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

Linda Axelsson, Jean-Baptiste Veron, Jonas Sävmarker, Jonas Lindh, Luke R. Odell, Mats Larhed *

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, BMC, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden

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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.

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

* Corresponding author. Tel.: +46 18471 4667; fax: +46 18471 4474.
E-mail address: mats.larhed@orgfarm.uu.se (M. Larhed).

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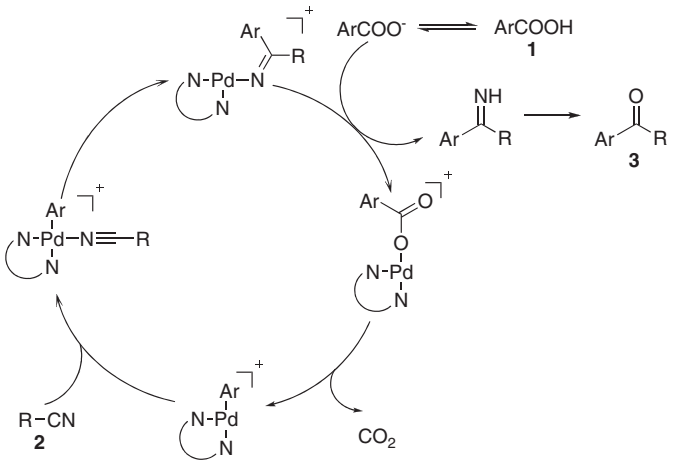


Figure 1. The proposed mechanism supported by MS-detected cationic palladium complexes.[23]

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

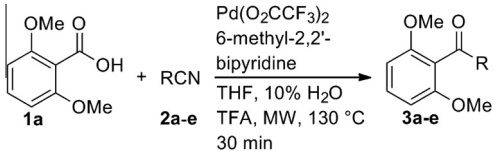
The addition of TFA has previously been shown to be beneficial for the palladium-catalyzed synthesis of aryl ketones from aryl sulfinates and organonitriles,[19] and we reasoned that this may also improve our current reaction, as addition of an acid helps to protonate and liberate the ketimine from the 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).

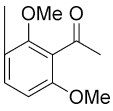
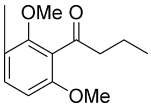
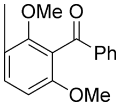
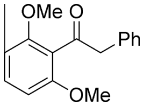
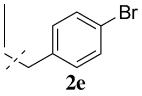
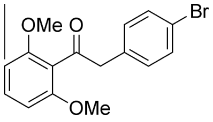
Notably, using the new protocol afforded aryl ketones **3a–c** in isolated yields that were either better (**3c**) or in the same range as the previous study.[23] Reducing the amount of nitrile from five to two equivalents had only a slight effect on the yield in some cases, for example **3d** was isolated 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

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 %).

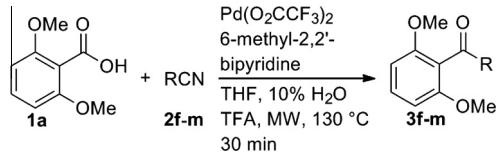
[g] Like[a] but nitrile (1 equiv), 2,6-dimethoxybenzoic acid (2 equiv).

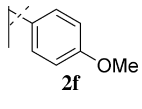
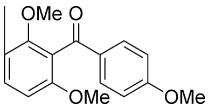
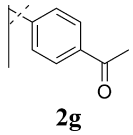
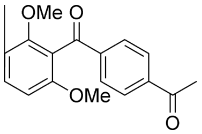
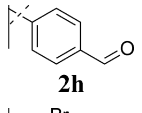
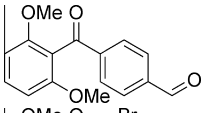
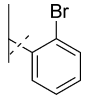
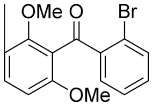
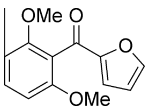
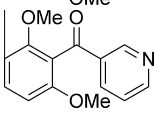
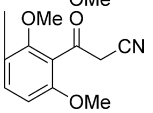
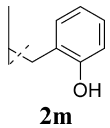
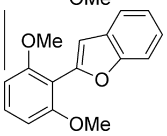
[h] Continuous-flow scale-out example using a flow of 0.5 mL/min of the reaction mixture, corresponding to 2 min in the MW heated zone, and with the temperature set at 210 °C. The stock solution consisted of 0.71 M **1a** (yield determining) in THF with 10% water, **2e** (5 equiv), TFA (25 equiv), $Pd(O_2CCF_3)_2$ (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**.

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

Table 2
Scope and limitations of the Pd(II)-catalyzed decarboxylative addition of 2,6-dimethoxybenzoic acid **1a** and nitriles **2f–m** producing **3f–m**



Entry	R	Product		Isolated yield (%)
1	 **2f**		**3f**	72[a]
2	 **2g**		**3g**	73[a]
3	 **2h**		**3h**	50[a]
4	 **2i**		**3i**	38[a]
5	 **2j**		**3j**	68[a]
6 7	 **2k**		**3k**	82[a] 83[b]
8	 **2l**		**3l**	42[a]
9 10 11	 **2m**		**3m**	47[c] 37[d] 53[e]

[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 (2 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] Like[a] but nitrile (5 equiv), Pd (2 mol %), and ligand (4.8 mol %).
[c] Like[a] but nitrile (1 equiv), 2,6-dimethoxybenzoic acid (2 equiv), and TFA (10 equiv), 1 h, 130 °C.
[d] Like[a] but nitrile (2 equiv), TFA (10 equiv), 1 h 130 °C.
[e] Like[a] but nitrile (2 equiv), TFA (3 equiv), no H_2O addition, dry THF, 1 h 130 °C.

obtained with both **3e** and **3i** without any Pd(0)-catalyzed reactions on the bromine. The use of dicyanide **2l** produced **3l** in a modest 42% yield and the diarylated compound was detected in trace amounts (according to LC–MS analysis, Table 2, entry 8).

Inspired by the work of Wang et al.,[22] an attempt was made to synthesize 2-(2,6-dimethoxyphenyl)benzofuran using our new protocol. However, it was necessary to increase the amount of TFA to 10 equiv to promote complete in situ cyclization of the 1-(2,6-dimethoxyphenyl)-2-(2-hydroxyphenyl)ethanone intermediate. This procedure afforded the desired product **3m** in 37% and 47% yields, using an excess of either the nitrile or benzoic acid, respectively (Table 2, entries 9 and 10). Competing formation of benzofuran-2(3*H*)-one, via hydrolysis of the nitrile **2m** and subsequent cyclization, was detected by LC–MS analysis. In an attempt to minimize byproduct formation, the number of equivalents of TFA was reduced from ten to three and dry THF was used, however, this strategy was only partly successful providing **3m** in 53% yield (Table 2, entry 11).

In cases where the nitrile is more expensive or more precious than the carboxylic acid, it may be desirable to reverse the stoichiometry and use the nitrile as the limiting reagent. When nitrile **2e** (2 mmol) was reacted with benzoic acid **1a** (1 mmol) it had a negative impact on the reaction outcome (78% vs 60%, Table 1, entries 10 and 11).

If the benzoic acid is available in excess concentration, problems with the competing background decarboxylation reaction decrease, but if the organonitrile is present in excess it is beneficial for coordination and insertion of the nitrile into the Pd-complex. Which of these two factors are the most important for the reaction outcome may differ with the benzoic acids and nitriles used.

Continuous flow microwave-assisted organic synthesis, CF-MAOS, can be used as a practical method for producing large quantities without the drawbacks of large-scale batch synthesis, that is, safety considerations, need for special and bulky equipment, etc., while still maintaining the shorter reaction times and energy efficiency associated with microwave chemistry.[29–31] Thus, an effort was made to include an example using a non-resonant microwave system for CF-MAOS.[29] A model reaction with 2,6-dimethoxybenzoic acid (**1a**) and 2-(4-bromophenyl)acetonitrile (**2e**) was chosen for a scale-out using a straight tubular reactor made of borosilicate glass (3 mm inner diameter, 200 mm long).

Unfortunately, Pd(0) precipitation on the reactor inner wall led to problems with local superheating and rupture of the reactor.[32,33] An increase in ligand concentration and decrease in Pd loading did not give a stable system amenable to safe and reliable upscaling. Although the addition of the palladium reoxidant, *p*-benzoquinone, led to a reduction in palladium precipitation, it also resulted in a significant decrease in product formation (according to GC-MS analysis). Finally, increasing the amount of TFA to 25 equivalents made upscaling possible at 0.5 mL/min, 210 °C and provided aryl ketone **3e** in a moderate 45% yield (Table 1, entry 12). Further optimization needs to be performed in order to use flow chemistry as an upscaling opportunity using this protocol.

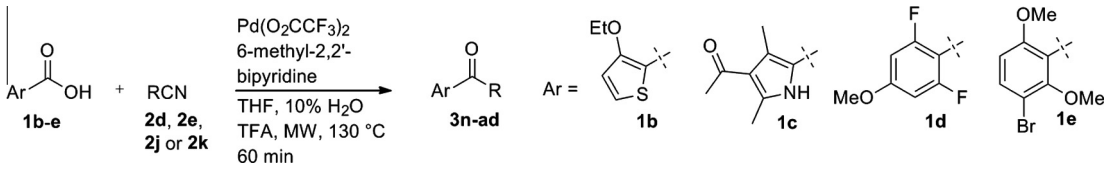
Next, an effort was made to further expand the batch reaction scope and evaluate additional benzoic acids using a selection of the nitriles from Tables 1 and 2. Thus, four diverse benzoic acids and four nitriles were chosen for investigation and the resulting (hetero)aryl ketone products are presented in Table 3. During initial attempts using the optimized conditions we noted a decrease in reactivity when using other less electron-rich carboxylic acids,[30,34] and therefore five equivalents of nitrile were used. The reactions were MW heated for one hour at 130 °C in order to achieve full conversion.

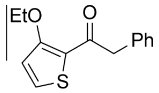
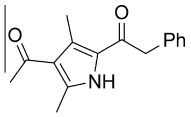
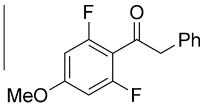
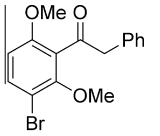
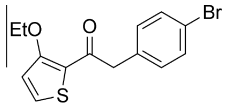
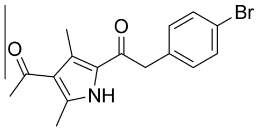
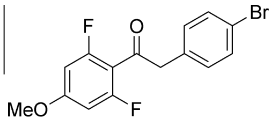
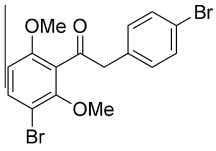
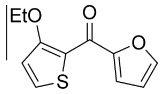
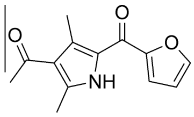
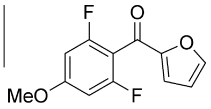
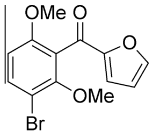
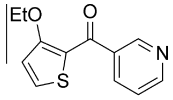
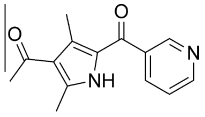
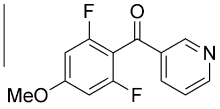
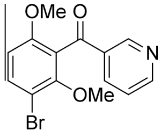
Rewardingly, most of the reactions occurred efficiently with various heterocyclic acids and nitriles. When 3-ethoxythiophene-2-carboxylic acid (**1b**) or 4-acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**1c**) was heated with the nitriles, 2-phenylacetonitrile (**2d**), 2-(4-bromophenyl)acetonitrile (**2e**), furan-2-carbonitrile (**2j**), and nicotinonitrile (**2k**), the reactions gave full conversion and the heteroaryl ketones **3n**, **3o**, **3v**, **3w**, **3z**, and **3ab** were isolated in moderate to good yields, 48–73% (Table 3).

In all the reactions involving 2-(4-bromophenyl)acetonitrile (**2e**), difficulties in removing the excess nitrile during product purification were encountered. Thus, these reactions were conducted using either two equivalents of nitrile (**3r**, 41% and **3s**, 70%) or a 2:1 excess of the benzoic acid substrate (**3t**, 76% and **3u**, 73%).

The less electron-rich carboxylic acids, 2,6-difluoro-4-methoxybenzoic acid (**1d**) and 3-bromo-2,6-dimethoxybenzoic acid (**1e**), exhibited lower reactivity and full conversion of the starting

Table 3
Pd(II)-catalyzed reaction between benzoic acids **1b–e** and nitriles **2d**, **2e**, **2j**, and **2k** producing ketones **3n–ad**



Product	Isolated yield (%)	Product	Isolated yield (%)	Product	Isolated yield (%)	Product	Isolated yield (%)
 **3n**	61[a]	 **3o**	73[a]	 **3p**	68[b]	 **3q**	68[b]
 **3r**	41[c]	 **3s**	70[c]	 **3t**	76[d]	 **3u**	73[d]
 **3v**	59[a]	 **3w**	64[a]	 **3x**	75[b]	 **3y**	36[b] 50[d]
 **3z**	48[a]	 **3ab**	66[a]	 **3ac**	26[b]	 **3ad**	9[b] 19[d]

[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. Benzoic acid **1b**, **1c**, **1d**, or **1e** (1 mmol), nitrile **2d**, **2e**, **2j**, or **2k** (5 equiv), TFA (1 equiv), and H_2O (200 μL) were added and the mixture exposed to MW heating for 1 h at 130 °C.
[b] Like[a] but THF (500 μL) and H_2O (50 μL).
[c] Like[a] but nitrile **2e** (2 equiv).
[d] Like[a] but THF (500 μL), H_2O (50 μL), benzoic acid **1b**, **1c**, **1d**, or **1e** (2 equiv) and nitrile **2e**, **2j**, or **2k** (1 equiv).

material was not observed (according to LC–MS analysis). A four-fold decrease in the amount of solvent improved the reaction outcome providing **3p**, **3q**, and **3x** in satisfactory yields, 68–75% (Table 3).

The disappointing yields of 26% and 9% for the synthesis of **3ac** and **3ad** might be a consequence of nitrogen coordination to palladium. Additionally, full conversion was not achieved in the synthesis of (3-bromo-2,6-dimethoxyphenyl)(furan-2-yl)methanone (**3y**), resulting in a low isolated yield of 36%. An attempt to improve the yield by having the benzoic acid in excess gave a slight increase in the isolated yield (50%). Finally, the same stoichiometry switch provided **3ad** in a slightly increased yield of 19%.

In conclusion, an improved, rapid, and straightforward protocol for decarboxylative Pd(II)-catalyzed addition reactions has been developed to synthesize aryl ketones from aryl carboxylic acids. Importantly, the reaction allowed the use of solid organonitriles in only a 2–5-fold excess. Employing THF as the solvent with one equivalent of TFA provided direct in situ hydrolysis. A total of 29 (hetero)aryl ketones were synthesized in moderate to excellent yields from five different *ortho*-functionalized benzoic acids and a wide variety of organonitriles.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.109.

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34. Using the protocol described in Table 3, conditions,[a] we also tried to synthesize aryl ketones using the following benzoic acids; 2,6-dimethoxynicotinic acid, 3-methylbenzofuran-2-carboxylic acid, 2,4,5-trimethoxybenzoic acid, 3-methylbenzo[*b*]thiophene-2-carboxylic acid, 4-methylthiazole-5-carboxylic acid, 2,4,6-trimethylbenzoic acid, 2-methoxy-4-methylbenzoic acid, and 3-methoxy-2-naphthoic acid. The aryl ketone products could be detected with all these benzoic acids, but the four chosen for further expansion showed the best conversion according to LC–MS analysis (Table 3).