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Role of base in palladium-catalyzed arylation of carbanions

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Abstract

The arylation reaction of carbanions, derived from certain sulfones, cyanoacetic ester and malononitrile, with aryl bromides (using the catalytic system of Pd_2dba_3/3L, L = PPh_3, P^tBu_3) as well as the reaction of the carbanions with one equivalent of 4-$CF_3C_6H_4$ $Pd(PPh_3)_2Br$ has been studied. These reactions proceed smoothly provided that the base stronger than the initial carbanion is present in the reaction mixture. In the absence of the above type of base the reactions do not proceed at all. Taking that into account we have proposed a novel mechanism of palladium-catalyzed arylation of CH-acids. The main feature of this mechanism is the accelaration of the reductive elimination due to the deprotonation of the intermediate $ArPdL_2CHXY$. The correlation between the carbanion reactivity and the pK_a values for related CH-acids as well as the ligand effect are discussed in the framework of the proposed mechanism.

Keywords: Palladium; Catalysis; Arylation; Sulfone; Phosphine ligand; Proton transfer

1. Introduction

The palladium-catalyzed arylation of CH-acids by aryl halides is a direct method of the introduction of a aryl group in the α-position of nitriles [1], ketones [2], aldehydes [3], amides [4], esters [5], nitroalkanes [5b,6], sulfones [7]. In most cases, the palladium-catalyzed arylation proceeds effectively only in the presence of electron-rich bulky phosphine ligands, which are supposed to reflect their influence on the reductive elimination stage [2c,8]. Meanwhile, some relatively strong CH-acids – functionalized nitriles [1a–1d] and sulfones [7] in particular – can be arylated just using triphenylphosphine as a ligand.

Studying the influence of the base upon the reactivity of sulfones in the arylation and using PPh_3 as a ligand, we unexpectantly found, that the reaction does not proceed without certain excess of the base. Thus, the role of the base in these reactions is more complicated than just a carbanion generation. In this article, an attempt has been made to explain this unusual phenomenon and, judging by the data obtained, to propose a novel mechanism of the palladium-catalyzed arylation of CH-acids.

2. Results and discussion

It is known, that the arylation of CH-acids by aryl halides is generally carried out using at least two equivalents of the base. One equivalent of the base is consumed in the deprotonation of the reaction product, which is a stronger CH-acid than the starting compound. It turned out, however, that if two equivalents (relative to the aryl halide) of the preformed anion of the starting CH-acid are used instead of two equivalents of the base, the palladium-catalyzed arylation of sulfones by aryl halides (4-bromobenzotrifluoride and 1-bromonaphtalene) using the PPh_3 ligand does not proceed at all. Meanwhile, in the presence of one equivalent of the CH-acid, two equivalents of the base, such as NaH, KO^tBu or NaHMDS, and PPh_3 almost complete conversion of the aryl bromide is achieved and the arylation product is formed (Scheme 1, Table 1).

This base effect phenomenon is observed not only with sulfones, but also with other CH-acids, such as cyanoacetic ester and malononitrile (Table 1, entries 5,

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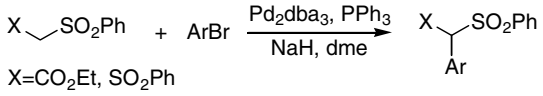


Scheme 1.

6), that is a double quantity of the base is required to carry out the reaction with these compounds.

Why does the arylation of CH-acid RH not proceed with their preformed salts? There could be two possible solutions of this problem: either the palladium complex $ArPdL_2Br$ formed in the oxidation addition does not react with the salt of the CH-acid under these conditions, or the product of the ligand substitution – $ArPdL_2R$ – is resistant to the reductive elimination.

In order to clarify this problem the stoichiometric reaction of the palladium complex $4\text{-}CF_3C_6H_4Pd(PPh_3)_2Br$ (prepared beforehand) and the salt $[PhSO_2CHCO_2Et]^-\ Na^+$ in dioxane at 70 °C has been studied. Surprisingly, no ligand exchange has occurred. The ^1H NMR and ^{19}F NMR displayed no visible changes, only the signals of starting materials being observed. However, upon the addition of the base (NaH or NaHMDS) to the reaction mixture, the reaction did take place, giving the salt of the arylated CH-acid. When NaH was used as a base, large quantities of $PhCF_3$, which is the product of the palladium complex reduction, were also formed (Scheme 2).

Reactions with another CH-acid – $C_6F_5CH_2SO_2CF_3$ – followed a similar pattern (DME, 80 °C), the only difference being, that in the absence of NaH the starting complex slowly decomposed, but did not give the arylation product. This product was formed only when NaH was added to the reaction mixture (Scheme 3).

Thus, the effect of the base in the catalytic and stoichiometric reactions turns out to be the same, namely – its presence affects the arylation reaction of the carbanion, provided that the base is stronger than the initial carbanion $[CHXY]^-$. This fact could be explained by assuming that the rate limiting stage of the arylation reaction is the reductive elimination, which is hampered in the neutral complex $ArPd(PPh_3)_2CHXY$ formed by weak sulfonic CH-acids. We suppose that, in the presence of a strong base, deprotonation takes place, leading to the formation of anionic palladium complex $[ArPd(PPh_3)_2CXY]^-$ which undergoes the reductive elimination. The Scheme 4 presents the catalytic cycle included the proton transfer stage (c).

According to the proposed arylation mechanism, however, it is not possible to explain why bromide in the $ArPdL_2Br$ complex is not exchanged in the stoichiometric reaction (Schemes 2 and 3). It is assumed that in case of stable carbanions used in this study, the step of the halogen substitution in the palladium complex is reversible (Scheme 4, Stage b) and the equilibrium is shifted towards the carbanion, and only the subsequent reductive elimination shifts this equilibrium. The similar equlibria, in which the order of ligand affinity to transition metal is opposite to the order of ligand pK_a values are known [9].

Table 1
Palladium-catalyzed arylation of CH-acids with aryl bromides[a]

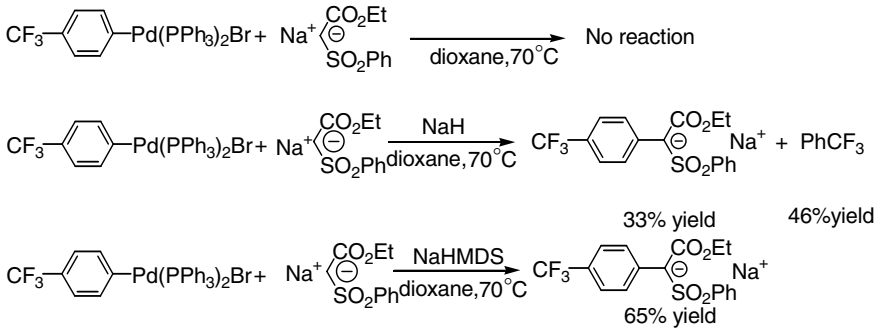
Entry	CH-acid	Conditions	Stoichiometric amount of the base (NaH)		Base (NaH) is present in excess	
			Time (h)	Conversion of ArBr, % (Yield, %)	Time (h)	Conversion of ArBr, % (Yield, %)
1	$PhSO_2CH_2CO_2Et$	1-bromonaphthalene, dioxane, $L = PPh_3$	12	5 (0)	12	82 (61)[b]
2	$PhSO_2CH_2CO_2Et$	$4\text{-}CF_3C_6H_4Br$, dioxane, L = DPPF	8	2	4	100 (77)
3	$(PhSO_2)_2CH_2$	$4\text{-}CF_3C_6H_4Br$, DME, $L = PPh_3$	12	13	4	100 (86)
4	$CF_3SO_2CH_2C_6F_5$	$4\text{-}CF_3C_6H_4Br$, DME, $L = PPh_3$	12	0	12	87 (81)
5	$NCCH_2COOEt$	$4\text{-}CF_3C_6H_4Br$, DME, $L = PPh_3$	12	0	15	86 (72)
6	$NCCH_2CN$	$4\text{-}CF_3C_6H_4Br$, DME, $L = PPh_3$	12	0	6	100 (84)
7	$PhSO_2CH_2CO_2Et$	$4\text{-}CF_3C_6H_4Br$, DME, $L = PPh_3$[c]	4	0	4	100 (70)
8	$PhSO_2CH_2CO_2Et$	$4\text{-}CF_3C_6H_4Br$, DME, $L = PPh_3$[d]	4	0	4	100 (56)

[a] Heating at 70 °C in dioxane or DME, aryl bromide – 0.5 mmol, Pd_2dba_3 – 2 mol%, L/Pd = 3:1, solvent – 4 ml; in the presence of the base excess: NaH – 1.25 mmol, CH-acid – 0.65 mmol; without of the base excess: NaH – 1.0 mmol, CH-acid – 1.25 mmol, see Section 3 for details.

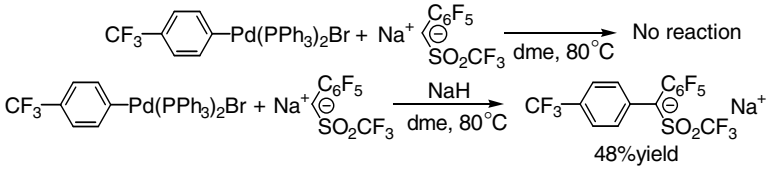
[b] Naphthalene forms in yield 20–24% as a consequence of side reaction – the reduction of ArBr.

[c] KO^tBu used as a base.

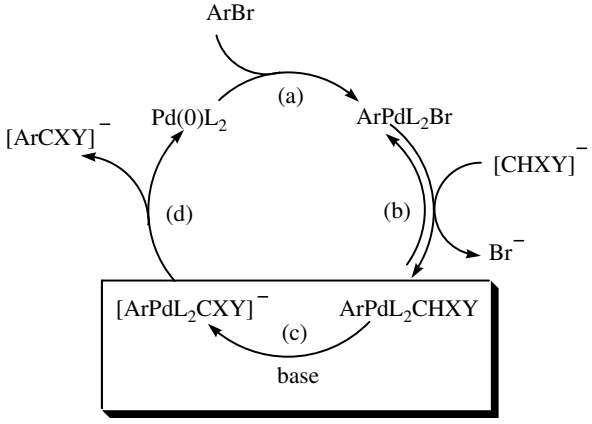
[d] NaHMDS used as a base.



Scheme 2.



Scheme 3.



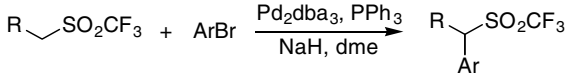
Scheme 4.

The suggestion that the $ArPd(PPh_3)_2CHXY$ complex in the case of the studied CH-acids has indeed to be deprotonated prior to the reductive elimination, is supported by the fact, that the reaction does not proceed with the CH-acids having tertiary carbon RSO_2-C(R′)HX, when the palladium complex cannot be deprotonated [7]. The fact, that the arylation reaction of sulfones proceeds exclusively as monoarylation, is due, in our opinion, to the same reason.

The role of the base in the reaction is apparently connected with the activation of the reductive elimination stage via the deprotonation of the $ArPd(PPh_3)_2$ CHXY complex, but it is not connected with the *cis–trans* isomerization of the complex, because the reaction of $PhSO_2CH_2CO_2Et$ and 4-$CF_3C_6H_4Br$ using DPPF as a bidentate ligand also requires a certain excess of the base to proceed (Table 1, entry 2).

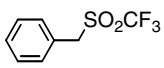
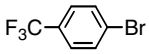
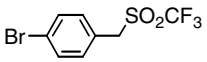
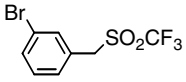
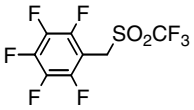
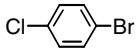
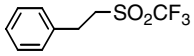
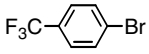
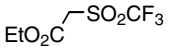
In the framework of the proposed mechanism the unusual dependence the reactivity of sulfones upon their pK_a could be also clearly explained. As it was shown earlier, the arylation reaction proceeds only with sulfones, which are relatively strong CH-acids ($pK_a < 13$) and correspondingly produce poorly nucleophilic carbanions. Meanwhile, weak CH-acids, such as CH_3SO_2Ph, $PhCH_2SO_2Ph$ and $C_6F_5CH_2SO_2Ph$ do not enter the reaction. The lack of reaction is not related with the difficulty of deprotonation of these compounds, because their sodium salts do not react either [7]. We suppose that this is caused by the difficulty of deprotonation of the palladium intermediate, because the latter is even a weaker CH-acid, than the corresponding initial sulfone. Deprotonation of the palladium intermediate can be effective only in the case of sulfones, which are strong CH-acids.

Following the proposed concept, it could be expected that increasing the acidity of sulfones, with the $PhSO_2$ group being changed to the more electron-withdrawing CF_3SO_2 group, would accelerate the arylation and allow to expand the range of substrates entering this reaction. And indeed, benzyltrifluoromethylsulfone and its derivatives (Scheme 5, Table 2, entries 1–5), unlike the corresponding benzylphenylsulfones [7], turned out to be active under the same conditions. The yields of monoarylated products are presented in Table 2.



Scheme 5.

Table 2
Palladium-catalyzed arylation of trifluoromethyl sulfones by aryl bromides

Entry	Sulfone	Aryl bromide	Time (h)	Yield (%)
1			20	67
2		-≫-	40	36
3		-≫-	14	30
4		-≫-	12	81
5	-≫-		24	48
6			24	0
7		-≫-	24	0

The reaction was carried out in DME at 70 °C; aryl bromide – 0.5 mmol, sulfone – 0.5 mmol, NaH – 1.5 mmol, Pd_2dba_3 – 2 mol%, $PPh_3/Pd = 3:1$, DME – 4 ml, see Section 3 for details.

However, the acidity of $PhCH_2CH_2SO_2CF_3$ is too low to make the reaction proceed (Table 2, entry 6). The reaction also does not proceed with a very strong CH-acid – $CF_3SO_2CH_2CO_2Et$ – which gives the weakest nucleophile after deprotonation (Table 2, entry 7).

In the light of the mechanism proposed, it seems important to study the influence of the ligands on the reactions. Using the palladium-catalyzed reaction of pentafluorobenzyl trifluoromethyl sulfone with 4-bromobenzotrifluoride as a model, it has been found, that even a significant change in the donating properties of the ligand only slightly influences the conversion of aryl halide. The only exception is the case of the bidentate ligand DPPBz when the reaction proceeds very slowly, this apparently being connected with a small value of the bite angle of this ligand (Table 3).

In general, both the yield of the arylated product, and the conversion of aryl bromide are only slightly influenced by the ligand nature, but the yield is somewhat lower when an electron-rich ligand P^tBu_3 is used. We can point out, that such effect of an electron-rich ligand is markedly different from that observed in the arylation of many other CH-acids. A large number of CH-acidic compounds, ketones, nitriles, esters, etc., were successfully arylated with high product yields using P^tBu_3 as a ligand [5a,5d,5e].

Table 3
Ligand effect in palladium-catalyzed arylation of pentafluorobenzyl triflone with 4-bromobenzotrifluoride[a]

Ligand L	Conversion of ArBr (%)	Yield (%)
$AsPh_3$	66	55
PFu_3	65	54
PPh_3	63	51
P^tBu_3	75	37
DBPBP[b]	51	40
DPPBz[c]	13	8

[a] The reaction was carried out at 75 °C for 5 h in DME; 4-bromobenzotrifluoride – 0.125 mmol, $C_6F_5CH_2SO_2CF_3$ – 0.16 mmol, NaH – 0.375, Pd_2dba_3 – 2 mol%, L/Pd = 3:1, DME – 1 ml.
[b] DBPBP – 2-(di- *t*-butylphosphino)biphenyl.
[c] DPPBz – 1,2-bis(diphenylphosphino)benzene.

In order to determine whether the features observed in the arylation reactions in the presence of PPh_3 also apply to the reactions using electron-rich bulky P^tBu_3 ligand, we studied the arylation reaction of several CH-acids using this ligand and varying the amount of the base – NaH (Table 4).

As it is shown above, in the presence of PPh_3 the studied CH-acids do not enter the arylation reaction without a certain excess of the base. When electron-rich bulky P^tBu_3 is used, some of the CH-acids behave in a similar way, that is, they are not arylated without

Table 4
Palladium-catalyzed arylation of CH-acids with aryl bromides[a]

Entry	CH-acid	Conditions	Stoichiometric amount of the base (Na		Base (NaH) is present in excess	
			Time (h)	Conversion of ArBr, % (Yield, %)	Time (h)	Conversion of ArBr, % (Yield, %)
1	$PhSO_2CH_2CO_2Et$	1-bromonaphthalene, $L = P^tBu_3$	17	55 (0)	12	100 (41)
2	$PhSO_2CH_2CO_2Et$	1-bromonaphthalene, L = DBPBP [b]	15	40 (0)	12	100 (49)
3	$NCCH_2COOEt$	4-$CF_3C_6H_4Br$, $L = P^tBu_3$	12	16 (15)	12	100 (80)
4	$NCCH_2CN$	4-$CF_3C_6H_4Br$, $L = P^tBu_3$	12	7	12	100 (82)
5	$PhSO_2CH(CH_3)CO_2Et$	4-$CF_3C_6H_4Br$, $L = P^tBu_3$	–	–	10	22 (0)

[a] Heating at 70 °C in dioxane, aryl bromide – 0.5 mmol, Pd_2dba_3 – 2 mol%, L/Pd = 3:1, dioxane – 4 ml; in the presence of the base excess: NaH – 1.25 mmol, CH-acid – 0.65 mmol; without of the base excess: NaH – 1.0 mmol, CH-acid – 1.25 mmol, see Section 3 for details.
[b] DBPBP – 2-(di-*t*-butylphosphino)biphenyl.

a certain excess of the base. The situation is somewhat different, however, in the case of cyanoacetic ester: a slow arylation reaction does take place without a certain excess of the base (Table 4, entry 3). The number of CH-acids was arylated with no excess of the base when the electron-rich ligands were used [1e,2b,5e]. The application of electron-rich bulky P^tBu_3 also enables one to carry out the arylation of some CH-acids having tertiary carbon, such as the derivatives of esters [5e], cyanoacetic ester, nitriles and fluoromalonic ester [10], though the corresponding sulfones do not enter this reaction (Table 4, entry 5). This data shows, that in principle, the reductive elimination from the Ar-PdL_2CHXY complex without a deprotonation step is possible for some CH-acids, provided that the electron-rich bulky phosphine ligands are used; however, when triphenylphosphine is used as a ligand, the deprotonation step is essential.

3. Experimental

3.1. Typical procedure for the palladium-catalyzed reaction of CH-acids with aryl bromides

The argon filled reactor equipped with condenser cooler and stirring bar was charged with 0.65 mmol of the CH-acid (Tables 1 and 2), 0.5 mmol of the aryl bromide, 1.25 mmol of NaH, $Pd_2dba_3 \cdot CHCl_3$ – 2 mol% and 0.06 mmol of the ligand (ligand/Pd = 3:1). The reaction mixture diluted with the degassed solvent (dioxane or DME, 4 ml) and degassed by three freeze-pump-thaw cycles. The reactor was refilled with argon and the reaction was carried out with stirring at 70 °C under positive argon pressure. In a few hours later GLC showed the absence of the starting aryl bromide. The reaction mixture was cooled to room temperature, mixed with brine, extracted with ether three times (3×10 ml). The extract was dried with Na_2SO_4 and was filtered. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel 40–100 μm, eluting with light petroleum ether:ethyl acetate mixture (v/v 4:1).

All products were purified with chromatography on silica gel and were characterized by elemental analysis, and ^1H, ^{19}F NMR and IR spectroscopy.

Acknowledgements

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