RSC Advances



PAPER

View Article Online
View Journal | View Issue



Cite this: RSC Adv., 2021, 11, 909

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

Antonio Arcadi, Da Giancarlo Fabrizi, Andrea Fochetti, Db Francesca Ghirga, Antonella Goggiamani, Da Antonia Iazzetti, Da Federico Marrone, Giulia Mazzoccanti Db and Andrea Serraiocco

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 $Pd_2(dba)_3/dppf$, while with sulfur, oxygen and carbo-nucleophiles $[Pd(\eta^3-C_3H_5)Cl]_2/XPhos$ is more efficient. The regiochemical outcome shows that the nucleophilic substitution occurs only on the benzylic position of the η^3 -(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.

Received 11th November 2020 Accepted 15th December 2020

DOI: 10.1039/d0ra09601f

rsc.li/rsc-advances

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, antifungal, 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 preformed 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 $\sigma 1$ receptor affinity and selectivity over the $\sigma 2$ 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

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 (Schema 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 bock 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 η^3 -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

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).

[&]quot;Dipartimento di Scienze Fisiche e Chimiche, Università degli Studi di L'Aquila, Via Vetoio, 67100 Coppito, AQ, Italy

^bDipartimento di Chimica e Tecnologie del Farmaco, Sapienza, Università di Roma, P.le A. Moro 5, 00185 Rome, Italy. E-mail: antonella.goggiamani@uniroma1.it

Center for Life Nano Science@Sapienza, Istituto Italiano di Tecnologia, Viale Regina Elena 291, 00161 Rome, Italy

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

1a. Our previous work

1b. Yoshida's work

1c. Our initial hypothesis

1d. This work

R = alk, Ph, H

NuH = N, S, O, C soft nucleophiles

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

$$X = 0$$
, NH, S

Fig. 1 Structure of the η^3 -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 bisphoshine ligands bearing an appropriate bite angle such us dppe and dppf¹⁷ and performing the reaction in MeCN at 120 $^{\circ}$ C in presence of K_2CO_3 (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 $[Pd_2(dba)_3, dppf, K_2CO_3, MeCN, 120\ ^{\circ}C]$ 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 $[Pd_2(dba)_3, dppf, K_2CO_3, MeCN, 120]$

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	$Pd_2(dba)_3/P(o-fur)_3^f$	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		HN_N-Et	20	87 (6aa)
2		HN_N_CI	16	78 (6ab)
3		HNNF 5c	24	76 (6ac)
4		Me Me Me 5d	8	88 (6ad)
5	OAc 2a	Ph HN N-Me	24	94 (6ae)
6		HN_N_F	20	91 (6af)
7		HN O	5	75 (6ag)
8		ⁿ Bu₂NH 5h	27	75 (6ah)
9		HN	24	92 (6ai)
10		Me NH	48	48 (6aj)
11	O ₂ N OAc	HN_N-Et	3	84 (6ba)
12	2b		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 $Pd_2(dba)_3$, 0.05 equiv. of dppf, 2 equiv. of 5, 2 equiv. of K_2CO_3 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 $[Pd(\eta^3-C_3H_5)Cl]_2$ as a precatalyst, previously used in sulfonvlation 15d,e and phosphonylation 15i 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(ally)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% vield 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 $[Pd(\eta^3-C_3H_5)Cl]_2/XPhos$, 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-polysubstituted 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 M_2CO_3 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 palladiumcatalyzed 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	<u></u> 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	$Pd_2(dba)_3/P(o-fur)_3$	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	$[Pd(\eta^3-C_3H_5)Cl]_2/SPhos$	THF	20	58	8
11	[Pd(η ³ -C ₃ H ₅)Cl] ₂ /SPhos	MeCN/THF	2	92^k	5
12	$[Pd(\eta^3-C_3H_5)Cl]_2/RuPhos$	MeCN/THF	3	70^k	23
13	[Pd(η³-C ₃ H ₅)Cl] ₂ /XPhos	MeCN/THF	1.5	98^k	Traces
14	[Pd(η^3 -C ₃ H ₅)(XPhos)Cl]	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 **K**₂CO₃ 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 sulfinates 7^a

$$R' + ArSO_2Na \xrightarrow{[Pd]} R' + O R' + O R'$$

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

^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 $[Pd(\eta^3-C_3H_5)]_2$, 0.05 equiv. of XPhos, 2 equiv. of 7, 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.

According to literature, $^{18a-d}$ the key intermediate of the functionalization of 2-benzofuranyl methyl acetates was suggested to be the η^3 -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

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.

Conclusions

In conclusion, we have developed a regioselective palladiumbenzylic-like nucleophilic substitution 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-2ylmethanol 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 6 Cation effect in palladium-catalyzed reaction of 2a with 9da

Entry	Base	Atomic radius (Å)	Yield ^b 10d (%)	Yield ^b 11a (%)	Yield ^b 11b (%)	10d/(11a + 11b)
1	${ m Li_2CO_3}$	0.76	_	_	_	_
2	Na_2CO_3	1.02	22	13	16	44/56
3	K_2CO_3	1.38	75	6	8	84/16
4	Rb_2CO_3	1.52	86	8	4	87/13
5	Cs_2CO_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. Yields are given for isolated products.

^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 $[Pd(\eta^3-C_3H_5)Cl]_2$, 0.05 equiv. of XPhos, 2 equiv. of 9, 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 11a and 11b were isolated respectively in 6 and 8% yield.

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

	R'-II O OAc + F	R"—EWG [Pd]	EWG F	R" -EWG
	2	12	13	
Entry	2	12	Time (h)	Yield ^b (%)
1		0—————————————————————————————————————	0.25	87 (13aa)
2		Me OEt	2	86 (13ab)
3	OAc OAc	EtO OEt	2	70 (13ac)
4		Me Me Me	1	97 (13ad)
5		EtO OEt	1	57 (13ae) °
6	O ₂ N OAC	Me Me SMe	1	98 (13bf)

 a Unless otherwise stated, reactions were carried out on a 0.4 mmol scale under an argon atmosphere at 120 $^\circ$ C using 0.025 equiv. of $[Pd(\eta^3-C_3H_5)Cl]_2$, 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) (CDCl₃): δ = 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); ¹³C NMR (100.6 MHz) (CDCl₃): δ = 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 [M + Na]⁺ calcd for C₉H₈O₂Na: 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 $\mu L, 5.170$ mmol, 1.1 equiv.) and triethylamine (350 $\mu L, 5.640$ 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 KHSO₄ (10% w/w), diluted with AcOEt and washed with a saturated NaHCO₃ solution and with brine. The

combined organic layer was dried over Na₂SO₄, 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; 1 H NMR (400.13 MHz) (CDCl₃): $\delta = 7.59$ (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) (CDCl₃): $\delta = 170.6$ (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 [M + Na]⁺ calcd for $C_{11}H_{11}O_3Na$: 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 Pd₂dba₃ (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.), K₂CO₃ (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 Et₂O, washed with a saturated NaHCO3 solution and with brine. The organic extract was dried over Na2SO4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on SiO₂ (25-40 μm), eluting with a 80/20 (v/v) n-hexane/AcOEt mixture ($R_{\rm f}=0.22$) 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) (CDCl₃): $\delta = 7.54$ (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); ¹³C NMR (100.6 MHz) (CDCl₃): $\delta = 155.1$ (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 [M + Na]⁺ calcd for C₁₅H₂₀N₂ONa: 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 $[Pd(\eta^3-C_3H_5)Cl]_2$ (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-tolylsulphinate **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

Paper

under reduced pressure. The residue was purified by chromatography on SiO_2 (25–40 µm), eluting with a 70/30 (v/v) n-hexane/AcOEt mixture ($R_{\rm f}=0.24$) 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.

Acknowledgements

Work carried out in the framework of PRIN 2017 (2017SXBSX\$) and the University "Sapienza", Rome.

Notes and references

1 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 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, Cagnotto, Т. 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; (1) 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. Faghih, 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. Despaux, 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. Ohtuska 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.

- 2 O. Saku, M. Saki, M. Kurokawa, K. Ikeda, T. Takizawa and N. Uesaka, *Bioorg. Med. Chem. Lett.*, 2010, 20, 1090.
- 3 (a) S. Rizzo, C. Riviare, L. Piazzi, 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.
- 4 (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; (1) 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. Leibeling, 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; (ν) 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. Mérour, *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. l. 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.
- (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.