

Sustainable Chemistry

Sustainable Synthesis of Aryl and Heteroaryl Aldehydes

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Aromatic aldehydes are important intermediates for the synthesis of valuable fine and specialty chemicals and many procedures for their preparation have been developed but, nowadays, most of these synthetic methods require large amounts of reagents and multiple steps, with production of wastes. In this paper, we focused on the synthesis of some (hetero)aromatic aldehydes, used either as industrial flavor/fragrances of commercial interest, such as Heliotropine[®], or as

key intermediates for the preparation of some APIs and of other fragrances such as Lioral[®] and Helional[®], by reductive carbonylation of halo derivative precursors. In order to carry out an easier and more applicable process, hydrogen donors, instead of gaseous flammable and explosive hydrogen, and recyclable phosphine free low metal content catalysts, were employed.

Introduction

Aryl and heteroaryl aldehydes are building blocks for the pharmaceutical, agrochemical, and fine-chemical industries.^[1,2] In particular, aromatic aldehydes represent valuable intermediates for the synthesis of aromas and fragrances and, sometimes, aldehydes themselves are interesting molecules with odorous notes or special flavors. A lot of odorous natural substances contain an aldehyde group, which seems to be important for primary olfactory reception.^[3] Today, most of perfume formulations possess at least a small quantity of an aldehyde, generally ranging in content from trace amounts to as high as one per cent in the so-called aldehydic perfumes.^[4] As a matter of fact, Chanel N°5, the sample number five selected in 1921 by Coco Chanel among ten perfume mixtures, contained the highest concentration of aldehydes. Moreover, aldehydes can be transformed in hemiacetals, acetals, or other derivatives to protect them to the oxidation and/or to have a slow release of the aldehydic fragrance due to hydrolysis of

these derivatives on the skin. Aldehydes can be also the precursors of alcohols, carboxylic acids and their esters, that are valuable ingredients for flavoring mixtures, too. Many procedures for the synthesis of aromatic aldehydes have been developed^[5] (Figure 1) but, nowadays, the synthesis on a large scale of aldehydes is still challenging in terms of efficiency and selectivity.^[6]

Oxidations or chlorination/hydrolysis reactions are commonly employed in the industrial production of aromatic aldehydes, but significant amounts of wastes are formed.^[5,6] Also, laboratory scale synthesis such as the Vilsmeier-Haack, Gattermann-Koch, Reimer-Tiemann, and Duff reactions require large amounts of reagents and multiple steps, with production of wastes.^[7,8] Most of these methods require the use of highly

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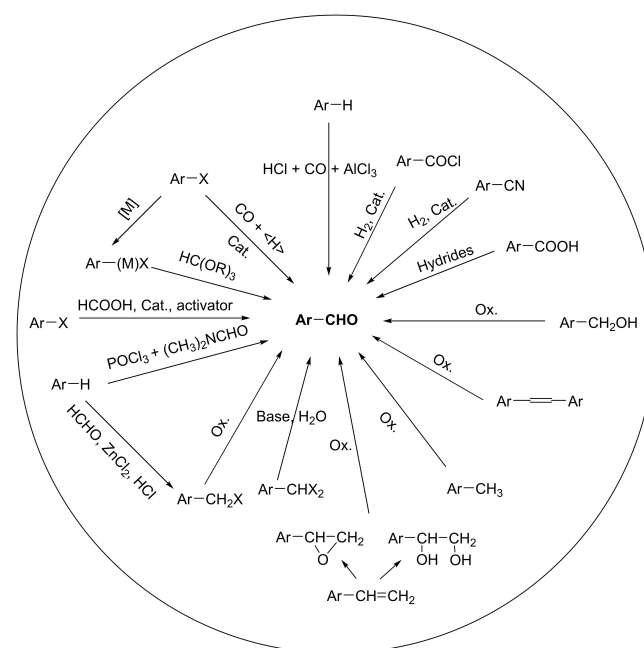


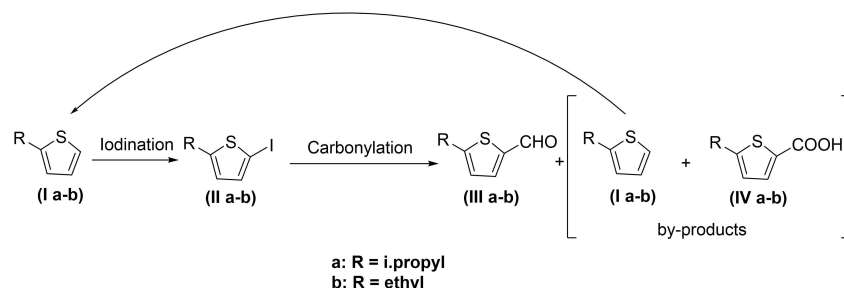
Figure 1. Main synthetic routes to aromatic aldehydes.

toxic and/or gaseous and/or unstable reagents, making storage and subsequent dosage in the reactive environment difficult.^[9,10] On an industrial level, the Vilsmeier-Haack reaction with DMF and phosgene requires special safety procedures and equipment, since N,N-dimethyl (chloromethylene)iminium chloride, formed from DMF and phosgene, reacts with DMF to give N,N-dimethylcarbamoyl chloride, a strongly carcinogenic compound,^[9] even if a clever solution was recently realized working under flow conditions.^[11] Furthermore, a final hydrolysis step is often necessary, consequently the disposal of the wastewater so produced is not a negligible problem. For instance, in the Vilsmeier-Haack reaction, performed with DMF/ POCl_3 , phosphoric acid is produced by hydrolysis. Hence, alternative routes to synthesize aldehydes have been developed in the past, including the reduction of carboxylic acids and their derivatives with hydrogen in the presence of suitable catalyst,^[12–14] and the palladium-catalyzed formylation of aryl halides.^[15–18] In 2006, Beller and collaborators developed a selective protocol for the reductive carbonylation of aromatic, heteroaromatic, and vinylic bromide substrates using syngas (CO/H_2 1:1), and a phosphine or phosphinite palladium homogeneous catalyst. This methodology was also applied on an industrial scale for the production of a specific aromatic aldehyde which serves as a drug intermediate,^[15–17] but the homogeneous catalyst is not easy to recycle. In the case of reductive carbonylation, CO is often used in combination with H-donors as tin hydrides, for instance.^[19–23] However, tin hydrides cannot be used today because of their toxicity and waste generation. Other reducing agents have been applied such as PMHS (polymethylhydrosiloxane)^[21] and other organosilanes^[23,24] in the presence of various palladium based catalytic systems. An accurate setting of the reaction parameters (catalyst, base, solvent, temperature, pressure, concentration) is fundamental for the transformation of (hetero)aryl halides into the corresponding aldehydes.^[25] Many efforts have been made to give life to new carbonylation protocols. In particular, new methodologies have been developed involving the use of suitable reagents capable of generating carbon monoxide *in situ* by the use of activators or by a simple thermal decomposition. As a matter of fact, formic acid was used as CO surrogate in the reductive carbonylation of aromatic halides catalyzed by $\text{Pd}(\text{OAc})_2$ with PPh_3 as ligand, DMF as the solvent and in the presence of dicyclohexylcarbodiimide (DCC) as formic acid activator.^[10] Noteworthy, some of the reagents used

(DMF and DCC) are toxic, and the replacement of the reaction solvent with a less impacting one caused a decrease in the aldehyde yield. Furthermore, the palladium-catalyzed reductive carbonylation of aryl bromides was carried out by using N-formyl saccharin as a CO precursor and a silane as a reducing agent.^[26] Other methodologies involved the use of acetic anhydride-based activators, showing a good reactivity and tolerance to functional groups, but a large amount of base was necessary to neutralize the acetic acid formed.^[10] An interesting carbonylation reaction employed formic acid as a CO surrogate and propylphosphonic anhydride as an activator; very good results both in terms of conversion and selectivity to the corresponding aldehydes have been obtained. However, also in this procedure the use of a homogeneous catalyst, palladium acetate, was required.^[27] Since many years, we are involved in the synthesis of fine chemicals including fragrances. Therefore, we decided to investigate the synthesis of two molecules, as aryl and heteroaryl aldehydes model, trying to improve the known palladium catalyzed reductive carbonylation. As a matter of fact, our goal was to apply more sustainable procedures avoiding the use of unsafe reagents and/or solvents and by using easily recyclable metal-based catalysts. In particular, we decided to investigate the synthesis of (hetero)aromatic aldehydes used either as industrial flavor/fragrances of commercial interest, such as Heliotropine[®], or as key intermediates for the preparation of some APIs, and of other fragrances such as Lioral[®]^[28] and Helional[®].^[29] Lioral[™] is a fragrance with a floral green scent reminiscent of lily of the valley, while Helional[®] presents a green, floral (cyclamen) odor profile with top notes of marine fresh, ozone and new mown hay and it is used in both feminine and masculine perfumes, shampoos, soaps etc. In this paper we report the results obtained in the reductive carbonylation by using carbon monoxide and hydrogen donor as TES in the presence of different palladium-based catalysts.

Results and Discussion

We proposed to study the reductive carbonylation of 2-iodo-5-isopropylthiophene (**II a**) and 2-iodo-5-ethylthiophene (**II b**) to the corresponding carbaldehydes (**III a**) and (**III b**), respectively (Scheme 1). 2-Isopropylthiophene (**I a**) is not commercially available and was synthesized by us (see experimental part); it is to note that some previous reported synthesis of this product



Scheme 1. Synthesis of 5-isopropylthiophen-2-carbaldehyde (**III a**) and 5-ethylthiophen-2-carbaldehyde (**III b**).

gave very low yield in our hands.^[28,30] Then, we prepared the two halo derivatives (**II a**) and (**II b**), by iodination of 2-isopropylthiophene (**I a**) and of the commercially available 2-ethylthiophene (**I b**), respectively. Iodination of (**I a**) and (**I b**) was carried out by using the NaIO₃/I₂ redox system in acetonitrile as the solvent.^[31] In both cases, conversion was quantitative and selectivity to (**II a**) and (**II b**), respectively, almost complete, being other mono iodo-isomers formed in negligible amount (< 1%). Noteworthy, di-iodinated compounds were never detected in the reaction mixture.

5-Isopropylthiophen-2-carbaldehyde (**III a**) is a fragrance with a potential industrial interest and also a valuable intermediate to synthesize Lioral®. 5-Ethylthiophen-2-carbaldehyde (**III b**) is an industrial flavor and can be formed by Maillard reaction during foods cooking.^[32,33] We focused on the reductive carbonylation of the iododerivatives (**II a**) and (**II b**) by using CO and H-donors. The advantage of H-donors is to avoid the use of gaseous, flammable, and explosive hydrogen and, if possible, to carry out the reaction under milder conditions of pressure and temperature. Basing on previous literature data, triethylsilane (TES) was used as H-donor, in the presence of the homogeneous catalyst Pd(PPh₃)₄ in acetonitrile, using HMPA as base.^[21] The reaction allowed to obtain a good conversion into the desired product (**IIIa**); however, the formation of triethylsilanol and hexaethyldisiloxane deriving from TES could make the purification product process complex and tedious. When in a comparison example PMHS, a byproduct of the silicone industry which is a cheap, easy to handle, and environmentally friendly reducing agent, was employed instead of TES not only the yield of the desired aldehyde was nearly quantitative (Table 1, run 1), but also volatile silicon-based by-products were not formed.

When DMF, instead of CH₃CN, and sodium carbonate, as base, were used, conversion did not change but selectivity was strongly lowered due to the formation of 30% of (**I a**) (Table 1, run 2). However, HMPA and DMF are not safe compounds, therefore we used the greener 2-MeTHF as solvent, always in the presence of sodium carbonate. The reaction, carried out at 80 °C and 1 MPa of CO pressure for 20 h and by using a substrate (**II a**)/catalyst molar ratio 180/1, afforded an almost complete substrate conversion (99%) with the exclusive formation of aldehyde (**III a**) (Table 1, run 3). Noteworthy, at these reaction conditions and by using safer reagents respect to those employed in the literature,^[21,34] substrate dehalogenation did not occur, being (**I a**) never detected in the reaction

mixture. Very similar results were obtained carrying out the carbonylation process on 5-iodo-2-ethylthiophene (**II b**), too. Due to the commercial availability of 2-ethylthiophene (**I b**), the starting material to get the iododerivative (**II b**), we continued our experimentation by using (**II b**) as model substrate. Despite the good results obtained by using PMHS as H-donor, we observed that, working on a small scale, the results were not always reproducible, depending on the PMHS supplier, and for this reason we decided to use TES for new experiments to easily find better procedure protocols. With the aim to perform a more sustainable process, we decided to use easily recoverable and recyclable palladium catalysts instead of the homogeneous Pd(PPh₃)₄. First, we studied the carbonylation reaction on 2-iodo-5-ethylthiophene (**II b**) catalyzed by 1.7% (Pd-EPS) or by (Met_x-EPS). These are heterogeneous biogenerated species, previously obtained by some of us, during citrate fermentation of *Klebsiella oxytoca* DSM 29614 in the presence of a palladium salt, in the case of (Pd-EPS)^[35,36] (see SI), or of different metals recovered from an exhausted catalytic converter, in the case of (Met_x-EPS)^[38,39] (see SI). Both these catalysts, had given very interesting results in the aqueous biphasic hydrogenation of different unsaturated substrates and in the hydrodehalogenation of 1260 Aroclor.^[35–40] In particular, in (Met_x-EPS), which contains different metals such as Al, Ce, W and the platinum-group metals Pd, Pt and Rh (1.9% Pd, 1.0% Pt and 0.25% Rh) (see SI), the co-presence of these noble transition metals could influence the catalysis by a synergic effect, leading to different activity and selectivity with respect to single metal species.^[38–40] Noteworthy, both catalysts require some water to exert their activity at the best,^[35–40] therefore the carbonylations were carried out in water/THF or in water/CPME at 80 °C in the presence of inorganic or organic bases. When 5 MPa of syngas (CO/H₂ = 1) were used, after 24 h at 80 °C and with a substrate (**II b**)/Pd molar ratio = 50/1, only about 20% of aldehyde (**III b**) was obtained, being 2-ethylthiophene (**I b**) and 5-ethylthiophene-2-carboxylic acid (**IV b**) the prevailing reaction products (data not reported in Table 2). In order to improve the aldehyde yield and to carry out the reaction in safer conditions, carbonylations were carried out by using TES instead of hydrogen and the results are described in Table 2.

The best results were obtained in the presence of the polymetallic catalyst (Met_x-EPS) when trioctyl amine (TOA) was used as the base. As a matter of fact, conversion was always complete and aldehyde (**III b**) yield reached 97–95%, working both in the presence of THF or in the greener solvent

Table 1. Carbonylation of 5-iodo-2-isopropylthiophene (**II a**) catalyzed by Pd(PPh₃)₄.^[a]

Run	Base	Solvent	(IIa)/cat. molar ratio	(IIa) conv. (%) ^[b]	(IIIa) yield (%) ^[b]	(Ia) yield (%) ^[b]
1	HMPA	CH ₃ CN	100/1	99	97	2
2 ^[c]	Na ₂ CO ₃	DMF	100/1	99	69	30
3 ^[d]	Na ₂ CO ₃	MeTHF	180/1	99	99	–

[a] Reaction conditions: substrate (**II a**) = 2 g (0.008 mol); PMHS = 3.36 mL; HMPA = 5.57 mL (HMPA/(**II a**) molar ratio 4/1); Pd(PPh₃)₄ = 0.092 g; CH₃CN = 10 mL; p(CO) = 1 MPa; T = 80 °C; t = 20 h; [b] Determined by GC; [c] same conditions of test 1 but 1.70 g of Na₂CO₃ (Na₂CO₃/(**II a**) molar ratio 2/1) was used instead of HMPA, and 10 mL of DMF were used instead of CH₃CN; [d] same conditions of test 1 but 1.70 g of Na₂CO₃ (Na₂CO₃/(**II a**) molar ratio 2/1) were used instead of HMPA, and 10 mL of 2-MeTHF were used instead of CH₃CN.

Table 2. Carbonylation of (II b) catalyzed by 1.7% (Pd-EPS) and by (Met_x-EPS) by using TES as H-donor.

Run	Catalyst	(II b)/Pd molar ratio	Base	(II b) conv. (%) ^[a]	(III b) yield (%) ^[a]	(I b) yield (%) ^[a]	(IV b) yield (%) ^[a]
1 ^[b]	Pd-EPS	100/1	Na ₂ CO ₃	99	88	3	8
2 ^[c]	Pd-EPS	100/1	Na ₂ CO ₃	99	82	–	17
3 ^[c]	Pd-EPS	100/1	Na ₂ CO ₃	98	85	Traces	13
4 ^[b]	Pd-EPS	100/1	Quinine	> 99	93	2	5
5 ^[c]	Pd-EPS	100/1	Quinine	99	81	9	9
6 ^[b]	Pd-EPS	500/1	Na ₂ CO ₃	97	76	17	4
7 ^[b]	Met _x -EPS	200/1	Na ₂ CO ₃	> 99	70	30	–
8 ^[b]	Met _x -EPS	500/1	Na ₂ CO ₃	> 99	67	33	–
9 ^[b]	Met _x -EPS	500/1	Quinine	> 99	76	24	–
10 ^[b]	Met _x -EPS	500/1	TOA	> 99	97	3	–
11 ^[d]	Met _x -EPS	500/1	TOA	> 99	95	5	–
12 ^[c]	Met _x -EPS	500/1	TOA	97	92	5	–
13 ^[c]	Met _x -EPS	500/1	TOA	97	88	9	–

[a] Determined by GC analysis; [b] Reaction conditions: substrate (II b) = 691 mg (2.89 mmol); TES = 4.0 g (34.4 mmol); Substrate/Base molar ratio = 2; p(CO) = 5 MPa; T = 80 °C; H₂O = 5 mL; THF = 5 mL; t = 22 h. [c] Reaction carried out by using the catalyst recovered from the previous experiment. [d] Same reaction conditions but H₂O (5 mL) and CPME (5 mL) were used.

cyclopentyl methyl ether (CPME) (Table 2, runs 10 and 11, respectively). The catalyst maintained a good activity in two recycle experiments, even if a slight increase of the dehalogenated by-product was observed (Table 2, runs 12 and 13). The best results obtained with TOA, in comparison with sodium carbonate and quinine, could be due to a more efficient sequestering capability of the formed HI, which is very probably responsible of a partial deactivation/loss of selectivity of this catalyst. Noteworthy, a much higher quantity of TES was required working with (Met_x-EPS) than with (Pd-EPS), perhaps due to an increased speed of decomposition of this reagent in the former case. The carbonylation of 2-iodo-5-ethylthiophene (II b) was also carried out by using the homemade catalyst 0.3% Pd/Al₂O₃ in the absence of any phosphine (Table 3). This low metal content catalyst was recently prepared by us^[41] (see SI) and used in the stereoselective semi-hydrogenation of 3-hexyn-1-ol to (Z)-3-hexen-1-ol, a very important fragrance with an herbaceous note.^[41]

A first reaction carried out at 80 °C, 5 MPa of CO, with a substrate/Pd molar ratio = 50/1, and by using an equimolar amount of TES with respect to substrate, gave a very low aldehyde (III b) yield (Table 3, run 1). By increasing TES amount

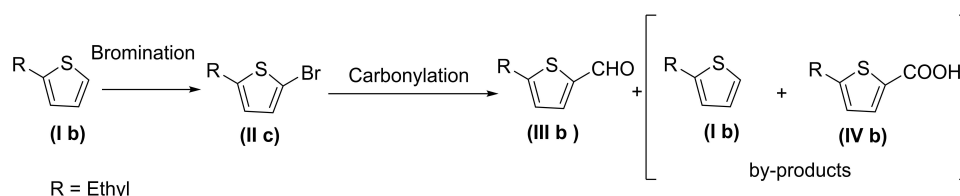
conversion increased and the best results were obtained with a strong excess of TES (TES/substrate molar ratio = 12). As a matter of fact, after 23 h at the above experimental conditions, 99% conversion was obtained, with 93% of (III b) and 6% of the dehalogenated product (I b) (Table 3, run 4). Noteworthy, in a recycling experiment, conversion remained unchanged and a slight increase of selectivity to (III b) was observed (run 5, Table 3). By comparison, we decided to carry out some reactions, catalyzed by 0.3% Pd/Al₂O₃, by using syngas instead of CO and TES. By working at 100 °C for 22 h at 5 MPa (CO/H₂ = 1/1), with a substrate/Pd molar ratio = 51 and in the presence of Na₂CO₃ (substrate/Na₂CO₃ (molar ratio) = 1/0.5), (II b) was completely converted into 2-ethylthiophene (I b), being the substrate dehalogenation the only reaction observed. Increasing CO/H₂ ratio (from 1/1 to 5/0.5), conversion was always complete but, at the best, aldehyde (III b) yield was 49%, being 51% of 2-ethylthiophene (I b) formed. These surprising and disappointing results^[2] underline a completely different behavior by changing the reducing agent from TES to hydrogen when this catalytic system is used. In order to improve the economy of the process, carbonylation was also studied by using the bromo-derivative (II c) as substrate (Scheme 2) and the results are reported in Table 4.

First, 2-ethylthiophene (I b) was efficiently brominated to 2-bromo-5-ethylthiophene (II c) by using HBr/H₂O₂ in CH₃CN/water mixture.^[42] Then, following a procedure reported in the literature,^[15] the bromo-derivative (II c) was carbonylated affording the desired aldehyde (III b) with 87% yield. However, this good result was obtained only in the presence of the homogeneous catalytic system Pd(OAc)₂/diadamantylbutylphosphine (DABP) and TMEDA as base, by using a substrate/catalyst molar ratio 4/1 (Table 4, run 1). Disappointingly, by increasing the substrate to catalyst molar ratio up to 40/1, the reaction did not occur at all (Table 4, run 2). By comparison with substrate (II b), the bromo-derivative (II c) was carbonylated in the presence carbon monoxide and TES, by using 0.3% Pd/Al₂O₃ as the catalyst and Na₂CO₃ as the base. A first reaction,

Table 3. Carbonylation of (II b) catalyzed by 0.3% Pd/Al₂O₃ by using TES as H-donor.^[a]

Run	TES/Substrate (molar ratio)	(II b) conv. (%) ^[b]	(I b) yield (%) ^[b]	(III b) yield (%) ^[b]
1	1	20	8	12
2	2	37	7	30
3	6	80	19	61
4	12	99	6	93
5 ^[c]	12	99	1	98

[a] Reaction conditions: substrate (II b) = 0.031 g (0.16 mmol); (II b)/Pd (molar ratio) = 50/1; T = 80 °C; p(CO) = 5 MPa; t = 23 h; MeTHF = 5 mL; substrate/Na₂CO₃ (molar ratio) = 1/0.5. [b] Determined by GC analysis. [c] Reaction carried out by using the catalyst recovered from the previous experiment.



Scheme 2. Synthesis of 5-ethylthiophen-2-carbaldehyde (III b).

Table 4. Carbonylation of 2-bromo-5-ethylthiophene (II c) by using TES as H-donor.

Run	Catalyst	Substrate/Cat (molar ratio)	T (°C)	(II c) conv. (%) ^[a]	(I b) yield (%) ^[a]	(III b) yield (%) ^[a]
1 ^[b]	Pd(OAc) ₂ /DABP	4	100	95	8	87
2 ^[b]	Pd(OAc) ₂ /DABP	40	100	–	–	–
3 ^[c]	0.3% Pd/Al ₂ O ₃	55	80	8	8	–
4 ^[c]	0.3% Pd/Al ₂ O ₃	55	120	18	18	–

[a] Determined by GC analysis. [b] Reaction conditions: substrate (II c) = 382 mg (2 mmol); p(H₂) = 1.5 bar; p(CO) = 1 bar; DABP = diadamantylbutylphosphine; TMEDA = 0.75 equiv.; Toluene = 2 mL. [c] Reaction conditions: substrate (II c) = 24.8 mg (0.13 mmol); TES = 183 mg (1.6 mmol); p(CO) = 5 MPa; t = 23 h; MeTHF = 5 mL; Na₂CO₃/substrate (molar ratio) = 2/1.

carried out at 80 °C and 5 MPa of CO for 23 h, gave a very low conversion (8%) and 2-ethylthiophene (II a) was the only reaction product (Table 4, run 3). By increasing the reaction temperature to 120 °C, substrate conversion reached 18% but, again, only 2-ethylthiophene (II a) was formed (Table 4, run 4).

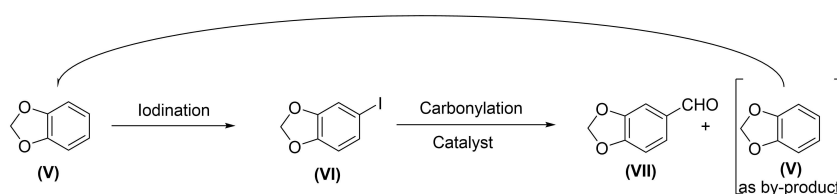
Besides alkyl thiophen carbaldehydes, our interest was also devoted to piperonal (VII) (also known as Heliotropine[®]), a valuable intermediate for the synthesis of Helional[®]. Furthermore, piperonal, is used as flavoring because of its floral odor similar to that of vanillin and cherry and it is also an important intermediate for the synthesis of some medicines and drugs.^[43] First, benzo[d][1,3]dioxole (V) was iodinated to 5-iodobenzo[d][1,3]dioxole (VI) in 92% yield by using the NaIO₃/I₂ system^[31] and subsequently reductively carbonylated to (VII) (Scheme 3).

The iodo derivative (VI) was initially carbonylated in the presence of the homogeneous catalyst Pd(PPh₃)₄ with a substrate/catalyst molar ratio 180/1. After 23 h at 1 MPa of CO and 80 °C, in the presence of TES as H-donor, substrate conversion was 66% (data non reported in the table) and after distillation under vacuum, pure piperonal (VII) was obtained in 53% yield. In the view of a more sustainable process, the homogeneous catalyst was replaced by more convenient heterogeneous catalysts; therefore, some reactions were carried out also using 0.3% Pd/Al₂O₃ or (Met_x-EPS), both successfully employed in the carbonylation of 5-iodo-2-ethylthiophene (II

b). Pd/Al₂O₃ catalyst gave quite unsatisfactory results both in terms of conversion and selectivity (Table 5, runs 1 and 2). When the polymeric species (Met_x-EPS) was used, aldehyde (VII) yield was strongly increased (Table 5, run 3). Very probably, the presence of the synergic effect of the different metals, besides palladium, present in the polymeric catalyst, accelerated the carbonylation rate with respect to the dehalogenation. Moreover, the catalyst maintained its activity and selectivity practically unchanged in a recycling experiment (Table 5, run 4). Very interestingly, when the reaction was carried out in the greener CPME/H₂O mixture and in the presence of TOA as the base, selectivity was strongly increased with respect to the experiment carried out with TEA in THF/H₂O (Table 5, cfr run 5 and 6). Noteworthy, the good activity and selectivity of the catalytic system was maintained practically unchanged in a recycling experiment (Table 5, run 6).

Conclusion

Using two model substrates, having different steric and electronics properties so to require a fine tuning in the synthetic protocols, a synthesis of two industrially important aldehydic compounds was realized by reductive carbonylation of aryl- and heteroaryl iodo precursors, using CO and silanes as reagents. The more relevant outcome of this research was that, besides conventional homogeneous catalysts, it was possible



Scheme 3. Synthesis of piperonal (VII).

Table 5. Reductive carbonylation of (VI) catalyzed by 0.3% Pd/Al₂O₃ and by Met_x-EPS by using TES as H-donor.

Run	T (°C)	Catalyst	(VI) conv. (%) ^[a]	(V) yield (%) ^[a]	(VII) yield (%) ^[a]
1 ^[b]	80	0.3% Pd/Al ₂ O ₃	82	19	63
2 ^[b]	100	0.3% Pd/Al ₂ O ₃	90	31	59
3 ^[c]	100	Met _x -EPS	> 99	13	87
4 ^[c,d]	100	Met _x -EPS	> 99	17	83
5 ^[c,e]	100	Met _x -EPS	> 99	21	79
6 ^[c,f]	100	Met _x -EPS	98	6	92
7 ^[c,d,f]	100	Met _x -EPS	95	5	90

[a] Determined by GC analysis. [b] Reaction conditions: substrate (VI) = 32.8 mg (0.13 mmol); 0.3% Pd/Al₂O₃ = 100.9 mg (0.0026 mmol Pd); (VI)/Cat. molar ratio = 50; TES/(VI) molar ratio = 12; substrate/Na₂CO₃ (molar ratio) = 1/2; p(CO) = 5 MPa; t = 23 h; Solvent (5 mL) = Me-THF. [c] (VI)/Cat. molar ratio = 500; THF/H₂O 1/1 (6 mL); [d] recycling experiment; [e] TEA as base; substrate/TEA (molar ratio) = 2; [f] Solvent CPME/H₂O 1/1 (6 mL) and TOA as base; substrate/TOA (molar ratio) = 2.

to use some phosphine free heterogeneous and easily recyclable catalysts. In our opinion, it represents an important new aspect and an improvement compared to the state of the art. Even if it is difficult, working on a small scale, to be able to quantize the sustainability of our protocol using green metrics such as Reaction Mass Efficiency or Process Mass Intensity (PMI), the use of a palladium-based catalyst with a low precious metal content and of a polymeric catalyst, consisting of platinum group metals recovered from exhausted catalytic converters, pave the way, on an industrial scale, for a more sustainable synthesis of many commercially important aldehydes.

Experimental Section

General

Methylenbenzo[d][1,3]dioxole was received from Endura S.p.A. (Italy), triethylsilane from AlzChem Group AG (Germany), 5% Pd/C (50% wet) and γ -Al₂O₃ from Chimet S.p.A. (Italy). 1.7% Pd-EPS,^[35] Met_x-EPS,^[38,39] and 0.3% Pd/Al₂O₃^[40] were prepared following reported procedures. CPME was received from IMCD Italia SpA. All the other reagents were Aldrich products. GC analyses were carried out on an Agilent 6850 A gaschromatograph (FFAP column 30 m × 0.25 mm × 0.25 μ m) and GC-MS analyses were performed by using an Agilent Technologies 7820 A GC System coupled with quadrupole mass spectrometer Agilent Technologies 5977B MSD (HP-5MS column 30 m × 0.25 mm × 0.25 μ m). NMR spectra were recorded by using a Bruker Avance 300 spectrometer working at 300 MHz.

Preparation of 2-isopropylthiophene (I a)

In a 1000 mL round bottom flask equipped with mechanical stirrer, 5 g (40 mmol) of 2-acetylthiophene and 200 mL of dry diethyl ether were placed under nitrogen. Subsequently, 16 mL of a 3 M solution of CH₃MgBr in Et₂O were added dropwise in 30 minutes at 5 °C. The reaction mixture was warmed at 25 °C for 2 h and then treated with a saturated solution of NH₄Cl (5 mL). The aqueous phase was extracted twice with diethyl ether (2 × 20 mL) and the collected organic phase was dried with Na₂SO₄, filtered and concentrated by rotavapor to give 5.4 g (95% yield) of 2-(thiophen-2-yl)propan-2-ol as a yellow liquid. In a Schlenk tube, 5 g (0.035 mol) of this tertiary alcohol, 1.03 g of 5% Pd/C (50% wet; substrate/catalyst molar ratio 140/1), 0.5 g of Amberlist-15[®] H⁺ form, 0.05 g of BHT, 1 mL of isopropylether and 30 mL of isooctane were added. The Schlenk

tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 0.5 MPa H₂ and stirred for 24 h at 25 °C. After this time the residual gas was released, and the mixture was analyzed by GC and GC-MS. 99% Conversion of the starting material was detected with the formation of 80% of (I a) and of 19% of undesired oligomeric by-products. The mixture was filtered to remove Amberlist-15[®] H⁺ and palladium catalyst and the solids were washed with 10 mL of diethyl ether three times. The recovered organic phase was washed with a 6 M KOH solution and subsequently with water until the pH was neutral, then dried on Na₂SO₄. After filtration and concentration of the solution by distillation at atmospheric pressure, pure (I a) was finally obtained by distillation under vacuum (33 °C/6 Pa) with 50% recovery. GC-MS^[44] and ¹H NMR^[45] data were in agreement with those reported in the literature.

Preparation of iodo derivatives (II a), (II b) and (VI)

Iodination of 2-isopropylthiophene (I a)

In a 250 mL jacket round bottom flask with two necks, equipped with magnetic stirrer and reflux condenser, 10 mL of water, 2.66 g of NaIO₃ (0.014 mol), 4.82 g of I₂ (0.019 mol), 20 mL of glacial acetic acid, 5 g (0.040 mol) of (I a) and 30 mL of ethyl acetate were introduced. Then, 1.4 mL of 98% sulfuric acid were slowly added. After 3 h at 30 °C conversion was practically quantitative and 30 mL of deionized water and 30 mL of 50% NaOH solution were added. Subsequently, 10.63 g (0.043 mol) of sodium thiosulfate were added and the organic phase was separated. The aqueous phase was extracted five times with 30 mL of ethyl acetate. The combined organic phases were dried on Na₂SO₄. After filtration, the solvent was removed by rotavapor and the sought product was obtained by distillation at reduced pressure (94 °C/13 Pa). Pure (II a) was obtained in 80% yield.

Adopting the same procedure, the iodination of 2-ethylthiophene (I b) and of methylenbenzo[d][1,3]dioxole (V) were carried out. After 3 h, conversion of (I b) into (II b) was 92% and after work-up, pure (II b) was obtained in 81% yield. After 20 h, conversion of (V) into (VI) was quantitative and after work-up, pure compound (VI) was obtained in 88% yield.

Compound (II a): ¹H NMR (300 MHz, CDCl₃): δ = 7.06 (d, 1H, J = 3.52 Hz), 6.51 (dd, 1H, J₁ = 3.52 Hz, J₂ = 0.9 Hz), 3.17 (m, 1H), 1.32 (d, 6H, J = 6.56 Hz). MS (70 eV): m/z: 252 [M]⁺; 237 [M, -CH₃]⁺; 126 [M, -I]⁺; 110 [M, -I, -CH₃]⁺.

Compound (II b): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 6.90 (d, 1H, J = 7.5 Hz), 6.56 (d, 1H, J = 7.5 Hz), 2.59 (q, 2H, J = 8 Hz), 1.24 (t, 3H, J = 8 Hz). MS (70 eV): m/z : 238 $[\text{M}]^+$, 112 $[\text{M}-\text{I}]^+$.

Compound (VI): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 7.14 (dd, 1H, J_1 = 8.1, J_2 = 1.6 Hz), 7.12 (d, 1H, J = 1.6 Hz), 6.59 (d, 1H, J = 8.1 Hz), 5.96 (s, 2H). MS (70 eV): m/z : 248 $[\text{M}]^+$, 190 $[\text{M}-\text{C}_2\text{H}_3\text{O}_2]^+$, 121 $[\text{M}-\text{I}]^+$, 79 $[\text{M}-\text{C}_3\text{H}_5\text{O}]^+$, 63 $[\text{M}-\text{CH}]^+$, 50 $[\text{M}-\text{C}_2\text{H}_2]^+$.

Preparation of 2-bromo-5-ethylthiophene (II c)

In a 50 mL round bottom flask equipped with magnetic stirrer and covered with aluminum foil, 1 g (0.009 mol) of 2-ethylthiophene (I b) was suspended in 3 mL of CH_3CN and 7 mL of water. A 48% aqueous solution of HBr (0.005 mol, 0.56 mL) and 30% aqueous solution of H_2O_2 (0.005 mol, 0.5 mL) was dropwised in 90 minutes. The reaction was carried out for 4 h at rt and monitored by GC and GC-MS. The detected conversion of 2-ethylthiophene (I b) was 91% (87% of 2-bromo-5-ethylthiophene (II c) and 4% of a di-brominated by-product). The crude mixture was treated with 10 mL of diethyl ether and the aqueous phase was separated. Subsequently, the aqueous phase was extracted three times with diethyl ether (3 \times 5 mL) and the recovered organic phases were dried over Na_2SO_4 . After filtration and concentration by rotavapor, the desired product (II c) was obtained in 81% yield by distillation at reduced pressure (30 $^\circ\text{C}/6$ Pa).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 6.86 (d, 1H, J = 3.6 Hz), 6.56 (dt, 1H, J_1 = 3.6 Hz, J_2 = 1.2 Hz), 2.80 (q, 2H, J = 7.6 Hz), 1.28 (t, 3H, J = 7.6 Hz). MS (70 eV): m/z : 190 $[\text{M}]^+$, 175 $[\text{M}-\text{CH}_3]^+$, 110 $[\text{M}-\text{Br}]^+$, 95 $[\text{M}-\text{Br}-\text{CH}_3]^+$.

Synthesis of aldehydes (III a), (III b) and (VII) by reductive carbonylation

Synthesis of 5-isopropylthiophen-2-carbaldehyde (III a) by reductive carbonylation of (II a) in the presence of PMHS, Na_2CO_3 and $\text{Pd}(\text{PPh}_3)_4$

In a Schlenk tube, 2 g (0.008 mol) of (II a), 0.051 g (0.044 mmol) of $\text{Pd}(\text{PPh}_3)_4$ ((II a)/catalyst molar ratio 180/1), 10 mL of Me-THF, 3.36 mL of PMHS and 1.70 g (0.016 mol) of Na_2CO_3 (base/(II a) molar ratio 2/1) were introduced under nitrogen. The Schlenk tube was then transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 1 MPa of CO and heated at 80 $^\circ\text{C}$ for 20 h under stirring. The reactor was then cooled to room temperature and the residual gases released. The crude mixture was filtered off and the recovered organic phase was analyzed by GC and GC-MS. Quantitative conversion of substrate (II a) into (III a) was obtained and, after distillation under vacuum (54 $^\circ\text{C}/6$ Pa), pure compound (III a) was obtained in 75% yield.

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 9.81 (s, 1H), 7.63 (d, 1H, J = 7.5 Hz), 6.95 (d, 1H, J = 7.5 Hz), 3.24 (m, 1H), 1.38 (d, 6H, J = 6.8 Hz). MS (70 eV): m/z : 154 $[\text{M}]^+$, 139 $[\text{M}-\text{CH}_3]^+$, 125 $[\text{M}-\text{CHO}]^+$, 111 $[\text{M}-\text{CH}_2\text{O}]^+$, 63 $[\text{M}-\text{CH}]^+$.

Synthesis of 5-ethylthiophene-2-carbaldehyde (III b) by reductive carbonylation of (II b) catalyzed by 1.7% (Pd-EPS)

In a Schlenk tube, 0.005 g of 1.7% (Pd-EPS) were stirred under nitrogen in 2 mL of distilled water for about 10 minutes. A solution of 0.025 g (0.0001 mmol) of (II b) in 2 mL of Me-THF ((II b)/Pd molar ratio 1000/1), 0.0212 g (0.0002 mol) of Na_2CO_3 , and 0.11 mL of TES

(d = 0.728 g/mL) were added. The Schlenk tube was transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 5 MPa CO and heated at 80 $^\circ\text{C}$ for 24 h under stirring. The reactor was then cooled to rt and the residual gases released. Diethyl ether was added, and the organic phase was separated, dried on Na_2SO_4 and analyzed by GC and GC-MS. Substrate conversion was almost quantitative to afford 88% of (III b), 3% of (I b) and 8% of (IV b). The catalyst containing aqueous phase was recycled for further experiments by adopting the above-described procedure. A similar procedure, but at different experimental condition, was used in the presence of (Met_x-EPS) as the catalyst (see Table 2).

Compound (III b): $^1\text{H NMR}$ (CDCl_3): δ = 9.74 (s, 1H, COH), 7.54 (d, 1H, J = 3.7 Hz), 6.85 (d, 1H, J = 3.7 Hz), 2.84 (q, 2H, J = 7.5 Hz), 1.27 (t, 2H, J = 7.5 Hz). MS (70 eV): m/z : 140 $[\text{M}]^+$, 125 $[\text{M}-\text{CH}_3]^+$, 111 $[\text{M}-\text{HCO}]^+$, 97 $[\text{M}-\text{CH}_3\text{CH}_2\text{HCO}]^+$.

Compound (IV b): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 7.73 (d, 1H, J = 3.8 Hz), 6.84 (d, 1H, J = 3.5 Hz), 2.85 (q, 2H, J = 7.6 Hz), 1.32 (t, 3H, J = 7.3 Hz). MS (70 eV): m/z : 156 $[\text{M}]^+$, 141 $[\text{M}-\text{CH}_3]^+$, 139 $[\text{M}-\text{OH}]^+$, 111 $[\text{M}-\text{COOH}]^+$, 97 $[\text{M}-\text{CH}_3\text{CH}_2\text{HCO}]^+$.

Synthesis of 5-ethylthiophene-2-carbaldehyde (III b) by reductive carbonylation of (II b) catalyzed by 0.3% $\text{Pd}/\text{Al}_2\text{O}_3$

In a Schlenk tube, 0.100 g of 0.3% $\text{Pd}/\text{Al}_2\text{O}_3$ ((II b)/catalyst molar ratio 50/1), a solution of 0.031 g (0.00013 mmol) of (II b) in 10 mL of Me-THF, 0.028 g (0.00026 mol) of Na_2CO_3 , and TES (TES/substrate molar ratio = 12) were added. The Schlenk tube was transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 5 MPa of CO and heated at 80 $^\circ\text{C}$ for 23 h under stirring. The reactor was then cooled to room temperature and the residual gases released. The organic phase was analyzed by GC and GC-MS. The results are reported in Table 3.

Synthesis of piperonal (VII) by reductive carbonylation of (VI) catalyzed by 0.3% $\text{Pd}/\text{Al}_2\text{O}_3$

In a Schlenk tube, a solution of 32.8 mg (0.13 mmol) of (VI) in 5 mL of Me-THF, 100.9 mg of 0.3% $\text{Pd}/\text{Al}_2\text{O}_3$ ((VI)/catalyst molar ratio 50/1), 30.1 g (0.26 mmol) of Na_2CO_3 , and 183.5 mg (1.56 mmol) of TES were added. The Schlenk tube was transferred into a 150 mL stainless steel autoclave under nitrogen, pressurized with 5 MPa of CO and heated at 80 $^\circ\text{C}$ for 23 h under stirring. The reactor was then cooled to room temperature and the residual gases released. The organic phase was analyzed by GC and GC-MS. The results are reported in Table 4. A similar procedure, but at different experimental conditions, was used in the presence of (Met_x-EPS) as catalyst (see Table 4).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ = 9.8 (s, 1H, CHO), 7.43 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.5 Hz), 7.35 (d, 1H, J = 1.5 Hz), 6.95 (d, 1H, J = 7.9 Hz), 6.10 (s, 2H). MS (70 eV): m/z : 150 $[\text{M}]^+$, 149 $[\text{M}-\text{H}]^+$, 121 $[\text{M}-\text{CHO}]^+$, 91 $[\text{M}-\text{CH}_2\text{O}]^+$, 63 $[\text{M}-\text{CH}]^+$.

Supplementary Information Summary

The catalysts preparation and characterization are reported in the supporting information.

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Conflict of Interest

The authors declare not conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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