Letter

Palladium-catalyzed carbonylation of aryl bromides and iodides with potassium phenoxides

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Abstract

Palladium-catalyzed aryloxycarbonylation of aryl bromides and iodides show contrastive reactivities with respect to the kind of phenoxides. The carbonylation of bromides with hindered potassium phenoxides in benzene gives ester products in high yields, while that with non-hindered PhOK gives almost no ester product under the same conditions. In contrast, the carbonylation of iodides with hindered potassium phenoxides gives no ester, while that with non-hindered PhOK provides ester products in high yields. Variant reductive elimination steps from aroyl palladium halide species to ester products and Pd(0) species are proposed depending on the steric and electronic properties of the phenoxides and aryl halides. They involve a stepwise ligand exchange path and a concerted path.

Keywords: Palladium-catalyzed carbonylation; Aryloxycarbonylation; Potassium phenoxides; Aryl bromides; Aryl iodides; 4-Bromo-biphenyl; Aryl esters; Phosphine ligands

1. Introduction

Palladium-catalyzed alkoxycarbonylation of aryl halides has been one of the useful methods for the synthesis of aryl carboxylic acid esters [1–5]. Aliphatic alcohols can be generally used as nucleophiles to give alkyl esters of aryl carboxylic acids. We have recently reported palladium-catalyzed efficient carbonylation of 4-bromobiphenyl (1a) with PhOH using a strong organic base [6]. This method was extended to the synthesis of aryl carboxylic acid aryl esters. Although various phenols can be used as nucleophiles, the carbonylation of bromide 1a did not

take place when hindered phenols such as 2,6-di-tert-butylphenols were used. This difficulty has been overcome by using potassium 2,6-di-tert-butylphenoxides without base, in place of corresponding hindered phenols with base [7], and the hindered ester 3b was obtained in high yield. On the other hand, the carbonylation of bromides with non-hindered PhOK gave almost no ester products.

The use of aryl iodides in this reaction showed additional interesting features about reactivity. For example, the carbonylation of iodides with hindered potassium phenoxides gives no ester, while that with non-hindered PhOK provides ester products in high yields. The unusual features of reactivity seems to be mainly related to

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the reductive elimination step from aroyl palladium halide species to ester products and Pd(0) species. However, there has been few detailed description of the reductive elimination step in the alkoxycarbonylation [8,9]. Furthermore, there has been no paper on the mechanism of carbonylation using metal phenoxide species as nucleophiles to our knowledge. We report herein the behavior of starting aryl bromides and iodides in the aryloxycarbonylation using potassium phenoxides and discuss the mechanism of this reaction.

2. Experimental

A typical procedure of phenoxycarbonylation with PhOK (**2a**) is as follows: In a 50 ml autoclave, CO was pressurized at 5 bar into a mixture of 4-iodobiphenyl (**1b**) (2.5 mmol) prepared by known method [10,11], docosane (internal standard, 1.25 mmol), 1,3-bis(diphenyl-phosphino)propane (dppp, 0.2 mmol), PdCl$_2$ (0.1 mmol), benzene (5 ml), and **2a** (3.0 mmol), prepared by treatment of phenol with 0.93 equiv. of KOH in aqueous methanol [12] followed by drying. The reaction vessel and contents were placed in a 100°C oil bath. After stirring for 2 h, capillary GC (Shimadzu GC14A; 0.2 mm × 12 m HP Ultra-1 column, 160–280°C) revealed a 100% conversion of iodide and a 97% yield of biphenyl-4-carboxylic acid phenyl ester (**3a**). Purification by column chromatography on silica gel gave product in almost the same yield as that determined by GC analysis. In all cases studied, carbonylation was 100% regiospecific. Procedure of aryloxycarbonylation with potassium 2,6-di-*tert*-butylphenols is described in our previous paper [7]. Physical properties of **3a** are given elsewhere [6] and those of **3b** and **3c** are given below.

3b: mp 179.5–180.5°C (recrystallized from ethanol). Anal. Calcd. for C$_{28}$H$_{32}$O$_2$: C, 83.96; H, 8.05. Found: C, 84.24; H, 8.14. MS m/z 400 (M$^+$), 181. IR (KBr): 1734 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 1.35 (18H, s), 2.36 (3H, s), 7.18

(2H, s), 7.37–7.53 (3H, m), 7.63–7.69 (2H, m), 7.75 (2H, dt, $J = 8.5$, 1.7 Hz), 8.31 (2H, dt, $J = 8.5$, 1.7 Hz). ^{13}C NMR (CDCl$_3$) δ: 21.56 (CH$_3$), 31.59 (6CH$_3$), 35.31 (2C), 127.06 (2CH), 127.31 (2CH), 127.45 (2CH), 128.25 (2CH), 128.95 (CH), 129.30 (C), 130.89 (2CH), 134.57 (C), 139.87 (C), 142.22 (2C), 145.90 (C), 146.11 (C), 166.78 (C=O).

3c: mp 74.5–75.5°C. Anal. Calcd. for C$_{14}$H$_{12}$O$_2$: C, 79.23; H, 5.70. Found: C, 79.24; H, 5.65. MS m/z 212 (M$^+$). IR (KBr): 1725 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ: 2.44 (3H, s), 7.19–7.31 (5H, m), 7.39–7.45 (2H, m), 8.08–8.11 (2H, m). ^{13}C NMR (CDCl$_3$) δ: 21.73 (CH$_3$), 121.74 (2CH), 125.75 (CH), 126.79 (C), 129.25 (2CH), 129.42 (2CH), 130.19 (2CH), 144.37 (C), 151.00 (C), 165.21 (C=O).

3. Results and discussion

The carbonylation of aryl halides (**1a–c**) with potassium aryloxides (**2a–b**) is shown in Eq. (1) and Table 1.

(Eq. 1)
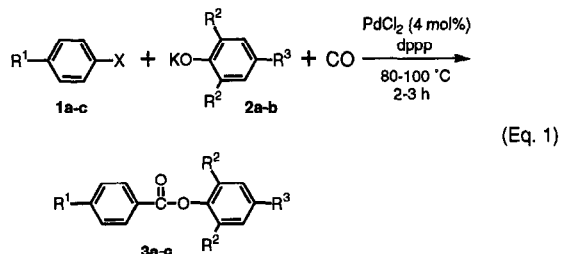
Bromide **1a** was readily carbonylated with hindered potassium 4-methyl-2,6-di-*tert*-butylphenoxide (**2b**) at 100°C in benzene under 5 bar of CO pressure to give corresponding hindered aryl ester **3b** in 84% yield (Table 1, run 1). The yields of ester **3b** were gradually decreased at lower temperatures (Table 1, run 2 and 3). Surprisingly, the reaction of **1a** with non-hindered PhOK (**2a**) gave phenyl ester **3a** in only 1% yield accompanied by the recovery
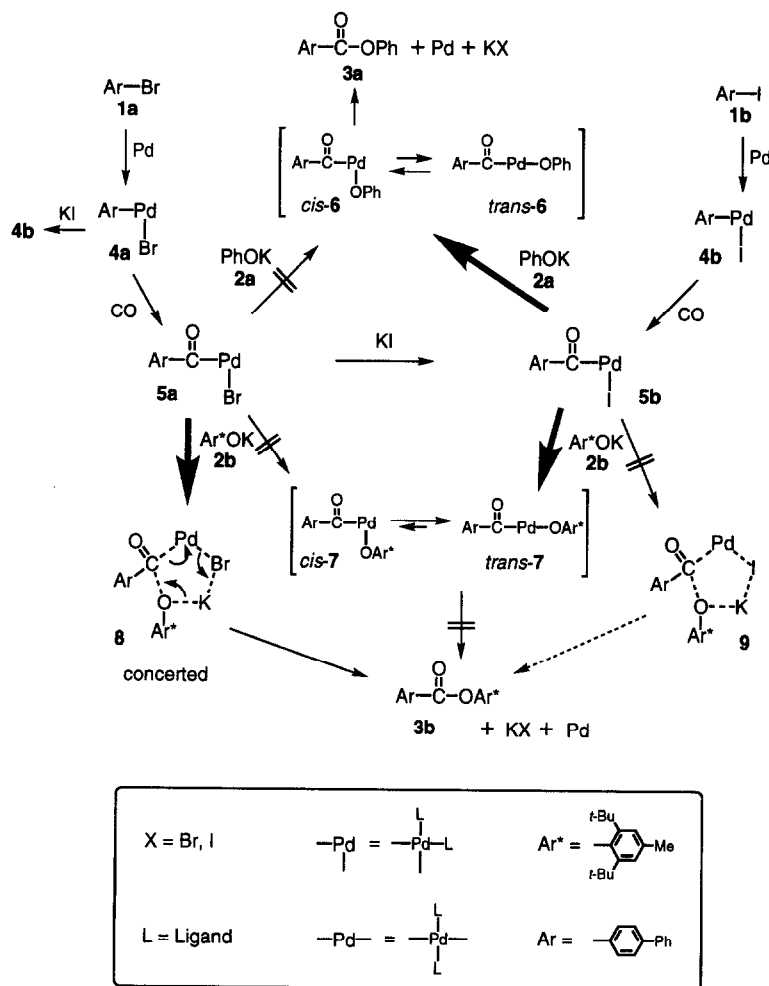
Table 1
Carbonylation of aryl halides (1) with potassium phenoxides (2) [a]

Run	1	X	R^1	2	R^2	R^3	Additive	Temp. (°C)	Time (h)	3	Yield (%) [b]	
											3	1
1	1a	Br	Ph	2b	t-Bu	Me	—	100	3	3b	84	8
2	1a	Br	Ph	2b	t-Bu	Me	—	90	3	3b	32	68
3	1a	Br	Ph	2b	t-Bu	Me	—	80	3	3b	3	97
4	1b	I	Ph	2b	t-Bu	Me	—	90	3	3b	0	78
5	1a	Br	Ph	2a	H	H	—	100	2	3a	1 (88) [c]	90 (12) [c]
6	1b	I	Ph	2a	H	H	—	100	2	3a	97	0
7	1a	Br	Ph	2a	H	H	KI	100	2	3a	50	42
8	1c	Br	Me	2a	H	H	—	100	2	3c	0	99
9	1d	I	Me	2a	H	H	—	100	2	3c	87	0

[a] Reactions were carried out in benzene unless otherwise noted.
[b] Yields were determined by GC.
[c] Yields for the reaction in DMF, given in parenthesis.

Scheme 1. Possible paths from 4-halobiphenyls to their aryl esters. Phosphine ligands are omitted for clarity.

of 1a in 90% (Table 1, run 5). Addition of KI (1 eq) improved the yield of 3a up to 50% (Table 1, run 7). The reaction in DMF also improved the yield drastically and gave 3a in 88% (Table 1, run 5). The analogous result is that the phenoxycarbonylation of 4-bromotoluene (1c) with non-hindered phenoxide 2a gave no ester product, and 1c was recovered in 99% (Table 1, run 8).

Next, we examined the reaction of iodides. Unlike the case of bromide 1a, the use of 4-iodobiphenyl (1b) and hindered phenoxide 2b gave no ester product at 90°C. On the other hand, the reaction of iodide 1b with non-hindered phenoxide 2a gave 97% of phenyl ester 3b. The phenoxycarbonylation of 4-iodo-toluene (1d) with 2a gave ester 3c in 87% (Table 1, run 9).

On the basis of these results, we considered the mechanism of aryloxycarbonylation of aryl halides with potassium phenoxides as shown in Scheme 1. It was quite interesting that bromide 1a and iodide 1b showed contrastive reactivities. When a hindered phenoxide 2b was used as a nucleophile, the hindered aryl ester 3b was obtained from bromide 1a in 32% yield at 90°C (Table 1, run 2), whereas it was not obtained at all from iodide 1b under the same conditions (Table 1, run 4). In contrast, when a non-hindered phenoxide 2a was used as a nucleophile, phenyl ester 3a was obtained from iodide 1b in 97% yield in benzene, whereas it was obtained from bromide 1a in only 1% under the same conditions. These results mean that the oxidative addition steps (from 1a–b to 4a–b in Scheme 1) do not determine the rate of this aryloxycarbonylation. If the oxidative addition is the rate-determining step, then the yields from iodides should be better than those from bromides in any case. It seems that the reductive elimination steps (from 5a–b to 3a–b in Scheme 1) are determining the order of reactivities.

It was also interesting that the yield of phenyl ester 3a from bromide 1a drastically increased from 1% to 50% in the presence of KI (Table 1,

run 5 and 7). This indicates that a partial halide exchange occurs on Pd(II) center in the bromo-intermediates 5a or 4a in Scheme 1 and that phenoxycarbonylation proceeds via an iodo-intermediate 5b, not directly from 5a. Ozawa et al. assumed the generation of a three-coordinate benzoyl palladium alkoxide which is to form ester product [8]. The formation process of this benzoyl palladium alkoxide corresponds to the exchange process to form intermediate 6 here. Ozawa et al. also reported the relative rates of ester formation in the reaction of trans-Pd(COPh)X(PPh$_3$)$_2$ (X = I, Br, Cl) with EtOH and Et$_3$N and that the reaction rates were in the order of X = I > X = Br > X = Cl [8]. We estimate this order may reflect the relative leaving group ability (nucleofugality) of halide ions, which is observed in the alkene-forming elimination reactions [13]. By analogy, we assume here that the exchange of iodide ligand in 5b with PhO$^-$ could readily take place, whereas that of bromide ligand in 5a with PhO$^-$ could not readily occur due to the relatively poor reactivity of the bromide. More polar media were expected to accelerate this substitution of polar species in the step from 5a to 6. In fact, the exchange of relatively low reactive bromide ligand in 5a with PhO$^-$ may have occurred in DMF. As a result, unlike in benzene, the reaction of bromide 1a with phenoxide 2a in DMF gave ester 3a in 88% yield (Table 1, run 5). The combined use of PhOH and an organic base instead of the use of 2a gave ester 3a in good yield even in benzene [6]. In this case, organic ammonium cations dissolving in benzene may have aided the polarity to the medium.

Another factor we should consider is the configuration of aroyl phenoxy palladium intermediate 6. It should be noted that the bisphosphines such as 1,3-bis(diphenylphosphino)propane (dppp) have been reported to have high catalytic activities in the carbonylation of aryl halides and triflates [14,15]. The enhancement of the activities must, in part, have been a consequence of the obligatory cis arrangement of the bisphosphine ligand by forming a six-

membered chelate in the square-planar aroyl palladium complex [15]. It can be assumed that aroyl phenoxy palladium intermediates **6** are under an equilibrium and reductive elimination takes place only from *cis*-**6**, forming phenyl ester **3a** and regenerating Pd(0) species [5]. The isomerization of trans species to the cis isomer during the reaction has been reported in several papers and considered to be involved in the dissociative process [9,16]. Therefore, it should also be estimated that bisphosphines do not always chelate to palladium center, but they sometimes function as monodentate ligands because the dissociation of a phosphine moiety and re-coordination of another phosphine moiety of another ligand molecule are possible under some conditions.

On the basis of these assumptions, the aryloxycarbonylation with hindered potassium 4-methyl-2,6-di-*tert*-butylphenoxide (**2b**, Ar*OK in Scheme 1) is explained as follows. In this case, the exchange of bromide or iodide in intermediate **5a** or **5b** with Ar*O$^-$ should be discussed in the same way as that with PhO$^-$. On the analogy of the relative ability of a halide as a leaving group, as discussed above, the exchange of iodide with Ar*O$^-$ (from **5b** to **7**) is estimated to be facile while that of bromide (from **5a** to **7**) is not. Nevertheless, hindered aryl ester **3b** is not obtained from iodide **1b** according to our result. This means that the equilibrium of *trans* and *cis* aroyl aryloxy palladium intermediates **7** is greatly shifted to *trans*-**7**, due to the steric hindrance between aroyl (ArCO) and aryloxy (Ar*O) groups. Reductive elimination could occur only from *cis*-**7** as described above. As a result, hindered esters **3b** could not be obtained from *trans*-**7** derived from iodide **1b**. However, we can not rule out the possibility that some electronic properties, rather than steric factors, control the step from intermediate **7** to ester **3b**. The hindered phenoxide **2b** has electron donating groups on *o*- and *p*-positions, while non-hindered phenoxide **2a** does not. The reductive elimination from intermediate **7** to ester **3b** could be much more

difficult than that from intermediate **6** to ester **3a**.

The fact that bromide **1a** was carbonylated with Ar*OK (**2b**) means that there is another path from aroyl bromo palladium intermediate **5a** to hindered aryl ester **3b**. It can be a concerted reaction (from **5a** to **3b** via **8**) including nucleophilic attack of Ar*O$^-$ to carbonyl group to form ester **3b**, regeneration of Pd(0) species, and elimination of bromide to form KBr. Ar*O$^-$ is bulky, but is still expected to be more nucleophilic than PhO$^-$ due to its electron-donating nature. As a result, the concerted path is feasible. In the case of iodide, the same concerted path (**5b** to **3b** via **9**) can be considered, but iodide is estimated to be so good leaving group that the exchange step from **5b** to **7** predominates.

4. Conclusion

There are large differences of reactivity between bromide and iodide, and between non-hindered PhOK and hindered potassium phenoxides, with regard to the carbonylation of aryl halides with metal phenoxide species. On the basis of these results, we propose the possible paths from aryl halides to aryl esters of aryl carboxylic acids. The descriptions of the oxidative addition (from **1a–b** to **4a–b**) and the CO insertion (from **4a–b** to **5a–b**) steps in this paper are common to those in many other papers on palladium-catalyzed alkoxycarbonylation. Regarding the reductive elimination step (from **5a–b** to **3a–b**), however, we can not explain our results before considering the variant paths which have never been reported so far. A stepwise ligand exchange path and a concerted path may be involved. In conclusion, it may be said that:

(1) There are two distinct paths of reductive elimination from an aroyl palladium intermediate to an ester product and Pd(0) species. These are a stepwise ligand exchange path and a concerted path. The selection of these paths seems

to depend on the steric and electronic properties of both aryl halides and phenolic nucleophiles.

(2) The effectiveness of the use of potassium phenoxides supports the hypothesis by Moser et al. [17] that direct reaction of alkoxide ion, rather than alcohol, with aroyl palladium complex is the principal mechanism of aryl carboxylic acid ester production in alkoxycarbonylation.

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