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Rhodium-Catalyzed Aerobic Coupling between Aldehydes and Arenesulfinic Acid Salts: A Novel Synthesis of Aryl Ketones

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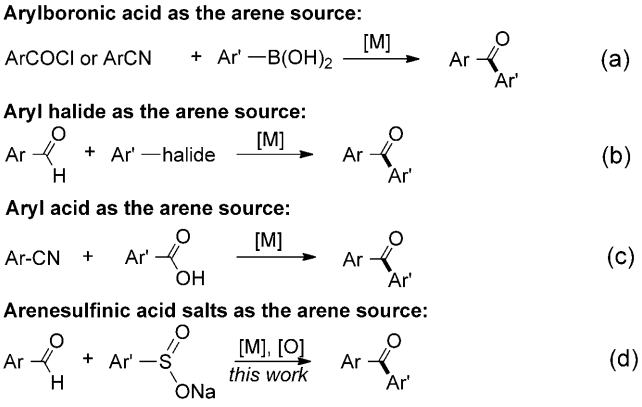
Abstract: A novel rhodium-catalyzed desulfinative coupling between aldehydes and arenesulfinic acid sodium salts was developed, generating a new protocol for the synthesis of aryl ketones. Most importantly, the coupling reaction uses molecular oxygen (O_2) as the oxidant and finally releases sodium hydrogen sulfate ($NaHSO_4$) from the reaction system; furthermore, this reaction occurs without the need for any additives.

Keywords: aldehydes; aryl ketones; arenesulfinic acid salts; coupling; desulfinative process; rhodium-catalyzed reaction

The aryl ketone moiety is one of the most common and fundamental building blocks occurring in many natural products, synthetic biologically active molecules,[1] and functional materials.[2] For organic chemists, it is also an extremely useful functional group for further manipulations.[3] Consequently, it continues to inspire the development of methods for the construction of this structural element. The traditional Friedel–Crafts acylation of aromatic compounds in the presence of Lewis acids such as $AlCl_3$ provides us with an efficient protocol for the synthesis of aryl ketones,[4] although the reaction sometimes fails with electron-deficient arenes and generally yields the desired products as isomeric mixtures.[5] The reactions of stoichiometric organometallic compounds with acid chlorides,[6] nitriles[7] or Weinreb amides[8] are also popular and well-known for the preparation of ketones. However, the poor functional group tolerance and strict handling requirement of the organometallic reagents limits their applications and thus there is a need for milder, cleaner and catalytic alternatives.[7]

During the last decade, transition metal catalysts have been utilized for the synthesis of aryl ketones. As a replacement of the organometallic reagents, arylboronic acids were introduced as a much milder arene source into the aryl ketone syntheses (Scheme 1, route a). In 1999, an efficient palladium-catalyzed cross-coupling reaction between arylboronic acids and acid chlorides to generate aryl ketones was reported by McCarthy's group.[9] Several years later, various catalytic systems were developed for aryl ketone syntheses from arylboronic acids and nitriles catalyzed by palladium,[10] rhodium[11] and nickel.[12] The use of arylboronic acids as the arene sources promises an applicable and efficient protocol for ketone syntheses, however, the boronic acids are comparably expensive and not so widely available.[13] As such, exploring and developing other arene sources instead of arylboronic acid is still highly desirable. In 2005, Chang reported a bimetallic system for the direct coupling of chelating aldehydes with iodoarenes or organostannanes as the arene sources to generate aryl ketones;[14] Xiao's group also disclosed an efficient cocatalysis of palladium-amine for the direct coupling of aldehydes with aryl bromides (Scheme 1, route b).[15] Very recently, carboxylic acids used as the



Scheme 1. Transition-metal catalyzed synthesis of aryl ketones by using different arene sources.

arene sources were illustrated by Larhed's group *via* palladium-catalyzed decarboxylative addition to nitriles affording the aryl ketones (Scheme 1, route c).[16] The most outstanding advantage of this protocol is that carboxylic acids are relatively cheap and widely commercially available, although it is mainly suitable for *ortho*-substituted electron-deficient benzoic acids and aliphatic nitriles.

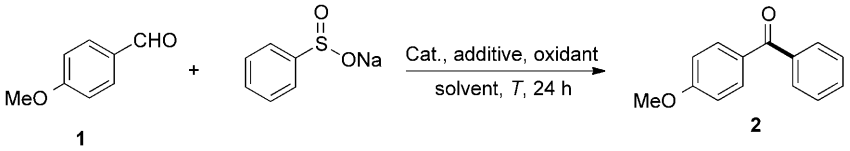
Previously, it was known that arenesulfonyl chlorides could act as aryl sources *via* desulfinative Heck-type reactions.[17] By contrast, the arenesulfinic acid salts are much more stable, and may also serve as the arene sources *via* the extrusion of SO_2. However, to the best of our knowledge, sulfinic acid salts are mainly used as sulfonylation reagents,[18] and seldom worked as the arene sources *via* desulfinative reactions.[19] Herein, we wish to introduce a novel rhodium-catalyzed coupling between aldehdyes and arenesulfinic acid salts as the novel arene sources under aerobic conditions, forming a novel strategy for aryl ketone synthesis (Scheme 1, route d).

Initially, the coupling of *p*-anisaldehyde and benzenesulfinic acid sodium salt was chosen as the model reaction to optimize the reaction conditions. The effects of catalysts, solvents, additives, oxidants, and reaction temperature were investigated. As shown in Table 1, we initially tested various ruthenium and rhodium catalysts for this desulfinative coupling reaction by using toluene as the solvent and TBP as the oxidant (entries 1–10). Among the ruthenium and rhodium catalysts explored, only three, $[RhCl(COD)]_2$, $[RhCl(C_2H_4)_2]_2$, and $RhCl(CO)(PPh_3)_2$, afforded the desired 4-methoxybenzophenone with 12%, 12% and 22% yields, respectively (entries 7, 8 and 10). Although $[RhCl(C_2H_4)_2]_2$ and $RhCl(CO)(PPh_3)_2$ afforded the same or a higher yield of the desired product, the competing homodecarbonylation product,[20] bis(4-methoxylphenyl)-methanone, was the major product in these cases (entries 7 and 8). Thus, $[RhCl(COD)]_2$ was selected for further optimization. Intriguingly, when air was used as the oxidant, it gave a 23% yield of 4-methoxybenzophenone (entry 13), whereas the use of TBHP and T-HYDRO® gave less than 10% of the product (entries 11 and 12). Furthermore, the reaction did not occur at all when carried out under argon without other additives (entry 14), indicating that O_2 may be a much better oxidant for this reaction. Indeed, the yield increased dramatically to 90% when 1 atm O_2 was employed as the oxidant (entry 15). The effect of solvents was also investigated. The yield decreased slightly when the reaction was carried out in benzene or PhCl (entries 16 and 17), while much lower yields were obtained in *o*-xylene, *p*-dioxane and mesitylene (entries 18–20). However, there was no positive effect when K_2CO_3, Na_2CO_3, K_3PO_4 and $NaHCO_3$ were added to the reaction system (entries 21–24). The reaction afforded slightly decreased yields when carried out at 160 °C and 170 °C, respectively (entries 25 and 26). In order to improve the solubility of benzenesulfinic acid sodium salt in the reaction system, H_2O was introduced; however, almost no desired product was detected (entry 27).[21] And when the catalyst was reduced to 5 mol%, the reaction still yielded 75% of the desired product (entry 28).

Hence, the scope of the direct desulfinative coupling with aldehydes was explored by using 10 mol% $[RhCl(COD)]_2$ as the catalyst, toluene as the solvent, 1 atm O_2 as the oxidant at 165 °C without any additive. As summarized in Table 2, the rhodium-catalyzed desulfinative coupling of benzenesulfinic acid sodium salt was successfully extended to various aldehyde substrates with different substituents on *para*-, *meta*- or *ortho*-position of the aromatic ring, and the desired aryl ketones were obtained in moderate to good yields (entries 2–9). The reaction could tolerate a range of functional groups on the aldehydes with coupling occurring in the presence of methoxy group (entries 2 and 7), methyl group (entry 3), carbon-halogen bonds (entries 4, 6, and 9), cyano group (entry 5) and trifluoromethyl group (entry 8), which promises further functionalizations of the aryl keto moieties. Aldehydes bearing electron-withdrawing groups such as halides, cyano and trifluoromethyl (entries 4–6, 8 and 9) showed lower reactivities than those with electron-donating groups such as methoxy and methyl (entries 2 and 3). The aldehydes with *ortho*-substituted groups on the aromatic ring gave lower yields (entries 7–9) possibly due to the increased steric effect (for examle, the aldehyde with methoxy group on the *ortho*-position and *para*-position afforded the aryl ketone in 77% and 90% yields, respectively). To expand the substrate scope, substituted arenesulfinic acid sodium salts and alkyl aldehydes were also examined under the optimal conditions. To our delight, Substituted arenesulfinic acid sodium salt, such as *p*-toluenesulfinic acid sodium salt, could undergo the desulfinative coupling efficiently (entry 10). An aliphatic aldehyde, such as *n*-hexanal, could also react, albeit giving the desired product in lower yields under the present conditions (entry 11). However, the reaction did not occur when an aliphatic sulfinic sodium salt such as *n*-$BuSO_2Na$ was treated with *p*-anisaldehyde under the optimal conditions (entry 12).

To explore the reaction mechanism for the synthesis of aryl ketones, the following control experiments were performed under the standard reaction conditions (Scheme 2). Coupling of *p*-anisaldehyde with sodium benzenesulfonate gave no desired 4-methoxybenzophenone and the result showed that the coupling reaction did not involve the oxidation of arenesulfinic sodium salt to sodium sulfonate (Scheme 2, reaction a). When benzenesulfinic sodium salt was coupled with 4-cyanobenzaldehyde, the reaction yield

Table 1. Optimization of the reaction conditions for the aryl ketone synthesis *via* the coupling of aldehyde with arenesulfinic acid salt.[a]



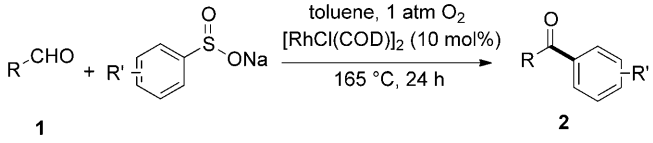
Entry	Cat.	Solvent	Additive	Oxidant	Yield [%][b]
1	$Ru_3(CO)_{12}$	toluene	–	TBP	trace
2	$Rh_6(CO)_{16}$	toluene	–	TBP	trace
3	$RhCl(PPh_3)_3$	toluene	–	TBP	trace
4	$Rh(CO)_2acac$	toluene	–	TBP	trace
5	$[RhCl(CO)_2]_2$	toluene	–	TBP	trace
6	$[RhCl_2Cp^*]_2$	toluene	–	TBP	trace
7	$[RhCl(COD)]_2$	toluene	–	TBP	12
8[c]	$[RhCl(C_2H_4)_2]_2$	toluene	–	TBP	12
9	$Rh(COD)_2BF_4$	toluene	–	TBP	trace
10[c]	$RhCl(CO)(PPh_3)_2$	toluene	–	TBP	22
11	$[RhCl(COD)]_2$	toluene	–	TBHP	<10
12	$[RhCl(COD)]_2$	toluene	–	T-HYDRO®	<10
13	$[RhCl(COD)]_2$	toluene	–	air	23
14[d]	$[RhCl(COD)]_2$	toluene	–	–	–
15	**$[RhCl(COD)]_2$**	**toluene**	**–**	**O_2**	**90**
16	$[RhCl(COD)]_2$	benzene	–	O_2	82
17	$[RhCl(COD)]_2$	PhCl	–	O_2	80
18	$[RhCl(COD)]_2$	*o*-xylene	–	O_2	50
19	$[RhCl(COD)]_2$	*p*-dioxane	–	O_2	trace
20	$[RhCl(COD)]_2$	mesitylene	–	O_2	27
21	$[RhCl(COD)]_2$	toluene	K_2CO_3	O_2	77
22	$[RhCl(COD)]_2$	toluene	Na_2CO_3	O_2	82
23	$[RhCl(COD)]_2$	toluene	K_3PO_4	O_2	25
24	$[RhCl(COD)]_2$	toluene	$NaHCO_3$	O_2	27
25[e]	$[RhCl(COD)]_2$	toluene	–	O_2	78
26[f]	$[RhCl(COD)]_2$	toluene	–	O_2	76
27[g]	$[RhCl(COD)]_2$	toluene	H_2O	O_2	trace
28[h]	$[RhCl(COD)]_2$	toluene	–	O_2	75

[a] *Reaction conditions:* anisaldehyde **1** (0.12 mmol), $PhSO_2Na$ (0.10 mmol), catalyst (10 mol%), solvent (0.50 mL), TBP (4 equiv.) or TBHP (4 equiv.) or T-HYDRO® (4 equiv.) or air (1 atm) or O_2 (1 atm), additive (2 equiv.), reaction temperature: 165 °C, reaction time: 24 h.
[b] Reported yields were based on $PhSO_2Na$ by ^1H NMR using an internal standard.
[c] Bis(4-methoxyphenyl)methanone was the major product.
[d] Reaction was carried out under argon.
[e] Reaction temperature: 160 °C.
[f] Reaction temperature: 170 °C.
[g] H_2O (10 μL).
[h] $[RhCl(COD)]_2$ (5 mol%).

45% of the desired ketone, without any product being detected *via* the reaction of benzenesulfinic sodium salt with the cyano group (Scheme 2, reactions b and c). Furthermore, the reaction of acetophenone with benzenesulfinic sodium salt under the optimal conditions yielded no 1,1-diphenylethanol (Scheme 2, reaction d). These results suggested that the reaction process most probably did not involve 1,2-addition of arylrhodium species with aldehyde followed by liberation of the product *via* a β-H elimination.

According to the results above, a tentative mechanism for the aryl ketone formation was proposed (Scheme 3). Initially, the coordination of aldehyde **1** to generated Rh(I) complex **3**, followed by C–H insertion of the aldehyde to get the Rh(III) hydride species **4**,[22] and the oxidation of **4** by O_2 may give the Rh(III)OOH complex **5**.[23] Next, reaction of complex **5** with arenesulfinic acid sodium salt effects the release of $NaHSO_4$ (see Supporting Information), generating complex **6**, which was followed by the re-

Table 2. Scope of rhodium-catalyzed coupling between aldehydes and arenesulfinic acid salts.[a]



1 2

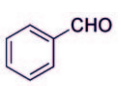
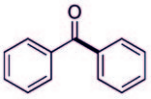
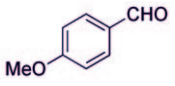
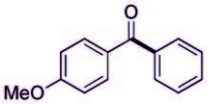
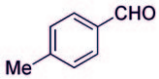
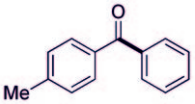
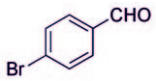
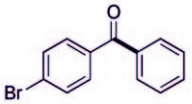
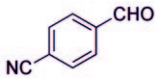
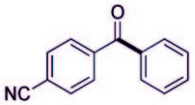
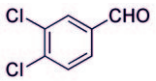
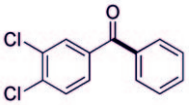
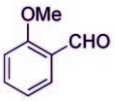
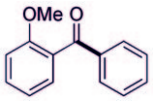
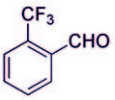
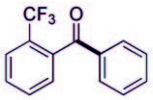
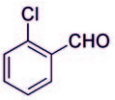
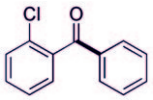
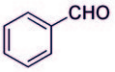
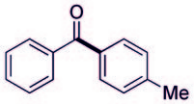
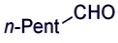
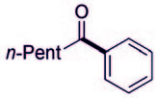
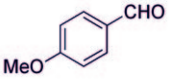
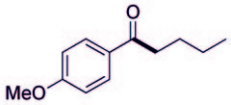
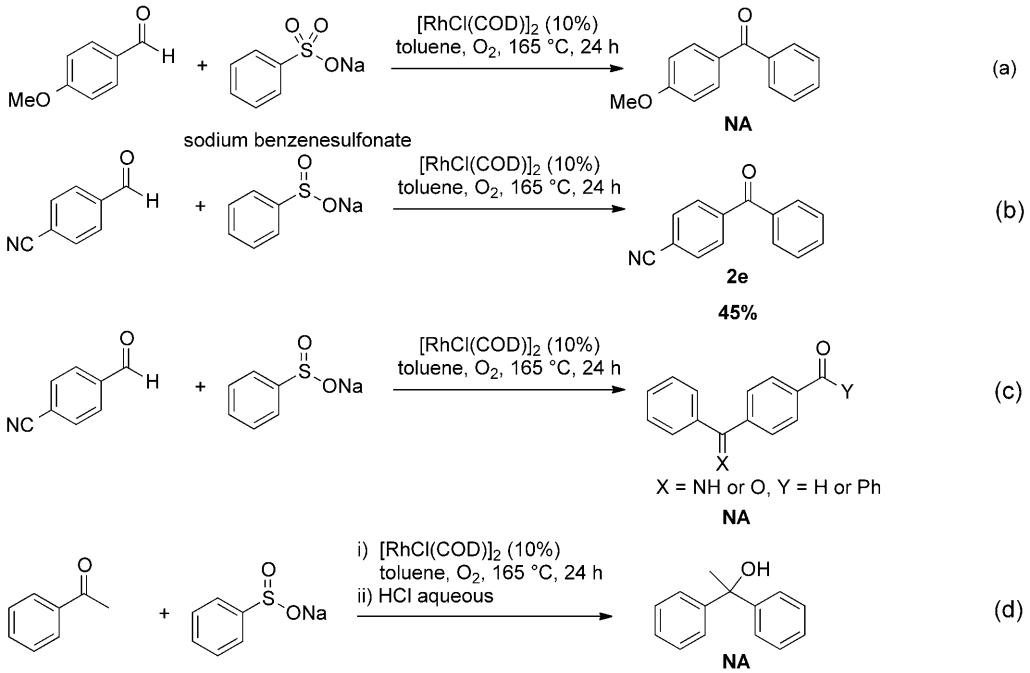
Entry	Aldehyde **1**	Product **2**	Yield [%][b]
1		**2a** 	82
2		**2b** 	90
3		**2c** 	80
4		**2d** 	67
5		**2e** 	45
6		**2f** 	63

Table 2. (Continued)

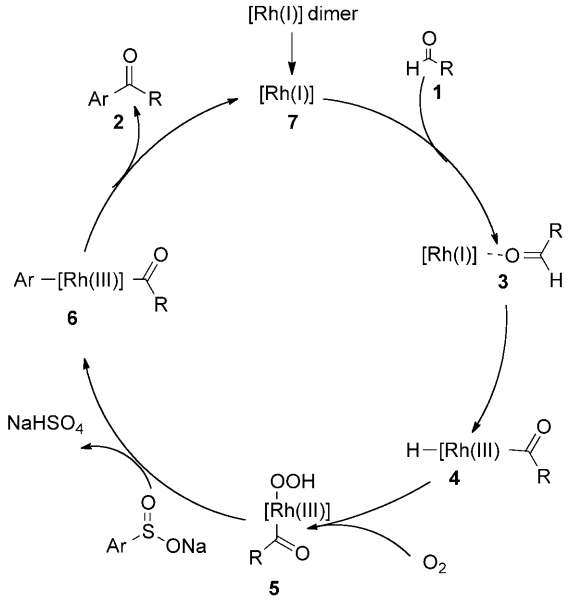
Entry	Aldehyde **1**	Product **2**	Yield [%][b]
7		**2g** 	77
8		**2h** 	50
9		**2i** 	43
10		**2c** 	79
11		**2j** 	23
12		**2k** 	0

[a] *Reaction conditions:* aldehyde **1** (0.12 mmol), $ArSO_2Na$ (0.10 mmol), catalyst (10 mol%), toluene (0.50 mL), O_2 (1 atm), reaction time: 24 h, reaction temperature: 165 °C.

[b] Reported yields were based on $ArSO_2Na$ by ^1H NMR using an internal standard.



Scheme 2. Investigation of the reaction mechanism for the ketone synthesis.



Scheme 3. Tentative mechanism for the rhodium-catalyzed coupling between aldehydes and arenesulfinic acid salts.

ductive elimination to the desired ketone product **2** and the regeneration of the Rh(I) catalyst **7**.

In summary, we have developed a novel rhodium-catalyzed coupling between aldehdyes and arenesulfinic acid sodium salts, generating a new protocol for aryl ketone synthesis. Most importantly, this desulfinative coupling reaction uses O_2 as the oxidant and releases $NaHSO_4$ from the reaction system; furthermore, this reaction occurred without any additives. Various functional groups on the aromatic ring are tolerated under the present coupling conditions, which indicates the potential wide applications of this reaction. Studies into the mechanism and further application of the reaction are ongoing in our laboratory.

Experimental Section

General Experimental Procedure

An oven-dried reaction vessel was charged with $[RhCl(COD)]_2$ (6.9 mg, 0.01 mmol, 10 mol%), benzenesulfinic acid sodium salt (0.10 mmol, 17 mg), and 4-methoxybenzaldehyde (0.12 mmol, 14 μL). After the vessel had been filled with O_2, dry toluene (0.5 mL) was added by syringe and the reaction mixture was stirred at room temperature for 5 min. Then the vessel was sealed, placed into an oil bath and heated to 165 °C. After 24 h, the resulting mixture was cooled to room temperature, filtered through a short silica gel pad and washed with ethyl acetate. The above solution was evaporated under vacuum. The yield of 4-methoxybenzophenone was determined by ^1H NMR using mesitylene as the internal standard. Then the mixture was purified by silica gel column with *n*-hexane/ethyl acetate (40:1) as the eluent to give the analytically pure 4-methoxybenzophenone.

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