Homogeneous Catalysis

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Rearrangement of 2-Aryloxybenzaldehydes to 2-Hydroxybenzophenones by Rhodium-Catalyzed Cleavage of Aryloxy C–O Bonds**

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The catalytic cleavage and functionalization of C–O bonds offer great potential for the utilization of biomass (e.g., carbohydrates and lignins) as renewable chemical feedstocks,[1] and broadening the diversity of functional molecules in the manufacture of pharmaceuticals and fine chemicals through the direct functionalization of alkyloxy- and aryloxy-containing natural products.[2] For transition-metal-catalyzed C–C bond formation by C_{Ar}–O bond cleavage, Wenkert et al. reported pioneering studies on the coupling of aryl ethers with Grignard reagents by employing a nickel catalyst.[3] Chemistry based on this cleavage-type remained dormant for nearly several decades until the appearance of improved catalyst systems involving less aggressive nucleophiles in recent years.[4] As illustrated in Figure 1, for instance, aryl triflates, sulfonates, and phosphates were successfully employed in the cross-coupling reactions by the direct activation of the C–O bonds.[5] Notably, the recent achievements indicated that aryl carbamate, carboxylates, and carbonate are also appropriate substrates for the C–O bond-cleavage-type chemistry.[6] In particular, anisole derivatives could also serve as a potential substrate for coupling reactions.[4,7] However, such reactivities still remain challenging because nearly all the reported C–O bond-cleavage-type reactions were performed by using nickel catalysts, and to the best of our knowledge, there are few examples on the cleavage of typically unreactive diaryl ether moieties.[8] Herein, we present an unprecedented rearrangement of 2-aryloxybenzaldehydes to 2-hydroxybenzophenones through the simultaneous rhodium-catalyzed cleavage of aryloxy C–O and aldehyde C–H bonds (Scheme 1). Furthermore, the reaction tolerates the presence of various catalytically reactive substituents such as aryl halides, nitriles, and esters.

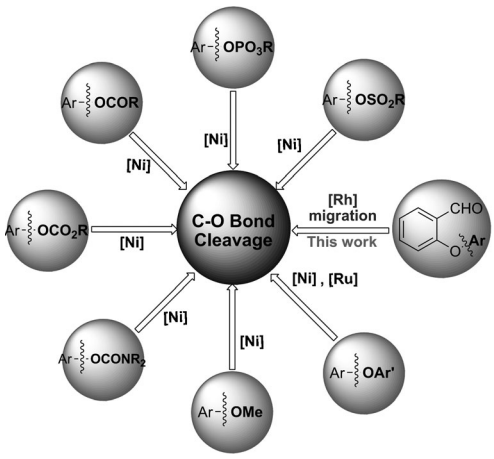
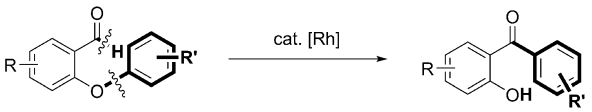


Figure 1. Transition-metal-catalyzed cleavage of C–O bonds.



Scheme 1. Rhodium catalyzed rearrangement through the cleavage of C–O and C–H bonds.

As a continuation of our studies into the decarbonylation reaction,[9] we reacted 2-(phenoxy)benzaldehyde (**1a**) under our previous decarbonylative coupling conditions. However, the expected decarbonylative coupling product was not observed; instead, the unexpected product **2a**, resulting from the rearrangement of the aryl group and the hydrogen atom by the cleavage of both the aryloxy C–O bond and aldehyde C–H bond, was detected in approximately 30% yield. Subsequently, optimization of this unprecedented rearrangement reaction was carried out with 2-(phenoxy)-benzaldehyde (**1a**), under argon in PhCl at 160°C by using TBP as the oxidant. A series of ruthenium and rhodium catalysts showed varying efficiencies in catalyzing the rearrangement reaction (Table 1, entries 1–10). Whereas all the ruthenium catalysts tested showed moderate catalytic activities (entries 1–3), the use of different rhodium catalysts had a drastic change in catalyzing the reaction (entries 4–10). By using $[\{RhCl(CO)_2\}_2]$ as the catalyst, the desired 2-hydroxybenzophenone (**2a**), was obtained in 53% yield (entry 4). Other rhodium catalysts having different ligands (such as acac, cod, PPh_3), counterions (such as BF_4^-), or higher-valent rhodium catalysts such as $[Cp^*Rh(MeCN)_3](SbF_6)_2$ were either much less effective than $[\{RhCl(CO)_2\}_2]$ or exhibited almost no catalytic activity (entries 5–10). Among the oxidants examined, TBP provided the best yield

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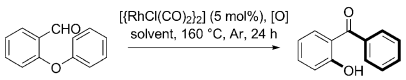
Table 1: Optimization of the rearrangement of 2-(aryloxy)benzaldehydes to 2-hydroxybenzophenones.[a]

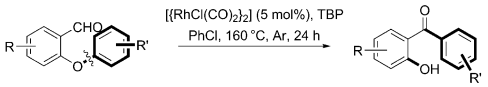


1a 2a

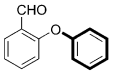
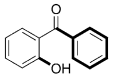
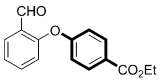
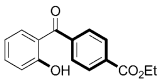
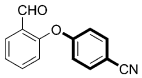
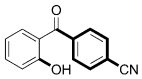
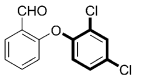
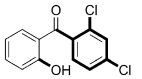
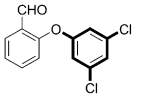
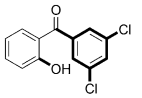
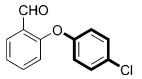
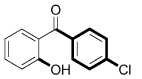
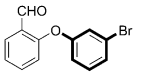
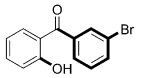
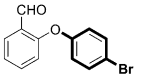
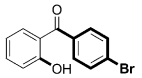
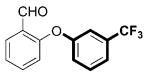
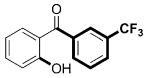
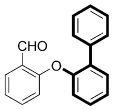
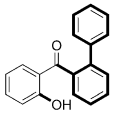
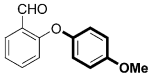
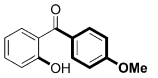
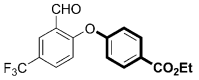
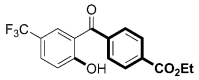
Entry	Catalyst	Solvent	[O]	Yield [%][b]
1	$[RuCl_2(PPh_3)_3]$	PhCl	TBP	22
2	$[\{Cp^*RuCl_2\}_2]$	PhCl	TBP	37
3	$[RuCl_2(CO)_3]$	PhCl	TBP	37
4	**$[\{RhCl(CO)_2\}_2]$**	**PhCl**	**TBP**	**53**
5	$[Rh(CO)_2acac]$	PhCl	TBP	< 10
6	$[\{RhCl(cod)\}_2]$	PhCl	TBP	12
7	$[RhCl(PPh_3)_3]$	PhCl	TBP	40
8	$[RhCl(CO)(PPh_3)_2]$	PhCl	TBP	12
9	$[Rh(cod)_2BF_4]$	PhCl	TBP	24
10	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	PhCl	TBP	trace
11	$[\{RhCl(CO)_2\}_2]$	PhCl	TBHP	< 10
12	$[\{RhCl(CO)_2\}_2]$	PhCl	DCP	< 10
13	$[\{RhCl(CO)_2\}_2]$	PhCl	*m*CPBA	trace
14	$[\{RhCl(CO)_2\}_2]$	benzene	TBP	35
15	$[\{RhCl(CO)_2\}_2]$	toluene	TBP	17
16	$[\{RhCl(CO)_2\}_2]$	DCE	TBP	11
17[c]	$[\{RhCl(CO)_2\}_2]$	PhCl	TBP	46
18[d]	$[\{RhCl(CO)_2\}_2]$	PhCl	TBP	46
19[e]	$[\{RhCl(CO)_2\}_2]$	PhCl	TBP	42
20[f]	$[\{RhCl(CO)_2\}_2]$	PhCl	TBP	21
21[g]	$[RhCl(CO)_2]_2$	PhCl	TBP	39
22[h]	$[\{RhCl(CO)_2\}_2]$	PhCl	TBP	< 10
23	$[\{RhCl(CO)_2\}_2]$	PhCl	–	trace
24	–	PhCl	TBP	trace

[a] Reaction conditions: **1a** (0.1 mmol), cat. (5 mol%), [O] (2.5 equiv), and solvent (0.25 mL) at 160°C for 24 h under argon. [b] Yield determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [c] *t*BuOH (1.0 equiv) as an additive. [d] H_2O (1.0 equiv) as an additive. [e] PivOH (1.0 equiv) as an additive. [f] DPPE (10 mol%) as the ligand. [g] $[\{RhCl(CO)_2\}_2]$ (2.5 mol%). [h] TBP (0.5 equiv). [O] = oxidant, acac = acetylacetonate, cod = 1,5-cyclooctadiene, Cp* = pentamethylcyclopentadienyl, DCE = 1,2-dichloroethane, DCP = dicumyl peroxide, DPPE = 1,2-bis(diphenylphosphino)ethane, *m*CPBA = 3-chlorobenzoperoxoic acid, PivOH = pivalic acid, TBP = *tert*-butyl peroxide, TBHP = *tert*-butyl hydroperoxide.

Table 2: Scope of the rhodium-catalyzed rearrangement of 2-(aryloxy)-benzaldehydes to 2-hydroxybenzophenones.[a]



1 2

Entry	1	2		Yield [%][b]
1			**2a**	51
2			**2b**	83
3			**2c**	71
4			**2d**	81
5			**2e**	86
6			**2f**	66
7			**2g**	60
8			**2h**	55
9			**2i**	60
10			**2j**	61
11			**2k**	40
12			**2l**	71

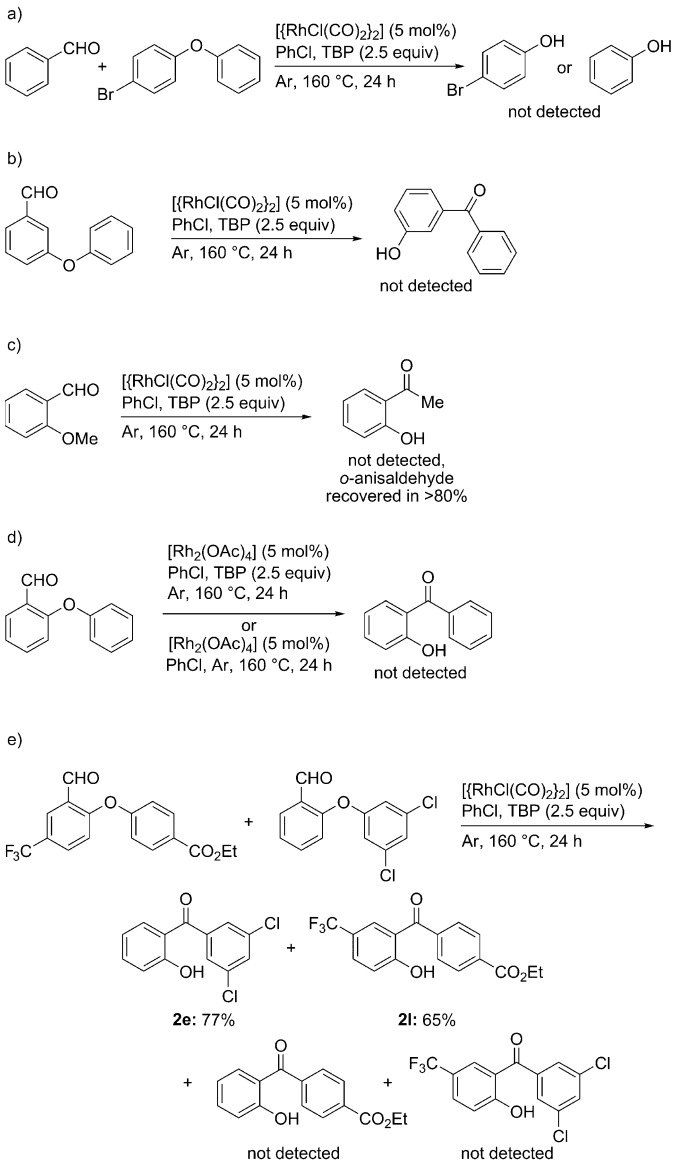
[a] Reaction conditions: **1** (0.20 mmol), $[\{RhCl(CO)_2\}_2]$ (5 mol%), TBP (2.5 equiv), PhCl (0.50 mL), at 160°C for 24 h under argon. [b] Yield of isolated product.

of the corresponding rearrangement product (entries 11–13). The use of different solvents also strongly influenced the reaction: When the reaction was carried out in benzene, toluene, or DCE the yield of the desired product decreased dramatically (entries 14–16). The introduction of some proton donors such as *t*BuOH, H_2O, or PivOH as additives slightly reduced the product yields (entries 17–19). Other endeavors to increase the yield of 2-hydroxybenzophenone were attempted. For instance, the addition of 10 mol% DPPE as the ligand did not improve this transformation (entry 20). When the reaction was conducted with a reduced amount of the catalyst (2.5 mol%) or TBP, the product yield was reduced (entries 21 and 22). Interestingly, a trace amount of the product was obtained when using either no catalyst or no TBP (entries 23–24).

With the optimized reaction conditions in hand, the substrate scope was explored at 160°C under argon using 5 mol% $[\{RhCl(CO)_2\}_2]$ as the catalyst, TBP as the oxidant, and PhCl as the solvent. As summarized in Table 2, this rearrangement was successfully performed with different substituents at the *para*, *meta*, or *ortho* position of the aryloxy unit, and the desired 2-hydroxybenzophenones were obtained in moderate to good yields (Table 2, entries 2–11). The reaction could tolerate a range of functional groups with rearrangement occurring in the presence of electron-withdrawing groups such as ester (entry 2), cyano (entry 3), halogen (entries 4–8), and trifluoromethyl groups (entry 9), as well as electron-donating groups such as phenyl (entry 10) and methoxy groups (entry 11), all of which promise additional functionalization of the products. Notably, the aryloxy

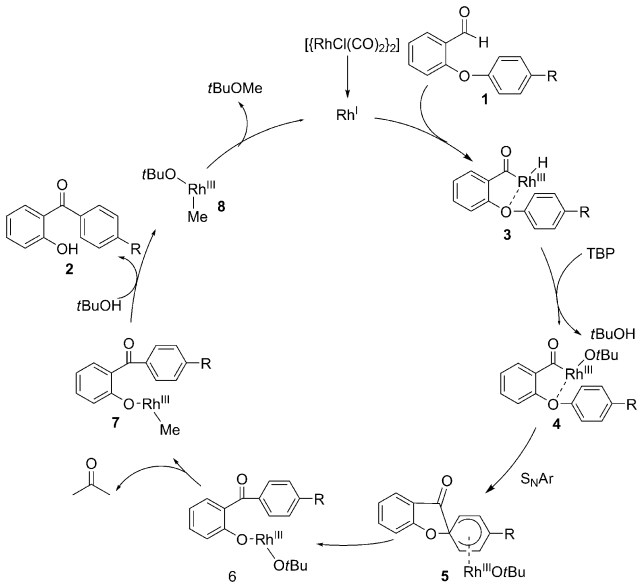
units with electron-withdrawing groups displayed higher reactivities than those with electron-donating groups (entries 2–11), as it is much easier to undergo the cross-dehydrogenative coupling reactions to 9*H*-xanthen-9-one derivatives with electron-donating substituents.[10] To expand the substrate scope, the benzaldehyde unit bearing a 4-CF_3 group underwent rearrangement smoothly to afford the desired ethyl 4-(2-hydroxy-5-(trifluoromethyl)benzoyl)benzoate in 71% yield (entry 12).

To explore the reaction mechanism for this rearrangement, control experiments were conducted under the standard reaction conditions (Scheme 2). The reaction of benzaldehyde with bromo biphenyl either gave no phenol or bromophenol (Scheme 2a). When 3-(phenoxy)benzaldehyde was subjected to the optimized reaction conditions, it also did not generate the C–O bond-cleavage product (Scheme 2b), thus demonstrating that the chelation to the rhodium catalyst by the CHO and 2-aryloxy groups is essential for the rearrangement. Meanwhile, when *o*-anisaldehyde was subjected to the standard reaction conditions, no 2′-hydroxyacetophenone was observed, thus indicating the important role of the 2-aryloxy group for this C–O bond-cleavage chemistry (Scheme 2c). Additionally, when $[Rh_2(OAc)_4]$ (usually employed in radical reactions involving nitroene or carbene radical species)[11] was used instead of $[\{RhCl(CO)_2\}_2]$, the desired product was not obtained, thus suggesting that this reaction may not involve a radical mechanistic pathway (although a radical mechanism cannot be excluded; Scheme 2d). Finally, a cross-experiment showed no cross-rearrangement product, thus indicating that this rearrangement most probably proceeded through an intramolecular process (Scheme 2e).



Scheme 2. Investigation of the mechanistic pathway for the rearrangement.

On the basis of the above investigations, a tentative mechanism for this aryloxy C–O bond-cleavage chemistry is depicted in Scheme 3. Initially, the chelating aldehyde C–H insertion of 2-(aryloxy)benzaldehydes **1** by Rh^I generates the Rh^{III} hydride species **3**.[12] Upon reaction with TBP, the



Scheme 3. Tentative mechanism for the rhodium-catalyzed rearrangement of 2-(aryloxy)benzaldehydes to 2-hydroxybenzophenones.

Rh^{III} complex **4** is formed, thus liberating one molecule of *t*BuOH. Then complex **4** may undergo an intramolecular S_NAr process to afford the complex **5** upon heating to 160 °C,[13] thereby generating the Rh^{III} complex **6** (an alternative process through 1,4-elimination of Ar–Rh–*t*OBu from **4** with subsequent conjugate addition of Ar–Rh–*t*OBu to the resulting enone species may be excluded based on the result of the cross-experiment), which could release one molecule of acetone (detected by GC-MS) to afford the Rh^{III}/Me complex **7**.[14] Finally, reaction of the previously formed *t*BuOH with complex **7** can release one molecule of the desired product **2** and form $[Rh^{III}(Me)(tOBu)]$ (**8**),[14e,f,15] which could regenerate the Rh^I catalyst through a reductive elimination process by releasing *t*BuOMe (detected by GC-MS).

In summary, we have developed a rhodium-catalyzed rearrangement of 2-(aryloxy)benzaldehydes to 2-hydroxybenzophenones, which serves as a novel aryloxy C–O bond-cleavage protocol that proceeds through a chelating strategy. This reaction can tolerate a variety of functional groups, thereby indicating the wide potential of applications for this reaction. Additional investigations into the mechanism and applications of the reaction are now ongoing in our laboratory.

Experimental Section

An oven-dried reaction vessel was charged with $[\{RhCl(CO)_2\}_2]$ (3.9 mg, 0.01 mmol, 5 mol%) and 2-(aryloxy)benzaldehydes (0.2 mmol). After the vessel was filled with argon, dry PhCl (0.5 mL) and TBP (100 uL, 2.5 equiv) were added by syringe sequentially under argon, and the reaction mixture was stirred at room temperature for 5 min. Then the vessel was sealed, placed into an oil bath, and heated at 160 °C for 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, and the residue was purified by column chromatography on silica gel with *n*-hexane/ethyl acetate (30:1 to 20:1) as the eluent to give the analytically pure 2-hydroxybenzophenones.

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