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From Benzofurans to Indoles: Palladium-Catalyzed Reductive Ring-Opening and Closure *via* β -Phenoxide Elimination

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Abstract. Benzofurans can undergo ring-opening by a palladium-catalyzed process resulting in C-O bond breaking. Benzofuran-tethered 2-iodoanilines give synthetically interesting 2-(3-indolylmethyl)phenols in an overall reductive process. Mechanistic studies suggest that this unusual reaction proceeds by carbopalladation of benzofuran giving a 3-palladated 2,3-dihydrobenzofuran intermediate, which then fragments by an uncommon *trans*-elimination of the phenoxide group β to the metal.

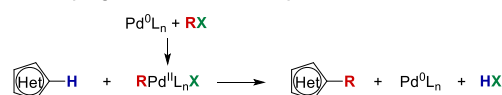
In this transformation, *N,N*-diisopropylethylamine acts as a base and as a reducing agent: it regenerates palladium(0) from palladium(II), thus allowing catalytic turnover.

Keywords: Heck reaction; palladium; benzofuran; ring opening; indole

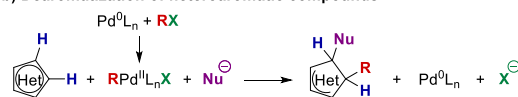
Introduction

In the realm of catalytic reactions involving organopalladium (II) species, unfunctionalized heteroaromatic compounds can have an ambivalent reactivity (Scheme 1), as they are potential substrates for both (a) C-H activation and formation of a new C-C bond with preservation of the aromatic character, *i.e.* direct coupling reactions;^[1] and (b) dearomatization via Heck-type carbopalladation.^[2]

a) Direct coupling of heteroaromatic compounds



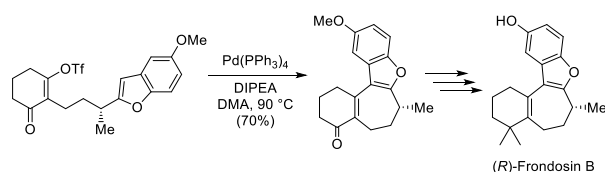
b) Dearomatization of heteroaromatic compounds



Scheme 1. Possible reactions of heteroarenes with organopalladium(II) species.

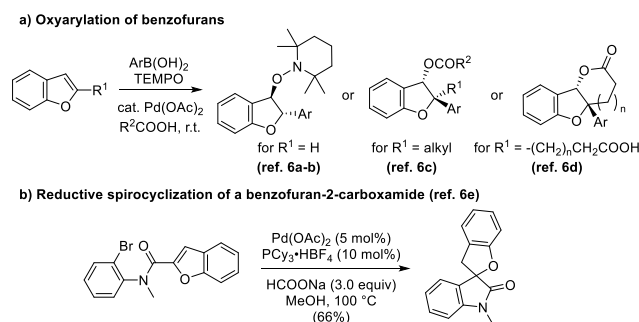
In this context, benzofurans have been shown to be suitable substrates for direct arylation reactions^[3] and an intramolecular ring closure of a vinyl

trifluoromethanesulfonate with a tethered benzofuran was applied by Trauner in the total synthesis of (*R*)-Fronodosin B (Scheme 2).^[4,5]



Scheme 2. Palladium-catalyzed C-H vinylation of a benzofuran as a key step in Trauner's total synthesis of (*R*)-Fronodosin B.^[4]

Some examples of palladium-catalyzed dearomative reactions involving benzofurans have also been reported.^[6] Studer and co-workers described a family of related palladium-catalyzed oxidative oxyarylations of benzofurans with arylboronic acids using TEMPO as a stoichiometric oxidant (Scheme 3, a)^[6a-d] and very recently Jia and co-workers^[6e] reported a single example of the cyclization of a benzofuran-2-carboxamide leading to a spiro-oxindole derivative (Scheme 3, b).^[7,8] In the latter example, sodium formate acts as a hydride donor in this overall reductive Heck-type reaction.



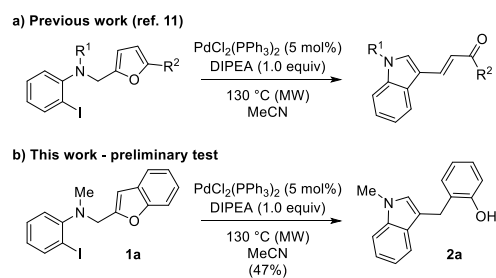
Scheme 3. Previous works on palladium-catalyzed dearomatizations of benzofurans.^[6]

Having a Dewar resonance energy (DRE) of 20.3 kcal mol⁻¹, benzofuran is considered less aromatic than indole (DRE = 23.8 kcal mol⁻¹).^[9] It is thus surprising that comparatively few examples of dearomative Heck reactions involving benzofurans have been described so far, taking into account that this chemistry is well developed for indoles.^[10] We report here a palladium-catalyzed reductive intramolecular Heck reaction of benzofurans which is terminated by an unusual fragmentation proceeding through β -aryloxy elimination. Suitably benzofuran-tethered 2-iodoanilines gave synthetically interesting 2-(3-indolylmethyl)phenols by double bond isomerization of the 3-alkylideneindolines formed as intermediates. To the best of our knowledge, this is the first example of fragmentation of the benzofuran nucleus under palladium catalysis.

Results and Discussion

Reaction Discovery and Optimization

A few years ago, we reported that furans bearing tethered *o*-iodoanilines undergo a PdCl₂(PPh₃)₂-catalyzed ring cleavage reaction leading to indoles featuring a pendant α,β -unsaturated carbonyl moiety when heated in MeCN in the presence of DIPEA (*N,N*-diisopropylethylamine) at 130 °C under microwave irradiation (Scheme 4, a).^[11] When we applied the same reaction conditions to the analogous benzofuran-containing substrate **1a**, we were pleased to isolate indole derivative **2a** in 47% yield (Scheme 4, b). Simple electron counting attests that this transformation is a reductive process (formally **1a** + H⁺ + 2e⁻ → **2a** + I⁻). The reactant **1a** is more oxidized than product **2a**, while our previously described fragmentation of furans was a redox-neutral transformation.^[11] Moreover, no cyclization product deriving from the direct arylation of benzofuran by activation of the C3-H bond could be identified in the reaction mixture, even though our experimental conditions were close to those used by Trauner to effect an intramolecular direct arylation (Scheme 2).^[4]

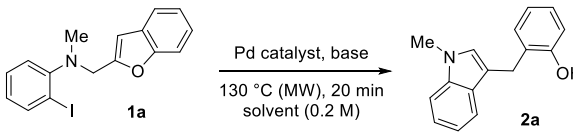


Scheme 4. Previously reported conditions for the palladium-catalyzed ring opening of furans and application to a benzofuran-containing substrate.

Building on this unexpected result, we first focused on finding optimal conditions for this transformation (Table 1, see Table S1 in the Supporting Information for an extended account). Increasing the amount of DIPEA from 1.0 to 2.0 equiv and substituting MeCN with EtCN as the solvent had a beneficial effect on yields, while other solvents (DMF, dioxane) proved less effective (entries 1 to 5). Tertiary (DIPEA, Et₃N) or secondary amines (*i*-Pr₂NH) are suitable bases (entries 3, 6 and 7), but the hindered base 2,2,6,6-tetramethylpiperidine and CsOAc gave almost no catalytic turnover (entries 8 and 9). Some palladium precatalysts different from PdCl₂(PPh₃)₂ were also tested. Phosphine-free PdCl₂(NCPh)₂ was completely unsuitable and palladium black was formed quickly upon heating along with no conversion of **1a**. Electron-rich alkyl phosphines (PCy₃ and *Pt*-Bu₃) and electron-poor P(4-CF₃-C₆H₄)₃ gave disappointing results (entries 11, 12 and 14). The combination of electron-rich P(4-MeO-C₆H₄)₃ with PdCl₂(NCPh)₂ and Pd(PPh₃)₄ were as efficient as the initially selected precatalyst (entries 13 and 15), but for practical

reasons we adopted PdCl₂(PPh₃)₂ instead of the more expensive substituted phosphine or the air-sensitive Pd(0) complex.

Table 1. Reaction optimization.



	Catalyst (mol%)	Base (equiv)	Solvent (wet) ^{a)}	Yield of 2a (%) ^{b)}
1	PdCl ₂ (PPh ₃) ₂ (5)	DIPEA (1.0)	MeCN	51 (47) ^{c)}
2	PdCl ₂ (PPh ₃) ₂ (5)	DIPEA (2.0)	MeCN	57
3	PdCl₂(PPh₃)₂ (5)	DIPEA (2.0)	EtCN	67^{d)} (65)^{e)}
4	PdCl ₂ (PPh ₃) ₂ (5)	DIPEA (2.0)	DMF	50
5	PdCl ₂ (PPh ₃) ₂ (5)	DIPEA (2.0)	1,4-dioxane	27
6	PdCl ₂ (PPh ₃) ₂ (5)	Et ₃ N (2.0)	EtCN	62
7	PdCl ₂ (PPh ₃) ₂ (5)	(<i>i</i> -Pr) ₂ NH (2.0)	EtCN	48
8	PdCl ₂ (PPh ₃) ₂ (5)	TMP ^{o)} (2.0)	EtCN	8
9	PdCl ₂ (PPh ₃) ₂ (5)	CsOAc (2.0)	EtCN	5
10	PdCl ₂ (NCPPh) ₂ (5)	DIPEA (2.0)	EtCN	0
11	PdCl ₂ (PCy ₃) ₂ (5)	DIPEA (2.0)	EtCN	25
12	Pd(dba) ₂ (5)	DIPEA (2.0)	EtCN	11
13	PdCl ₂ (NCPPh) ₂ (5)	DIPEA (2.0)	EtCN	68
14	PdCl ₂ (NCPPh) ₂ (5)	DIPEA (2.0)	EtCN	16
15	Pd(PPh ₃) ₄ (5)	DIPEA (2.0)	EtCN	67

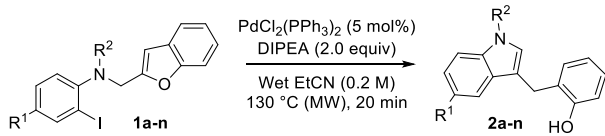
^{a)} All solvents were *not* dried, no precautions were taken to exclude air and moisture. The use of thoroughly dried MeCN or EtCN lead to reproducibility issues and once an explosion of the reaction vessel occurred due to deposition of a Pd mirror and excessive MW heating. Solvents were thus deliberately moistened with 1% of water. The role of water in the formation of Pd(0) from Pd(II) precursors has been elucidated.^[12] ^{b)} Determined by GLC with octadecane as an internal standard, unless otherwise stated. Reactions performed on 0.1 mmol scale. ^{c)} Isolated yield. ^{d)} Average of four determinations, standard deviation: 0.5. ^{e)} 2,2,6,6-Tetramethylpiperidine.

The most efficient and practical protocol was thus based on the use of PdCl₂(PPh₃)₂ in combination with DIPEA in wet EtCN at 130 °C under microwave irradiation. Lowering the temperature resulted in poorer yields (See the Supporting Information, Table S1). The optimized conditions were applied to a set of benzofuran-tethered 2-iodoanilines (Table 2).

Several different alkyl substituents on nitrogen were tolerated (Table 2), but the reaction was not efficient for the *N*-acetyl substrate **1o** and for *N*-unsubstituted **1n**. This transformation was also compatible with esters (entry 9), unprotected alcohols (entry 10) and *tert*-butyldimethylsilyl ethers (entries 8 and 11). Both electron-releasing (entries 6-11, 13) and electron-withdrawing groups (entries 2, 5) could be present on the iodoarene moiety of the substrate without significantly affecting the results. However, the nitro-substituted substrate **1l** gave a modest yield (entry 12).

Our procedure, thus, gives access to indoles decorated with diverse substituents on the carbocyclic ring. The 2-(3-indolylmethyl)phenol structural motif so formed is present in some active pharmaceutical ingredients and it is a useful intermediate for further transformations.^[13]

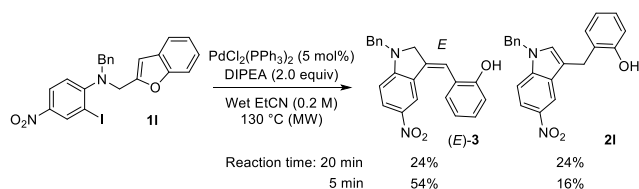
Table 2. Scope of the palladium-catalyzed benzofuran ring-opening indole ring-closure reaction.



	Subs. t.	Prod.	R ¹	R ²	Yield (%) ^{a)}
1	1a	2a	H	Me	65
2	1b	2b	F	Me	64
3	1c	2c	H	Bn	71
4	1d	2d	H	<i>n</i> -Octyl	68
5	1e	2e	F	PMB	76
6	1f	2f	OMe	(2-Naphthyl)CH ₂ -	54
7	1g	2g	OMe	Bn	58
8	1h	2h	Me	TBDMSO-(CH ₂) ₆ -	55
9	1i	2i	Me	BzO-(CH ₂) ₆ -	62
10	1j	2j	Me	HO-(CH ₂) ₆ -	48
11	1k	2k	Me	TBDMSO-(CH ₂) ₄ -	55
12	1l	2l	NO ₂	Bn	24
13	1m	2m	NH(BOC)	Bn	50
14	1n	2n	H	Ac	trace ^{b)}
15	1o	2o	H	H	0

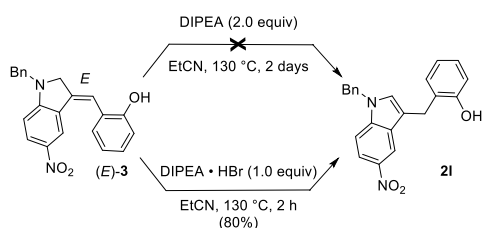
^{a)} Isolated yields. ^{b)} Determined by NMR analysis of the crude reaction mixture.

With the aim of finding the reason why **2l** was obtained in such a modest yield, we analyzed more in detail the crude reaction mixture resulting from the application of the optimized conditions to **1l**. Besides **2l**, the isomeric product **3** could be isolated by careful separation by flash chromatography (Scheme 5). Shortening the reaction time from 20 minutes to only 5 minutes allowed isolating pure **3** in 54% yield together with a small amount of **2l**. Interestingly, in every case **3** was obtained as a pure stereoisomer, the configuration being established to be *E* by NOE experiments and by the analysis of ³J_{CH} (see the Supporting Information for detailed NMR analyses). It is worth noting that the *E* isomer was not expected to be the thermodynamically most stable one, as elementary considerations and theoretical calculations^[14] point out. No isomerization from (*E*)-**3** to (*Z*)-**3** should thus be possible in the conditions of the reaction and the formation of (*E*)-**3** is under kinetic control.



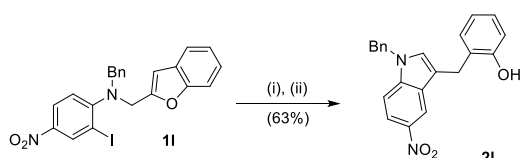
Scheme 5. Isomeric products arising from the benzofuran ring-opening reaction of **11**. Isolated yields are reported.

We speculated that (*E*)-**3** is an intermediate that is converted into indole **21** by double bond migration. Taking into account the K_2CO_3 -mediated isomerization of related compounds reported by Kim and co-workers,^[15] we first guessed that DIPEA might be an effective catalyst for this base-promoted process at the temperature at which the reaction is performed. A straightforward test demonstrated that this is not the case (Scheme 6), but heating in the presence of the ammonium salt DIPEA·HBr effected the conversion of (*E*)-**3** to **21** in 80% yield, as determined by 1H NMR analysis (Scheme 6). Considering that HI is formally produced during the catalytic reaction, we concluded that most likely the isomerization takes place under acid catalysis in the reaction medium.



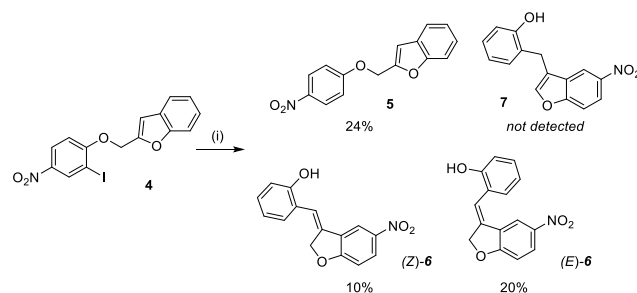
Scheme 6. Conditions for the isomerization of (*E*)-**3** into **21**. NMR yield reported.

With this information in hand, we devised an efficient protocol for the synthesis of **21**. After applying our optimized conditions to **11**, DIPEA·HBr (1.0 equiv) was added to the crude reaction mixture and heating was continued. The desired product **21** was finally isolated in 63% yield (Scheme 7), this time in line with the results obtained for the other examples listed in Table 2.



Scheme 7. Improved one-pot protocol for the synthesis of **21**. Conditions: (i) $PdCl_2(PPh_3)_2$ (5 mol%), DIPEA (2.0 equiv), wet EtCN, 130 °C, 20 min; (ii) DIPEA·HBr (1.0 equiv), 130 °C, overnight.

Aiming to verify whether it is essential to have a nitrogen atom in the side chain of the benzofuran, substrate **4** was synthesized and tested under the optimized conditions (Scheme 8). After work-up, three main isomeric products could be identified by NMR spectroscopy and mass spectrometry analyses of partially purified samples, namely the dehalogenated compound **5** and alkenes (*Z*)-**6** and (*E*)-**6**. Remarkably, benzofuran **7** could not be detected in any useful amount. We speculate that cyclization is hampered for conformational reasons in the case of this ether substrate, so the reduction forming **5** – which we did not observe in significant amount for substrates **1a-m** – is competitive in this case. Most likely (*E*)-**6**, which is expected to be the less thermodynamically stable stereoisomer^[14] is formed first, in analogy to what observed for the reaction of substrate **11**, and then isomerizes to (*Z*)-**6**.



Scheme 8. Attempted Pd-catalyzed ring-opening reaction of ether substrate **4**. Conditions: (i) $PdCl_2(PPh_3)_2$ (5 mol%), DIPEA (2.0 equiv), wet EtCN, 130 °C, 1 h; NMR yields reported.

Increasing the tether length as in substrate **9** resulted in reductive deiodination, as observed for the *N*-unsubstituted substrate **10** (Figure 1). These results highlight that a tertiary amine tether of appropriate length is crucial for the dearomatization to take place efficiently.

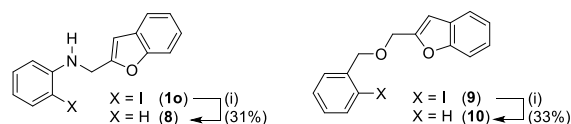
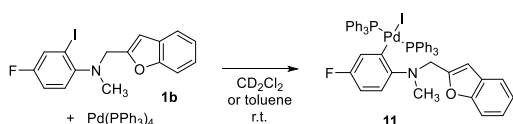


Figure 1. Reductive deiodination of compounds **10** and **9** under the standard conditions: (i) $PdCl_2(PPh_3)_2$ (5 mol%), DIPEA (2.0 equiv), wet EtCN, 130 °C, 20 min; isolated yields reported.

Mechanistic Insights

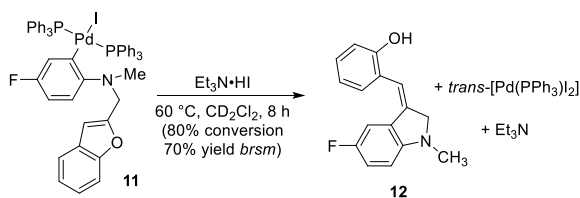
To gain insight into the mechanism of the transformation under study, we first considered the oxidative addition of compound **1b** to $Pd(PPh_3)_4$ as a source of Pd(0). The fluorine-tagged **1b** was chosen to follow the reaction also by ^{19}F NMR.

A solution of Pd(PPh₃)₄ (20 mM in CD₂Cl₂)^[16] was treated with **1b** (2.0 equiv). After about 1 h at room temperature and heating at 50 °C for a few minutes, the *trans*-[ArPd^{II}(PPh₃)₂I] complex **11** was formed in almost quantitative yield, as attested by multinuclear NMR analysis (Scheme 9). The organometallic nature of this complex was confirmed by the strongly shielded aromatic resonances in the ¹H spectrum due to the ring directly attached to the metal (see the Supporting Information, Figure S1) and by the shielding of the ¹⁹F NMR resonance ($\delta = -123.8$ ppm, to be compared with $\delta = -118.3$ for **1b**). Only one singlet ($\delta = 21.85$ ppm) was present in the ³¹P NMR spectrum of this complex, compatibly with the *trans* geometry. The reaction observed is analogous to that of simple iodoarenes.^[17] Complex **11** was not stable and it decomposed slowly on standing at room temperature. It was nonetheless possible to isolate it in the solid state – albeit only in 19% yield – by switching to toluene as solvent and by performing the crystallization at low temperature (–20 °C).



Scheme 9. Reaction of compound **1b** with Pd(PPh₃)₄.

To study its reactivity, complex **11** was generated *in situ* from Pd(PPh₃)₄ (40 mM in CD₂Cl₂) and **1b** (1.5 equiv). Et₃N·HI was then added (2.5 equiv) as a mild source of HI,^[18] and the resulting mixture was heated at 60 °C for 8 h. After cooling, a precipitate of *trans*-[Pd(PPh₃)₂I₂]·(CD₂Cl₂) in the form of orange-red needles was produced.^[19] Analysis of the supernatant revealed that 80% of **11** had been converted to a mixture of products, the major being compound **12** (Scheme 10), which was obtained in 70% yield (based on converted **11**), as assessed by ¹⁹F NMR spectroscopy. No trace of indole **2b** could be identified by NMR analysis (¹H and ¹⁹F) of the *crude* reaction mixture.^[20]

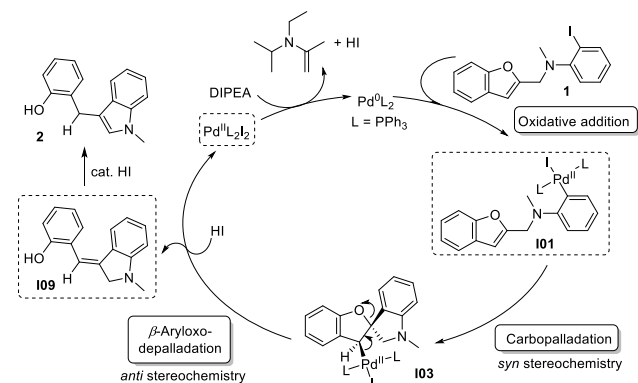


Scheme 10. Thermal decomposition of complex **11** in the presence of Et₃N·HI.

Based on the data collected, the catalytic cycle illustrated in Scheme 11 can be put forward. Intermediates that have been isolated or characterized spectroscopically are shown in dashed rectangles. The

first step is the oxidative addition of the iodoarene substrate to Pd(0). The resulting arylpalladium(II) complex **101** evolves through a carbopalladation of the C=C double bond of benzofuran, giving the *spiro* organopalladium intermediate **103**. As it usually happens,^[21] this reaction should proceed in a *syn* fashion. *Anti* β-phenoxypalladation would deliver the indole having the exocyclic double bond with the observed *E* stereochemistry (**109**).

This step can be thought as the reverse of the key step of the Wacker-Hoechst process, *i.e.* the addition of an oxygen nucleophile to a Pd(II)-alkene complex. The latter reaction would deliver a Pd(II) species, that needs to be reduced back to Pd(0) to allow catalytic turnover. We propose that DIPEA can act as a reducing agent, being in turn oxidized to the corresponding iminium ion. It has already been demonstrated that DIPEA can fulfill this role.^[22] Moreover, other amines having α hydrogens can replace DIPEA (Et₃N, *i*Pr₂NH, Table 1, entries 6-7), while 2,2,6,6-tetramethylpiperidine – having no α hydrogens – and CsOAc gave almost no catalytic turnover (Table 1, entries 8-9). The final step of this catalytic process is the acid-catalyzed isomerization of the exocyclic double bond of intermediate **109** (cf. Scheme 6), which re-establishes aromaticity and delivers the indole **2**, *i.e.* the end product of the reaction.^[23]



Scheme 11. Proposed catalytic cycle.

To get a better understanding of these experimental results, we resorted to a theoretical study of the reaction at the DFT level. Compound **1a** and trimethylamine (TMA) were selected as model substrates and PH₃ as a model ligand. The reaction proceeds in five key steps: i) formation of a spiro adduct **103** (Figure 2), ii) ring-opening of the benzofuran, iii) elimination of the 3-vinylidene indoline (**109**, Figure 2), iv) isomerization of the exocyclic double bond of the 3-alkylidene indoline **109** into indole and v) catalyst regeneration. The Gibbs free energy profile for the first three steps is shown in Figure 2, while the alkene isomerization and the catalyst regeneration are shown in Figure S5 and S6 in the Supporting Information.

The first step corresponds to the oxidative addition of the Pd⁰L₂ catalyst in the carbon-iodine bond to form complex **I01** (Figure 2). A rotation along a C-N bond occurs along with the loss of one ligand to adopt the reactive conformation **I02**. Spiro compound **I03** is thus formed through a migratory insertion. The free energy barrier of the latter is only 8.4 kcal mol⁻¹. The spiro compound can further evolve directly through the **TS34'** transition state with a barrier of 10.8 kcal mol⁻¹ (Figure 2, blue dashed line). Interestingly, this path leads to **I04'**, whose Lewis structure corresponds to a methylene quinone rather than a phenolate. (See

Supporting Information, Figure S4)^{8]b}: The complexation of **I04'** with the amine base leads to phenolate **I05**. Alternatively, the spiro ring-opening could occur through activation by an ammonium ion that engages in hydrogen-bonding with the oxygen atom (Figure 2, solid black lines). Although this path is not favored with the chosen model amine, it could be competitive when using other bases. The spiro ring-opening with the participation of a water molecule is not favored either (see the Supporting Information, Figure S8).

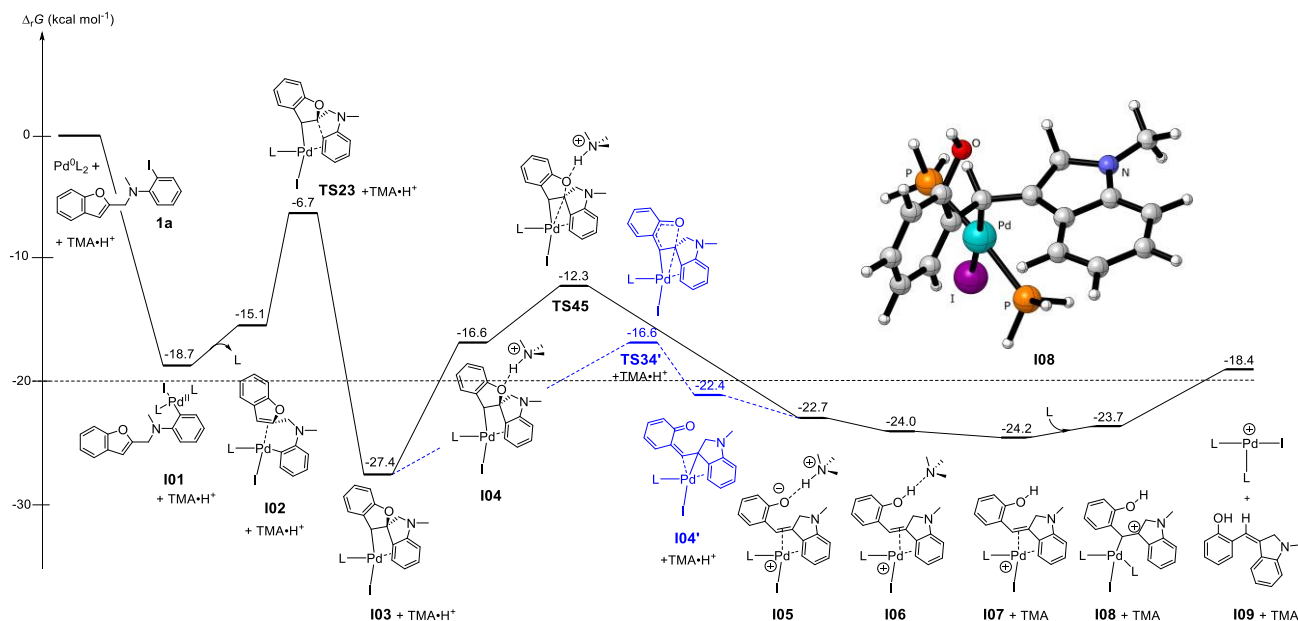


Figure 2. Free energy profile (kcal mol⁻¹) for the benzofuran opening and release of the 3-alkylidene indoline **I09** intermediate. The direct opening is shown in blue with dashed lines while the acid assisted path is shown in solid black lines. Structure of complex **I08** is shown as an inset to illustrate the pre-organisation of the CC bond towards the *E* alkene **I09**.

The next step consists in the protonation of phenolate **I05** by the ammonium (**I06**), generating **I07** and the free amine. The binding of a second phosphine to the palladium center (**I08**) followed by the dissociation of the alkene affords the cationic [Pd^{III}L₂I]⁺ complex and the (*E*)-3-alkylidene indoline **I09**. The final alkene isomerization leading to indole **2a** proceeds smoothly ($\Delta_rG = 4.5$ kcal mol⁻¹, See the Supporting Information, Figure S5) and it is exergonic by 16.3 kcal mol⁻¹. The regeneration of the Pd⁰L₂ active catalyst is achieved by oxidation of the amine into an iminium ion (see the Supporting Information, Figure S6). The full catalytic cycle thus corresponds to a reaction free energy of 57.2 kcal mol⁻¹ with the highest free energy barrier of only 17.5 kcal mol⁻¹, compatibly with the good isolated yields.

We then considered the reaction with oxygen analogue **4**, focusing solely on formation of the spiro compound and the isomerization of the 3-alkylidene dihydrobenzofuran (**6**) towards the expected benzofuran product (**7**). The first step requires a barrier of 11.4 kcal mol⁻¹, higher than the 8.4 kcal/mol one observed for **1a** (see Figure S7 in Supporting

Information). The spirocycle forming carbometallation for **4** is thus 45 times slower than that corresponding **1a** at the temperature of the reaction (130 °C). An analogous picture is also obtained for the *N*-unsubstituted substrate **1o** (See the Supporting Information, Figure S5). The higher reactivity of **1a** could also be attributed to the pre-organization induced by the *N*-Me group via a Thorpe-Ingold-type effect. Concerning the end product-forming step, the acid-catalyzed isomerization of the exocyclic double bond leading to benzofuran **7** is exergonic by only 6.6 kcal mol⁻¹, but it requires the formation of highly unstable cations at 27.5 kcal mol⁻¹ (See Supporting Information, Figure S5). These calculations provide a plausible explanation why benzofuran **7** could not be formed from **4** under the standard conditions and why **1o** does not display the same reactivity as its *N*-substituted derivatives.

Conclusion

To conclude, a novel Pd-catalyzed ring-opening of benzofuran derivatives was disclosed to afford a straightforward access to the 2-(3-indolylmethyl)phenol scaffold, which is a structural motif of biological interest. To the best of our knowledge, this reaction constitutes the first example of a metal-catalyzed ring-opening of these heterocyclic scaffolds. A study combining both experimental results and theoretical calculations has been carried out to understand in detail the mechanism of this unusual transformation. Two key points are to be highlighted: 1) amine bases such as DIPEA act as reducing agents in this process; 2) cleavage of the benzofuran ring takes place by a *syn* Heck-type carbopalladation of the heteroaromatic ring giving a spirocyclic 3-palladated 2,3-dihydrobenzofuran intermediate, followed by *anti* β -phenoxydepalladation, which is an uncommon process in palladium chemistry. Interestingly, direct arylation of the benzofuran nucleus through C-H activation does not take place under the reported reaction conditions.

Experimental Section

General procedure for the Pd-catalyzed ring-opening of *N*-(2-benzofurylmethyl)-2-iodoanilines – Synthesis of 2-(3-indolylmethyl)phenols

A microwave tube of suitable volume (capable of withstanding pressure up to 20 bar) equipped with a magnetic stirring bar was charged with the appropriate substrate dissolved in EtCN (5.0 mL per mmol of substrate) and water (50 μ L per mmol of substrate), then *N,N*-diisopropylethylamine (DIPEA, Hünig's base, 2.0 equiv) and PdCl₂(PPh₃)₂ (0.05 equiv) were introduced. No special precautions were adopted to exclude air. The tube was hermetically sealed and heated at 130 °C in a microwave apparatus.

After stirring for 20 minutes at the prescribed temperature, the tube was cooled to room temperature, opened and the mixture was diluted with CH₂Cl₂ (10 mL per mmol of substrate) and water (10 mL per mmol of substrate). Phases were separated, and the aqueous layer was extracted with more CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried over MgSO₄ and evaporated at reduced pressure. The residue was purified by flash chromatography on silica gel.

2-((1-Methyl-1*H*-indol-3-yl)methyl)phenol (2a)

The reaction of **1a** (179 mg, 0.493 mmol) according to the general procedure (flash chromatography eluent: toluene) gave the title compound in the form of a pale yellow oil (76.5 mg, 65%).

¹H NMR (300 MHz, CDCl₃): δ = 7.53 (d, *J* = 7.9 Hz, 1H), 7.33–7.04 (m, 5H), 6.89 (td, *J* = 7.4, 1.3 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.78 (br s, 1H), 4.99 (br s, 1H), 4.10 (s, 2H), 3.71 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 154.5, 137.6, 130.7, 128.0, 127.7, 127.2, 126.6, 122.2, 121.0, 119.4, 119.3, 116.2, 111.8, 109.5, 32.8, 27.1 ppm. HRMS (EI) *m/z*: [M]⁺ Calcd for C₁₆H₁₅NO 237.1154; Found 237.1151. Spectral data are in agreement with the literature.^[13c]

Computational Details

All calculations were done with the Gaussian09 package.^[24] Following previous works on similar reactions, the BP86 functional^[25] was chosen.^[26] The 6-311++G(2d,p) basis set was selected for C, N, O, and H atoms. The LANL2TZ(f) basis set was used for the Pd atom^[27] and the LANL08(d) basis set for P and I atoms with associated effective core potentials,^[28] as obtained from the EMSL Basis Set Exchange website.^[29] Geometry optimizations were conducted using the default convergence criteria followed by frequency calculations to ensure the nature of the stationary points. A single imaginary frequency was obtained for each transition state structure. Solvent effects were taken into account by using a polarizable continuum model (IEF-PCM)^[30] as implemented in Gaussian09 for acetonitrile. Transition state structures have been drawn with CYLview.^[31]

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From Benzofurans to Indoles: Palladium-catalyzed Reductive Ring-Opening and Closure *via* β -Phenoxide Elimination

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