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Mini review

Multiple arylation of carbonyl compounds via palladium catalysis

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Abstract

The palladium catalyzed direct arylation of carbonyl compounds using aryl halides has recently been developed. While most of works for the reaction focused on monoarylation at α-position of the carbonyl group, we succeeded in performing the introduction of several aryl groups to the substrates by single treatment. Thus, for example, in the presence of excess of aryl halides acetophenone undergoes arylation not only on the α-position, but also on the *ortho*-position to produce tetraarylated products. In this short account are summarized our recent results for multiple arylation of a number of ketones, amides, and α,β-unsaturated carbonyl compounds.

Keywords: Aryl halides; Arylation; Carbonyl compounds; Palladium and compounds

1. Introduction

Palladium-catalyzed arylation reactions using aryl halides are now recognized to be highly useful for making aromatic fine compounds [1,2]. For example, the reaction of alkenes (the Mizoroki–Heck reaction) and that of organoboron compounds (the Suzuki–Miyaura reaction) are very often employed.

So far the palladium catalyzed cross-coupling of aryl halides with carbonyl compounds has also been developed. Takahashi and coworkers reported that cyanoacetate esters and malononitrile undergo direct substitutive arylation at the central carbon on treatment with aryl iodides in the presence of a base [3]. Meanwhile, the α-arylation of less acidic simple ketones could be carried out only indirectly. For the reaction masked ketone enolates such as silyl enol ethers [4] and enol acetates [5] were used in the presence of a tin source.

Recently, it was reported by several groups including ours that ketones can effectively undergo direct intermolecular α-arylation, in which ketones themselves are employed [6–8]. We also demonstrated the regioselective γ-arylation of α,β-unsaturated carbonyl compounds [9]. The reactions are considered to involve the coupling of enolates and dienolates, respectively, with arylpalladium species generated in situ (Scheme 1).

On the other hand, we reported that the arylation of phenolic substrates such as 2-phenylphenols and 1-naphthols occurs regioselectively via cleavage of the aromatic C–H bonds at the spatially neighboring positions of phenolic function. For instance, the former substrates **2** undergo arylation on the 2′-positions on treatment with aryl iodides **1** in the presence of a palladium catalyst and a base to form the corresponding diarylated products **3** (Scheme 2) [6a,6b]. The coordination of phenolic oxygen of **2** to intermediary arylpalladium species appears to be the key for the coupling, as shown in Scheme 3. Interestingly, it was also found that phenol (**4**) itself is multiply arylated around the oxygen up to five times by treatment with excess aryl bromides to selectively give 2-biphenyl-6-terphenylphenols **5** (Scheme 4) [10]. The reaction is considered to involve two mechanistic patterns; i.e. the reaction of arylpalladium intermediates with (a) phenolates at the *ortho*-position, this being similar to the α-arylation of ketones (Scheme 1), and (b) thus formed 2-phenylphenols as in Scheme 3. Consequently, one may expect that enolate oxygen from an aromatic ketone can function like phenolate oxygen to bring about not only α-arylation, but also aromatic arylation. Since the sequential multiple arylation appears to be useful as a synthetic method of oligophenyl compounds [11,12], we examined the reaction of ketones and other

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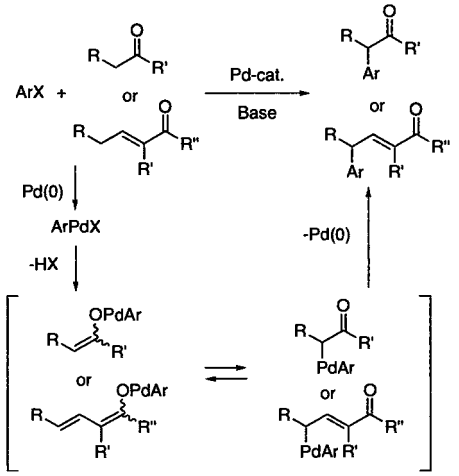
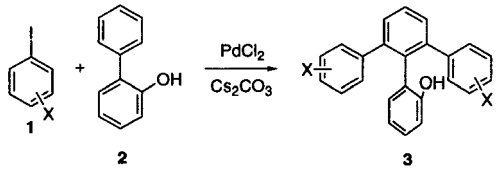
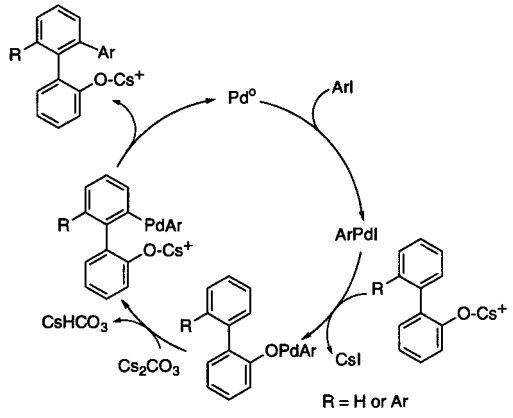
carbonyl compounds with excess aryl bromides. In this account are briefly summarized the results.



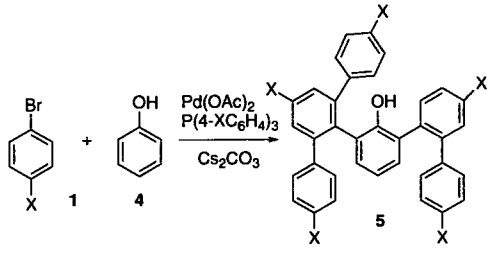
Scheme 1.



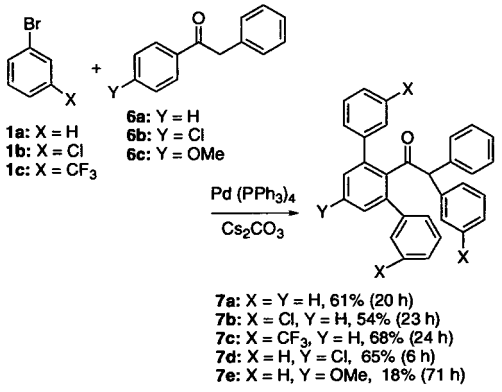
Scheme 2.



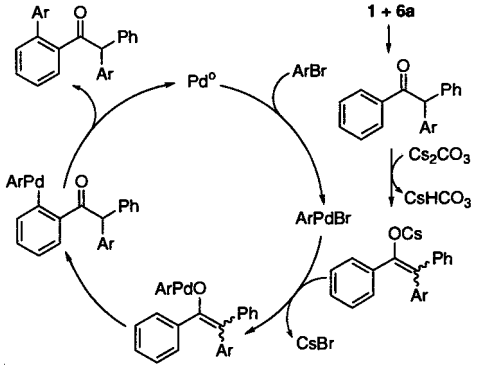
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

2. Benzyl phenyl ketones and benzanilides

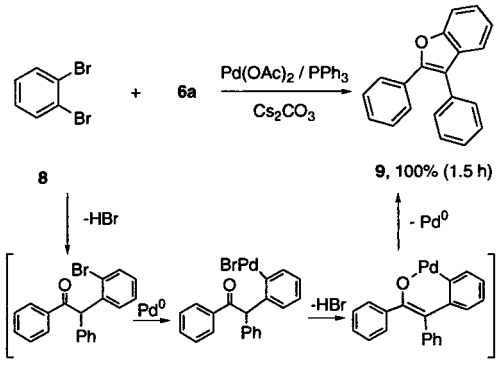
The first example of multiple arylation based on our strategy described above is that using benzyl phenyl ketones **6**. The reaction of **6** with four equivalents of aryl bromides **1a**–**c** and Cs_2CO_3 as base in the presence of a catalytic amount of $Pd(PPh_3)_4$ in refluxing *o*-xylene affords expected triarylation products **7** (Scheme 5) [13]. The use of a bulky phosphine P(*o*-Tolyl)$_3$ together with $Pd(OAc)_2$ and a less effective base K_2CO_3 in place of $Pd(PPh_3)_4$ and Cs_2CO_3, respectively, gives the corresponding monoarylated products on the α-position almost exclusively, the arylation on the *ortho*-position leading to **7** being suppressed.

A plausible mechanism for the formation of **7** is shown in Scheme 6. As described above, α-arylation of ketones proceeds via the reaction of arylpalladium species with enolates generated in situ in the presence of a base (Scheme 1) [6–8]. The *ortho*-arylation is considered to involve the coordination of enolate oxygen to arylpalladium species and the subsequent *ortho*-palladation as the key steps.

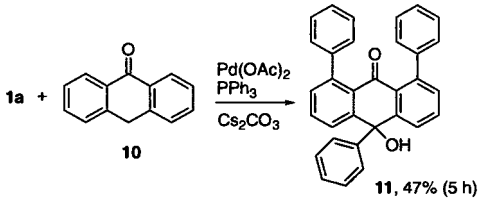
It should be noted that benzyl 4-chlorophenyl ketone (**6b**) reacts with **1a** considerably faster than **6a**, whereas the 4-methoxy derivative **6c** is consumed very slowly (Scheme 5). These results suggest that an electron-withdrawing substituent on the phenyl ketone enhances

ortho-arylation, possibly by promoting enolate formation.

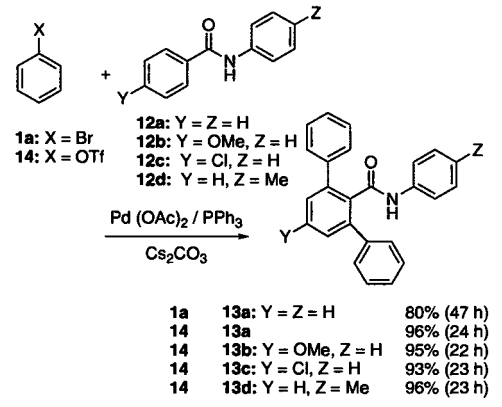
One may conceive that the use of *o*-dibromobenzene (**8**) as halide results in formation of a six-membered cyclic ketone via sequential α- and *ortho*-arylative coupling. Unexpectedly, not the double C–C coupling but



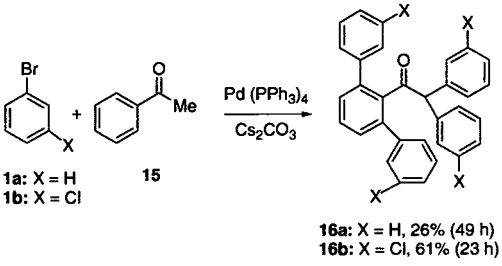
Scheme 7.



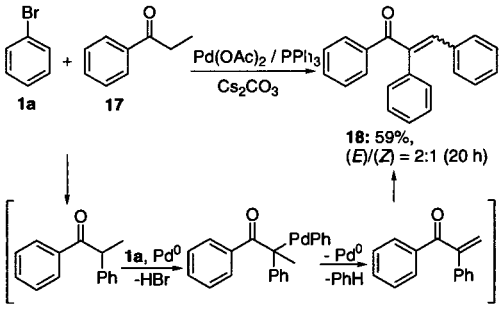
Scheme 8.



Scheme 9.



Scheme 10.



Scheme 11.

the successive formation of C–C and C–O bonds occurs in the reaction of **8** with **6a** to give 2,3-diphenylbenzo[*b*]furan (**9**) quantitatively (Scheme 7) [6c]. Thus, in the intramolecular case [14], the second arylation preferably takes place on the enolate oxygen [15] rather than on the *ortho*-carbon.

A cyclic ketone, anthrone (**10**), which is a structural relative of benzyl phenyl ketones **6**, also reacts with **1a** (Scheme 8). The ketone **10** undergoes triphenylation at the 1-, 8- and 10-positions, which parallels the reaction of **6**. However, the 10-position is unexpectedly hydroxylated. The hydroxyl group may come from the base or adventitious water, but the mode of its addition is not clear.

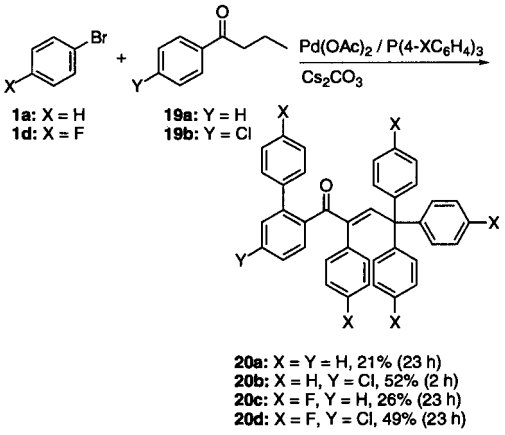
Benzanilide **12a** is similarly phenylated on two *ortho*-positions of the carbonyl group by treatment with **1a** in the presence of $Pd(OAc)_2$-PPh_3 to give a 2,6-diphenylbenzoic acid derivative **13a** (Scheme 9) [16]. Note that this kind of compound is a useful building block for preparing cyclophanes and related cyclic compounds having a terphenyl moiety with functionality [17]. The reaction can be conducted under relatively mild conditions when phenyl triflate **14** is used as phenylation reagent (110 °C, 24 h), compared with those for the reaction using **1a** (150 °C, 47 h). *N*-Arylation is not observed under both conditions [18].

3. Other alkyl phenyl ketones

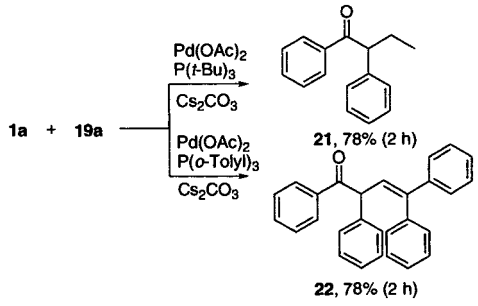
Acetophenone (**15**) undergoes sequential arylation on the α- and *ortho*-positions in a similar manner to that of **6** to give the corresponding tetraarylated products **16** (Scheme 10) [13].

On the other hand, the reaction of longer alkyl phenyl ketones having β-hydrogens with aryl bromides **1** involves oxidative unsaturation of the alkyl moiety that occurs prior to *ortho*-arylation. The unsaturation accompanied by β-hydrogen elimination is well-known [1]. Thus, treatment of propiophenone (**17**) with four equivalents of **1a** in the presence of $Pd(OAc)_2$-PPh_3 and Cs_2CO_3 gives 1,2,3-triphenyl-2-propen-1-one (**18**) as a (*E*)–(*Z*) mixture (Scheme 11) [19].

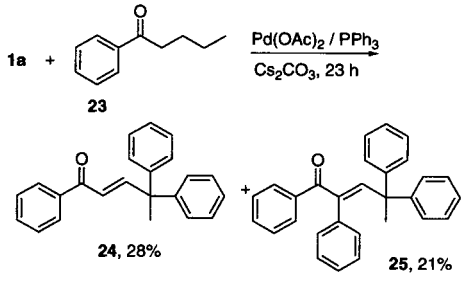
After α-phenylation of **17**, the enolate from the primary product reacts with phenylpalladium bromide to form an alkylphenylpalladium intermediate. Then, elimination of PhPdH occurs to give 1,2-diphenyl-2-propen-1-one with the liberation of Pd(0) species and benzene. The α,β-unsaturated ketone undergoes the second phenylation as in the usual Mizoroki–Heck type reaction via carbopalladation.



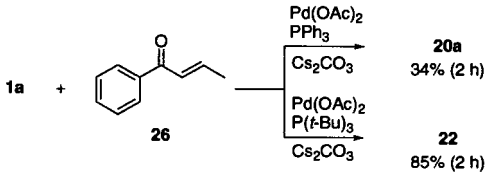
Scheme 12.



Scheme 13.



Scheme 14.



Scheme 15.

Treatment of butyrophenone (**19a**) with 7.5 equivalents of **1a** in the presence of $Pd(OAc)_2$-PPh_3 and Cs_2CO_3 gives a pentaphenylated compound **20a**, along with tri- and tetraphenylated products (Scheme 12). Thus, in this case, not only arylation on the α- and γ-positions accompanied by unsaturation, but also *ortho*-arylation takes place as in the reactions of **6**, **10**, **12**, and **15**.

The reactions of 4-chlorophenyl propyl ketone (**19b**) with **1a** using PPh_3 and of **19a** and **19b** with 4-bromofluorobenzene (**1d**) using $P(4\text{-}FC_6H_4)_3$ give the corresponding pentaarylated products **20b**–**d**. The latter phosphine should be used for the reaction with **1d** to avoid the contamination of phenyl group from PPh_3 [12]. It has been observed that **19b** affords considerably enhanced yields of **20**. This implies that the 4-chloro substituent promotes *ortho*-arylation, as in the reaction of benzyl phenyl ketones **6** (Scheme 5).

It is of particular interest that treatment of **19a** with six equivalents of **1a** using $P(o\text{-Tolyl})_3$ and $P(t\text{-Bu})_3$ in place of PPh_3 affords mono- and triphenylated products **21** and **22**, respectively, as the predominant products (Scheme 13).

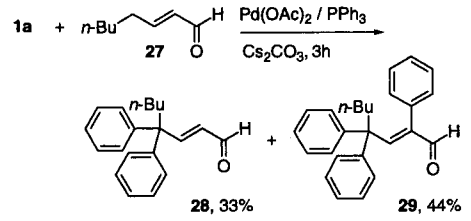
These facts suggest that the steric bulkiness of ligands appears to be the major factor affecting the degree of multiple arylation. Thus, unsaturation of **21** and further γ-phenylation of **22**, as well as *ortho*-phenylation can be suppressed selectively by selecting ligands appropriately.

The reaction of valerophenone (**23**) with **1a** using PPh_3 as ligand gives a mixture of γ,γ-diphenylated product **24** and α,γ,γ-triphenylated one **25** (Scheme 14).

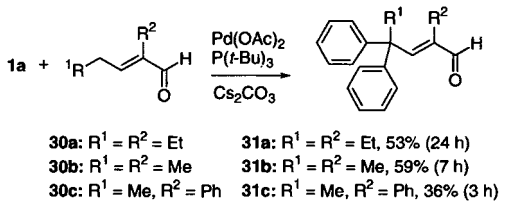
It is reasonable to consider that the initial unsaturation of **23** followed by γ,γ-diphenylation leads to **24**. The triphenylated compound **25** can be formed by either α-phenylation followed by unsaturation and γ,γ-diphenylation or initial unsaturation followed by α,γ,γ-triphenylation. Therefore, in the reaction of **19**, an alternative route involving initial unsaturation other than the route via **21** should be taken into consideration. Indeed, this is supported by the reaction of (*E*)-1-phenyl-2-buten-1-one (**26**) as the intermediate (vide infra, Scheme 15).

4. α,β-Unsaturated carbonyl compounds

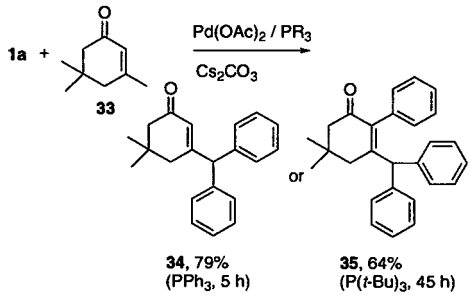
Various α,β-unsaturated carbonyl compounds can also undergo multiple arylation. The reaction of (*E*)-1-phenyl-2-buten-1-one (**26**) with 7.5 equivalents of **1a** gives **20a** (Scheme 15) as in the reaction using **19a** (Scheme 12). This indicates that as described above, the arylation of **19** may, at least in part, proceed after unsaturation of the propyl group.



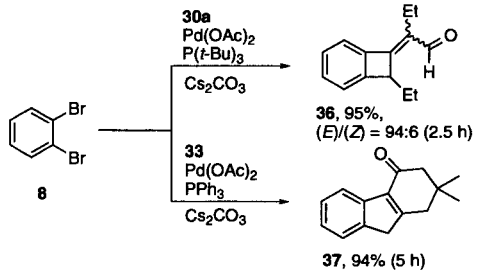
Scheme 16.



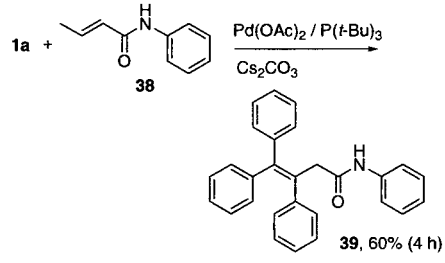
Scheme 17.



Scheme 18.



Scheme 19.



Scheme 20.

It is of interest that the reaction using P(*t*-Bu)$_3$ gives **22** as the single major product. The conditions employed are similar to those for the reaction of **19a** in which the monophenylated product **21** is produced as the principal one. These results suggest that the bulky ligand can effectively enhance α,γ,γ-triphenylation of the α,β-unsaturated ketone to **22**, while its further transformations to **20a**, as well as the unsaturation of **21** are suppressed [7,8].

Treatment of (*E*)-2-octenal (**27**) with four equivalents of **1a** using Pd(OAc)$_2$-PPh$_3$ gives a mixture of γ,γ-diphenylated product **28** and α,γ,γ-triphenylated one **29** in comparable yields (Scheme 16). This parallels the reaction of **23** (Scheme 14).

The reaction of (*E*)-2-ethyl-2-hexenal (**30a**) proceeds smoothly in DMF rather than in *o*-xylene, which is the choice of solvent for all other reactions described above. At 80 °C, the use of P(*t*-Bu)$_3$ as ligand brings about the expected γ,γ-diphenylated product **31a** (Scheme 17), while using PPh$_3$ under same conditions results in the selective formation of γ-monophenylated product, (*E*)-2-ethyl-4-phenyl-2-hexenal (**32**) [9].

The reactions of (*E*)-2-methyl-2-pentenal (**30b**) and (*E*)-2-phenyl-2-pentenal (**30c**) using P(*t*-Bu)$_3$ in DMF give the corresponding γ,γ-diphenylated products, **31b** and **31c**, as expected. In the reaction of isophorone (**33**), the use of PPh$_3$ and P(*t*-Bu)$_3$ leads to the selective formation of γ,γ-diphenylated product **34** and α,γ,γ-triphenylated one **35**, respectively (Scheme 18).

The intramolecular 'diarylation' of **30a** using dibromobenzene **8** exhibits different regioselectivity compared with that of the intermolecular diarylation (Scheme 17 vs. Scheme 19) [6c], as in the reaction of **6a** (Scheme 5 vs. Scheme 7). Treatment of **30a** with one equivalent of **8** gives a four-membered cyclic product **36**, via γ- and β-arylations. Meanwhile, **33** undergoes γ- and α-arylations to give a five-membered product **37** [6c].

The reaction of (*E*)-*N*-phenyl-2-butenamide (**38**) using P(*t*-Bu)$_3$ in *o*-xylene unexpectedly gives β,γ,γ-triphenylated product **39** (Scheme 20), while using PPh$_3$ is formed a complex mixture. In this special case, β-phenylation via carbopalladation may initially occur.

5. Conclusions

We have demonstrated that alkyl aryl ketones, benzanilides, and α,β-unsaturated carbonyl compounds can be multiply arylated by simple one-pot treatment using excess aryl bromides in the presence of palladium catalysts. This appears to provide a straightforward method for preparing a number of designed oligoaryl compounds.

Acknowledgements

We are grateful to our coworkers for their contribution to this study. Their names are described in the

references listed below. This work was partly supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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