (dd, $J_1 = 7.7$ Hz, $J_2 = 0.5$ Hz, 1H), 7.51 (dd, $J_1 = 8.2$ Hz, $J_2 = 0.7$ Hz, 1H), 7.33 (td, $J_1 = 7.3$ Hz, $J_2 = 1.3$ Hz, 1H), 7.26 (td, $J_1 = 7.5$ Hz, $J_2 = 1.0$ Hz, 1H), 6.80 (s, 1H), 5.23 (s, 2H), 2.14 (s, 3H); ^{13}C NMR (100.6 MHz) (CDCl_3): $\delta = 170.6$ (q), 155.2 (q), 151.9 (q), 127.9 (q), 124.9 (CH), 123.0 (CH), 121.3 (CH), 111.4 (CH), 107.0 (CH), 58.6 (CH₂), 20.9 (CH₃); HRMS: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{11}\text{O}_3\text{Na}$: 213.0522; found: 213.0523.

Typical procedure for the preparation of 1-(benzofuran-2-ylmethyl)-4-ethylpiperazine **6aa**

In a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar Pd_2dba_3 (9.2 mg, 0.010 mmol, 0.025 equiv.) and dppf (11.1 mg, 0.020 mmol, 0.05 equiv.) were dissolved at room temperature with 1.0 mL of anhydrous MeCN. Then, benzofuran-2-ylmethyl acetate **2a** (76.0 mg, 0.4 mmol, 1.0 equiv.), *N*-ethylpiperazine **5a** (152 mL, 0.80 mmol, 2.0 equiv.), K_2CO_3 (165.6 mg, 1.20 mmol, 2.0 equiv.), and 1.0 mL of solvent were added. The mixture was stirred for 24 h at 100 °C under Ar. After this time, the reaction mixture was cooled to room temperature, diluted with Et_2O , washed with a saturated NaHCO_3 solution and with brine. The organic extract was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 μm), eluting with a 80/20 (v/v) *n*-hexane/AcOEt mixture ($R_f = 0.22$) to obtain 84.9 mg (87% yield) of 1-(benzofuran-2-ylmethyl)-4-ethylpiperazine **6aa**.

6aa. Pale yellow oil; 87% yield (84.9.0 mg); IR (neat): 2935, 2810, 1454, 1254, 1163, 941 cm^{-1} ; ^1H NMR (400.13 MHz) (CDCl_3): $\delta = 7.54$ (d, $J = 7.4$ Hz, 1H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.31–7.18 (m, 2H), 6.62 (s, 1H), 3.72 (s, 2H), 2.87–2.27 (m, 10H), 1.10 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (100.6 MHz) (CDCl_3): $\delta = 155.1$ (q), 154.4 (q), 128.3 (q), 123.9 (CH), 122.6 (CH), 120.7 (CH), 111.3 (CH), 105.7 (CH), 55.5 (CH₂), 53.1 (CH₂), 52.6 (CH₂), 52.2 (CH₂), 11.9 (CH₃); HRMS: m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$: 267.1468; found: 267.1471.

Typical procedure for the preparation of 2-(tosylmethyl) benzofuran **8aa**

In a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (3.7 mg, 0.010 mmol, 0.025 equiv.) and XPhos (9.5 mg, 0.020 mmol, 0.05 equiv.) were dissolved at room temperature with 0.5 mL of anhydrous THF under Ar. Then, benzofuran-2-ylmethyl acetate **2a** (76.0 mg, 0.4 mmol, 1.0 equiv.), sodium 4-tolylsulphinatate **7a** (142.5 mg, 0.80 mmol, 2.0 equiv.), K_2CO_3 (110.4 mg, 0.80 mmol, 2.0 equiv.), and 1.0 mL of anhydrous MeCN were added. The mixture was stirred for 1 h at 120 °C under Ar. After this time, the reaction mixture was cooled to room temperature, diluted with Et_2O , washed with brine. The organic extract was dried over Na_2SO_4 , filtered and concentrated



under reduced pressure. The residue was purified by chromatography on SiO₂ (25–40 μm), eluting with a 70/30 (v/v) *n*-hexane/AcOEt mixture (*R_f* = 0.24) to obtain 112.2 mg (98% yield) of 2-(tosylmethyl)benzofuran **8aa**.

8aa. Pale yellow solid; 98% yield (0.112 g); mp: 194–195 °C; IR (neat): 1451, 1310, 1144, 1084 cm⁻¹; ¹H NMR (400.13 MHz) (CDCl₃): δ = 7.57 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.23–7.11 (m, 4H), 6.59 (s, 1H), 4.45 (s, 2H), 2.35 (s, 3H); ¹³C NMR (100.6 MHz) (CDCl₃): δ = 155.2 (q), 145.3 (q), 145.1 (q), 135.3 (q), 129.8 (CH), 128.5 (CH), 127.9 (q), 124.9 (CH), 123.1 (CH), 121.2 (CH), 111.3 (CH), 108.9 (CH), 56.5 (CH₂), 21.7 (CH₃); HRMS: *m/z* [M + Na]⁺ calcd for C₁₆H₁₄O₃SNa: 309.0556; found: 309.0551.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- For recent review, see: (a) H. Khanam and Shamsuzzaman, *Eur. J. Med. Chem.*, 2015, **97**, 483; (b) Y.-H. Miao, Y.-H. Hu, J. Yang, T. Liu, J. Sun and X.-J. Wang, *RSC Adv.*, 2019, **9**, 27510. For specific paper, see: (c) D. B. Judd, M. D. Dowle, D. Middlemiss, D. I. C. Scopes, B. C. Ross, T. I. Jack, M. Pass, E. Tranquillini, J. E. Hobson, T. A. Panchal, P. G. Stuart, J. M. S. Paton, T. Hubbard, A. Hilditch, G. M. Drew, M. J. Robertson, K. L. Clark, A. Travers, A. A. E. Hunt, J. Polley, P. J. Eddershaw, M. K. Bayliss, G. R. Manchee, M. D. Donnelly, D. G. Walker and S. A. Richards, *J. Med. Chem.*, 1994, **37**, 3108; (d) D. Middlemiss, S. P. Watson, B. C. Ross, M. D. Dowle, D. I. C. Scopes, J. G. Montana, P. Shah, G. C. Hirst, T. A. Panchal, J. M. S. Paton, M. Pass, T. Hubbard, J. Hamblett, K. S. Cardwell, T. I. Jack, G. Stuart, S. Coote, J. Bradshaw, G. M. Drew, A. Hilditch, K. L. Clark, M. J. Robertson, M. K. Bayliss, M. Donnelly, E. Palmer and G. R. M. Manchee, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 589; (e) P. R. Halfpenny, D. C. Horwell, J. C. Hunter and D. C. Rees, *J. Med. Chem.*, 1990, **33**, 286; (f) W.-J. Song, X.-D. Yang, X.-H. Zeng, X.-L. Xu, G.-L. Zhang and H.-B. Zhang, *RSC Adv.*, 2012, **2**, 4612; (g) S. Butini, S. Gemma, G. Campiani, S. Franceschini, F. Trotta, M. Borriello, N. Ceres, S. Ros, S. S. Coccone, M. Bernetti, M. D. Angelis, M. Brindisi, V. Nacci, I. Fiorini, E. Novellino, A. Cagnotto, T. Mennini, K. Sandager-Nielsen, J. T. Andreasen, J. Scheel-Kruger, J. D. Mikkelsen and C. Fattorusso, *J. Med. Chem.*, 2009, **52**, 151; (h) S. A. Galal, A. S. Abd El-All, M. M. Abdallah and H. I. El Diwani, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2420; (i) S. M. Bakunova, S. A. Bakunov, T. Wenzler, T. Barszcz, K. A. Werbovetz, R. Brun, J. E. Hall and R. R. Tidwell, *J. Med. Chem.*, 2007, **50**, 5807; (j) A. E. Kozikowsky, *WO 010008*, 2006 (*Chem. Abstr.*, 2006, **144**, 164278); (k) R. E. Ziegert, K. Knepper and S. Brease, *J. Comb. Chem.*, 2005, **7**, 147; (l) J. J. Marugan, C. Manthey, B. Anaclerio, L. Lafrance, T. Lu, T. Markotan, K. A. Leonard, C. Crysler, E. Eisennagel, M. Dasgupta and B. Tomczuk, *J. Med. Chem.*, 2005, **48**, 926; (m) G. A. Gfesser, R. Faghieh, Y. L. Bennani, M. P. Curtis, T. A. Esbenshade, A. A. Hancock and M. D. Cowart, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 2559; (n) M. Wahab Khan, M. Jahangir Alam, M. A. Rashid and R. Chowdhury, *Bioorg. Med. Chem.*, 2005, **13**, 4796; (o) M. Cowart, J. K. Pratt, A. O. Stewart, Y. L. Bennani, T. A. Esbenshade and A. A. Hancock, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 689; (p) M. D. Collini, D. H. Kaufman, E. S. Manas, H. A. Harris, R. A. Henderson, Z. B. Xu, R. J. Unwalla and C. P. Miller, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 4925; (q) K. Kawasaki, M. Masabuchi, K. Morikami, S. Sogabe, T. Aoyama, H. Ebiike, S. Niizuma, M. Hayase, T. Fujii, K. Sakata, H. Shindoh, Y. Shiratori, Y. Aoki, T. Ohtsuka and N. Shimma, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 87; (r) R. Fleischer and M. Wiese, *J. Med. Chem.*, 2003, **46**, 4988; (s) L. Bettinetti, K. Schlotter, H. Hubner and P. Gmeiner, *J. Med. Chem.*, 2002, **45**, 4594; (t) J.-L. Peglion, B. Goument, N. Despau, V. Charlot, H. Giraud, C. Nisole, A. N. Tancredi, A. Dekeine, M. Bertrand, P. Genissel and M. J. Millan, *J. Med. Chem.*, 2002, **45**, 165; (u) S. Yoo, S.-H. Kim, S.-H. Lee, N.-J. Kim and D.-W. Lee, *Bioorg. Med. Chem.*, 2000, **8**, 2311; (v) T. Nagahara, Y. Yokoyama, K. Inamura, S. Katakura, S. Komoriya, H. Yamaguchi, T. Hara and M. Iwamoto, *J. Med. Chem.*, 1994, **37**, 1200; (w) M. Masubuchi, H. Ebiike, K. Kawasaki, S. Sogabe, K. Morikami, Y. Shiratori, S. Tsujii, T. Fujii, K. Sakata, M. Hayase, H. Shindo, Y. Aoki, T. Ohtsuka and N. Shimma, *Bioorg. Med. Chem.*, 2003, **11**, 4463; (x) A. Gangjee, R. Devraj, J. J. McGuire and R. L. Kisliuk, *J. Med. Chem.*, 1995, **38**, 3798.
- O. Saku, M. Saki, M. Kurokawa, K. Ikeda, T. Takizawa and N. Uesaka, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1090.
- (a) S. Rizzo, C. Riviare, L. Piazzoli, A. Bisi, S. Gobbi, M. Bartolini, V. Andrisano, F. Morroni, A. Tarozzi, J.-P. Monti and A. Rampa, *J. Med. Chem.*, 2008, **51**, 2883; (b) Z. Lu, G. R. Ott, R. Anand, R.-Q. Liu, M. B. Covington, K. Vaddi, M. Qian, R. C. Newton, D. D. Christ, J. Trzaskos and J. J.-W. Duan, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1958; (c) H. J. Ha, D. W. Kang and H. M. Kim, *J. Med. Chem.*, 2018, **61**, 396.
- (a) A. P. Kozikowski, D. Ma, L. Du, N. E. Lewin and P. M. Blumberg, *Pure Appl. Chem.*, 1994, **66**, 2087; (b) T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles*, 1988, **27**, 2225; (c) C. P. Dell, *Sci. Synth.*, 2001, **10**, 11; (d) S. Cacchi, G. Fabrizi and A. Goggiamani, *Heterocycles*, 2002, **56**, 613; (e) X.-L. Hou, Z. Yang and H. N. C. Wong, *Prog. Heterocycl. Chem.*, 2003, **15**, 167; (f) S. Schröter, C. Stock and T. Bach, *Tetrahedron*, 2005, **61**, 2245; (g) J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, New York, 2000; (h) S. Cacchi, G. Fabrizi and A. Goggiamani, *Curr. Org. Chem.*, 2006, **10**, 1423; (i) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol.*



- Chem.*, 2011, **9**, 641; (j) S. Priyadarshini, P. J. Amal Joseph, P. Srinivas, H. Maheswaran, M. Lakshmi Kantam and S. Bhargava, *Tetrahedron Lett.*, 2011, **52**, 1615; (k) C.-H. Lin, Y.-W. Wang and C.-F. Lee, *Eur. J. Org. Chem.*, 2010, **23**, 4368; (l) E. A. Jaseer, D. J. C. Prasad and G. Sekar, *Tetrahedron*, 2010, **66**, 2077; (m) J. Liu, W. Chen, Y. Ji and L. Wanga, *Adv. Synth. Catal.*, 2012, **354**, 1585; (n) A. Carrüer, D. Brinet, J.-C. Florent, P. Rousselle and E. Bertounesque, *J. Org. Chem.*, 2012, **77**, 1316; (o) B. Yin, C. Cai, G. Zeng, R. Zhang, X. Li and H. Jiang, *Org. Lett.*, 2012, **14**, 1098; (p) M. Leibelng, M. Pawliczek, D. Kratzert, D. Stalke and D. B. Werz, *Org. Lett.*, 2012, **14**, 346; (q) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Comb. Chem. High Throughput Screening*, 2012, **15**, 451; (r) C. Li, Y. Zhang, P. Li and L. Wang, *J. Org. Chem.*, 2011, **76**, 4692; (s) S. Wang, P. Li, Y. Lin and L. Wang, *Org. Lett.*, 2011, **13**, 5968; (t) Y. Luo and J. Wu, *Org. Lett.*, 2011, **13**, 5558; (u) L. Wu, X. Shi, X. Xu, F. Liang and G. Huang, *J. Chem. Sci.*, 2011, **123**, 697; (v) V. Guilarte, M. P. Castroviejo, E. Alvarez and R. Sanz, *Beilstein J. Org. Chem.*, 2011, **7**, 1255; (w) E. Rasolofonjatovo, A. Hamze, O. Provot, J. Joanna Wdzieczak-Bakala, J. Dubois, J.-D. Brion and M. Alami, *Eur. J. Org. Chem.*, 2011, 4868; (x) A. Arcadi, F. Blesi, S. Cacchi, G. Fabrizi, A. Goggiamani and F. Marinelli, *J. Org. Chem.*, 2013, **78**, 4490.
- 5 For functionalization of benzo[b]furan system via benzofuryl halides or triflates, see: (a) T. Bach and M. Bartels, *Synlett*, 2001, 1284; (b) T. Bach and M. Bartels, *Synthesis*, 2003, 925; (c) R. L. Hudkins, J. L. Diebold and F. D. Marsh, *J. Org. Chem.*, 1995, **60**, 6218; (d) T. R. Kelly, A. Szabados and Y.-J. Lee, *J. Org. Chem.*, 1997, **62**, 428; (e) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli and L. Moro, *Synlett*, 1999, 1432; (f) F. Kerrigan, C. Martin and G. H. Thomas, *Tetrahedron Lett.*, 1998, **39**, 2219; (g) A. Arcadi, F. Blesi, S. Cacchi, G. Fabrizi and A. Goggiamani, *Tetrahedron Lett.*, 2011, **52**, 5149.
- 6 For functionalization of benzo[b]furan system via benzofurylstannanes, see: (a) J. F. Einhorn, P. Demerseman and R. Royer, *Synthesis*, 1984, 978; (b) H. Nakamura, M. Aizawa, D. Takeuchi, A. Murai and O. Shimoura, *Tetrahedron Lett.*, 2000, **41**, 2185; "Palladium in Heterocyclic Chemistry 26, Second Edition: A Guide For The Synthetic Chemist (*Tetrahedron Organic Chemistry*)".
- 7 For functionalization of benzo[b]furan system via benzofurylboronic acids, see: (a) B. Joseph, B. Malapel and J.-Y. Mérou, *Synth. Commun.*, 1996, **26**, 3289; (b) A. S. Ionkin and W. J. Marshall, *Organometallics*, 2004, **23**, 3276.
- 8 For functionalization of benzo[b]furan system via benzofurylzinc compound, see: I. S. Mann, D. A. Widdowson and J. M. Clough, *Tetrahedron*, 1991, **47**, 7981; A. Seggio, A. Jutand, G. Priem and F. Mongin, *Synlett*, 2008, 2955.
- 9 For direct CH activation, see: (a) A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani and Y. Aoyagi, *Heterocycles*, 1990, **31**, 195; (b) T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn and B. DeBoef, *Org. Lett.*, 2007, **9**, 3137; (c) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2008, **47**, 1473; (d) R. Cano, J. M. Perez, D. J. Ramon and G. P. McGlacken, *Tetrahedron*, 2016, **72**, 1043.
- 10 I. A. Moussa, S. D. Banister, C. Beinat, N. Giboureau, A. J. Reynolds and M. Kassiou, *J. Med. Chem.*, 2010, **53**, 6228.
- 11 S. Cacchi, G. Fabrizi, E. Filisti, A. Goggiamani, A. Iazzetti and L. Maurone, *Org. Biomol. Chem.*, 2012, **10**, 4699.
- 12 I. Ambrogio, S. Cacchi and G. Fabrizi, *Org. Lett.*, 2006, **8**, 2083.
- 13 (a) S. Cacchi, G. Fabrizi, A. Iazzetti, C. Molinaro, R. Vediglione and A. Goggiamani, *Adv. Synth. Catal.*, 2015, **357**, 1053; (b) S. Cacchi, G. Fabrizi, A. Goggiamani, C. Molinaro and R. Vediglione, *J. Org. Chem.*, 2014, **79**, 1053; (c) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti and R. Vediglione, *Synthesis*, 2017, **49**, 4163.
- 14 (a) M. Yoshida, Y. Morishita, M. Fujita and M. Ihara, *Tetrahedron Lett.*, 2004, **45**, 1861; (b) M. Yoshida, Y. Morishita, M. Fujita and M. Ihara, *Tetrahedron*, 2005, **61**, 4381.
- 15 (a) R. Kuwano, Y. Kondo and Y. Matsuyama, *J. Am. Chem. Soc.*, 2003, **125**, 12104; (b) A. M. Johns, J. W. Tye and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 16010; (c) R. Kuwano and Y. Kondo, *Org. Lett.*, 2004, **6**, 3545; (d) R. Kuwano, Y. Kondo and T. Shirahama, *Org. Lett.*, 2005, **7**, 2973; (e) M. Yokogi and R. Kuwano, *Tetrahedron Lett.*, 2007, **48**, 6109; (f) A. Najib, K. Hirano and M. Miura, *Org. Lett.*, 2017, **19**, 2438; for review, see: (g) B. Liégault, J.-L. Renaud and C. Bruneau, *Chem. Soc. Rev.*, 2008, **37**, 290; (h) R. Kuwano, *Synthesis*, 2009, **7**, 1049; (i) J. Le Bras and J. Muzart, *Eur. J. Org. Chem.*, 2016, 2565; (j) R. Kuwano and H. Kusano, *Chem. Lett.*, 2007, **36**, 528; (k) R. Kuwano and H. Kusano, *Org. Lett.*, 2008, **10**, 1979; (l) Y. Makida, K. Usui, S. Ueno and R. Kuwano, *Chem. Lett.*, 2017, **46**, 1814.
- 16 (a) G. Primault, J.-Y. Legros and J.-C. Fiaud, *J. Organomet. Chem.*, 2003, **687**, 353; (b) J.-Y. Legros, G. I. Primault, M.-A. Toffano, M. Rivière and J.-C. Fiaud, *Org. Lett.*, 2000, **2**, 433; (c) A. Boutros, J. Y. Legros and J. C. Fiaud, *Tetrahedron Lett.*, 1999, **40**, 7329; (d) S. Tabuchi, K. Hirano and M. Miura, *Angew. Chem., Int. Ed.*, 2016, **55**, 6973.
- 17 Bite angles of DPPE and DPPF in the palladium dichloride complexes are 86° and 99°, respectively: (a) W. L. Steffen and G. J. Palenik, *Inorg. Chem.*, 1976, **15**, 2432; (b) T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, 1984, **106**, 158.
- 18 (a) I. Ahmad and W. Shagufta, *Int. J. Pharmacol. Pharm. Sci.*, 2015, **7**, 19; (b) D. C. Meadows and J. Gervay-Hague, *Med. Res. Rev.*, 2006, **26**, 793; (c) M. Butawan, L. R. Benjamin and J. R. Bloomer, *Nutrients*, 2017, **9**, 290; (d) X. Chen, S. Hussain and S. Parveen, *Curr. Med. Chem.*, 2012, **19**, 3578.
- 19 (a) N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon Press, Oxford, 1993; (b) G. Le Duc, E. Bernoud, G. Prestat, S. Cacchi, G. Fabrizi, A. Iazzetti, D. Madec and G. Poli, *Synlett*, 2011, **20**, 2943; (c) A. Shavnya, K. D. Hesp, V. Mascitti and A. C. Smith, *Angew. Chem., Int. Ed.*, 2015, **54**, 13571; (d) A. Shavnya, S. B. Coffey, A. C. Smith and V. Mascitti, *Org. Lett.*, 2013, **15**, 6226; (e) M. W. Johnson,



- S. W. Bagley, N. P. Mankad, R. G. Bergman, V. Mascitti and F. D. Toste, *Angew.Chem. Int. Ed.*, 2014, **53**, 4404; *Angew.Chem.*, 2014, **126**, 4493; (f) E. J. Emmett, B. R. Hayter and M. C. Willis, *Angew. Chem., Int. Ed.*, 2014, **53**, 10204; (g) C. S. Richards-Taylor, D. C. Blakemore and M. C. Willis, *Chem. Sci.*, 2014, **5**, 222.
- 20 (a) D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722; see also: (b) X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 6653; (c) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685; (d) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461; (e) D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 6338.
- 21 A. J. DeAngelis, P. G. Gildner, R. Chow and T. J. Colacot, *J. Org. Chem.*, 2015, **80**, 6794.
- 22 K. R. McGarry, M. McDaniel, B. C. Chan and A. R. O'Connor, *Polyhedron*, 2016, **114**, 101.
- 23 (a) S. G. Modha, V. P. Mehtazb and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 5042; (b) D. H. Ortgies, A. Hassanpour, F. Chen, S. Woo and P. Forgione, *Eur. J. Org. Chem.*, 2016, 408; (c) X. Zhou, J. Luo, J. Liu, S. Peng and D. Deng, *Org. Lett.*, 2011, **13**, 1432; (d) B. Liu, Q. Guo, Y. Cheng, J. Lan and J. You, *Chem.–Eur. J.*, 2011, **17**, 13415; (e) F. Zhao, Q. Tan, F. Xiao, S. Zhang and G. Deng, *Org. Lett.*, 2013, **15**, 1520.
- 24 For the competitive *O/S*-attack of the ambident sulfinate anion in palladium catalyzed cross coupling reactions with aryl halides see: (a) S. Cacchi, G. Fabrizi, A. Goggiamani and L. M. Parisi, *Org. Lett.*, 2002, **4**, 4719; (b) S. Cacchi, G. Fabrizi, A. Goggiamani and L. M. Parisi, *Synlett*, 2003, **3**, 361; (c) S. Cacchi, G. Fabrizi, A. Goggiamani and L. M. Parisi, *J. Org. Chem.*, 2004, **69**, 5608.
- 25 I. Ambrogio, S. Cacchi, G. Fabrizi, A. Goggiamani and A. Iazzetti, *Eur. J. Org. Chem.*, 2015, 3147.

