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Palladium-Catalyzed Cross-Dehydrogenative Coupling of *o*-Xylene: Evidence of a New Rate-Limiting Step in the Search for Industrially Relevant Conditions

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An efficient cross-dehydrogenative coupling of *o*-xylene under neat conditions, which brings important industrial benefits towards the synthesis of a monomer used in polyimide resins, is reported. The catalyst based on the combination of Pd/N ligand/carboxylate = 1:1:2 does not require a Cu cocatalyst and proceeds at 11 bar of O_2 pressure. Evaluation of the deuterium kinetic isotope effect (KIE) provides evidence for three different rate-determining steps, which depend on the reaction conditions (medium, temperature). Under the reported neat conditions, the dissociation of a carboxylate-bridged dimer to generate a more reactive monometallic Pd species is proposed to be the rate-limiting step.

Introduction

The biaryl unit is an important structural motif in various products of high commercial importance.[1] Although Suzuki coupling is used widely to access high-end, small-scale biaryls, such as pharmaceutical intermediates,[2] efforts have been made to develop alternative catalytic strategies for biaryl synthesis to meet the more stringent cost and waste requirements associated with large-scale chemicals, such as monomers. A major step forward is the "direct arylation" approach, which bypasses the need for boronic acids as a nucleophilic coupling partner. Additionally, the cross-dehydrogenative coupling (CDC) of arenes eliminates the need for electrophilic ArX coupling partners.[3] Provided that an economically and ecologically feasible terminal oxidant such as O_2 is used, in principle, CDC meets all the requirements for the low-cost, bulk-scale manufacture of biaryls.[4]

The Pd/Cu-catalyzed aerobic CDC of dimethyl phthalate presents a case in point practiced industrially.[5] The target product, that is, tetramethyl (1,1′-biphenyl)-3,3′,4,4′-tetracarboxylate (**1**), is an intermediate for 4,4′-biphthalic anhydride (**3**), which serves as a monomer in the production of a high-performance polyimide (Upilex®; Scheme 1, Route A).[6] This polymer would benefit from a significant decrease of cost if the anhydride could be formed from 3,3′,4,4′-tetramethyl-1,1′-biphenyl (**2**) generated by the CDC of *o*-xylene (Scheme 1, Route B). Early attempts to achieve a sufficiently selective CDC of *o*-xylene were not successful because, in contrast to phthalate, *o*-xylene suffers from competing, selectivity-eroding benzylic oxidation during Pd/Cu-catalyzed aerobic CDC (Scheme 2 a).[7,8]

A significant step forward in the development of aerobic CDC of *o*-xylene was achieved by Stahl et al. who found that the regio- and chemoselectivity increase to comparable values obtained with phthalate by the use of 2 equivalents of 2-fluoropyridine as a ligand (Scheme 2 b) instead of phenanthroline, which is employed in the current industrial process.[9,10] In contrast to the neat conditions employed industrially for the CDC of phthalate, 2-fluoropyridine-based catalysis is performed in acetic acid as the solvent. Industrial applicability would benefit significantly from aerobic catalysis that works efficiently under solvent-free conditions. The use of neat *o*-xylene as the reaction medium instead of acetic acid not only simplifies downstream processing and lowers the corrosivity, and thereby, also the capital investment, but it also leads to a sufficient space–time yield. As the CDC of arenes to yield biaryls is stopped at a low conversion to suppress the over-arylation of the product, space–time yields in the presence of a solvent tend to be below an economically feasible level.

The results of our search for an aerobic CDC catalyst system in neat *o*-xylene have been published in patents filed in 2015 and 2016.[11,12] An important finding disclosed in the first patent is the use of a palladium carboxylate catalyst in the presence of 1 equivalent of an N-donor ligand, such as pyridine. At a Pd/N ratio of 1, no Cu cocatalyst is required under neat conditions. To ensure catalyst robustness, one should avoid the use of carboxylate anions or N ligands that can undergo cyclopalladation. Other salient features include the control of the activity and regio- and chemoselectivity by the proper design of the electronics and sterics of the anion and ligand, and the dependence of the optimum carboxylate on

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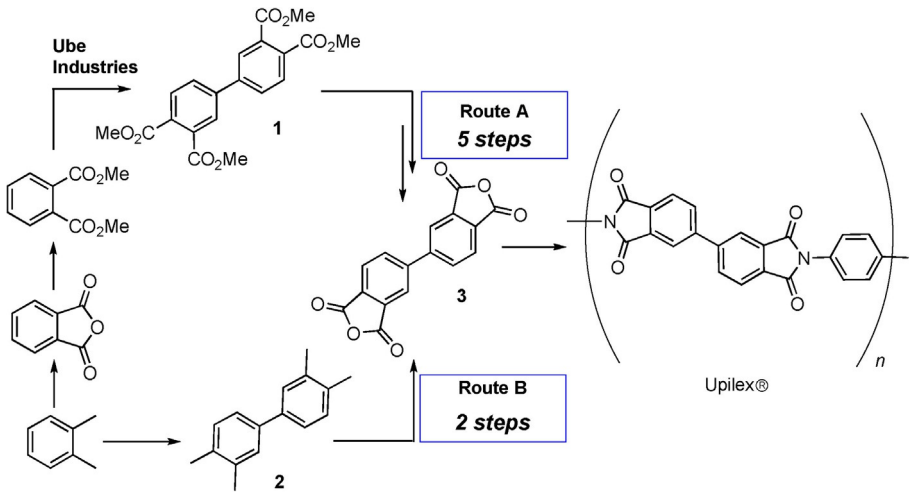
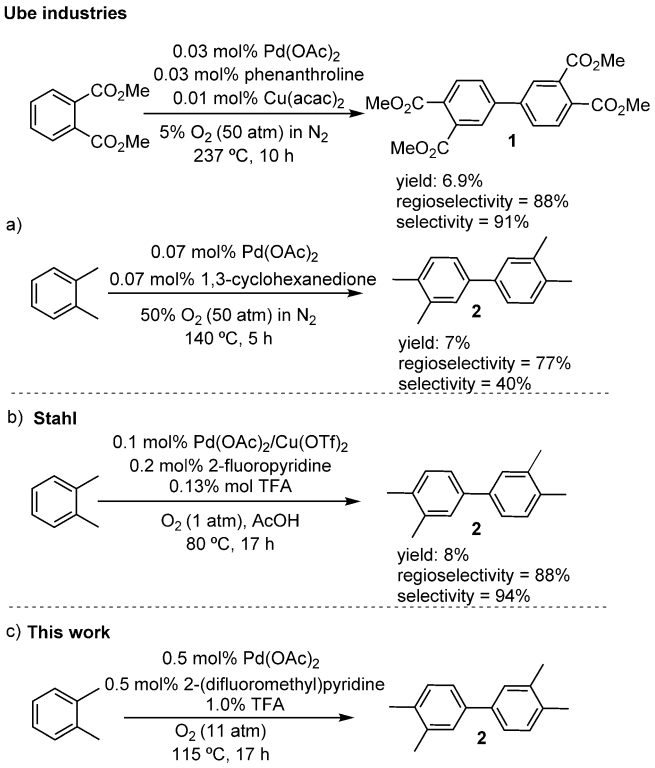


Scheme 1. Current and proposed alternative routes for the industrial synthesis of 4,4′-biphthalic anhydride.



Scheme 2. Developed catalyst for the CDC of arenes towards the synthesis of 4,4′-biphthalic anhydride.

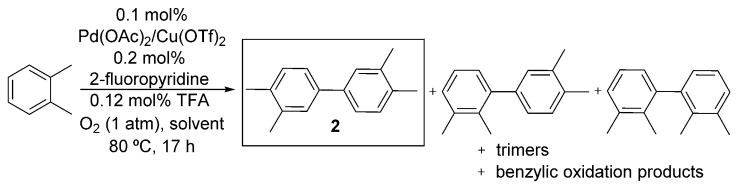
the O_2 pressure. In this article, we report additional results on the CDC of neat *o*-xylene with Pd/N = 1:1 catalysts (Scheme 2c) with a particular focus on a comparison with Pd/N = 1:2 catalysis and neat versus solvent conditions. Evaluation of the deuterium kinetic isotope effect (KIE) with the use of [D_{10}]*o*-xylene provided evidence for three different rate-determining steps, which depends on the catalyst and reaction conditions.

Results and Discussion

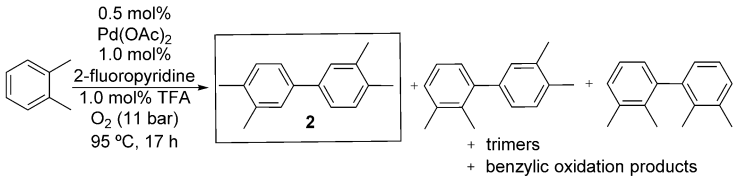
Considering the promising results reported with 2-fluoropyridine as a ligand in acetic acid as the solvent,[9a] we started by exploring Pd catalysts based on 2-fluoropyridine under neat conditions (Table 1). If we used the optimum catalyst composition reported for the aerobic CDC of *o*-xylene in acetic acid as the reaction medium, that is, 0.10 mol% $Pd(OAc)_2$, 0.20 mol% 2-fluoropyridine, 0.12 mol% CF_3CO_2H, and 0.1 mol% $Cu(OTf)_2$ under neat conditions (17 h, 1 bar O_2, 80 °C), the regio- and chemoselectivity were much lower than those reported if the reaction was performed in acetic acid. In addition, the yield decreased to a very low value (Table 1, entry 1 vs. 2). The omission of the $Cu(OTf)_2$ cocatalyst improved the selectivities slightly without affecting the yield (Table 1, entry 3). The yields and selectivities were restored to significant values by increasing the temperature (95 °C), O_2 pressure (11 bar), $Pd(OAc)_2$ loading (0.5 mol%), and amount of CF_3CO_2H (1.0 mol%; Table 1, entry 4). The selectivities eroded significantly if the ligand was omitted under these conditions (Table 1, entry 5). However, a decrease of the amount of ligand from 1.0 to 0.5 mol% (Pd/N = 1:1) boosted the yield significantly without compromising the selectivities (Table 1, entry 6).

After we had identified conditions that led to useful yields and selectivities under neat conditions, we embarked on an extensive screening of pyridines to further optimize the catalyst performance (Figure 1). These ligands were screened under both Pd/N = 1:1 and 1:2 conditions, and the yields are shown as dark gray (Pd/N = 1:2) and light gray (Pd/N = 1:1) bars. For the catalyst with a Pd/N ratio of 1, selectivity ratios are displayed in this graph as orange markers. To emphasize performance differences between the various ligands, selectivities are expressed as the more sensitive ratio of the desired product(s) to the undesired products rather than as a percentage of the total desired plus undesired products. Regioselectivities are expressed as the "regioratio", that is, yield(**2**)/yield(BP^u), in which BP^u is the sum of the undesired regiomeric 2,3,3′,4′/2,2′,3,3′-tetramethyl-1,1′-biphenyl byproducts. Chemoselectivities are expressed as the "chemoratio", that is, yield(2+BP^u)/

Table 1. Influence of the reaction conditions in the CDC coupling of *o*-xylene.



Entry	Remarks	Ar–Ar yield [%][a,b]	Regioselectivity [%][b,c]	Chemoselectivity [%][b,d]
1	AcOH	8.0	88	94
2	No solvent	0.9	67	74
3	No solvent/No Cu	0.9	70	76



4	No remarks	12.6	89	83
5	No ligands	11.9	62	46
6	Ligand/Pd ratio = 1 (0.5 mol%)	17.6	83	79

[a] Collective biaryl yield. [b] Determined by using GC, internal standard = *n*-dodecane. [c] Regioselectivity is the percentage of dimer **2** relative to all dimers. [d] Chemoselectivity is the percentage of all dimer isomers relative to all products formed (dimers, trimers, benzylic oxidation…).

yield(Balc+Bald+Bza+trimers), in which Balc is 2-methylbenzyl alcohol, Bald is 2-methylbenzaldehyde, Bza is 2-methylbenzoic acid, and trimers are all of the isomers with a molecular weight that corresponds to hexamethylterphenyl. Below we summarize some notable findings related to this screening:

- Under Pd/N = 1:2 conditions, pyridines that can be expected to coordinate well to Pd^{II} (i.e., those that are sufficiently electron-rich and devoid of steric hindrance near the N atom) fail to generate active catalysts (Figure 1, L1, L3, L4, L14, L16).
- Electron-poor pyridines that can be expected to coordinate less strongly induce significant yields to biaryls under Pd/N = 1:2 conditions (Figure 1, L2, L6, L8, L11, L12, L17), especially in the case of strong electron-withdrawing *ortho* substituents (Figure 1, L5, L7, L9, L10, L13, L15).
- Those pyridines for which the collective biaryl yield under Pd/N = 1:2 conditions almost equals that under 1:1 conditions, tend to show low regio- and chemoratios (Figure 1, L5, L9, L10, L13).

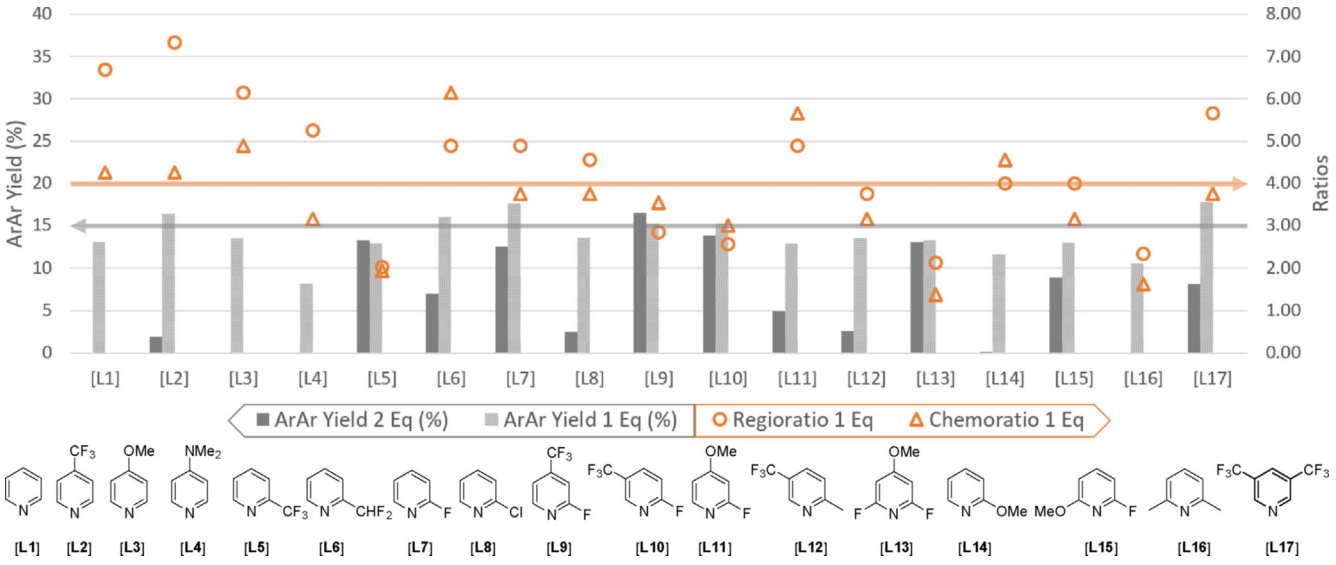


Figure 1. Screening of pyridine ligands.

- Under Pd/N = 1:1 conditions, the electronic effect of changing the *meta* or *para* substituents on the pyridine ligand is relatively small. In the absence of *ortho* substituents, the activity benefits from the presence of electron-withdrawing substituents (Figure 1, L2, L17).
- Pyridines devoid of *ortho* substituents tend to show higher regioratios and increased tendencies towards benzylic oxygenation (see Supporting Information for further details; Figure 1, L1–L4, L17).[13]
- In some cases, the reaction is very sensitive to minor changes of the ligand. For example, the replacement of one F atom by a H atom from 2-(trifluoromethyl)pyridine (L5) to 2-(difluoromethyl)pyridine (L6) leads to a threefold decrease in the trimer formation in agreement with the fact that less electron-withdrawing ligands form less active catalysts that are not so prone to over-arylation (see Supporting Information for further details).

The two horizontal gray and orange arrows on the graph correspond to the minimum criteria to be met by a pyridine ligand to be taken further in subsequent optimizations: collective biaryl yield >15%, regio- and chemoratio >4. Pyridines that lead to a collective biaryl yield >15% and at least one of the ratios >4 are those devoid of too much steric hindrance near the N atom and of a too-strong-electron-withdrawing substitution pattern although it is still more electron-poor than pyridine. These are 4-(trifluoromethyl)pyridine (L2), 2-(difluoromethyl)pyridine (L6), 2-fluoropyridine (L7), and 3,5-bis(trifluoromethyl)pyridine (L17). Both the regio- and chemoratio exceed 4 only with 4-(trifluoromethyl)pyridine and 2-(difluoromethyl)-pyridine. The latter ligand was used in additional experiments because of the somewhat higher regioratio.

If we apply otherwise the same Pd/N = 1:1 conditions as for the ligand screening, a temperature optimization from 85–150 °C was performed for the CDC of *o*-xylene under the influence of the 2-(difluoromethyl)pyridine-based catalyst (Table S4). The collective biaryl yield increased from 13% at 85 °C to 29% at 125 °C and decreased to 15% upon a further increase of the temperature to 150 °C. This may be indicative of catalyst deactivation by Pd black formation at too high temperatures. The regioselectivity was fairly constant over this temperature range, but the chemoselectivity tended to decrease above 115 °C. We judged this temperature to offer the best compromise between optimum activity and selectivity requirements.

At 115 °C/11 bar O_2 and with a $Pd(OAc)_2$ loading of 0.5 mol% as in the above experiments, we then varied the amount of CF_3CO_2H relative to added $Pd(OAc)_2$ from 0 to 50 equivalents (Table S6). In line with our earlier findings,[11] at this high O_2 pressure, the collective biaryl yield benefits from the addition of up to 2 equivalents of a strong carboxylic acid such as CF_3CO_2H. More CF_3CO_2H decreases both the yield and regioselectivity without affecting the chemoselectivity significantly. With 2 equivalents of CF_3CO_2H, the collective biaryl yield reached 26% with a regio- and chemoratio of 5.7 and 6.1, respectively.[14]

To gain insight into the nature of the rate-determining step, the order of the reaction on the Pd and deuterium KIEs were examined. The order of the reaction was determined by the initial rate method under the optimized Pd/N = 1:1 neat conditions described above. The kinetic data indicate a first-order dependence on [Pd] (see Supporting Information).

Deuterium KIEs were determined under various conditions by measuring the conversion obtained at low reaction times with *o*-xylene and [D_{10}]*o*-xylene independently (Table 2).[15] Under the optimized Pd/N = 1:1 neat conditions described above for 2-(difluoromethyl)pyridine as the ligand (0.5 mol% $Pd(OAc)_2$, 0.5 mol% 2-(difluoromethyl)pyridine, 1.0 mol% CF_3CO_2H, 17 h, 11 bar O_2, 115 °C), a KIE of 1.6 was obtained for the CDC reaction (Table 2, entry 1). If the catalyst loading was decreased to 0.1 mol%, the KIE vanished (k_H/k_D = 1.0; Table 2, entry 2). After the restoration of the catalyst loading to 0.5 mol%, we measured the KIEs in the presence of three solvents (50 vol%). In acetic acid, the KIE increased significantly (k_H/k_D = 10–11; Table 2, entry 3). If we replaced acetic acid by non-protic but more polar propylene carbonate, the KIE decreased (k_H/k_D = 2.0; Table 2, entry 4). In non-protic, nonpolar hexafluorobenzene, a very low KIE (k_H/k_D = 1.3; Table 2, entry 5) close to that under neat conditions (Table 2, entries 1 and 2) was obtained.

Table 2. Results of the KIE evaluations.[a]

Entry	Ligand[b]	Equivalents of ligand[c]	$Pd(OAc)_2$ [mol%]	Equivalents of CF_3CO_2H[c]	Solvent[d] (50 vol%)	T [°C]	P_{O_2} [bar]	Equipment[e]	KIE
1	F_2	1	0.5	2	No	115	11	A	1.6
2	F_2	1	**0.1**	2	No	115	11	A	1.0
3	F_2	1	0.5	2	**AA**	115	11	A	10/11[f]
4	F_2	1	0.5	2	**PC**	115	11	A	2.0
5	F_2	1	0.5	2	**F6**	115	11	A	1.3
6	**2F**	**2**	**0.1**	**1.2**	**AA**	**80**	**1**	**B**	20
7	2F	2	0.1	1.2	AA	**80**	**1**	**A**	22
8	2F	2	0.1	1.2	AA	80	**11**	A	20/17[f]
9	2F	2	0.1	1.2	AA	**115**	11	A	12/14[f]
10	2F	2	0.1	1.2	AA	115	**1**	A	15/12[f]

[a] A variable in a row is of bold type if it has been changed compared to the preceding row. [b] F_2 = 2-(difluoromethyl)pyridine; 2F = 2-fluoropyridine. [c] Relative to Pd. [d] AA = acetic acid; F6 = hexafluorobenzene; PC = propylene carbonate. [e] A = autoclave; B = balloon. [f] Duplicate experiment.

The foregoing KIE values with 2-(difluoromethyl)pyridine under Pd/N = 1:1 conditions at 115 °C/11 bar O_2 differ markedly from those obtained by Stahl et al. with 2-fluoropyridine under Pd/N = 1:2 conditions in acetic acid at 80 °C/1 bar O_2.[9b] An unusually large KIE range (k_H/k_D = 18–25) was measured for the latter system if it was applied at various Pd catalyst concentrations. These very high KIE values were ascribed to rate-limiting bimetallic transmetallation, which was supported by additional kinetic measurements that showed a square dependence on [Pd]. In addition to employing 2-fluoropyridine at a Pd/N = 1:2 ratio and 80 °C/1 bar O_2, the KIE study by Stahl on this catalyst system also differed from our study with 2-(difluoromethyl)pyridine in that the Pd/CF_3CO_2H ratio was approximately 1:1 instead of 1:2. We decided to extend our KIE evaluations to this 2-fluoropyridine-based catalyst system, and we focused on the study of its behavior at an elevated temperature and/or pressure compared to the earlier study. From this, we hoped to learn the cause of the near-absence of KIEs under our conditions without a protic and/or polar solvent (Table 2, entries 1, 2, and 5) as compared to the very high KIE values obtained by Stahl et al.[9b] In particular, we aimed to understand whether the large differences in KIEs were due to the use of different catalysts or to the change in reaction conditions.

First, we determined the KIE values under the conditions as employed earlier by Stahl et al.[9b] If we used either a glass vessel connected to a balloon filled with O_2 (Table 2, entry 6) or an autoclave operated at 1 bar O_2 (Table 2, entry 7) we obtained very high KIE values that are fully in accordance with those reported by Stahl et al.[9b] These high values were retained in experiments performed in duplicate, but at 11 bar O_2 instead of 1 bar O_2 (Table 2, entry 8). If the temperature was increased to the value employed in our KIE evaluations with the 2-(difluoromethyl)pyridine-based catalyst system, the KIE decreased markedly to a very similar value to that obtained with this ligand in acetic acid medium (Table 2, entry 9 vs. 3). This suggests that at least if we use acetic acid as the solvent, the KIE is determined largely by the temperature of the reaction, irrespective of which of the two catalyst systems is used.[16] However, in acetic acid, the O_2 pressure does not have a significant effect on the KIE (Table 2, entries 7 and 9 vs. 8 and 10).

The (near) absence of a KIE (Table 2, entries 1, 2, and 5) and first-order dependency on Pd under neat or apolar C_6F_6 solvent conditions may be explained by the rate-limiting dissociation of a carboxylate-bridged dimer under such conditions (see Supporting information for a full kinetic analysis that demonstrates that such a rate-determining step indeed leads to a first-order reaction in Pd). These apolar media disfavor the dissociation of dimeric species into two monometallic species by the solvent-assisted dissociation of carboxylate bridges, as demonstrated for dimeric $[Pd(RCO_2)_2PMe_2Ph]_2$ tertiary phosphine complexes.[17] In the absence of solvolytic assistance, we propose the formation of two monometallic Pd species that contain a κ^2-(O,O)-bound carboxylate.[18] Arene C–H activation only takes place after the formation of a sufficiently reactive, monometallic Pd^{II} species with a weakly bound solvent molecule or κ^2-(O,O) carboxylate. This is in line with a concerted metalation–deprotonation (CMD) mechanism as this requires the simultaneous presence of a vacant site (in the form of a weakly bound functionality) for the incoming arene and a non-bridged carboxylate that accepts the proton liberated upon arene palladation.[19,20]

The generation of a monometallic species by the breaking of the carboxylate bridges is facilitated by the use of coordinating solvents (e.g., propylene carbonate or acetic acid), which induce a switch to other kinetic regimes in which the dimer dissociation is no longer rate-determining. In the case of non-protic but polar propylene carbonate (Table 2, entry 4), the KIE value is at the lower limit of the range observed previously for Pd-based oxidative arene coupling reactions (k_H/k_D = 2–25),[9b,21] which suggests rate-limiting C–H activation (k_H/k_D = 2–5).[21c] For protic acetic acid (Table 2, entry 3), the KIE value approaches the lower limit of the range expected for rate-limiting bimetallic transmetallation (k_H/k_D = 9–25).[9b]

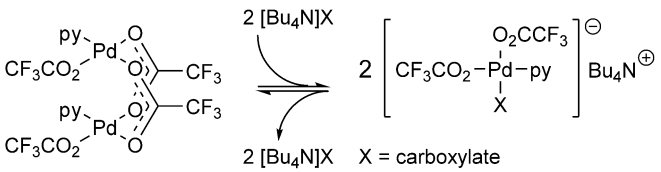
We sought to get further evidence for the presence of dimeric Pd species by adding various (soluble) tetrabutylammonium salts, that is, the tetrafluoroborate, trifluoroacetate, and acetate salts (Table 3). At least for the two carboxylates, it may be anticipated that these have sufficient coordinative strength to induce the (partial) breaking of a trifluoroacetate-bridged dimer into two monometallic tricarboxylate palladate species (in which the remaining coordination site is occupied by the pyridine ligand; Scheme 3).

Compared to the monometallic species that are obtained by bridge cleavage by (neutral) solvent molecules, such negatively charged monometallic palladate species can be expected to be much less electrophilic, and therefore, much less active in a subsequent arene palladation.

Table 3. Effect of tetrabutylammonium salts addition.[a]

Entry	Pd source[b]	Equivalents of CF_3CO_2H[c]	$[Bu_4N]X$[d]	Ar–Ar yield [%][e]
1	TFA	–	–	18.9
2	TFA	–	$X = BF_4^-$	8.2
3	TFA	–	$X = TFA^-$	1.3
4	TFA	–	$X = AcO^-$	0.3
5	Acetate	2	–	22.0
6	Acetate	2	$X = BF_4^-$	7.2
7	Acetate	2	$X = TFA^-$	4.4
8	Acetate	2	$X = AcO^-$	1.5

[a] Conditions: Pd source (0.5 mol%), 2-(difluoromethyl)pyridine (0.5 mol%), $[Bu_4N]X$ (1.0 mol%), and optional CF_3CO_2H (1.0 mol%) in *o*-xylene (1 mL) were stirred for 17 h at 115 °C/11 bar O_2. [b] TFA = $Pd(CF_3CO_2)_2$; Acetate = $Pd(CH_3CO_2)_2$. [c] Relative to Pd. [d] $TFA^- = CF_3CO_2^-$. [e] Collective biaryl yield.



Scheme 3. Dissociation of the dimeric, carboxylate-bridged Pd complex induced by tetrabutylammonium salts.

The effect of additional tetrabutylammonium salts was tested on 2-(difluoromethyl)pyridine-based catalyst systems under Pd/N = 1:1 conditions with either $Pd(CF_3CO_2)_2$ or $Pd(CH_3CO_2)_2$ as the Pd source, the latter in the presence of 2 equivalents CF_3CO_2H to allow the in situ generation of $Pd(CF_3CO_2)_2$. The addition of 2 equivalents of $[Bu_4N]BF_4$ to these systems led to a significant reduction of the collective biaryl yield after 17 h compared to the blank reactions without this additive (Table 3, entries 1 and 5 vs. 2 and 6). These results demonstrate that even an additive such as $[Bu_4N]BF_4$, which has ionic constituents that are both typically regarded to be noncoordinating towards Pd^{II}, exerts a deactivating effect on the CDC process, at least under the solvent-free conditions tested. A significant further reduction of the collective biaryl yield resulted from the addition of $[Bu_4N]CF_3CO_2$ (Table 3, entries 3 and 7) and in particular $[Bu_4N]CH_3CO_2$ (Table 3, entries 4 and 8). Clearly, the collective biaryl yield follows the coordinative strength of the anion inversely ($CH_3CO_2^- > CF_3CO_2^- > BF_4^-$), in line with the hypothesis that the anion-induced dissociation of a carboxylate-bridged dimer is accompanied by reduced catalyst activity because of the build-up of less-reactive palladate species. This deactivating effect of the addition of coordinating anions (as their tetrabutylammonium salts) is very similar to the deactivating effect of using twice the amount of a well-coordinating pyridine, which also results in the formation of well-defined, but unreactive monometallic rather than dimeric Pd species.[18]

Conclusions

The use of Pd/N = 1:1 rather than Pd/N = 1:2 conditions expands the range of pyridines that act as efficient ligands for the palladium carboxylate catalyzed cross-dehydrogenative coupling (CDC) of *o*-xylene without a Cu cocatalyst under neat conditions. Both features, in particular the use of solvent-free conditions, lead to important industrial benefits. We have also formulated some trends with regard to the control of the activity, regioselectivity, and chemoselectivity as a function of electronic and steric features of the pyridine ligand. Preferred pyridines, such as 2-(difluoromethyl)pyridine, lack too much steric hindrance near the N atom and a too-strong-electron-withdrawing substitution pattern. The optimum choice of the (in situ generated) palladium carboxylate depends on the O_2 pressure. High O_2 pressures allow the use of 2 equivalents of trifluoroacetic acid relative to Pd to increase the electrophilicity of the Pd^{II} center. At lower O_2 pressures, strongly electrophilic Pd^{II} is not tolerated because reductive catalyst deactivation by Pd black formation then outcompetes the aerobic reoxidation of Pd^0 to Pd^{II}. Evaluation of the kinetic isotope effects (KIEs) revealed that the kinetics of the Pd/N = 1:1 catalyst system under neat conditions are different from those of neat arene systems with acetylacetone as the ligand ($k_H/k_D \approx 2–5$) or those of Pd/N = 1:2 systems in the presence of acetic acid as solvent studied previously. Although for the latter bimetallic transmetallation was proposed to be the rate-limiting step to explain the very high KIE values ($k_H/k_D = 9–25$),[9b] the present solvent-free Pd/N = 1:1 system is characterized by a rate-limiting step without a KIE ($k_H/k_D \approx 1$). The dissociation of a carboxylate-bridged dimer to generate a much more reactive monometallic Pd species is proposed as a new rate-limiting arene CDC step to explain the near-absence of a KIE and other experimental observations. The intermediate KIE value ($k_H/k_D = 2$) observed with a Pd/N = 1:1 catalyst system if propylene carbonate was used as the solvent is in line with yet another kinetic regime, that is, rate-limiting C–H activation.[9b,21c] Thus, the present study underlines the impact of the reaction conditions (medium, temperature) besides the catalyst system on the kinetic regime. Finally, although the CDC of dimethyl phthalate is estimated to be operated on a kiloton scale,[22] the process is performed with remarkably low Pd turnover numbers.[6e–g] The key to achieve sufficient process economics is Pd recovery and recycling.[4c,23] This needs to be addressed in subsequent process research together with the development of an efficient protocol for the aerobic oxidation of **2** to **3**.

Experimental Section

Note on safety: although we performed thousands of experiments at elevated temperatures and O_2 pressures (up to 11 bar) without any explosion, a detailed safety analysis should be performed before such hazardous conditions are applied. Experiments should only be performed in proper equipment that can withstand the pressure increase in case of an unintended explosion.

In a disposable culture tube, palladium acetate (0.041 mmol), 2-(difluoromethyl)pyridine (0.041 mmol), trifluoroacetic acid (0.082 mmol), and *o*-xylene (1 mL) were combined. The reaction tube was placed in a seven-well aluminum block, which was introduced into the autoclave. The autoclave was purged with O_2 for 2 min, and then the pressure was increased to 11 bar of O_2. The autoclave was placed inside a preheated aluminum block, and the reaction was stirred at 115 °C for 17 h. After that time, the autoclave was removed from the aluminum block and allowed to reach RT before the pressure was released. *n*-Dodecane was added to the reaction mixture as internal standard, and the mixture was filtered through a Celite plug and rinsed with AcOEt. Samples were evaluated by using GC.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: biaryls · C–H activation · cross-dehydrogenative coupling · industrial chemistry · palladium

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[13] As benzylic oxygenation and trimer formation respond differently to the nature of the pyridine ligand, chemoratios (which take into account both types of byproducts) vary in a more unpredictable way with the pyridine structure than regioratios.

[14] From previous observations[9a] at lower O_2 pressures, the addition of an equivalent amount of a strong carboxylic acid is preferred. As the electrophilicity of the Pd^{II} center increases with the amount of added strong acid, and thereby its propensity to reductive catalyst deactivation by Pd black formation, the latter probably outcompetes aerobic re-oxidation of Pd^0 to Pd^{II} at low O_2 pressures.

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