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An improved palladium(II)-catalyzed method for the synthesis of aryl ketones from aryl carboxylic acids and organonitriles

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ABSTRACT

A palladium(II)-catalyzed decarboxylative protocol for the synthesis of aryl ketones has been developed. The addition of TFA was shown to improve the reaction yield and employing THF as solvent enabled the use of solid nitriles and in only a small excess. Using this method, five different benzoic acids reacted with a wide range of nitriles to produce 29 diverse (hetero)aryl ketone derivatives in up to 94% yield.

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The use of aryl carboxylic acids as aryl palladium precursors has attracted significant attention. Compared to other aryl sources, aryl carboxylic acids offer a number of significant advantages including wide commercial availability, low cost, low toxicity, and high chemical stability. Moreover, gaseous CO_2 is the only byproduct produced when the aryl palladium species is formed. Since the groundbreaking decarboxylative Heck-type reaction reported by Myers and co-workers in 2002, a multitude of palladium(II)-catalyzed decarboxylative reactions, including Heck-type and cross-coupling processes, have been discovered.[1–6]

Numerous natural products and pharmaceuticals contain an aryl ketone, often with a substituent at one or both *ortho* positions.[7,8] Furthermore, they often serve as precursors to various important heterocyclic systems including imidazoles,[9] isoxazoles,[10] indoles,[11] and pyrazoles.[12] Previously, the synthesis of aryl ketones from benzoic acids has been limited to harsh methods requiring stoichiometric organolithium reactants,[13] or Friedel–Crafts acylations[14] that are often moisture sensitive and suffer from a lack of regio- and chemoselectivity. More recently, arylstannanes have been used to prepare sterically hindered aryl ketones from acid chlorides, however this procedure suffers from the drawbacks associated with handling toxic tin by-products.[15] Thus, the development of new methods for the preparation of aryl ketones is of significant interest.

The palladium-catalyzed insertion of nitriles, first discovered in 1970,[16] is an attractive strategy for generating the aryl ketone motif due to the often widespread availability and low cost of the nitrile reaction partners. Thus, effective protocols are available utilizing a range of aryl palladium precursors.[17–22] In 2010, Lindh et al.[23] published the synthesis of aryl ketones from aryl carboxylic acids via a Pd(II)-catalyzed decarboxylation followed by addition to a nitrile, protonation of the ketimine intermediate, and hydrolysis to give the aryl ketone product. Importantly, sterically congested aryl ketones could be synthesized as the benzoic acid needs to have an activating *ortho* substituent to facilitate the decarboxylation process. To complement the suggested mechanism based on MS-detected cationic palladium complexes (Fig. 1),[23] DFT calculations on sterically congested aromatic substrates have been carried out to improve the detailed understanding of the process.[24]

However, in the protocol of Lindh et al., the nitriles were used as solvents and the scope was thus limited to liquid substrates.[23] Accordingly, we sought to expand the scope of this procedure to enable the use of solid nitriles as reaction partners and to decrease the amount of nitrile required for a productive reaction. As a starting point for our investigation, 2,6-dimethoxybenzoic acid (**1a**, 0.5 mmol) and phenylacetonitrile (**2d**, 5 equiv), were chosen as model substrates for a solvent screen, since these substrates were among the most high yielding in the previous study.[23] A catalytic system consisting of $Pd(O_2CCF_3)_2$ (8 mol %) and 6-methyl-2,2′-bipyridine, (9.6 mol %) was employed. Among the solvents evaluated[25] a mixture of THF/water (10/1) performed best and product **3d** was isolated in 68% yield (Table 1, entry 4), after microwave

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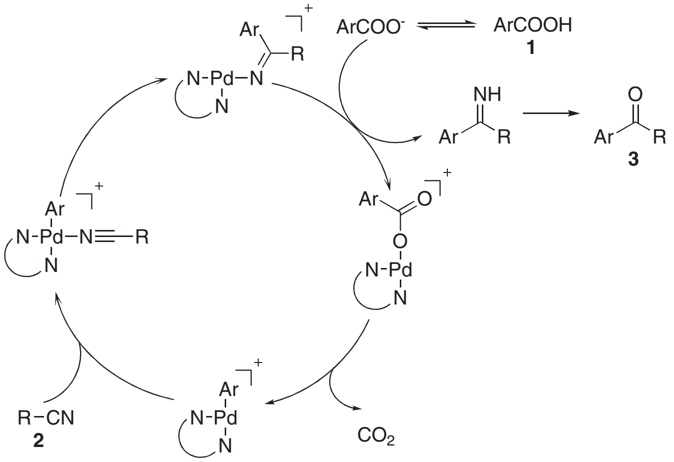
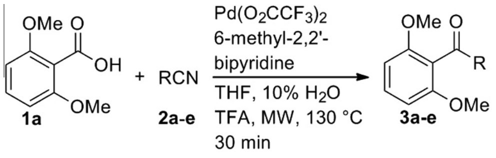
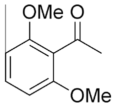
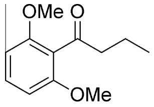
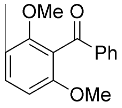
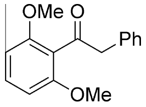
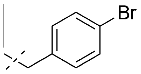
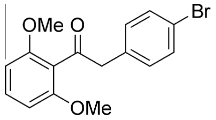


Figure 1. The proposed mechanism supported by MS-detected cationic palladium complexes.[23]

Table 1
Optimization of the conditions for the Pd(II)-catalyzed decarboxylative addition of 2,6-dimethoxybenzoic acid (**1a**) and nitriles **2a–e** producing **3a–e**



Entry	R	Product		Isolated yield (%)
1	Me **2a**		**3a**	71[a,b]
2	Pr **2b**		**3b**	64[c,b]
3	Ph **2c**		**3c**	82[a,b]
4	Bn **2d**		**3d**	68[d]
5				86[c]
6				89[a,b]
7				84[e]
8				76[f]
9				94[a]
10	 **2e**			78[c]
11				60[g]
12				45[h]

[a] A microwave vial was charged with $Pd(O_2CCF_3)_2$ (8 mol %), 6-methyl-2,2′-bipyridine (9.6 mol %), and THF (2 mL), and the mixture was stirred for 5 min. 2,6-Dimethoxybenzoic acid (1 mmol), nitrile (5 equiv), TFA (1 equiv), and H_2O (200 μL) were added and the mixture exposed to MW heating for 30 min at 130 °C.

[b] The highest yields obtained by Lindh et al. were 94% for **3a**, 73% for **3b**, 20% for **3c**, and 73% for **3d**.

[c] Like[a] but nitrile (2 equiv).

[d] Like[a] but no TFA, only conducted on a 0.5 mmol scale, 130 °C for 4 h, followed by addition of formic acid (1 mL) and the mixture was heated to 130 °C for 15 min.

[e] Like[a] but nitrile (2 equiv), Pd (4 mol %) and ligand (4.8 mol %).

[f] Like[a] but Pd (2 mol %) and ligand (4.8 mol %).

[g] Like[a] but nitrile (1 equiv), 2,6-dimethoxybenzoic acid (2 equiv).

[h] Continuous-flow scale-out example using a flow of 0.5 mL/min of the reaction mixture, corresponding to 2 min in the MW heated zone, and with the temperature set at 210 °C. The stock solution consisted of 0.71 M **1a** (yield determining) in THF with 10% water, **2e** (5 equiv), TFA (25 equiv), $Pd(O_2CCF_3)_2$ (4 mol %), and 6-methyl-2,2′-bipyridine (9.6 mol %). The yield is based on the work-up of an aliquot of 14 mL of the solution with the theoretical yield of 1 mmol of **3e**.

(MW) heating[26] at 130 °C for four hours followed by hydrolysis with formic acid.

The addition of TFA has previously been shown to be beneficial for the palladium-catalyzed synthesis of aryl ketones from aryl sulfinates and organonitriles,[19] and we reasoned that this may also improve our current reaction, as addition of an acid helps to protonate and liberate the ketimine from the intermediate Pd-complex (a role otherwise given solely to the benzoic acid). In addition, TFA facilitates the hydrolysis of the ketimine to form the ketone.[23,24] Gratifyingly, the addition of one equivalent of TFA led to an increase in the isolated yield of **3d** (89%) and allowed the reaction time to be shortened to 30 minutes as well as promoting in situ hydrolysis (Table 1, entry 6).

Notably, using the new protocol afforded aryl ketones **3a–c** in isolated yields that were either better (**3c**) or in the same range as the previous study.[23] Reducing the amount of nitrile from five to two equivalents had only a slight effect on the yield in some cases, for example **3d** was isolated in 86% yield compared to 89% when two and five equivalents of **2d** were used, respectively (Table 1, entries 5 and 6). In other reactions the effect was more pronounced: two equivalents of 2-(4-bromophenyl)acetonitrile (**2e**) provided **3e** in 78% yield, whereas five equivalents gave **3e** in a 94% yield (Table 1, entries 9 and 10). Unfortunately, the presence of large amounts of excess nitrile often led to difficulties during the purification process and therefore most of the reactions were conducted using two equivalents of nitrile.

In an attempt to reduce catalyst loading the synthesis of **3d** was conducted with $Pd(O_2CCF_3)_2$ (4 mol %) and ligand (4.8%) instead of 8 mol % and 9.6%, respectively. This resulted in a slight decrease in the yield from 86% to 84% (Table 1, entries 5 and 7). A further decrease to 2 mol % of Pd-catalyst produced **3d** in a lower 76% yield (Table 1, entry 8). The synthesis of **3k** was not affected by the reduction to 4 mol % of the Pd-catalyst (Table 2, entries 6 and 7). When the reaction was carried out with less reactive substrates (see Table 3) there was a notable difference in conversion (according to LC–MS analysis) between 4% and 8 mol % of Pd-catalyst. Accordingly, in order to develop and evaluate a robust protocol, most of the experiments in Tables 1 and 2 were run with 8 mol % of $Pd(O_2CCF_3)_2$.

Having identified suitable conditions, we next set about exploring the scope and limitations of the method (Table 2). The protocol seemed robust concerning electronic effects as the electron-rich nitrile **2f** provided **3f** in a 72% yield, whereas **3g** was isolated in 73% yield using the electron-poor nitrile **2g** (Table 2, entries 1 and 2). The aldehyde-containing nitrile **2h** returned only a modest yield of **3h** (50%, Table 2, entry 3) due to the competing Pd(II)-catalyzed insertion of the aldehyde,[27,28] which furnished an alcohol in trace amounts that could be detected by LC–MS analysis. Heterocyclic nitriles were also well tolerated and the electron-rich furan-2-carbonitrile (**2j**) gave **3j** in 68% yield, whereas the yield obtained with electron-poor nicotinonitrile (**2k**) was slightly higher, 82% (Table 2, entries 5 and 6).

To our surprise the sterically hindered aryl ketone **3i** was isolated in 38% yield, despite the presence of two *ortho*-methoxy groups on the benzoic acid and an *ortho*-bromo substituent on the benzonitrile (Table 2, entry 4). Full chemoselectivity was

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