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Full Article

Palladium(II)-Catalyzed Desulfitative Synthesis of Aryl Ketones from Sodium Arylsulfinates and Nitriles: Scope, Limitations and Mechanistic Studies

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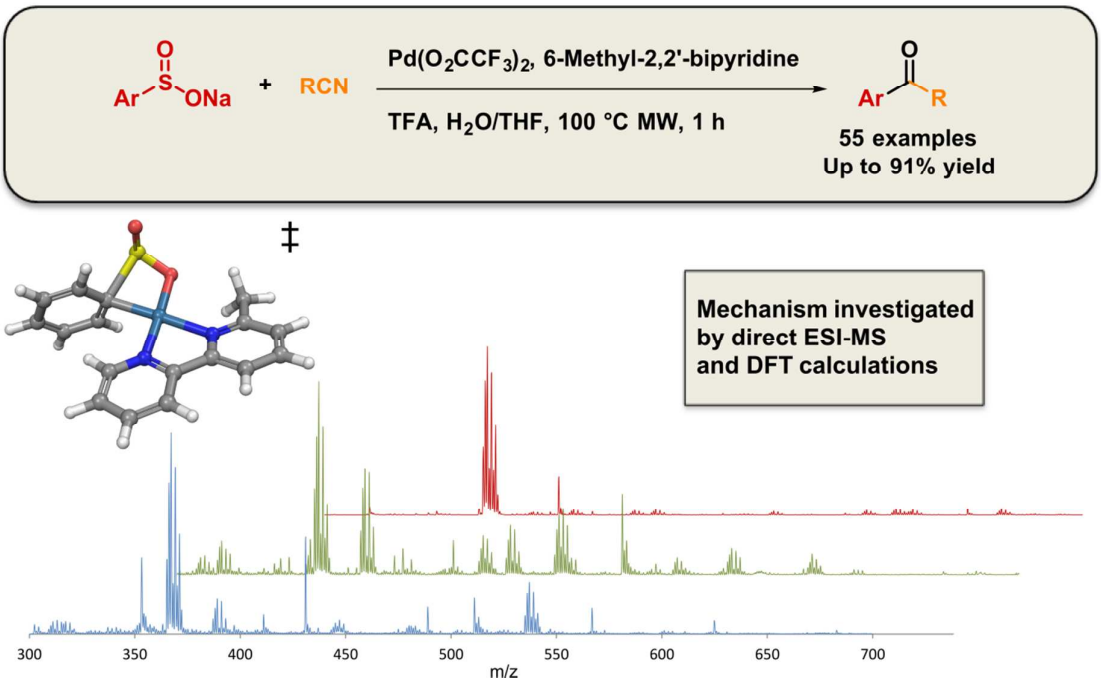
Graphical abstract



Abstract

A fast and efficient protocol for the palladium(II)-catalyzed production of aryl ketones from sodium arylsulfinates and various organic nitriles under controlled microwave irradiation has been developed. The wide scope of the reaction has been demonstrated by combining 14 sodium arylsulfinates and 21 nitriles to give 55 examples of aryl ketones. One additional example illustrated that through the choice of the nitrile reactant, benzofurans are also accessible. The reaction mechanism was investigated by electrospray ionization mass spectrometry (ESI-MS) and DFT calculations. The desulfitative synthesis of aryl ketones from nitriles was also compared to the corresponding transformation starting from benzoic acids. Comparison of the energy profiles indicates that the free energy requirement for decarboxylation of 2,6-dimethoxybenzoic acid and especially benzoic acid are higher than the corresponding desulfitative process for generating the key aryl palladium intermediate. The detected palladium(II) intermediates and the DFT calculations provide a detailed understanding of the catalytic cycle.

Keywords: palladium, catalysis, desulfination, arylsulfinates, aryl ketones, microwave, ESI-MS, density functional theory, mechanism

Introduction

The aryl palladium precursor of choice for palladium(II)-catalyzed reactions has long been aryl boronic acids since these are widely commercially available, tolerate a broad variety of functional groups and are relatively non-toxic.[1] However, the shelf life of aryl boronic acids is limited as trimeric cyclic anhydrides are formed and many boronic acids are not easy to handle due to their waxy appearance.[2] Thus, different alternative aryl boron derivatives such as aryl trifluoroborates[2] and aryl MIDA esters[3] have been investigated as improved and more stable arylating agents.

Throughout the years we have investigated various aryl palladium precursors such as aryl boronic acids[4,5], aryltrifluoroborates[2,6] and more recently benzoic acids for Pd(II)-catalyzed Heck arylations[7], synthesis of aryl amidines[8] and aryl ketones[9]. Although aryl carboxylic acids may undergo decarboxylation to form an aryl palladium complex, the use of aryl carboxylic acids for palladium-catalyzed decarboxylative coupling reactions is limited to electron rich, sterically congested *ortho* substituted substrates or the use of a Cu decarboxylative co-catalyst.[8,10,11] The limitations of Pd(II)-catalyzed decarboxylative coupling reactions prompted us to investigate alternative aryl palladium precursors. Based on a literature report by Garves[12] and preliminary DFT calculations we hypothesized that arylsulfinic acids could be used as aryl palladium precursors through the loss of SO_2 without the requirement of activating *ortho* substituents. The carbopalladation of nitriles by aryl palladium complexes has been effected by employing different arylating agents[13–19] and is an interesting route to aryl ketones. Thus, we initiated a preparative investigation and communicated our initial findings concerning the use of sodium arylsulfinates and nitriles for the Pd(II)-catalyzed synthesis of aryl ketones[20] simultaneously as Wang[21] and Deng[22].

After these initial reports sodium arylsulfinates have proven to be useful for different types of reactions, ranging from the production of biaryls through homocoupling[23] to the synthesis

of caffeine analogues[24]. Other examples of Pd-catalyzed synthesis of biaryls using arylsulfinates include coupling with aryl halides[25–27] or aryl triflates[28] in addition to Hiyama-type cross-coupling reactions[29].

Desulfitative Heck type reactions have been developed[30–33]. Using different protocols conjugate addition could be achieved instead[34,35]. Also, desulfitative hydroarylation has been effected using sodium arylsulfinates as arylating agents in the presence of diarylacetylenes to yield trisubstituted alkenes[36].

Recently, Pd-catalyzed desulfitative arylation through C-H-activation of heteroarenes such as azoles[37,38] and indoles[39,40] has attracted notable attention. Also, C-H activation of electron poor polyfluoroarenes and coupling with sodium arylsulfinates has been reported.[41]

We have focused our efforts in investigating and optimizing the Pd(II)-catalyzed desulfitative synthesis of aryl ketones. This functionality is a common functional group in pharmaceuticals[42–44] and natural products[45–47], and the introduction of a ketone functionality also opens up for a range of subsequent reactions in multi-step synthesis.

Herein, we report the mechanistic investigation and the scope of the microwave (MW) assisted synthesis of aryl ketones by Pd(II)-catalyzed addition of sodium arylsulfinates to organic nitriles and subsequent hydrolysis.

Results and discussion

Initial DFT investigation of arylsulfinates as arylating agents

Previous calculations of Pd(II)-mediated decarboxylation of benzoic acid analogues have shown that the π-systems of the carboxyl group and aryl group are approximately orthogonal in the transition state (TS).[11,48,49] Thus, the energy required to reach the TS will include the energy required to disrupt the stabilization obtained from the aryl–carboxyl conjugated system. The sterical hindrance provided by *ortho* substituents in benzoic acid analogues should hinder this stabilization and thus lower the required energy to reach the TS. In fact, *ortho* substituents in benzoic acid analogues, such as 2,6-dimethoxybenzoic acid, are a prerequisite for productive reactions relying on Pd(II)-mediated decarboxylation. We hypothesized that arylsulfinic acids could be utilized as analogous aryl acids in the reaction and thus avoid the strong stabilization from the aryl–carboxyl interaction, even without *ortho* substituents. In order to investigate the difference in stabilization energy from the interaction between the aryl group and the acidic group in benzenesulfinic acid (the corresponding acid of **1e**), benzoic acid, and 2,6-dimethoxybenzoic acid the energy requirements for dihedral angle rotation of the acidic groups in the aryl acids were investigated using DFT calculations. The results of the calculations are presented in Figure 1.

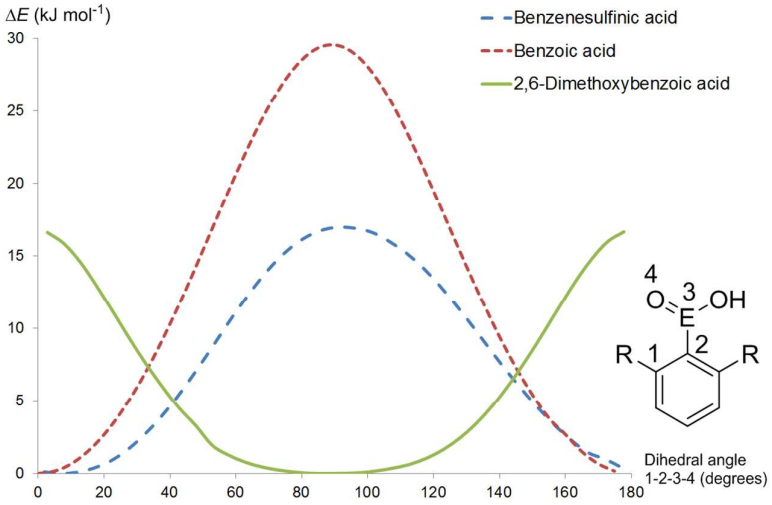


Figure 1. Energy diagram of the dihedral angle scan of benzenesulfinic acid, benzoic acid and 2,6-dimethoxybenzoic acid.

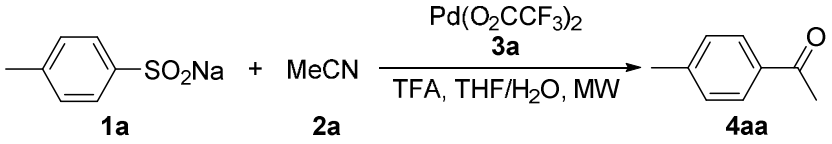
From the dihedral scans it is clear that there is a substantial difference in energy stabilization between the investigated aryl acids. In benzoic acid the lowest energy is obtained when the phenyl ring and the carboxyl group are coplanar and the maximum energy is reached when the groups are orthogonal. On the contrary, for 2,6-dimethoxybenzoic acid the coplanar geometry is the energy maximum while the orthogonal geometry is the energy minimum in the calculations, as a consequence of the steric hindrance from the two *ortho*-methoxy substituents. In line with the discussion above regarding the geometry of the activated complex at the TS for decarboxylation the *ortho* substituents are clearly lowering the required energy in Pd(II)-mediated decarboxylation. The trigonal pyramidal geometry of the sulfinic acid moiety makes a direct dihedral angle comparison to the trigonal planar carboxylic acid moiety difficult. The calculated energy maximum for benzenesulfinic acid occurs when the SO bond is orthogonal to the phenyl. However the energy requirement for the dihedral angle rotation is substantially lower for benzenesulfinic acid with a maximum energy requirement of 17 kJ mol^{-1} compared to 30 kJ mol^{-1} for benzoic acid. Because of the

lower energy requirement to arrange a suitable geometry in the activated complex towards the TS, benzenesulfinic acid may be a more productive aryl source compared to benzoic acid.

Optimization of reaction conditions

The starting point for optimizing the conditions for the desulfitative addition of 4-methylbenzenesulfinate (**1a**) to acetonitrile (**2a**) was the protocol previously developed for Pd(II)-catalyzed decarboxylative addition to nitriles.[9] This protocol proved inefficient for the transformation and only traces of the desired product **4aa** was observed. Thus, the catalyst loading was increased to 8% (12% ligand), the excess of the nitrile reactant was decreased to 5 equiv, the amount of water was increased, THF was used as a cosolvent and TFA was added to effect *in situ* hydrolysis of the intermediate ketimine (see Table 1). The stoichiometry of TFA proved to be crucial – the use of 1 equiv furnished 19% (entry 2) while increasing the amount to 10 equiv yielded 87% of the desired aryl ketone **4aa** (entry 4). Increasing the amount of TFA further did not improve the yield of **4aa** (entry 5).

Table 1. Preparation of aryl ketone 4aa by palladium(II)-catalyzed desulfitative reaction between 1a and 2a using varying amounts of TFA.

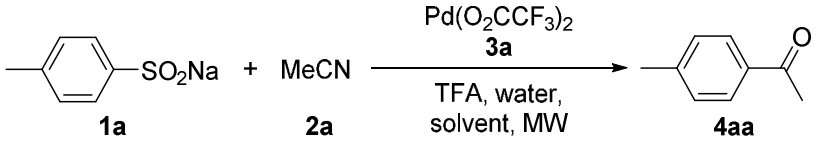


Entry	Amount of TFA	Yield[a]
1	0 equiv	Traces[b]
2	1 equiv	19%
3	5 equiv	72%
4	10 equiv	87%
5	20 equiv	83%

[a] Isolated yield, > 95% purity. Reaction conditions: A 0.5-2 mL process vial was charged with **1a** (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol, 8%), **3a** (0.06 mmol, 12%), H_2O/THF: 1/1 (1.4 mL), **2a** (2.5 mmol, 5 equiv) and the specified amount of TFA. The sealed vial was heated in a MW reactor at 100 °C for 1 h. [b] According to GCMS.

Different solvents were screened and the solvent system with equal amounts of water and tetrahydrofuran (THF) proved to be the most suitable for the reaction. However, the use of the corresponding water/1,4-dioxane system resulted in similar yield, see Table 2 (entries 4 and 5). More polar solvents seemed to favor the reaction. The use of neat water as the solvent resulted in excessive hydrolysis of nitrile **2a** under these conditions (analysis by LCMS showed significant formation of the corresponding amide).

Table 2. Preparation of aryl ketone 3aa by palladium(II)-catalyzed desulfitative reaction between 1a and 2a using different solvents.

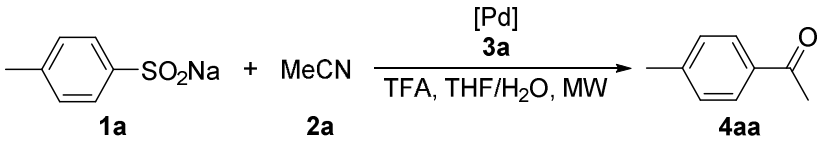


Entry	Solvent	Yield[a]	Entry	Solvent	Yield[a]
1	THF	39%	6	Isobutanol	64%
2	Dioxane	43%	7	DMF	54%
3	Water	28%	8	DME	28%
4	Water/THF (1:1)	87%	9	NMP	17%
5	Water/Dioxane (1:1)	77%	10	DMSO	5%

[a] Isolated yield, > 95% purity. Reaction conditions: A 0.5-2 mL process vial was charged with **1a** (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol, 8%), **3a** (0.06 mmol, 12%), solvent (1.4 mL), **2a** (2.5 mmol, 5 equiv) and TFA (5 mmol, 10 equiv). One equivalent of H_2O was added to the reaction mixtures not using H_2O as solvent. The sealed vial was heated in a MW reactor at 100 °C for 1 h.

Having identified a suitable medium for the reaction, different palladium sources were screened (see Table 3). $Pd(O_2CCF_3)_2$ was found to be more efficient than $Pd(O_2CCH_3)_2$ (compare entry 1 and 2), and as expected $PdCl_2$ was not an efficient catalyst for the transformation (entry 5). Although $Pd(dba)_2$ is a palladium(0) complex the use of this precatalyst provided a 32% yield of product **4aa** under these conditions (entry 4). When no palladium source was added to the reaction mixture no product formation was observed.

Table 3. Preparation of aryl ketone 3aa by palladium(II)-catalyzed desulfitative reaction between 1a and 2a using different palladium sources.



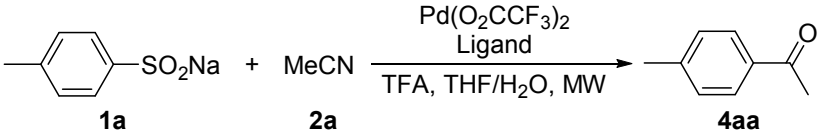
1a **2a** **4aa**

Entry	Pre-catalyst	Yield[a]
1	$Pd(O_2CCF_3)_2$	87%
2	$Pd(O_2CCH_3)_2$	47%
3	$Pd(OH)_2$	47%
4	$Pd(dba)_2$	32%
5	$PdCl_2$	5%

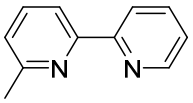
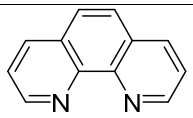
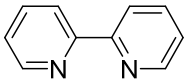
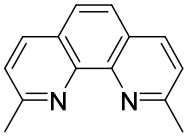
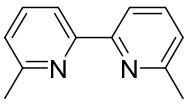
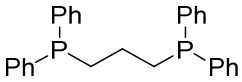
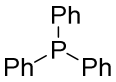
[a] Isolated yield, > 95% purity. Reaction conditions: A 0.5-2 mL process vial was charged with **1a** (0.5 mmol), the specified palladium source (0.04 mmol, 8%), **3a** (0.06 mmol, 12%), H_2O/THF: 1/1 (1.4 mL), **2a** (2.5 mmol, 5 equiv) and TFA (5 mmol, 10 equiv). The sealed vial was heated in a MW reactor at 100 °C for 1 h.

A number of common ligands used in transition metal catalysis were screened but only the use of 6-methyl-2,2'-dipyridyl (**3a**) as the ligand provided a satisfying yield, see Table 4. The methyl group in **3a** appears to be very important for high catalyst efficiency in the corresponding decarboxylative reaction.[9] Interestingly, the introduction of a second methyl group drastically decreases the efficiency of the catalytic system. This difference also exists in the decarboxylative coupling with nitriles[9] but seems to be greater for sulfinates than carboxylic acids. None of the phosphine ligands that were tested proved to provide effective catalysts for the transformation.

Table 4. Preparation of aryl ketone 3aa by palladium(II)-catalyzed desulfitative reaction between 1a and 2a using different ligands.



1a **2a** **4aa**

Entry	Ligand	Yield[a]	Entry	Ligand	Yield
1	 **3a**	87%	6	 **3f**	31%
2	 **3b**	39%	7	 **3g**	8%
3	 **3c**	8%	8	 **3h**	n.d.[b]
4	 **3d**	15%	9	Dppf **3i**	n.d.[b]
5	DMSO **3e**	10%	10	No ligand	Traces[b]

[a] Isolated yield, > 95% purity. Reaction conditions: A 0.5-2 mL process vial was charged with **1a** (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol, 8%), ligand (0.06 mmol, 12%), H_2O/THF: 1/1 (1.4 mL), **2a** (2.5 mmol, 5 equiv) and TFA (5 mmol, 10 equiv). The sealed vial was heated in a MW reactor at 100 °C for 1 h. [b] According to GCMS.

Investigation of scope and limitations

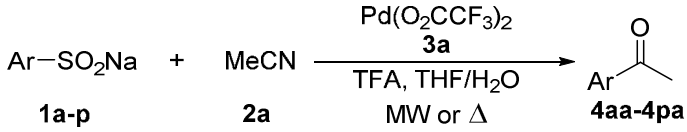
A limited number of sodium arylsulfinates have previously been evaluated for the desulfitative addition to nitriles and therefore we decided to evaluate the scope of the reaction by allowing various sodium arylsulfinates to react with acetonitrile under the optimized conditions. As depicted in Table 5 both electron donating aryl substituents *e.g.* 4-methoxy (entry 1) and moderately electron withdrawing substituents *e.g* 4-chloro (entry 6) are tolerated. Compounds containing these substituents may be converted into the corresponding aryl ketones in good yields (79% for either sodium arylsulfinate mentioned above). Reactions were also performed under conventional heating, but consistently resulted in lower yield (entries 1, 5 and 6). The difference is probably due to a higher reaction temperature using the MW reactor than using conventional heating where the thermometer measures the temperature of the metal block, not the temperature of the reaction mixture[50,51]. The reaction mixture is also heated *in situ* using the MW reactor, in contrast to conventional heating where the walls of the reaction vessel are heated which may result in decomposition of the catalyst[52,53].

Interestingly, sodium 2,4,6-trimethylbenzenesulfinate (entry 11), whose analogue is a reactive substrate in the decarboxylative reaction[9], only affords 5% yield of the desired aryl ketone. The reactivity of arylsulfinates seems truly orthogonal to carboxylic acids as *ortho*-substitution hinders the reaction while unsubstituted substrates work well. It is worth mentioning that aryl halides are tolerated as compounds containing 4-chloro and 4-fluoro substituents, respectively, give satisfying yields (entry 6 and 7). This indicates that competing Pd(0)-catalyzed processes are not a significant issue. However, moving the chloro substituent to the *meta* position drastically decreases the yield of the desired aryl ketone as the reaction results in significant biaryl formation through homocoupling of the arylsulfinate. Very

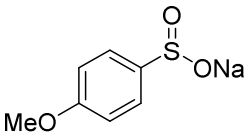
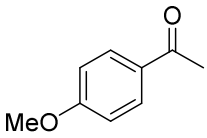
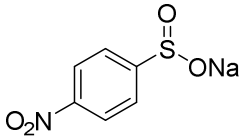
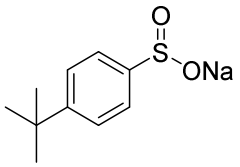
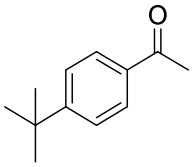
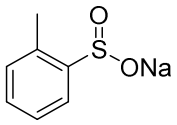
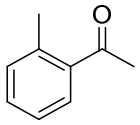
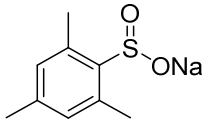
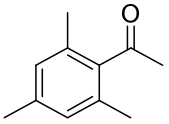
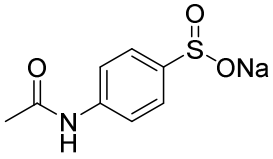
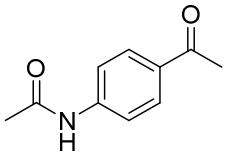
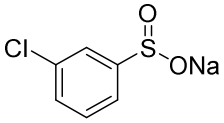
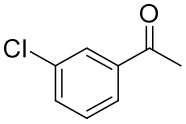
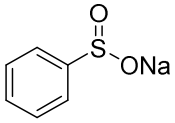
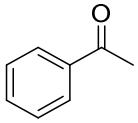
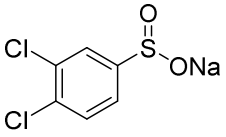
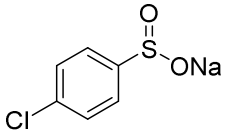
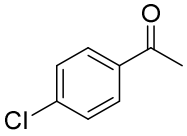
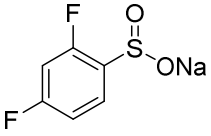
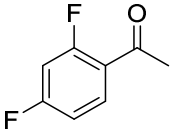
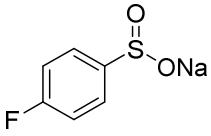
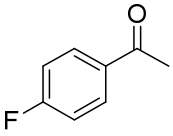
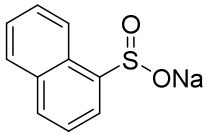
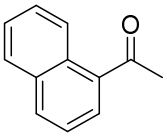
electron poor aryl sulfinates provided poor yields and analysis by GC-MS revealed that 4-trifluoromethylbenzenesulfinate and sodium 4-nitrobenzenesulfinate are even more prone to biaryl formation.

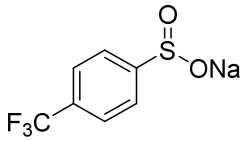
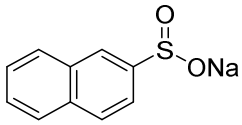
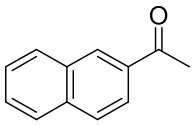
It was observed that 4-acetamidobenzenesulfinate is hydrolyzed and protodesulfinated to form aniline under the optimized conditions. However, when the amount of water was reduced to 0.2 mL and the amount of **2a** was increased to 2 mL 57% of the desired product could be isolated (entry 4). In addition to substituted benzenesulfinates, 1- and 2-naphthylsulfinate can successfully be employed in the synthesis of the corresponding ketones (entry 15 and 16).

Table 5. Preparation of aryl ketones by palladium(II)-catalyzed desulfitative reaction between different sodium arylsulfinates with 2a.



1a-p **2a** **4aa-4pa**

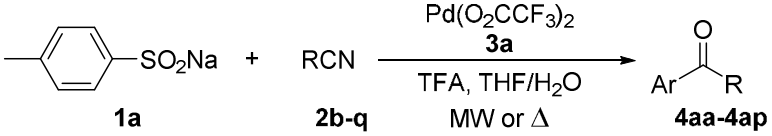
Entry	$ArSO_2Na$	Product	Yield[a]	Entry	$ArSO_2Na$	Product	Yield
1	 **1b**	 **4ba**	79%[b]/ 31%[c]	9	 **1i**	Not detected	-
2	 **1c**	 **4ca**	51%[b]	10	 **1j**	 **4ja**	66%[b]
3	**1a**	**4aa**	87%[b]	11	 **1k**	 **4ka**	5%[b]
4	 **1d**	 **4da**	Traces[b]/ 57%[d]	12	 **1l**	 **4la**	12%[b]
5	 **1e**	 **4ea**	77%[b]/ 61%[c]	13	 **1m**	Traces[e]	-
6	 **1f**	 **4fa**	79%[b]/ 49%[c]	14	 **1n**	 **4na**	18%[b]
7	 **1g**	 **4ga**	73%[b]	15	 **1o**	 **4oa**	71%[b]

8	 **1h**	Not detected	-	16	 **1p**	 **4pa**	30%[b]

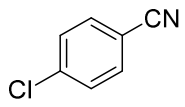
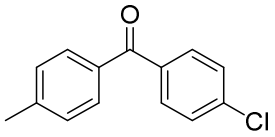
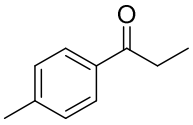
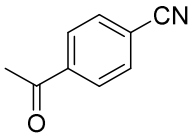
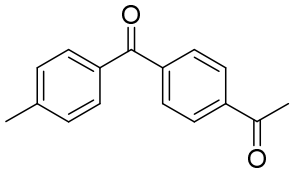
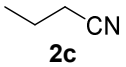
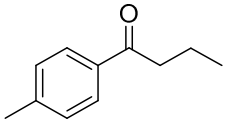
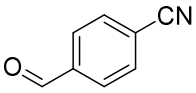
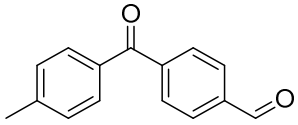
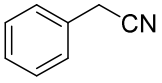
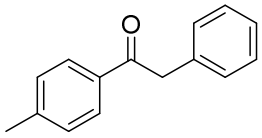
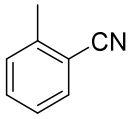
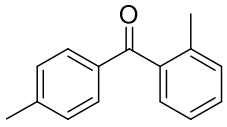
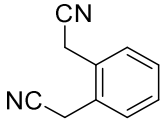
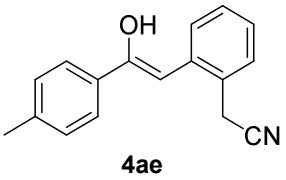
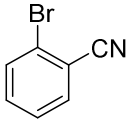
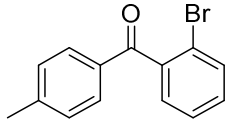
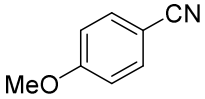
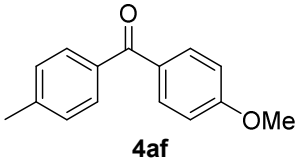
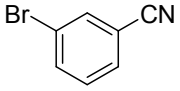
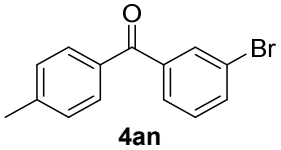
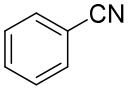
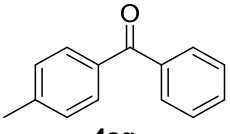
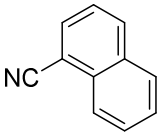
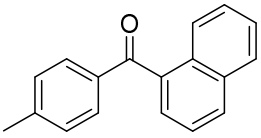
[a] Isolated yield, > 95% purity. [b] Reaction conditions: A 0.5-2 mL process vial was charged with sodium arylsulfinate (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol, 8%), **3a** (0.06 mmol, 12%), H_2O/THF: 1/1 (1.4 mL), **2a** (2.5 mmol, 5 equiv) and TFA (5 mmol, 10 equiv). The sealed vial was heated in a MW reactor at 100 °C for 1 h. [c] Same conditions as [b], except heated in a heating block at 100 °C for 16 h. [d] Same conditions as [b], except performed in 2 ml **2a** with 0.2 ml water. [e] According to GCMS.

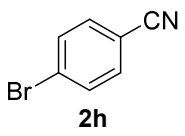
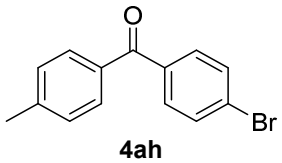
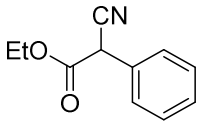
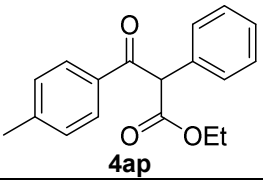
Next, the scope of the nitrile coupling partner was investigated. Aliphatic, benzylic and aromatic nitriles were allowed to react with **1a** to provide the corresponding products, see Table 6. Aromatic nitriles with electron donating groups such as 4-methoxy (entry 6) or electron withdrawing groups such as 4-acetyl (entry 10) worked well (68% and 61%, respectively), demonstrating the wide scope of the reaction. The use of 4-formyl benzonitrile resulted in a lower yield compared to 4-acetyl benzonitrile, probably because of side reactions of the formyl group (entry 11). Again, the Pd(II)-catalyzed reaction displayed excellent chemoselectivity as reactions with arylhalide nitriles showed no traces of homocoupling or dehalogenation. Also, no difference in reactivity between the regioisomers of bromobenzonitrile was observed (entries 8, 12 and 13). The product from the reaction with the bifunctional nitrile 2,2'-(1,2-phenylene)diacetonitrile (entry 5) resulted in monocoupling under these conditions and was isolated as the enol in 31% yield. The use of the sterically hindered ethyl 2-cyano-2-phenylacetate (entry 15) afforded satisfying yield of the desired product and no hydrolysis of the ethyl ester was observed.

Table 6. Preparation of aryl ketones by palladium(II)-catalyzed desulfitative reaction between 1a with different nitriles.



1a **2b-q** **4aa-4ap**

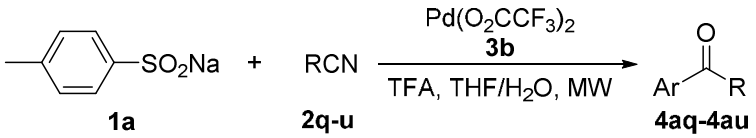
Entry	RCN	Product	Yield[a]	Entry	RCN	Product	Yield
1	**2a**	**4aa**	87%[b]	9	 **2i**	 **4ai**	62%[b]
2	 **2b**	 **4ab**	91%[b]/ 83%[c]	10	 **2j**	 **4aj**	51%[b]
3	 **2c**	 **4ac**	91%[b]	11	 **2k**	 **4ak**	42%[b]
4	 **2d**	 **4ad**	87%[b]	12	 **2l**	 **4al**	62%[b]
5	 **2e**	 **4ae**	31%[b]	13	 **2m**	 **4am**	70%[b]
6	 **2f**	 **4af**	68%[b]	14	 **2n**	 **4an**	67%[b]
7	 **2g**	 **4ag**	89%[b]/ 74%[c]	15	 **2o**	 **4ao**	42%[b]

8	 **2h**	 **4ah**	68%[b]	16	 **4ap**	 **4ap**	49%[b]

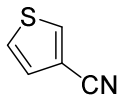
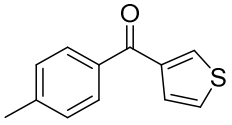
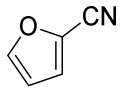
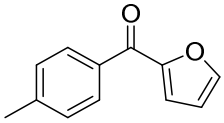
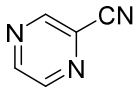
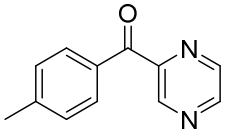
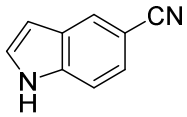
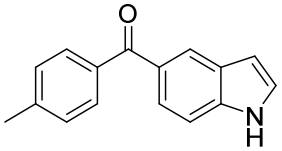
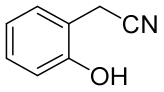
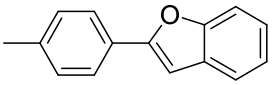
[a] Isolated yield, > 95% purity. [b] Reaction conditions: A 0.5-2 mL process vial was charged with **1a** (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol, 8%), **3a** (0.06 mmol, 12%), H_2O/THF: 1/1 (1.4 mL), nitrile (2.5 mmol, 5 equiv) and TFA (5 mmol, 10 equiv). The sealed vial was heated in a MW reactor at 100 °C for 1 h. [c] Same conditions as [b], except heated in a heating block at 100 °C for 16 h.

To further demonstrate the usefulness of the reaction, different heterocyclic nitriles were investigated. The synthesis of 2-arylbenzofurans by desulfitative coupling with 2-(gem-dibromovinyl)phenols was recently reported[54] and as shown in Table 7 the desulfitative coupling of sodium arylsulfinate with (2-hydroxyphenyl)acetonitrile **2v** could also be used to access this class of compounds. The product **4au** is formed by aryl ketone formation and subsequent intramolecular condensation.

Table 7. Preparation of heteroaryl ketones and benzofuran by palladium(II)-catalyzed desulfitative reaction between 1a with different nitriles.



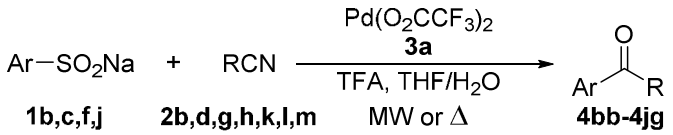
1a **2q-u** **4aq-4au**

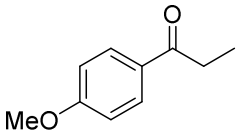
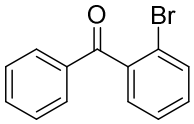
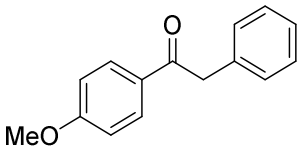
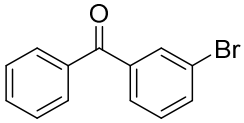
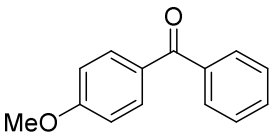
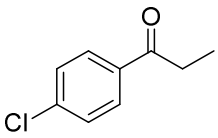
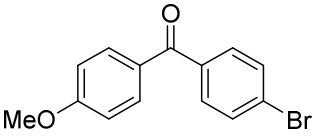
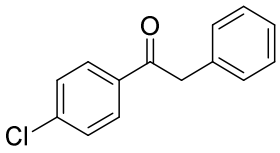
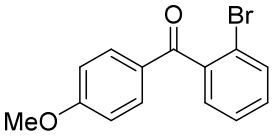
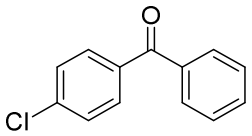
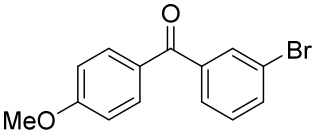
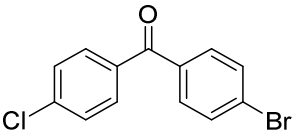
Entry	RCN	Product	Yield[a]
1	 **2q**	 **4aq**	67%[b]
2	 **2r**	 **4ar**	53%[b]
3	 **2s**	 **4as**	40%[b]
4	 **2t**	 **4at**	50%[b]
5	 **2u**	 **4au**	49%[b]

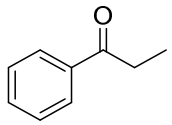
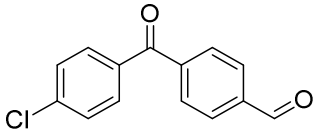
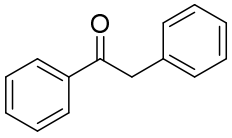
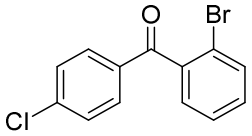
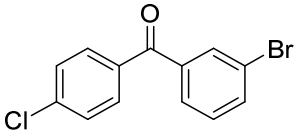
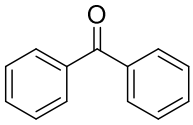
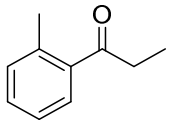
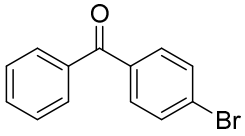
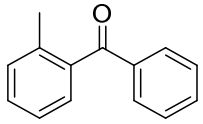
[a] Isolated yield, > 95% purity. Reaction conditions: A 0.5-2 mL process vial was charged with **1a** (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol, 8%), **3a** (0.06 mmol, 12%), H_2O/THF: 1/1 (1.4 mL), nitrile (2.5 mmol, 5 equiv) and TFA (5 mmol, 10 equiv). The sealed vial was heated in a MW reactor at 100 °C for 1 h.

The results in Table 8 illustrates that electron rich and moderately electron poor sodium arylsulfinates can be combined with any of a number of aromatic and aliphatic nitriles to give the corresponding aryl ketones in 51-89% yields of **4bb-4jg**. Aryl ketone **4bg** was synthesized in satisfying yield by combining 4-methoxybenzene sulfinate (**1b**) with benzonitrile (**2g**) (entry 3) and could also be synthesized from benzenesulfinate (**1e**) and 4-methoxybenzonitrile (**2f**) (entry 9). However, using the more electron rich sodium arylsulfinate resulted in higher yield which is consistent with the trend shown in Table 5. The consistently high yields underscore the usefulness of this swift and straightforward reaction protocol.

Table 8. Preparation of aryl ketones by palladium(II)-catalyzed desulfitative reaction between different sodium arylsulfinates and nitriles.



Entry	$ArSO_2Na$	RCN	Product	Yield[a]	Entry	$ArSO_2Na$	RCN	Product	Yield
1	**1b**	**2b**	 **4bb**	66[b]/ 64%[c]	12	**1c**	**2l**	 **4el**	62%[b]
2	**1b**	**2d**	 **4bd**	77%[b]/ 56%[c]	13	**1c**	**2m**	 **4em**	58%[b]
3	**1b**	**2g**	 **4bg**	74%[b]/ 65%[c]	14	**1f**	**2b**	 **4fb**	73%[b]/ 73%[c]
4	**1b**	**2h**	 **4bh**	62%[b]	15	**1f**	**2d**	 **4fd**	66%[b]/ 58%[c]
5	**1b**	**2l**	 **4bl**	62%[b]	16	**1f**	**2g**	 **4fg**	77%[b]/ 55%[c]
6	**1b**	**2m**	 **4bm**	62%[b]	17	**1f**	**2h**	 **4fh**	51%[b]

7	**1c**	**2b**	 **4eb**	89%[b]	18	**1f**	**2k**	 **4fk**	53%[b]
8	**1c**	**2d**	 **4ed**	76%[b]/ 22%[c]	19	**1f**	**2l**	 **4fl**	89%[b]
9	**1c**	**2f**	**4bg**	62%[b]	20	**1f**	**2m**	 **4fm**	54%[b]
10	**1c**	**2g**	 **4eg**	70%[b]	21	**1j**	**2b**	 **4jb**	66%[b]
11	**1c**	**2h**	 **4eh**	61%[b]	22	**1j**	**2g**	 **4jg**	84%[b]

[a] Isolated yield, > 95% purity. [b] Reaction conditions: A 0.5-2 mL process vial was charged with sodium arylsulfinate (0.5 mmol), $Pd(O_2CCF_3)_2$ (0.04 mmol, 8%), **3a** (0.06 mmol, 12%), H_2O/THF: 1/1 (1.4 mL), nitrile (2.5 mmol, 5 equiv) and TFA (5 mmol, 10 equiv). The sealed vial was heated in a MW reactor at 100 °C for 1 h. [c] Same conditions as [b], except heated in a heating block at 100 °C for 16 h.

Mechanistic investigation

Density functional theory study

In order to further study the mechanism of the Pd(II)-mediated desulfitative reaction and compare with the corresponding decarboxylative reaction we initiated a theoretical investigation by means of DFT calculations. Particularly we were interested in a computational understanding of the desulfination step, which has not previously been described. In addition to benzenesulfinic acid and benzoic acid, 2,6-dimethoxybenzoic acid was also included in the investigation since this is a well-known substrate in productive decarboxylative reactions. A 1:1 THF:water mixture was used in the experimental reaction protocol but since solvent mixtures were not supported in the calculations, water was chosen as the solvent for the computational study.

The calculations were initiated from complex **I** (see Figure 2) in which **3a** is associated to $Pd(O_2CCF_3)_2$. The calculated energies in the reactions are reported relative to this complex. For the reaction employing benzenesulfinic acid stepwise ligand exchange via dissociation of trifluoroacetate and association of **1b** (complexes **II** to **IVa**) gave the positively charged complex **IVa** as the lowest found energy minimum prior to the desulfination TS. In **IVa** both oxygen atoms in the sulfinic moiety are coordinated to the two vacant sites on Pd(II). In order to proceed over **TS-Ia** the binding mode of benzenesulfinate is altered into complex **VIa** to allow for an interaction between Pd(II) and the phenyl group. From complex **VIa** 19.3 kJ mol^{-1} is required to reach **TS-Ia**. The total energy required for the desulfination step (**IVa** to **TS-Ia**) is calculated to 46.5 kJ mol^{-1}. From **TS-Ia** the Pd–phenyl intermediate **VIIa** is formed and replacing SO_2 with the nitrile (**2a**) gives complex **VIIIa**, which was the lowest energy minimum found after desulfination.

Comparisons of the energy profile for desulfination of benzenesulfinic acid with decarboxylation of benzoic acid and 2,6-dimethoxybenzoic acid in Figure 2 shows that the energy required for decarboxylation of benzoic acid (117.9 kJ mol^{-1}, **Vb** to **TS-Ib**) is 2.5 times higher than desulfination (46.5 kJ mol^{-1}, **IVa to TS-Ia**). It should be noted that the lowest energy minimum found prior to **TS-Ib** is the neutral complex **Vb** and that this energy comparison of a neutral and a cationic complex is associated with a higher degree of computational uncertainty, compared to the case of desulfination. However, the free energy requirement for decarboxylation of benzoic acid should still be significantly higher compared to desulfination because of the large energy difference between them. Decarboxylation of 2,6-dimethoxybenzoic acid is also higher in energy than desulfination, at 66.1 kJ mol^{-1} going from **VIc** to **TS-Ic**. The geometries of the activated complexes at the TSs for decarboxylation and desulfination are depicted in Figure 3. Studies on desulfination and decarboxylation of methyl acids in Cu-catalyzed systems have shown the same trend with desulfination having a lower free energy requirement.[55]

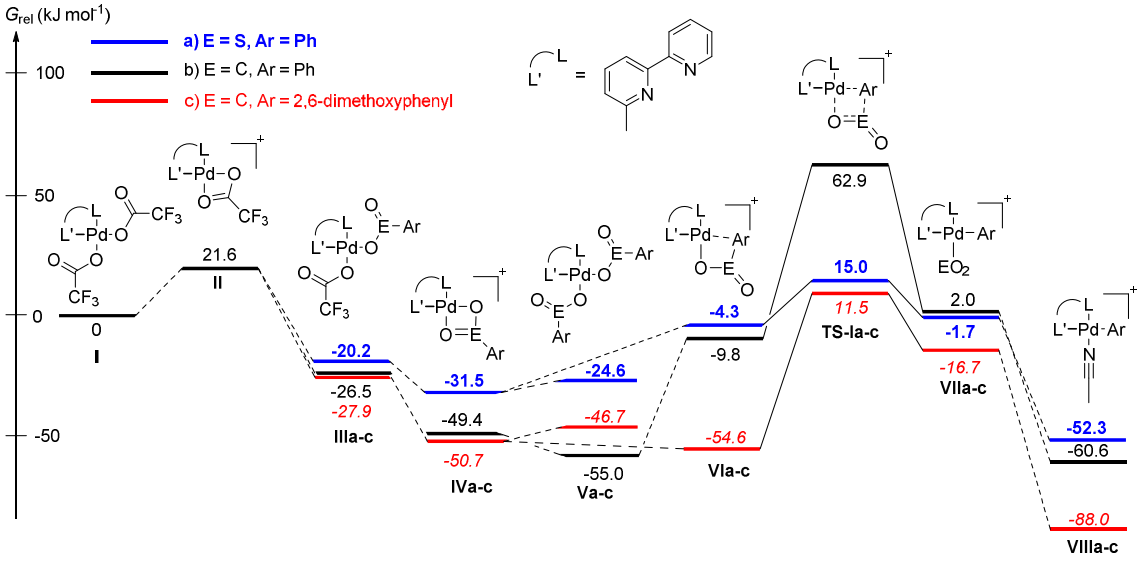


Figure 2. Free energy profiles of the Pd(II)-mediated desulfination and decarboxylation steps.

a) b)

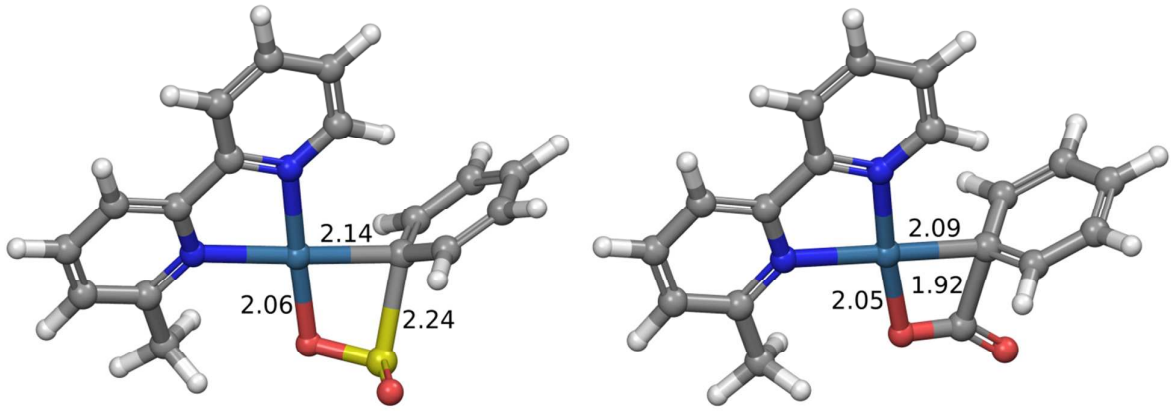


Figure 3. Geometry of the activated complexes for a) desulfination of benzenesulfinic acid **1e** (**TS-Ia**), b) decarboxylation of benzoic acid (**TS-Ib**). Selected bond lengths (Å) are shown.

Complex **VIII** constitutes the starting point for the carbopalladation step (Figure 4). We have previously shown that the carbopalladation of cyanamides is facilitated by a high electron density on the aryl group.[8] This trend seems to be consistent also with nitriles. The free energy requirement for carbopalladation of acetonitrile (**VIII** to **TS-II**) with phenyl was calculated to 99.1 kJ mol^{-1} and the corresponding carbopalladation with 2,6-dimethoxyphenyl was calculated to 81.6 kJ mol^{-1}, which shows a clear advantage when using 2,6-dimethoxybenzoic acid as substrate. For the desulfitative reaction the free energy requirement for the backward reaction from **VIII**, which leads back to **Va**, is lower in energy compared to the forward carbopalladation step. However, the forward reaction from **VIII** leads to lower free energy and thus provides a driving force for the reaction.

From complex **IX**, formation of the imine and subsequent hydrolysis proceeds to give the aryl ketone product. In the calculated model reaction the imine released after **IX** and ammonia

formed during hydrolysis leave the catalytic cycle as neutral species. In the experimental desulfitative protocol the added 10 equiv TFA will protonate these species but this is not computationally investigated herein. Finally, a new aryl acid is coordinated to Pd and this constitutes the corresponding starting point for desulfination/decarboxylation (**IVa**,**Vb** or **VIc**) in the next catalytic cycle.

Assuming that either desulfination/decarboxylation or carbopalladation provides the highest energy requirements in the reaction the calculations suggest that the rate determining step of the reaction depends on which aryl acid is used. For benzoic acid, which is not a productive reactant in the reaction investigated herein, decarboxylation is clearly the rate determining step with a required energy of 117.9 kJ mol^{-1} compared to 99.1 kJ mol^{-1} for carbopalladation. On the other hand, carbopalladation of the nitrile is calculated to be the rate determining step when using either benzenesulfinic acid or 2,6-dimethoxybenzoic acid with a free energy requirement of 99.1 kJ mol^{-1} and 81.6 kJ mol^{-1}, respectively, compared to 46.5 kJ mol^{-1} and 66.1 kJ mol^{-1}, respectively, for desulfination and decarboxylation.

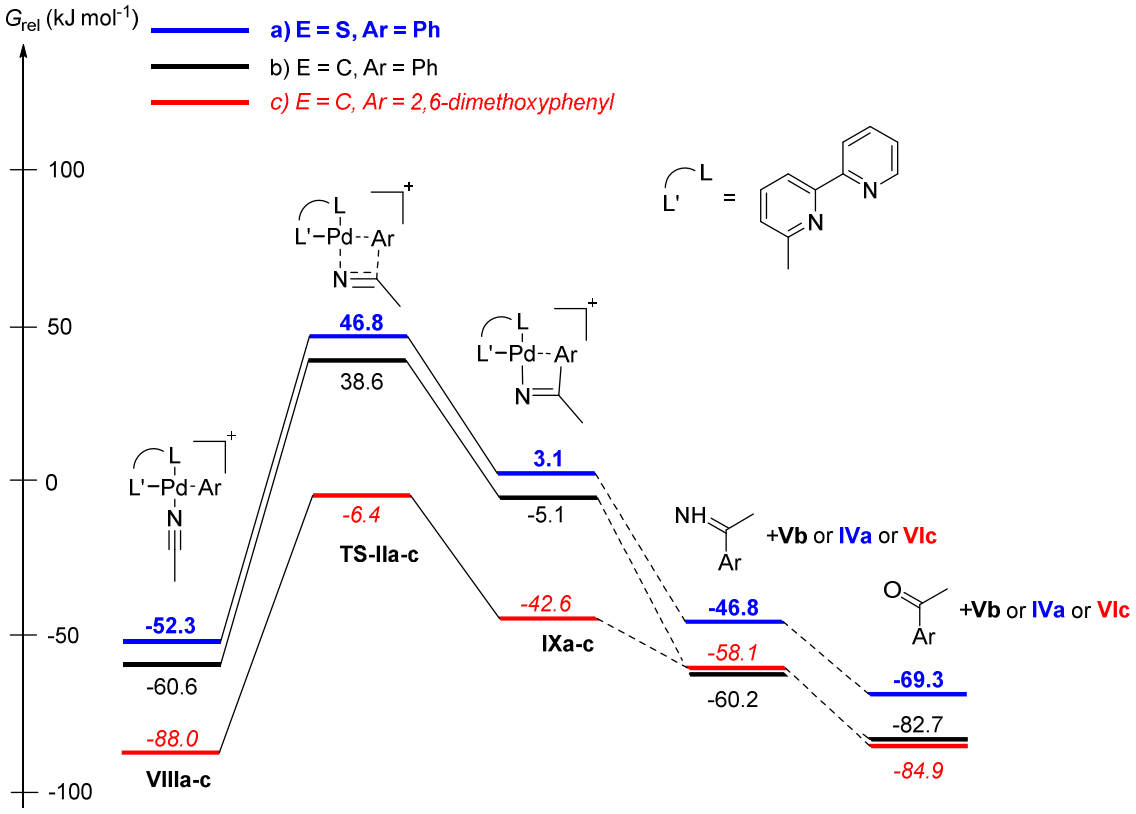


Figure 4. Free energy profile for carbopalladation of acetonitrile followed by product release and hydrolysis.

Electrospray mass spectrometry (ESI-MS) study

To give further experimental insight into the reaction pathway, an electrospray ionization mass spectrometry (ESI-MS) study was conducted. This soft ionization technique only gives few fragmentation products and can be a useful tool to directly detect and study charged reaction intermediates[56–58]. In this case, most of the proposed organometallic intermediates in the Pd(II)-catalyzed reaction are cationic and can be directly analyzed.

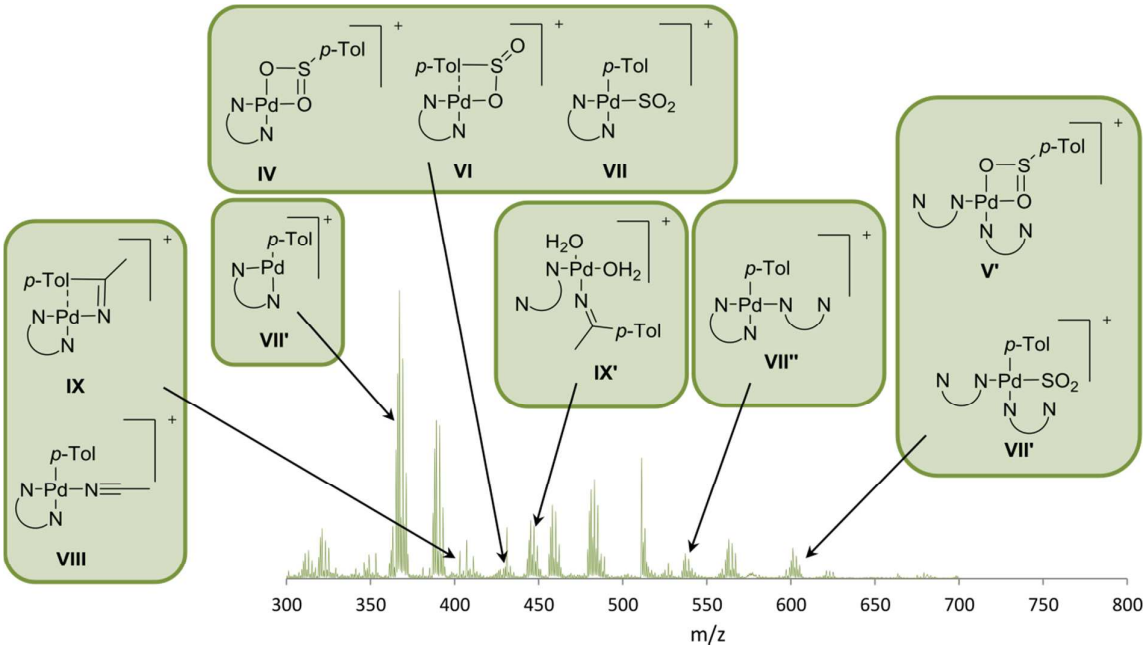
The reaction of **1a** and **2a** with **3a** as the ligand was chosen as the model reaction. The reaction mixture was heated at 100 °C for 10 minutes and an aliquot was diluted 10 times with **2a** and was analyzed directly by ESI-MS. The ESI-MS(+) spectrum showed signals with the characteristic isotopic pattern of singly charged mono-palladium complexes and few non-

palladium complexes or ions were observed (see Figure 5). The signals that showed the isotopic pattern of palladium were further analyzed by MS-MS selecting the isotopic peaks containing ^{106}Pd and ^{108}Pd and some cases further analysis in MS^3 mode was performed to further assign the composition of the intermediates. Neutral loss experiments, monitoring the loss of 41 Da and 64 Da corresponding to the loss of acetonitrile and SO_2 respectively, were also performed to verify the identity of some of the proposed Pd(II) complexes.

When the ESI-MS experiments were carried out with **1e** as the substrate the corresponding cations were also recorded. Similarly, when the reaction was carried out using phenanthroline (**4f**) as the supporting ligand, the expected m/z ratios could also be detected although the intensities were significantly lower (see supporting information). For all the reactions studied, the major signal in the ESI-MS(+) spectrum corresponded to the complex with a free coordination site where Pd(II) supported by the ligand binds the aryl group. This observation is likely due to formation of the complex in the mass spectrometer since the coordination strength of neutral SO_2 and nitrile ligands to Pd(II) is weak.

The identified complexes were assigned (**IV-IX**) based on their proposed role in the mechanism according to the DFT study. Complexes **IV** and **VII** were found independently during the ESI-MS study through different techniques (i.e., neutral loss of arylsulfinate and SO_2, respectively) and can therefore be differentiated despite the fact that they have identical masses. When the corresponding ESI-MS(-) scan was performed no anionic palladium complexes could be detected.

a)



b)

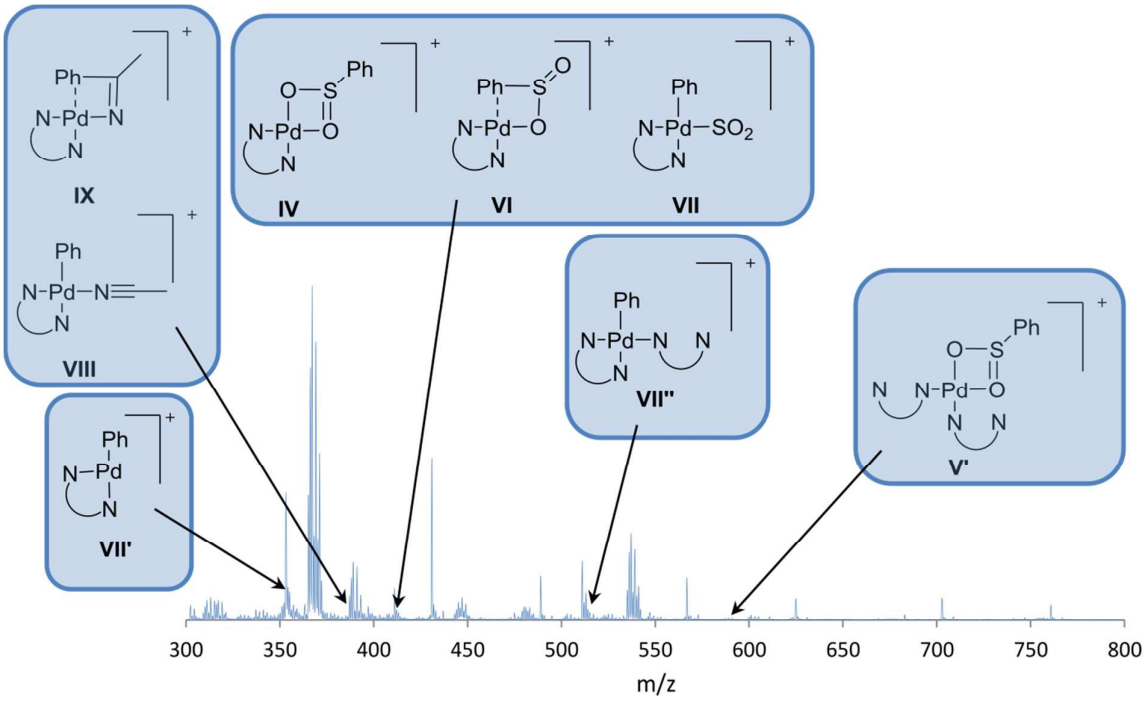
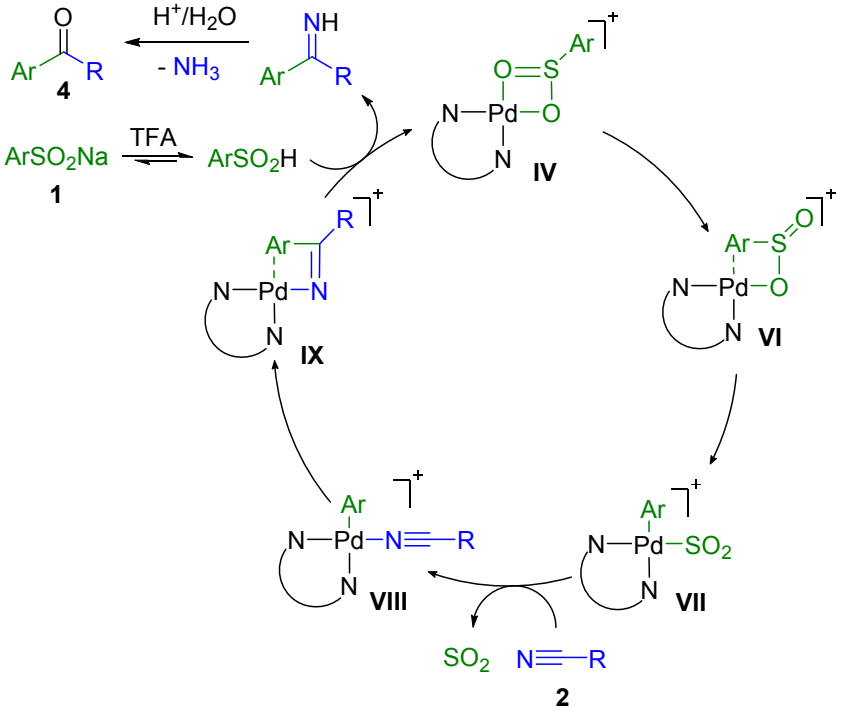


Figure 5. Direct ESI-MS spectra for the desulfitative reaction of a) arylsulfinate **1a** and nitrile **2a** with **3a** as the ligand, b) arylsulfinate **1b** and nitrile **2a** with **3a** as the ligand.

The proposed reaction mechanism from the ESI-MS results and DFT calculations is in accordance with the previously suggested mechanism (see Figure 6). The arylsulfinate is coordinated to the Pd(II) center to give complex **V**. Rearrangement occurs to give **VI** and desulfination gives **VII**. From this complex, substitution of SO_2 by the nitrile **2** gives complex **VIII**. Thereafter, carbopalladation of the nitrile, which is likely the rate determining step, gives **IX**. After release of the imine and catalyst regeneration, hydrolysis occurs to form the desired aryl ketone **4**.

Figure 6. Proposed reaction mechanism.



Conclusions

A robust ligand-mediated Pd(II)-catalyzed protocol that is fast and efficient for the synthesis of a wide range of aryl ketones was developed. The developed protocol provides a useful complement to previous decarboxylative reactions as no *ortho* substituents are required. Desulfination of the benzenesulfinic acid was investigated using DFT calculations and compared to decarboxylation aryl acids. The calculations show that Pd(II)-catalyzed desulfination of aryl sulfinic acids is a viable route to aryl Pd(II) intermediates, on par with decarboxylation of *ortho* substituted benzoic acids. Experimental support for the proposed reaction mechanism was further provided by direct ESI-MS studies.

Experimental Section

General Information

The MW reactions were performed in a Biotage single-mode MW reactor producing controlled irradiation at 2450 MHz with a power of 0–400 W. The reaction temperature was determined using the built-in online IR-sensor. MW mediated reactions were performed in sealed Smith process vials designed for 0.5-2 mL reaction volumes. Analytical TLC was performed using aluminum-backed 0.2 mm silica gel 60 F-254 plates and visualization was performed with UV light (λ = 254 nM). GC–MS analyses were performed with a CP-SIL 8 CB Low Bleed (30 m × 0.25 mm) capillary column using a 70–300 °C temperature gradient or and EI ionization at 70 eV. Analytical UHPLC–MS was performed with an ion trap mass spectrometer and UV-DAD detection using a C18 column (50 × 3 mm). Acetonitrile in 0.05% aqueous formic acid was used as mobile phase at a flow rate of 1.5 mL/min. Silica gel 60 (40–63 μm) was purchased from Sigma Aldrich. Nuclear magnetic resonance (NMR) spectra were recorded on an NMR spectrometer at 400 MHz for ^{1}H and at 100.5 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm and referenced indirectly to TMS via the residual solvent signals (^{1}H, $CDCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.16 ppm). All final compounds were ≥95% pure as determined by NMR. Palladium catalysts were purchased from Sigma-Aldrich or Strem Chemicals. All reagents and solvents are commercially available and were used as received. The sodium salts of 4-methylbenzenesulfinic acid (**1a**), benzenesulfinic acid (**1e**), 4-chlorobenzenesulfinic acid (**1f**) and 4-fluorobenzenesulfinic acid (**1g**) are commercially available. All other sulfinic acids are known compounds and were prepared using a modified literature procedure.[59] All aryl ketone products **4** except **4ae** are known compounds.

Experimental

General Procedure for the Preparation of Sodium Arylsulfinates

The aryl sulfonyl chloride (10.0 mmol, 1.0 equiv) was dissolved in 30 mL water. Sodium sulfite (16.0 mmol, 1.6 equiv) and sodium bicarbonate (16.0 mmol, 1.6 equiv) were added and the reaction mixture was refluxed for 3 h. The water was evaporated and ethanol was added to the residue. The suspension was heated for 10 minutes, cooled and filtered through a 20 μm polyethylene frit. This was repeated twice with the residue from the filtration. The ethanol fractions were combined and the solvent was evaporated under vacuum and the sodium arylsulfinates were isolated as white powders.

General Procedure A: Synthesis of Aryl Methyl Ketones under MW heating

$Pd(O_2CF_3)_2$ (13.3 mg, 0.08 mmol) and 6-methyl-2,2'-bipyridine (10.2 mg, 0.06 mmol) were weighed in a 2-5 ml Smith MW vial. 0.7 ml of THF and 0.7 ml of deionized water were added and the solution was stirred vigorously for 1 minute. **1a** (89.0 mg, 0.5 mmol) and **2g** (257.8 mg, 2.5 mmol) were added. Finally TFA (570.1 mg, 5.0 mmol) was added and the vial was capped quickly under air. The reaction mixture was irradiated for 1 hour at 100 °C. The reaction mixture was allowed cool to room temperature and was poured into 6 ml of 2 M NaOH solution followed by extraction with 3×10 ml DCM. The organic layer was dried over $MgSO_4$, the drying agent was filtered off and the crude product was deposited on a minimum amount of celite. Purification by column chromatography using 20-50% DCM in pentane afforded **4ag** in 89% yield as a white powder.

General Procedure B: Synthesis of Aryl Methyl Ketones under conventional heating

Same procedure as above but heating was performed in a heating block at 100 °C for 16 h. Purification by column chromatography using 20-50% DCM in pentane afforded **4ag** in 74% yield as a white powder.

4'-Methylacetophenone (4aa) [CAS: 122-00-9]: Synthesized from **1a** and **2a** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3aa** as a colorless liquid (58.3 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 – 7.83 (m, 2H), 7.27 – 7.23 (m, 2H), 2.56 (s, 4H), 2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 197.8, 143.8, 134.7, 129.2, 128.4, 26.5, 21.6.

4'-Methoxyacetophenone (4ba) [CAS: 100-06-1]: Synthesized from **1b** and **2a** according to general procedure A and B. Purifications were performed by column chromatography using pentane/dichloromethane as the solvent to give **4ba** as a colorless liquid (59.3 mg, 79%, for procedure A; 17.7 mg, 31%, for procedure B); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 – 7.89 (m, 2H), 6.94 – 6.89 (m, 2H), 3.85 (s, 3H), 2.53 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.7, 163.4, 130.5, 130.3, 113.6, 55.4, 26.3.

4'-Tertbutylacetophenone (4ca) [CAS: 943-27-1]: Synthesized from **1c** and **2a** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ca** as a colorless liquid (45.2 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 – 7.86 (m, 2H), 7.52 – 7.43 (m, 2H), 2.58 (s, 3H), 1.34 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 198.0, 156.9, 134.8, 128.4, 125.6, 35.2 , 31.2, 26.7.

4'-acetamidoacetophenone (4da) [CAS: 2719-21-3]: Synthesized from **1d** and **2a** using the same procedure as A but using 2 ml **2a** and 0.2 ml water as the solvent. Purification was

performed by column chromatography using pentane/dichloromethane as the solvent to give **4da** as a white solid (50.5 mg, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 – 7.88 (m, 2H), 7.87 (s, 1H), 7.64 – 7.61 (m, 2H), 2.57 (s, 3H), 2.21 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 197.3, 168.9, 142.6, 132.9, 129.9, 119.0, 26.6, 24.9.

Acetophenone (4ea) [CAS: 98-86-2]: Synthesized from **1e** and **2a** according to general procedure A and B. Purifications were performed by column chromatography using pentane/dichloromethane as the solvent to give **4ea** as a colorless liquid (46.3 mg, 77%, for procedure A; 36.6 mg, 61%, for procedure B); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.99 – 7.91 (m, 2H), 7.60 – 7.50 (m, 1H), 7.50 – 7.40 (m, 2H), 2.59 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 198.1, 137.0, 133.0, 128.5, 128.2, 26.5.

4'-Chloroacetophenone (4fa) [CAS: 99-91-2]: Synthesized from **1f** and **2a** according to general procedure A and B. Purifications were performed by column chromatography using pentane/dichloromethane as the solvent to give **4fa** as a colorless liquid (61.1 mg, 79%, for procedure A; 37.9 mg, 49%, for procedure B); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 – 7.83 (m, 2H), 7.41 – 7.37 (m, 2H), 2.56 – 2.53 (m, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.6, 139.4, 135.3, 129.6, 128.7, 26.4.

4'-Fluoroacetophenone (4ga) [CAS: 403-42-9]: Synthesized from **1g** and **2a** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ga** as a colorless liquid (50.4 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 – 7.94 (m, 2H), 7.18 – 7.08 (m, 2H), 2.59 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.5, 165.8 (d, $J_{F\text{-}C}$ = 254.6 Hz), 133.6 (d, $J_{F\text{-}C}$ = 3.1 Hz), 130.9 (d, $J_{F\text{-}C}$ = 9.3 Hz), 115.6 (d, $J_{F\text{-}C}$ = 21.9 Hz), 26.5.

2'-Methylacetophenone (4ja) [CAS: 577-16-2]: Synthesized from **1j** and **2a** according to general procedure A. Purification was performed by column chromatography using

pentane/dichloromethane as the solvent to give **4ja** as a colorless liquid (44.2 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 – 7.68 (m, 1H), 7.41 – 7.36 (m, 1H), 7.29 – 7.23 (m, 2H), 2.59 (s, 3H), 2.53 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 202.4, 138.5, 137.4, 132.0, 131.7, 129.4, 125.7, 29.4, 21.6.

2',4',6'-Trimethylacetophenone (4ka) [CAS: 1667-01-2]: Synthesized from **1k** and **2a** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ka** as a colorless liquid (4.1 mg, 5%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (s, 2H), 2.46 (s, 3H), 2.28 (s, 3H), 2.22 (s, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 208.8, 140.0, 138.5, 132.5, 128.6, 32.4, 21.2, 19.3.

3'-Chloroacetophenone (4la) [CAS: 99-02-5]: Synthesized from **1l** and **2a** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4la** as a colorless liquid (9.5 mg, 12%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 – 7.90 (m, 1H), 7.87 – 7.79 (m, 1H), 7.58 – 7.50 (m, 1H), 7.44 – 7.39 (m, 1H), 2.60 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.7 , 138.6 , 134.9 , 133.0 , 129.9 , 128.4 , 126.4 , 26.6.

2,4-Difluoroacetopheone (4na) [CAS: 364-83-0]: Synthesized from **1n** and **2a** according to general procedure A. Purifications were performed by column chromatography using pentane/dichloromethane as the solvent to give **4na** as a colorless liquid (14.2 mg, 18%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.90 (m, 1H), 6.99 – 6.92 (m, 1H), 6.90 – 6.84 (m, 1H), 2.62 (d, J_{F-H} = 5.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.4 (d, J_{C-F} = 3.9 Hz), 167.3 (d, J_{C-F} = 12.3 Hz), 164.6 (dd, J_{C-F} = 31.3, 12.4 Hz), 161.9 (d, J_{C-F} = 12.6 Hz), 132.8 (dd, J_{C-F} = 10.6, 4.0 Hz), 112.3 (dd, J_{C-F} = 21.5, 3.5 Hz), 104.9 (dd, J_{C-F} = 27.7, 25.4 Hz), 31.4 (d, J_{C-F} = 7.4 Hz).

1-(Naphthalen-1-yl)ethanone (4oa) [CAS: 941-98-0]: Synthesized from **1o** and **2a** according to general procedure A. Purification was performed by column chromatography

using pentane/dichloromethane as the solvent to give **4oa** as a colorless liquid (60.8 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.80 – 8.73 (m, 1H), 8.03 – 7.84 (m, 1H), 7.66 – 7.56 (m, 1H), 7.58 – 7.49 (m, 1H), 7.54 – 7.45 (m, 1H), 2.75 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 201.9, 135.5, 134.1, 133.1, 130.2, 128.8, 128.5, 128.2, 126.5, 126.1, 124.4, 30.1.

1-(Naphthalen-2-yl)ethanone (4pa) [CAS: 93-08-3]: Synthesized from **1p** and **2a** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4pa** as a colorless liquid (25.6 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 – 8.46 (m, 1H), 8.06 – 8.02 (m, 1H), 7.99 – 7.95 (m, 1H), 7.91 – 7.86 (m, 2H), 7.64 – 7.52 (m, 2H), 2.73 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 198.2, 135.7, 134.6, 132.7, 130.3, 129.7, 128.6, 128.5, 127.9, 126.9, 124.0, 26.8.

4'-Methylpropiophenone (4ab) [CAS: 5337-93-9]: Synthesized from **1a** and **2b** according to general procedure A and B. Purifications were performed by column chromatography using pentane/dichloromethane as the solvent to give **4ab** as a colorless liquid (67.4 mg, 91%, for procedure A; 61.4 mg, 83%, for procedure B); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 – 7.84 (m, 2H), 7.26 – 7.23 (m, 2H), 2.97 (q, $^{3}J_{HH}$ = 7.3 Hz, 2H), 2.40 (s, 3H), 1.21 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 200.5, 143.5, 134.4, 129.2, 128.1, 31.6, 21.6, 8.3.

4'-Methylbutyrophenone (4ac) [CAS: 4160-52-5]: Synthesized from **1a** and **2c** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ac** as a colorless liquid (73.8 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 – 7.83 (m, 2H), 7.26 – 7.22 (m, 2H), 2.93 – 2.88 (m, 2H), 2.39 (s, 3H), 1.81 – 1.70 (m, 2H), 1.02 – 0.97 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 200.2, 143.6, 134.8, 129.3, 128.3, 40.5, 21.7, 18.0, 14.0.

4'-Methyl-2-phenylacetophenone (4ad) [CAS: 451-40-1]: Synthesized from **1a** and **2d** according to general procedure A. Purification was performed by column chromatography

using pentane/dichloromethane as the solvent to give **4ad** as a white powder (91.4 mg, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 – 7.92 (m, 2H), 7.36 – 7.25 (m, 7H), 4.27 (s, 2H), 2.41 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 197.2, 143.9, 134.7, 134.0, 129.4, 129.3, 129.2, 128.7, 128.5, 128.5, 126.7, 45.3, 21.5.

2-(2-(2-Hydroxy-2-(4'-tolyl)vinyl)phenyl)acetonitrile (4ae): Synthesized from **1a** and **2q** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ae** as a colorless liquid (51.1 mg, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.49 (m, 2H), 7.39 – 7.28 (m, 4H), 7.26 – 7.22 (m, 2H), 6.79 (s, 1H), 3.60 (s, 2H), 2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 170.2, 139.6, 136.7, 134.7, 134.7, 131.6, 129.8, 129.0, 128.7, 127.8, 127.3, 126.5, 114.7, 43.0, 21.3. HRMS (ESI) calcd for C17H16NO $[M + H]^+$ m/z 250.1232, found m/z 250.1241.

4-Methoxy-4'-methylbenzophenone (4af) [CAS: 23886-71-7]: Synthesized from **1a** and **2f** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4f** as a white solid (76.9 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 – 7.78 (m, 2H), 7.70 – 7.65 (m, 2H), 7.29 – 7.23 (m, 2H), 7.00 – 6.90 (m, 2H), 3.86 (s, 3H), 2.42 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.2, 162.9, 142.5, 135.4, 132.3, 130.4, 129.9, 128.8, 113.4, 55.4, 21.5.

4-Methylbenzophenone (4ag) [CAS: 134-84-9]: Synthesized from **1a** and **2g** according to general procedure A and B. Purifications were performed by column chromatography using pentane/dichloromethane as the solvent to give **4ag** as a white powder (82.4 mg, 84%, for procedure A; 72.6 mg, 74%, for procedure B); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.77 (m, 2H), 7.75 – 7.71 (m, 2H), 7.59 – 7.54 (m, 1H), 7.49 – 7.44 (m, 2H), 7.30 – 7.26 (m, 2H), 2.43 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.3, 143.1, 137.9, 134.8, 132.1, 130.2, 129.8, 128.9, 128.1, 21.6.

4-Bromo-4'-methylbenzophenone (4ah) [CAS: 76693-57-7]: Synthesized from **1a** and **2h** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4h** as a white powder (93.2 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 – 7.67 (m, 2H), 7.67 – 7.63 (m, 2H), 7.63 – 7.58 (m, 2H), 7.30 – 7.26 (m, 2H), 2.43 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.2, 143.5, 136.6, 134.4, 131.4, 131.4, 130.1, 129.0, 127.1, 21.6.

4-Chloro-4'-methylbenzophenone (4ai) [CAS: 5395-79-9]: Synthesized from **1a** and **2i** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ai** as a white solid (71.5 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.71 (m, 2H), 7.71 – 7.67 (m, 2H), 7.49 – 7.40 (m, 2H), 7.33 – 7.25 (m, 2H), 2.44 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.2, 143.5, 138.5, 136.2, 134.5, 131.3, 130.1, 129.1, 128.5, 21.7.

4-Acetyl-4'-methylbenzophenone (4aj) [CAS: 127118-95-0]: Synthesized from **1a** and **2j** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4aj** as a white solid (61.7 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 – 8.01 (m, 2H), 7.83 – 7.80 (m, 2H), 7.72 – 7.68 (m, 2H), 7.30 – 7.26 (m, 2H), 2.65 (s, 3H), 2.43 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 197.6, 195.7, 144.0, 141.8, 139.4, 134.3, 130.4, 130.0, 129.3, 128.2, 27.0, 21.8.

4-Formyl-4'-methylbenzophenone (4ak) [CAS: 211106-76-2]: Synthesized from **1a** and **2k** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ak** as a white solid (47.3 mg, 42 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.22 (s, 1H), 8.11 – 8.09 (m, 2H), 8.08 – 8.07 (m, 2H), 8.01 – 8.00 (m, 2H), 7.99 – 7.97 (m, 2H), 2.55 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.6, 191.8, 144.3, 143.1, 138.4, 134.2, 130.5, 130.3, 129.6, 129.4, 21.8.

2-Methyl-4'-methylbenzophenone (4al) [CAS: 1140-16-5]: Synthesized from **1a** and **2m** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4am** as a colorless oil (64.8 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 – 7.67 (m, 2H), 7.40 – 7.34 (m, 1H), 7.31 – 7.21 (m, 5H), 2.42 (s, 3H), 2.31 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 198.5, 144.2, 139.1, 136.6, 135.3, 131.0, 130.4, 130.1, 129.3, 128.4, 125.3, 21.8, 20.0.

2-Bromo-4'-methylbenzophenone (4am) [CAS: 67104-64-7]: Synthesized from **1a** and **2m** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4am** as a white solid (96,3 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 – 7.69 (m, 2H), 7.65 – 7.62 (m, 1H), 7.43 – 7.38 (m, 1H), 7.36 – 7.31 (m, 2H), 7.28 – 7.24 (m, 2H), 2.42 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.4, 144.7, 140.9, 133.6, 133.1, 130.9, 130.3, 129.3, 128.8, 127.1, 119.4, 21.7.

3-Bromo-4'-methylbenzophenone (4an) [CAS: 102092-51-3]: Synthesized from **1a** and **2n** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4an** as a white solid (92.2 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 – 7.90 (m, 1H), 7.72 – 7.66 (m, 4H), 7.37 – 7.32 (m, 1H), 7.31 – 7.27 (m, 2H), 2.44 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.7, 143.7, 139.8, 134.9, 134.2, 132.6, 130.2, 129.7, 129.1, 128.3, 122.4, 21.6.

Naphthalen-1-yl(4'-tolyl)methanone (4ao) [CAS: 62723-07-3]: Synthesized from **1a** and **2o** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ao** as a white solid (51.9 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 – 8.02 (m, 1H), 8.04 – 7.96 (m, 1H), 7.96 – 7.88 (m, 1H), 7.82 – 7.74 (m, 2H), 7.60 – 7.44 (m, 4H), 7.30 – 7.22 (m, 2H), 2.44 (s, 3H). $^{13}C\{^{1}H\}$ NMR

(101 MHz, $CDCl_3$) δ = 197.8, 144.3, 136.9, 135.9, 133.8, 131.1, 130.7, 129.3, 128.5, 127.4, 127.2, 126.5, 125.9, 124.5, 21.9.

Ethyl 3-oxo-2-phenyl-3-(4'-tolyl)propanoate (4ap) [CAS: 613667-48-4]: Synthesized from **1a** and **2p** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ao** as a colorless liquid (69.4 mg, 49%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 – 7.84 (m, 2H), 7.45 – 7.37 (m, 2H), 7.40 – 7.31 (m, 2H), 7.34 – 7.25 (m, 1H), 7.26 – 7.18 (m, 2H), 4.29 – 4.17 (m, 2H), 2.37 (s, 3H), 1.28 – 1.22 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 193.0, 169.0, 144.6, 133.3, 133.3, 129.7, 129.5, 129.2, 128.9, 128.1, 61.8, 60.6, 21.8, 14.2.

Thiophen-3-yl(4'-tolyl)methanone (4aq) [CAS: 118993-65-0]: Synthesized from **1a** and **2q** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4aq** as a colorless liquid (68.2 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 – 7.88 (m, 1H), 7.80 – 7.73 (m, 2H), 7.62 – 7.55 (m, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.24 (m, 2H), 2.44 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 189.9, 143.2, 141.6, 136.0, 133.5, 129.7, 129.2, 128.8, 126.2, 21.8.

Furan-2-yl(4'-tolyl)methanone (4ar) [CAS: 13365-62-3]: Synthesized from **1a** and **2r** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ar** as a colorless liquid (49.4 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 – 7.85 (m, 2H), 7.71 – 7.66 (m, 1H), 7.33 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 6.61 – 6.55 (m, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 182.4, 152.6, 146.9, 143.5, 134.7, 129.6, 129.2, 120.2, 112.2, 21.8.

Pyrazin-2-yl(4'-tolyl)methanone (4as) [CAS: 89815-16-7]: Synthesized from **1a** and **2s** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4as** as a white solid (39.6 mg, 40%); ^{1}H

NMR (400 MHz, $CDCl_3$) δ = 9.23 – 9.18 (m, 1H), 8.78 – 8.72 (m, 1H), 8.69 – 8.63 (m, 1H), 8.01 – 7.94 (m, 1H), 7.31 – 7.28 (m, 2H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 191.9, 150.4, 146.6, 146.0, 144.7, 143.0, 133.0, 131.1, 129.2, 21.9.

(1H-Indol-5-yl)(4'-tolyl)methanone (4at) [CAS: 215668-16-9]: Synthesized from **1a** and **2t** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4at** as a white solid (59.50 mg, 50%); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.75 (s, 1H), 8.16 – 8.10 (m, 1H), 7.81 – 7.71 (m, 3H), 7.47 – 7.40 (m, 1H), 7.33 – 7.25 (m, 3H), 6.65 – 6.62 (m, 1H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 197.5, 142.5, 138.4, 136.3, 130.3, 130.1, 128.9, 127.2, 125.9, 125.2, 124.3, 111.1, 104.2, 21.8.

Benzofuran-2-yl(4'-tolyl)methanone (4au) [CAS: 41967-43-5]: Synthesized from **1a** and **2u** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4au** as a colorless liquid (51.1 mg, 49%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.79 – 7.75 (m, 2H), 7.59 – 7.55 (m, 1H), 7.54 – 7.49 (m, 1H), 7.30 – 7.26 (m, 2H), 7.26 – 7.24 (m, 1H), 7.24 – 7.20 (m, 1H), 6.99 – 6.95 (m, 1H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 156.3, 154.9, 138.7, 129.6, 129.5, 127.9, 125.0, 124.1, 123.0, 120.9, 111.2, 100.7, 47.0, 21.5.

4'-Methoxypropiophenone (4bb) [CAS: 121-97-1]: Synthesized from **1b** and **2b** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4bb** as a colorless liquid (54.2 mg, 66%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.96 – 7.91 (m, 2H), 6.94 – 6.89 (m, 2H), 3.85 (s, 3H), 2.94 (q, J = 7.3 Hz, 2H), 1.20 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 199.4, 163.2, 130.2, 130.0, 113.6, 55.4, 31.4, 8.4.

4'-Methoxy-2-phenylacetophenone (4bd) [CAS: 1023-17-2]: Synthesized from **1b** and **2d** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4bd** as a white solid (87.1 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.03 – 7.98 (m, 2H), 7.36 – 7.22 (m, 5H), 6.95 – 6.90 (m, 2H), 4.24 (s, 2H), 3.86 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.1, 163.5, 134.9, 130.9, 129.6, 129.3, 128.6, 126.7, 113.7, 55.4, 45.2.

4'-Methoxybenzophenone (4bg) [CAS: 611-94-9]: Synthesized from **1b** and **2g** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4bg** as a white solid (78.5 mg, 74%); Also synthesized from **1e** and **2f** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4bg** as a white solid (65.8 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 – 7.81 (m, 2H), 7.77 – 7.74 (m, 2H), 7.58 – 7.53 (m, 1H), 7.49 –7.44 (m, 2H), 6.98 – 6.94 (m, 2H), 3.88 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.5, 163.2, 138.2, 132.5, 131.8, 130.1, 129.7, 128.1, 113.5, 55.4.

4-Bromo-4'-methoxybenzophenone (4bh) [CAS: 54118-75-1]: Synthesized from **1b** and **2h** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4bh** as a white solid (90.3 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.76 (m, 2H), 7.64 – 7.58 (m, 4H), 6.98 – 6.93 (m, 2H), 3.88 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.3, 163.4, 136.9, 132.4, 131.4, 131.2, 129.7, 126.8, 113.6, 55.5.

2-Bromo-4'-methoxybenzophenone (4bl) [CAS: 59142-63-1]: Synthesized from **1b** and **2l** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4bl** as a white solid (90.3 mg, 62%); ^{1}H

NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.76 (m, 2H), 7.67 – 7.61 (m, 1H), 7.45 – 7.38 (m, 1H), 7.36 – 7.30 (m, 2H), 6.97 – 6.91 (m, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.6, 164.3, 141.3, 133.2, 132.8, 131.0, 129.3, 128.9, 127.3, 119.6, 114.1, 55.7.

3-Bromo-4'-methoxybenzophenone (4bm) [CAS: 54118-76-2]: Synthesized from **1b** and **2m** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4bm** as a white solid (90.2 mg, 62%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 – 7.86 (m, 1H), 7.83 – 7.77 (m, 2H), 7.72 – 7.63 (m, 2H), 7.38 – 7.31 (m, 1H), 7.01 – 6.94 (m, 2H), 3.89 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.0, 163.7, 140.3, 134.9, 132.7, 132.6, 130.0, 129.6, 128.3, 122.6, 113.9, 55.7.

Propiophenone (4eb) [CAS: 93-55-0]: Synthesized from **1e** and **2b** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4eb** as a colorless liquid (65.9 mg, 89%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.94 (m, 2H), 7.57 – 7.52 (m, 1H), 7.47 – 7.42 (m, 2H), 3.00 (q, J = 7.2 Hz, 2H), 1.22 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 200.7, 136.9, 132.8, 128.5, 127.9, 31.7, 8.2.

1,2-diphenylethan-1-one (4ed) [CAS: 451-40-1]: Synthesized from **1e** and **2d** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4ed** as a white solid (74.6 mg, 76%); ^1H NMR (400 MHz, $CDCl_3$) δ = 8.05 – 8.01 (m, 2H), 7.61 – 7.52 (m, 1H), 7.51 – 7.42 (m, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.23 (m, 3H), 4.30 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 197.5, 136.6, 134.5, 133.1, 129.4, 128.6, 128.6, 128.6, 126.8, 45.5.

Benzophenone (4eg) [CAS: 119-61-9]: Synthesized from **1e** and **2g** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4eg** as a white solid (65.9 mg, 70%); ^1H NMR

(400 MHz, $CDCl_3$) δ = 7.83 – 7.78 (m, 4H), 7.61 – 7.55 (m, 2H), 7.50 – 7.44 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.6, 137.5, 132.3, 129.9, 128.2.

4-Bromobenzophenone (4eh) [CAS: 90-90-4]: Synthesized from **1e** and **2h** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4eh** as a white solid (79.6 mg, 61%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.75 (m, 2H), 7.70 – 7.65 (m, 2H), 7.64 – 7.61 (m, 2H), 7.61–7.57 (m, 1H), 7.52 – 7.46 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.5, 137.1, 136.3, 132.6, 131.6, 131.5, 129.9, 128.4, 127.4.

2-Bromobenzophenone (4el) [CAS: 13047-06-8]: Synthesized from **1e** and **2l** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4el** as a white solid (80.6 mg, 62 %); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.84 – 7.80 (m, 2H), 7.66 – 7.63 (m, 1H), 7.63 – 7.57 (m, 1H), 7.49 – 7.43 (m, 2H), 7.42 – 7.39 (m, 1H), 7.38 – 7.33 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.9, 140.8, 136.2, 133.8, 133.3, 131.3, 130.3, 129.1, 128.7, 127.3, 119.6.

3-Bromobenzophenone (4em) [CAS: 1016-77-9]: Synthesized from **1e** and **2m** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4em** as a white solid (75.7 mg, 58%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.95 – 7.92 (m, 1H), 7.81 – 7.76 (m, 2H), 7.73 – 7.69 (m, 2H), 7.63 – 7.58 (m, 1H), 7.53 – 7.46 (m, 2H), 7.38 – 7.33 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.2, 139.6, 137.0, 135.4, 132.9, 132.9, 130.1, 130.0, 128.7, 128.6, 122.7.

4'-Chloropropiophenone (4fb) [CAS: 6285-05-8]: Synthesized from **1f** and **2b** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4fb** as a white solid (61.5 mg, 73%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 – 7.83 (m, 2H), 7.43 – 7.35 (m, 2H), 2.94 (q, J = 7.2 Hz, 2H),

1.19 (t, J = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 199.6, 139.2, 135.1, 129.3, 128.8, 31.7, 8.0.

4'-Chloro-2-phenylacetophenone (4fd) [CAS: 1889-71-0]: Synthesized from **1f** and **2d** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4fd** as a white solid (76.1 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 – 7.93 (m, 2H), 7.45 – 7.40 (m, 2H), 7.37 – 7.31 (m, 2H), 7.30 – 7.24 (m, 3H), 4.26 (s, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 196.3, 139.5, 134.8, 134.1, 130.0, 129.3, 128.9, 128.7, 127.0, 45.5.

4-Chlorobenzophenone (4fg) [CAS: 134-85-0]: Synthesized from **1f** and **2g** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4fg** as a white solid (83.4 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 – 7.70 (m, 4H), 7.61 – 7.55 (m, 1H), 7.51 – 7.42 (m, 4H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 195.3, 138.8, 137.1, 135.8, 132.5, 131.3, 129.8, 128.5, 128.3.

4-Bromo-4'-chlorobenzophenone (4fh) [CAS: 27428-57-5]: Synthesized from **1f** and **2h** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4fh** as a white solid (75.4 mg, 51%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 – 7.70 (m, 2H), 7.66 – 7.61 (m, 4H), 7.48 – 7.44 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.3, 139.1, 135.9, 135.4, 131.7, 131.4, 131.3, 128.7, 127.7.

4-Formyl-4'-chlorobenzophenone (4fk) [CAS: 81223-65-6]: Synthesized from **1f** and **2k** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4fk** as a white solid (64.8 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.13 (s, 1H), 8.03 – 7.98 (m, 2H), 7.92 – 7.87 (m, 2H), 7.78 –

7.72 (m, 2H), 7.51 – 7.46 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.7, 191.6, 142.3, 139.8, 138.8, 135.2, 131.6, 130.3, 129.7, 129.1.

2-Bromo-4'-chlorobenzophenone (4fl) [CAS: 99585-64-5]: Synthesized from **1f** and **2l** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4fl** as a white solid (131.5 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 – 7.72 (m, 2H), 7.67 – 7.63 (m, 1H), 7.47 – 7.40 (m, 3H), 7.40 – 7.36 (m, 1H), 7.35 – 7.32 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.8, 140.5, 140.3, 134.6, 133.4, 131.7, 131.5, 129.2, 129.1, 127.5, 119.6.

3-Bromo-4'-chlorobenzophenone (4fm) [CAS: 75762-56-0]: Synthesized from **1f** and **2m** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4fm** as a white solid (79.8 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 – 7.87 (m, 1H), 7.78 – 7.64 (m, 4H), 7.50 – 7.45 (m, 2H), 7.40 – 7.33 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 194.0, 139.5, 139.2, 135.6, 135.3, 132.8, 131.5, 130.1, 129.0, 128.5, 122.8.

2'-Methylpropiophenone (4jb) [CAS: 2040-14-4]: Synthesized from **1j** and **2b** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4jb** as a white solid (48.9 mg, 66 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 – 7.60 (m, 1H), 7.38 – 7.33 (m, 1H), 7.28 – 7.22 (m, 2H), 2.91 (q, J = 7.3 Hz, 2H), 2.49 (s, 3H), 1.20 (t, J = 7.3 Hz, 3H. $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 205.3, 138.3, 138.0, 132.0, 131.2, 128.4, 125.8, 34.9, 21.4, 8.5.

2'-Methylbenzophenone (4jg) [CAS: 131-58-8]: Synthesized from **1j** and **2g** according to general procedure A. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4jg** as a white solid (82.4 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 – 7.80 (m, 2H), 7.62 – 7.55 (m, 1H), 7.48 – 7.43 (m, 2H), 7.42 –

7.36 (m, 1H), 7.34 – 7.27 (m, 2H), 7.27 – 7.22 (m, 1H), 2.34 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 198.7, 138.7, 137.8, 136.8, 133.20, 131.1, 130.3, 130.2, 128.6, 128.5, 125.3, 20.1.

Density functional theory (DFT) calculations

All energy calculations were performed using Jaguar.[60] Geometry optimization in the gas phase and vibrational analysis were performed using the B3LYP hybrid functional[61–63] with the LACVP* basis set, which uses an effective core potential[64] for Pd and the 6-31G* for all heavy atoms. The optimized geometries were subjected to a single point calculation using LACVP**+ for the final energies. In the relaxed coordinate scan (5 degrees resolution) of the dihedral angle in benzenesulfinic acid, benzoic acid, and 2,6-dimethoxybenzoic acid the geometry optimization were performed using the LACVP**+ basis set. The solution phase energy was calculated in a single-point energy calculation utilizing the PBF solvation model[65,66] for water as implemented in Jaguar 7.6. The final free energies was obtained by adding the thermodynamic correction from the vibrational analysis in the gas phase at 373.15 K and dispersion correction calculated using DFT-D3[67] to the solution phase energy. The TSs were determined to be connected to their corresponding reactants and products via QRC calculations[68], which is shown by solid lines in the energy diagrams. The TSs were confirmed to have exactly one imaginary frequency in the vibrational analysis and the stationary minima were confirmed to have no imaginary frequencies.

ESI-MS study

The reaction mixture was diluted tenfold with acetonitrile after 10 min of microwave heating in a sealed vessel at 100 °C and introduced by continuous infusion with the aid of a syringe pump at a flow-rate of 5 μL/min through a fused silica capillary (with a 50 μm inner and a 184 μm outer diameter). The ion source used was a Turbo V source in positive ESI mode. The following MS conditions were used: temperature (TEM) off, curtain gas (CUR) 15 psi, ion source gas 1 (GS1) 7 psi, ion source gas 2 (GS2) 10 psi, ion spray voltage (IS) 5500 V, the declustering potential (DP) was 20 V and entrance potential (EP) 10 V for all measurements. MS data were collected in enhanced MS mode (EMS) and MS/MS data were collected in enhanced product ion mode (EPI) and neutral loss mode. The collision gas parameter (CAD) was set to an arbitrary number, 11, for EMS (linear ion trap MS scan) and high for the EPI, which corresponds to a pressure reading of $3.9 \cdot 10^{-5}$ Torr. The collision energy (CE) was 20-30 eV for all experiments aside from the EMS where it was set to 10 eV. The isotopic ions with the strongest and the second strongest intensity for each palladium complex (containing ^{106}Pd and ^{108}Pd, respectively) were selected for further MS/MS-(+), MS/MS/MS-(+) or neutral loss (m/z = e.g. 41; 64) analyses.

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Supporting Information: ^{1}H and ^{13}C NMR spectra, energies and coordinates of reported complexes and ESI-MS(+), ESI-MS-MS(+) and ESI-MS^{3}(+) spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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