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Direct Synthesis of Aryl Ketones by Palladium-Catalyzed Desulfinative Addition of Sodium Sulfinates to Nitriles

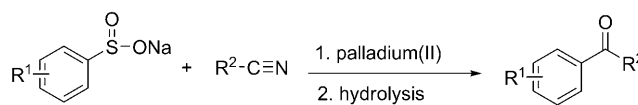**Jing Liu,[a] Xianya Zhou,[a] Honghua Rao,[b] Fuhong Xiao,[a] Chao-Jun Li,*[b] and Guo-Jun Deng*[a]**

Aryl ketones are fundamental intermediates in many types of organic compound, for example, pharmaceuticals, fragrances, and natural products.[1] Classical routes to synthesize aryl ketones mainly rely on the Friedel–Crafts acylation of aromatic compounds in the presence of corrosive AlCl$_3$[2] and the oxidation of the corresponding secondary alcohols.[3] Transition-metal-catalyzed reactions provide many opportunities for the synthesis of aryl ketones.[4] Among them, hydroacylation is a useful synthetic method for preparing aryl ketones from aldehydes and olefines through C–H bond activation and subsequent addition.[5]

Nitriles are normally very stable and widely commercially available. The nucleophilic addition of organometallic reagents to nitriles is an old and well-known reaction for ketone preparation. However, application of this addition reaction has been limited by poor functional group tolerance.[6] In recent years, the transition-metal-catalyzed addition reaction has resulted in great progress in the synthesis of aryl ketones from nitriles. One of the pioneering works involving the use of nitriles as the starting materials for aryl ketone synthesis was developed by Larock et al. by using palladium as the catalyst. Arylboronic acids and even arene C–H bonds were successfully added to nitriles to generate various aryl ketones by the hydrolysis of the intermediate ketimine in trifluoroacetic acid.[7] Later, Lu and Zhao,[8] Miura et al.,[9] and others[10] developed various catalytic systems for aryl ketone synthesis from nitriles and arylboronic acids, catalyzed by palladium or rhodium. Cheng et al. developed a nickel-catalyzed addition of arylboronic acids to nitriles by using ZnCl$_2$ as the Lewis acid, under mild conditions.[11] However, arylboronic acids normally require several

steps to synthesize from arenes (via the halide and then reaction with borate by using stoichiometric magnesium),[12] although newer methods of direct boronic acid formation from C–H bonds have recently been explored.[13] In 2010, Larhed et al. developed a palladium-catalyzed decarboxylative addition of benzoic acids to nitriles, and various aryl ketones can be synthesized with this method.[14] One of the main advantages of this method is that the carboxylic acids used for this transformation are comparably cheap and are commercially available.[15] However, this method is mainly suitable for *ortho*-functionalized electron-rich benzoic acids and aliphatic nitriles.

Arenesulfonyl chlorides are active compounds and are used as starting materials for preparing compounds containing a sulfonyl group.[16] They are also used as aryl sources for C–C bond-forming reactions through desulfinative Heck-type reactions under harsh conditions ($>130\,°C$).[17] Compared to the active and moisture sensitive arenesulfonyl chloride, sulfinic acid sodium salts are comparably stable and easy to handle. Thus, sulfinic acid sodium salts have the potential to serve as the ideal aryl source for C–C bond-forming reactions through release of SO$_2$. However, sulfinic acids (or their sodium salts) are mainly used as sulfonylation reagents[18] and rarely used as the aryl source in desulfinative reactions.[19] Recently, we developed a palladium-catalyzed desulfinative Heck-type reaction of aromatic sulfinic acid sodium salts with various olefins under mild conditions.[20] Herein, we report the direct synthesis of aryl ketones by palladium-catalyzed desulfinative addition of aryl sulfinic acid sodium salts to nitriles under mild conditions (Scheme 1).

We began our investigation by screening various palladium salts for the desulfinative addition reaction between benzonitrile (**1a**) and *p*-toluenesulfinic acid sodium salt (**2a**) in the presence of trifluoroacetic acid, and the results are summarized in Table 1. If benzonitrile was reacted with **2a** (2 equiv) in the presence of Pd(OAc)$_2$ (5 mol%) and 1,10-phenanthroline (1,10-phen; 10 mol%) in 1,4-dioxane/water (3:2), the desired product was observed in 53% yield, as de-
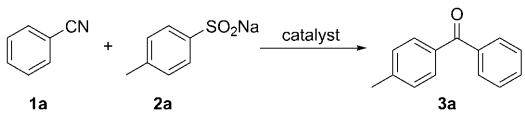
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Scheme 1. General reaction scheme.

Table 1. Optimization of the reaction conditions.[a]

	Catalyst	Ligand	Solvent	Yield [%][b]
1	Pd(OAc)$_2$	1,10-phen	1,4-dioxane	53
2	Pd(O$_2$CCF$_3$)$_2$	1,10-phen	1,4-dioxane	54
3	PdCl$_2$	1,10-phen	1,4-dioxane	41
4	[Pd(acac)$_2$]	1,10-phen	1,4-dioxane	42
5	[Pd$_2$(dba)$_3$]	1,10-phen	1,4-dioxane	58
6	[Pd(cod)Cl$_2$]	1,10-phen	1,4-dioxane	52
7	[Pd(NH$_3$)$_4$Cl$_2$]	1,10-phen	1,4-dioxane	40
8	PdO	1,10-phen	1,4-dioxane	70
9	Pd(OH)$_2$	1,10-phen	1,4-dioxane	91
10	Pd(OH)$_2$	dipyridine	1,4-dioxane	60
11	Pd(OH)$_2$	DMAP	1,4-dioxane	2
12	Pd(OH)$_2$	DBU	1,4-dioxane	trace
13	Pd(OH)$_2$	PPh$_3$	1,4-dioxane	trace
14	Pd(OH)$_2$	1,10-phen	DMF	3
15	Pd(OH)$_2$	1,10-phen	anisole	45
16	Pd(OH)$_2$	1,10-phen	diglyme	56
17	Pd(OH)$_2$	1,10-phen	THF	67
18[c]	Pd(OH)$_2$	1,10-phen	1,4-dioxane	71
19[d]	Pd(OH)$_2$	1,10-phen	1,4-dioxane	63
20[e]	Pd(OH)$_2$	1,10-phen	1,4-dioxane	47

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol %), ligand (10 mol %), CF$_3$CO$_2$H (0.2 mL), solvent (0.3 mL), H$_2$O (0.2 mL), 110 °C, 20 h, under air; acac = acetylacetone, dba = dibenzylideneacetone, cod = 1,5-cyclooctadiene, DMAP = 4-dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] GC yield based on **1a**. [c] 1,4-Dioxane/H$_2$O = 1:1. [d] At 90 °C. [e] No CF$_3$CO$_2$H was used.

tected by GC-MS and ^{1}H NMR methods (Table 1, entry 1). Subsequently, various palladium salts were tested for this desulfinative addition reaction and moderate yields were observed (Table 1, entries 2–7). The reaction yield can be improved to 70 % if PdO was used (Table 1, entry 8). However, the best yield was obtained with Pd(OH)$_2$ as the catalyst, for which the desired product was obtained in 91 % yield (Table 1, entry 9). Other ligands were also investigated for this transformation but were less efficient (Table 1, entries 10–13). The effect of solvents on this reaction was also investigated. A low yield was obtained if the reaction was carried out in DMF (Table 1, entry 14) although the reactions in anisole, diglyme, and THF gave the desired product in moderate yields (Table 1, entries 15–17). The ratio of 1,4-dioxane to water also affected the reaction yield significantly, decreasing it to 71 % if the ratio of was changed to 1:1 (Table 1, entry 18). Decreasing the reaction temperature also decreased the yield (Table 1, entry 19). Trifluoroacetic acid played an important role in this addition reaction and only 47 % yield was achieved in its absence (Table 1, entry 20).[21]

Next, the desulfinative addition of p-toluenesulfinic acid sodium salt **2a** to various nitriles was conducted under the optimized conditions, and the results are summarized in Table 2. The palladium-catalyzed desulfinative addition reaction was successfully extended to various substituted aryl

nitriles **1b–g**, and various asymmetric diaryl ketones were obtained in moderate to good yields (Table 2, entries 2–7). A series of functional groups, including methyl, methoxy, fluoro, chloro, and acetyl, were tolerated under the optimized reaction conditions. A moderate yield was obtained when 2-methylbenzonitrile was reacted with **2a** (Table 2, entry 8). Aliphatic nitriles also worked well for this reaction. Phenylacetonitrile and its substituted derivatives were

Table 2. Desulfinative addition of **2a** with various nitriles.[a]

	Nitrile		Product		Yield [%][b]
1	Ph—CN	**1a**		**3a**	78
2		**1b**		**3b**	72
3		**1c**		**3c**	80
4		**1d**		**3d**	81
5		**1e**		**3e**	73
6		**1f**		**3f**	74
7		**1g**		**3g**	60
8		**1h**		**3h**	51
9	Ph~CN	**1i**		**3i**	82
10		**1j**		**3j**	80 (78)[c]
11		**1k**		**3k**	85
12		**1l**		**3l**	83
13		**1m**		**3m**	82
14		**1n**		**3n**	70

Table 2. (Continued)

	Nitrile		Product		Yield [%][b]
15[d]	∼∼CN	**1o**		**3o**	42
16[d]	⟨⟩₆CN	**1p**		**3p**	52
17[d]	⟨⟩₈CN	**1q**		**3q**	65

[a] Reaction conditions, unless otherwise noted: **1** (0.2 mmol), **2a** (0.4 mmol), Pd(OH)$_2$ (5 mol%), 1,10-phen (10 mol%), CF$_3$CO$_2$H (0.2 mL), 1,4-dioxane (0.3 mL), H$_2$O (0.2 mL), 110°C, 20 h, under air. [b] Isolated yield based on **1**. [c] The yield in parenthesis was on a 5 mmol scale. [d] Pd(OH)$_2$ (10 mol%) and 2,2′-bipyridine (10 mol%) were used.

smoothly reacted with **2a** and gave the corresponding alkyl aryl ketones in good yields (Table 2, entries 9–14). Pentanenitrile, octanenitrile, and decanonitrile were also reacted with **2a**, although under modified reaction conditions, and gave the desired products in 42, 52, and 65% yield, respectively (Table 2, entries 15–17).

Additionally, the results of the reaction between various aryl sulfinic acid sodium salts and 4-methylbenzonitrile (**1b**) are presented in Table 3. Benzenesulfinic acid sodium salt (**2b**) was successfully reacted with **1b** and gave the corresponding product in 76% yield (Table 3, entry 1). Various functional groups, including methoxy, *tert*-butyl, fluoro, bromo, and trifluoromethyl, were tolerated, and the desired products were obtained in moderate to good yields (Table 3, entries 2–6). A more bulky substrate, 2-naphthylsulfinic acid sodium salt (**2h**), also efficiently reacted with **1b** and gave the product in 53% yield (Table 3, entry 7).

A plausible mechanism to rationalize this transformation is illustrated in Scheme 2. Similar to the Pd^{II}-catalyzed decarboxylative addition of benzoic acids to nitriles,[14] the proposed mechanism involves the following six steps: 1) coordination of the arenesulfinic acid (or its sodium salt) to palladium(II) to give complex **I**; 2) the desulfinative reaction of the sulfinic acid to generate aryl–palladium complex **II**; 3) coordination of the nitrile group to form complex **III**; 4) 1,2-carbopalladation of the nitrile to generate ketimine complex **IV**; 5) protonation of the ketimine by the acid to give the free ketimine and a palladium(II) species; and 6) hydrolysis of the ketimine under acidic conditions to afford the desired final aryl ketone.

In summary, we have developed a new Pd-catalyzed method that allows the direct synthesis of aryl ketones from aromatic sulfinic acid sodium salts and inexpensive nitrile compounds. Ligands and solvents played an important role in the reaction yield. A combination of Pd(OH)$_2$ and 1,10-phenanthroline in 1,4-dioxane/water (3:2) in air gave the desired product in the best yield. Aromatic and aliphatic nitriles were successfully reacted with arenesulfinic acid

Table 3. Desulfinative addition of **1b** with various sodium sulfinates.[a]

	Sodium sulfinate		Product		Yield [%][b]
1	⟨⟩SO$_2$Na	**2b**		**3r**	76
2	MeO–⟨⟩SO$_2$Na	**2c**		**3s**	65
3	tBu–⟨⟩SO$_2$Na	**2d**		**3t**	73
4	F–⟨⟩SO$_2$Na	**2e**		**3u**	61
5[c]	Br–⟨⟩SO$_2$Na	**2f**		**3v**	50
6	F$_3$C–⟨⟩SO$_2$Na	**2g**		**3w**	35
7	⟨⟨⟩⟩SO$_2$Na	**2h**		**3x**	53

[a] Reaction conditions, unless otherwise noted: **1b** (0.2 mmol), **2** (0.4 mmol), Pd(OH)$_2$ (5 mol%), 1,10-phen (10 mol%), CF$_3$CO$_2$H (0.2 mL), 1,4-dioxane (0.3 mL), H$_2$O (0.2 mL), 110°C, 20 h, under air. [b] Isolated yield based on **1b**. [c] Anisole was used instead of 1,4-dioxane.
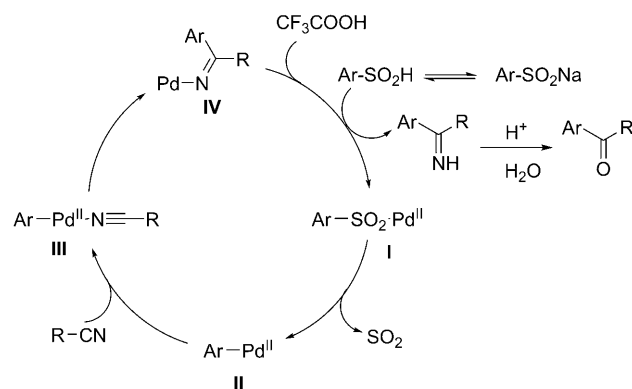
Scheme 2. Proposed mechanism.

sodium salts to form aryl ketones in moderate to good yields. This procedure provides a rapid and convenient method for the small-scale synthesis of aryl ketones.[22] Our current efforts are focused on further mechanistic studies to improve the catalytic efficiency and to overcome limitations in substrate scope.

Experimental Section

Representative experimental procedure (3a, CAS: 134–84–9): A reaction vessel (10 mL) was charged with a mixture of palladium hydroxide

(1.4 mg, 0.01 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), sodium *p*-toluenesulfinate (**2a**, 71.2 mg, 0.4 mmol), benzonitrile (**1a**, 20 μL, 0.2 mmol), and trifluoroacetic acid (0.2 mL) in 1,4-dioxane/water (0.5 mL, 3:2). The reaction vessel was closed and the resulting solution was stirred at 110 °C for 20 h. After cooling to room temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 50:1) to give **3a** as a white solid (30.5 mg, 78 %).

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