

Note

# Electrosynthesis of heteroaromatic aldehydes by palladium-catalyzed carbonylation of heteroaromatic iodides in the presence of formic acid

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## Abstract

The palladium-catalyzed electrocarbonylation of heteroaromatic iodides, performed in the presence of formic acid under one atmosphere of carbon monoxide, affords heteroaromatic aldehydes in moderate to good yields. It has been developed a new application of palladium-catalyzed formylation using carbon monoxide, formic acid and tertiary amines as ligands under electrochemical reducing conditions.

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## 1. Introduction

Aromatic heterocycles like furan, thiophene and pyridine, are important starting materials for syntheses of various biologically and physiologically active compounds [1]. Therefore, the functionalization of these compounds, widely used in pharmaceutical and fine chemistry, is an important goal in organic chemistry. Among these functionalizations, the reaction of formylation leads to important synthons in organic synthesis. This formylation can be achieved using carbon monoxide and palladium catalyst [2]. Palladium complexes have been used in the carbonylation reactions of aryl halides and 2-iodothiophene, with carbon monoxide in high yields, using high temperature and Pd(0) and Pd(II) complexes as catalyst [3], while moderate yields are reported using bimetallic Pd–Ru catalyst and high pressure of CO/H<sub>2</sub> mixture [4].

In this paper we report the electrocarbonylation of heteroaromatic iodides using a palladium complex as catalyst,

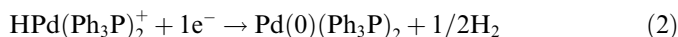
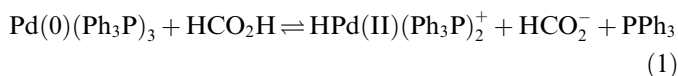
tertiary amines as ligands, formic acid as hydrogen source and CO (1 atm). This way, the reaction offers two advantages; the first is proceeding under atmospheric pressure of carbon monoxide, whereas the formylation using H<sub>2</sub> as hydrogen source generally requires high pressures of carbon monoxide [5], the second is working without phosphines as ligands. Phosphine ligands are generally present in palladium complexes and they give excellent results in many reactions. However, phosphine ligands are sensitive to air, which limits their synthetic applications significantly. Therefore, the development of phosphine-free palladium catalysts would be significant [6].

The initial concept was based upon an electrochemical reduction of acylpalladium intermediates generated in situ from aryl halides, palladium and carbon monoxide, followed by the protonation of the resultant anionic species; when *n*-Bu<sub>4</sub>NHSO<sub>4</sub> and HClO<sub>4</sub> were used as proton sources, aromatic aldehydes were obtained in low yields [7]. Apparently, the reduction of the arylpalladium complex, formed via initial oxidative insertion of palladium(0) into the carbon–halogen bond, is faster than its reaction with CO to afford the corresponding acylpalladium complex.

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A dramatic change in the mechanism occurred by switching to formic acid. As a matter of fact, the synthesis of aryl aldehydes from aryl halides, CO and formic acid is formally an hydride transfer from  $\text{HCOO}^-$ . Formate ions cannot be supplied directly from formic acid; in fact, the dissociation constant of formic acid in DMF is too low to allow it to be the direct source of formate ions [8]. Moreover, formic acid cannot be the direct source of formate ions by electrochemical reduction of its protons. Indeed, the electrolyses were carried out at a potential of  $-1.2$  V vs. SCE, whereas the electrochemical reduction of formic acid under the same conditions, in the absence of palladium, occurred at  $-2.0$  V vs. SCE. It is apparent that under our electrolytic conditions, palladium must play a second crucial role in supplying the reaction medium with formate ions. In fact, the reaction between  $\text{Pd}(0)(\text{Ph}_3\text{P})_3$  (that derives from a dissociation equilibrium of  $\text{Pd}(0)(\text{PPh}_3)_4$ ) and formic acid – presumably via the low ligated complex  $\text{Pd}(0)(\text{Ph}_3\text{P})_2$  – affords a formate anion and the cationic palladium(II) hydride (Eq. (1)).



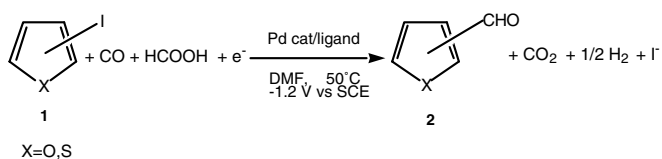
On the basis of its reduction potential ( $-0.84$  V vs. SCE),  $\text{HPd}(\text{Ph}_3\text{P})_2^+$  is reducible under our electrolytic conditions (Eq. (2)). Consequently, the equilibrium sketched in Eq. (1) is continuously displaced to its right-hand side, generating a small but constant flux of formate ions. The result is that formate ions are generated at an adequate rate via a combination of chemical and electrochemical steps, at a potential where the direct reduction of formic acid to formate and  $\text{H}_2$  cannot occur [8]. When the electrochemical reduction of aryl halides was carried out under 1 atm of CO, in the presence of catalytic amount of  $\text{PdCl}_2(\text{PPh}_3)_2$  and formic acid, aromatic aldehydes were isolated in high yields [9].

On the basis of these results, we report a  $\text{Pd}(\text{OAc})_2$  and amine catalytic system for formylation of some aromatic heterocycles like iodofuran, iodothiophene and iodopyridine, in order to test the effectiveness of this electrochemical method.

## 2. Results and discussion

Thiophene was used as a model compound to study solvents and ligands influence on the reaction. The process is outlined in the following reaction (Scheme 1).

The following general procedure was used: in a cell with three separated compartments [10], kept at  $50.0 \pm 0.1$  °C,



Scheme 1.

the electrolysis was carried out on a solution of 2-iodothiophene (0.50 mmol), in  $30 \text{ dm}^3$  of solvent containing  $n\text{-Bu}_4\text{NBF}_4$  (TBAF,  $0.20 \text{ mol dm}^{-3}$ ) as supporting electrolyte, in the presence of  $\text{Pd}(\text{OAc})_2$  (0.05 mmol), formic acid (1.50 mmol) and a tertiary amine (0.10 mmol), under 1 atmosphere of carbon monoxide at  $-1.2$  V vs. SCE. A graphite electrode, of apparent area  $3 \text{ cm}^2$ , was used as working electrode. The counter-electrode was a Pt wire and the reference was a saturated calomel electrode (SCE). At first, we have applied to 2-iodothiophene the same reaction conditions used with arylhalides, i.e., DMF/0.2 M TBAF as solvent,  $\text{Pd}(\text{OAc})_2$  as catalyst, CO and HCOOH (Table 1, entry 1). Unlike aryl iodides, 2-iodothiophene gave poor yields in aldehyde (25%), so we tried to vary some parameters in order to increase the yields. Many solvents were used, with no or little increments in the yield of thiophene-2-carbaldehyde (Table 1, entries 1–5), so we screened several amines with different sterical bulk as ligands. The catalytic activity increases with increasing bulk around the nitrogen atom (even if the results suggest other factors may be involved in the activity of these amines; in fact, it cannot be excluded an action as a base). For example, 4-dimethylaminopyridine (DMAP), *N,N*-diisopropylethylamine (DIPEA) and 1,8-diazabicyclo-[5,4,0]-undec-7-ene (DBU) showed no activity in the reaction (Table 1, entries 6–8), while the bulkier 1,4-diazabicyclo-[2,2,2]-octane (DABCO) gave the best result. A synergistic effect of DABCO as ligand and DMF (in which  $\text{HCOO}^-$  is highly soluble) as solvent results in 81% yield of aldehyde for 2-iodothiophene (Table 1, entry 9). The position of the iodine atom on the molecule of thiophene seems not to be important; in fact, starting from 3-iodothiophene, the corresponding aldehyde was obtained in 82% yield (Table 1, entry 10).

The reactivity of 5-butyl-2-iodofuran is slightly lower than iodothiophenes. When this reaction was carried out on this oxygenated compound, the results confirmed the hypothesis that DMF/DABCO system gives the best result, with 72% yield (Table 1 entries 11–13).

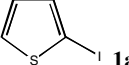
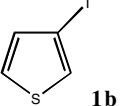
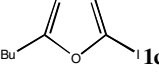
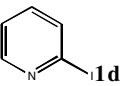
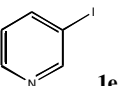
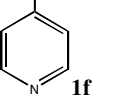
Because of their  $\pi$ -electron deficient nature, halopyridines normally react slowly to the insertion of carbon monoxide into arylpalladium(II) complexes (formed by initial oxidative insertion of palladium(0) into the carbon–halogen bond) [9]. Generally, high pressures of carbon monoxide are required to suppress side-reactions. In fact, not significant yields are obtained for this class of heterocycles. However, using our conditions, under atmospheric pressure of carbon monoxide we obtained moderate yield of 3-pyridinecarbaldehyde (35%, Table 1, entry 17). This result is very significant because the  $\beta$ -position results to be less reactive to oxidative addition of Pd(0) [11].

The proposed mechanism of the electrosynthesis of aldehydes is outlined in Scheme 2 [9].

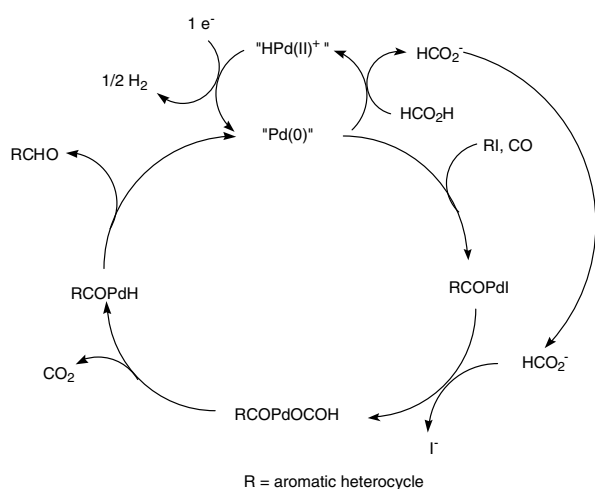
## 3. Conclusions

We have obtained in moderate to good yields heteroaromatic aldehydes from iodothiophens, iodofuran and

Table 1  
Palladium-catalyzed formylation of iodo-heteroaromatics in CO atmosphere in the presence of HCOOH, Pd(OAc)<sub>2</sub>, TBAF as supporting electrolyte

Entry	Substrate	Solvent	Ligand	Time (h)	Aldehyde 2, yield (%)	Starting material
1		DMF		5	25	65
2	<b>1a</b>	DMSO		4	28	70
3	<b>1a</b>	C <sub>2</sub> H <sub>5</sub> CN		2.5	Traces	Traces
4	<b>1a</b>	CH <sub>3</sub> NO <sub>2</sub>		3.5	3	Traces
5	<b>1a</b>	CH <sub>3</sub> CN		2.5	16	–
6	<b>1a</b>	DMF	DMAP	5	19	33
7	<b>1a</b>	DMF	DIPEA	2.5	24	71
8	<b>1a</b>	DMF	DBU	4	30	47
9	<b>1a</b>	DMF	DABCO	4	81	12
10		DMF	DABCO	5	82	12
11		CH <sub>3</sub> CN		3	32	–
12	<b>1c</b>	DMSO		5	Traces	Traces
13	<b>1c</b>	DMF	DABCO	5	72	Traces
14		CH <sub>3</sub> CN		5	Traces	>90
15	<b>1d</b>	DMSO		4	Traces	>90
16	<b>1d</b>	DMF	DABCO	4	Traces	>90
17		DMF	DABCO	5	35	Traces
18		DMF	DABCO	4	Traces	>95

Yields determined by HPLC, yields relative to starting **1**.



Scheme 2.

iodopyridines using an electrochemical method to generate formate ions under very mild conditions. The result is that formate ions are generated at an adequate rate via a combination of chemical and electrochemical steps, at a potential where the direct reduction of formic acid to formate ion cannot occur. In this reaction the palladium catalyst plays a triple role: activation of the iodoheterocycle by oxidative addition of Pd(0), activation of CO to form an acylpalladium complex and activation of formic acid to generate formate ions.

#### Acknowledgements

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