Remarkable ligand effect on the palladium-catalyzed double carbonylation of aryl iodides†

Muneaki Iizuka and Yoshinori Kondo*

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The use of *t*-Bu_3P as a ligand dramatically improved the generality of the double carbonylation of aryl iodides, and $Mo(CO)_6$ was also found to be effective as a CO source in the system.

The palladium-catalyzed carbonylation of aryl halides in the presence of carbon monoxide is an important methodology for the preparation of carbonyl containing derivatives.[1] The procedure usually tolerates a wide range of functionalities and has been employed for the synthesis of many biologically active molecules. The palladium-catalyzed double carbonylation of aryl halides has also been extensively studied. After the early reports on double carbonylation,[2] extensive mechanistic investigations were carried out.[3] It has been reported that the smooth formation of an aroylpalladium intermediate **3** is the key to the successful double carbonylation of an aryl halide.[3g] The migration step, forming **3** from the intermediate **2**, is critically influenced by the electron density of the aryl moiety. Therefore, aryl halides with electron withdrawing groups have been regarded as unfavorable substrates for double carbonylation.[3g] In order to overcome this limitation, double carbonylation was investigated using various ligands and bases, and the remarkable facilitating effect of *t*-Bu_3P was demonstrated.

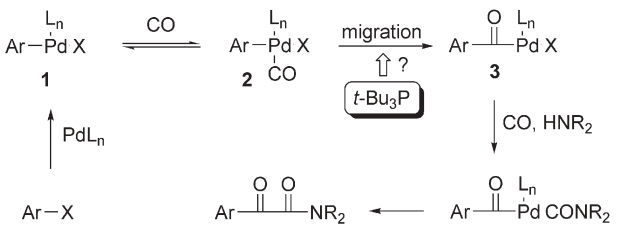

Fig. 1

In recent years, *t*-Bu_3P has been shown to exhibit a unique reactivity in a variety of palladium-catalyzed coupling reactions.[4] The use of *t*-Bu_3P has mainly focused on the coupling reaction of aryl chlorides and aryl bromides, and the lower reactivity against bromides has been commented-on in some palladium-catalyzed coupling reactions.[5] Although *t*-Bu_3P was employed in carbonylation reactions in some recent papers, no significant ligand effect has been demonstrated for the carbonylation of aryl iodides.[6]

For double carbonylation, it was recently reported that the Pd/PPh_3/DABCO/THF system[7] is effective for aryl iodides without electron withdrawing groups and the reaction was conducted at room temperature under an atmospheric pressure of carbon monoxide. However, the protocol is only applicable to those aryl iodides without electron withdrawing groups.

In our initial investigation of double carbonylation, we chose 4-iodonitrobenzene (**4**) as a substrate for carbonylation. Introduction of an electron withdrawing substituent, such as a nitro group at the *para* position, increases the reactivity of palladation but decreases the selectivity of α-ketoamide formation. Namely, 4-iodonitrobenzene can be regarded as the most unfavorable substrate for double carbonylation and the most suitable, challenging substrate for the optimization experiment of selective double carbonylation. The choice of an amine as a nucleophile is important, and the steric bulkiness of amines has a great influence on the formation of α-ketoamides.[3g] Pyrrolidine was chosen as a nucleophile because of its tendency in a previous report to give the amide rather than the α-ketoamide, taking the most unfavorable case into consideration.[3g] The choice of base is also considered to be important for the selectivity, and DBU is known to be favorable for single carbonylation from the results of a previous report.[7]

When the reaction of **4** and pyrrolidine in the presence of $Pd_2(dba)_3$, PPh_3 and DBU was carried out at room temperature, single carbonylation proceeded smoothly to give amide **6**, as expected from the previous reports (Table 1, entry 1). No formation of the double carbonylated α-ketoamide was observed. Other ligands such as DPPF and DPPP were examined, and they also showed similar single carbonylation selectivity (Table 1, entries 2 and 3). To our surprise however, when *t*-Bu_3P was used as a ligand, the selectivity dramatically changed, and the double carbonylation product **5** was predominantly formed (Table 1, entry 4). On the other hand, the similar, basic, bulky ligand Cy_3P showed a different selectivity from *t*-Bu_3P, and the formation of amide **6** was found to be favorable (Table 1, entry 5). Commercially available $Pd(t\text{-}Bu_3P)_2$ showed almost the same selectivity as $Pd_2(dba)_3$/2*t*-Bu_3P (Table 1, entry 6). When the base was switched to Et_3N from DBU, the selectivity changed towards the formation of amide **6**, and the reaction became slow (Table 1, entry 7). DABCO was found to be suitable for single carbonylation when combined with *t*-Bu_3P, in contrast to the previous report,[7] and inorganic bases such as Cs_2CO_3 and K_3PO_4 were also favorable for single carbonylation (Table 1, entries 8, 9 and 10). Other amine nucleophiles were examined for carbonylation, and

Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki Aza Aoba 6-3, Aoba-ku, Sendai 980-8578, Japan. E-mail: ykondo@mail.pharm.tohoku.ac.jp; Fax: (+81) 22-795-6804; Tel: (+81) 22-795-6804

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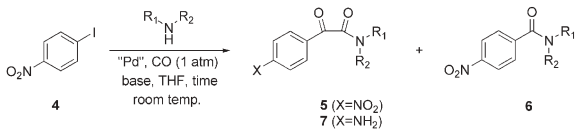
Table 1



						Product distribution[a]				
Entry	"Pd"	R_1	R_2	Base	Time/h	**4**	**5**	**6**	**7**	Yield of **5** (%)[b]
1	$Pd_2(dba)_3$/2PPh_3	–$(CH_2)_4$–		DBU	3	0	0	100	0	—
2	$Pd_2(dba)_3$/DPPF	–$(CH_2)_4$–		DBU	14	0	0	100	0	—
3	$Pd_2(dba)_3$/DPPP	–$(CH_2)_4$–		DBU	14	0	0	100	0	—
4	$Pd_2(dba)_3$/2*t*-Bu_3P[c]	–$(CH_2)_4$–		DBU	3	0	80	10	10	73 (**5a**)
5	$Pd_2(dba)_3$/2Cy_3P	–$(CH_2)_4$–		DBU	24	0	0	100	0	—
6	Pd(*t*-$Bu_3P)_2$	–$(CH_2)_4$–		DBU	2	0	80	12	8	77 (**5a**)
7	Pd(*t*-$Bu_3P)_2$	–$(CH_2)_4$–		Et_3N	24	22	13	72	0	—
8	$Pd_2(dba)_3$/2*t*-Bu_3P[c]	–$(CH_2)_4$–		DABCO	24	17	15	68	0	—
9	Pd(*t*-$Bu_3P)_2$	–$(CH_2)_4$–		Cs_2CO_3	1.5	0	25	75	0	—
10	Pd(*t*-$Bu_3P)_2$	–$(CH_2)_4$–		K_3PO_4	1.5	0	56	44	0	—
11	Pd(*t*-$Bu_3P)_2$	H	*n*-Bu	DBU	12	—	—	—	—	45 (72)[d] (**5b**)
12	Pd(*t*-$Bu_3P)_2$	H	*t*-Bu	DBU	7	—	—	—	—	55 (65)[d] (**5c**)
13	Pd(*t*-$Bu_3P)_2$	Et	Et	DBU	9	—	—	—	—	85 (**5d**)

[a] Estimated by ^{1}H-NMR. [b] Isolated yields. [c] HBF_4 salt was used. [d] Cs_2CO_3 was used in the case of values in parentheses.

the α-ketoamides were obtained in good selectivities (Table 1, entries 11, 12 and 13). The exact role of *t*-Bu_3P in the double carbonylation is still under investigation to determine the underlying rationale of the selectivity, but the assistance of a migration from the intermediate **2** to **3** is considered to be one of the factors, as suggested in Fig 1.

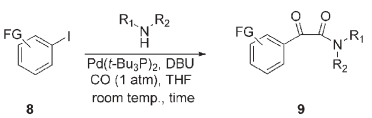
The double carbonylation of other aryl halides with other functional groups (FGs) was also examined using pyrrolidine or *n*-butylamine as the nucleophile. Aryl halides with electron withdrawing groups such as ethoxycarbonyl or cyano underwent double carbonylation in high yields in the presence of Pd(*t*-$Bu_3P)_2$ and DBU (Table 2, entries 1, 2, 3 and 4). Iodobenzene and 4-iodoanisole were also converted into the α-ketoamide selectively by this new catalyst system (Table 2, entries 5, 6, 7 and 8). *Ortho* substituents did not affect the double carbonylation, and the reaction of methyl 2-iodobenzoate proceeded smoothly to give the α-ketoamide (Table 2, entry 9).

Recently, *in situ* generation of CO has been investigated, with $Mo(CO)_6$ being regarded as an excellent CO generator.[8] However, conventionally, a high temperature was required to release CO molecules using microwave irradiation. We recently reported that CH_3CN is effective for releasing CO from $Mo(CO)_6$, but that the generation of CO from $Mo(CO)_6$ at room temperature has yet to be accomplished.[9]

When the conventional catalyst system using PPh_3 was employed, the carbonylation was quite slow due to the reluctant release of CO from $Mo(CO)_6$ (Table 3, entries 1 and 2). When our new protocol using *t*-Bu_3P was employed, the double carbonylation proceeded smoothly at room temperature to give **10** in good yield (Table 3, entry 3). When the base was switched to DABCO from DBU, the amide **11** was obtained as a main product (Table 3, entry 4).

In summary, the use of *t*-Bu_3P as a ligand has dramatically improved the generality of the double carbonylation of aryl iodides. The facilitated formation of aroylpalladium species, at present, are presumed to be responsible for the observed selectivity, but further careful investigations are necessary for a more fundamental understanding of the real effect that *t*-Bu_3P has on these carbonylation reactions. Further investigations on the scope and limitations of *t*-Bu_3P-assisted double carbonylation,‡ and mechanistic studies are now under way.

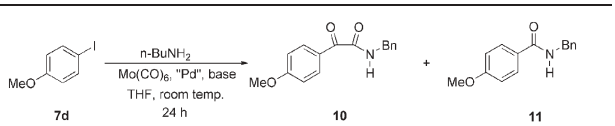
Table 2



Entry	FG	**8**	R_1	R_2	Time/h	**9**	Yield (%)[a]
1	4-CN	**8a**	–$(CH_2)_4$–		1.5	**9a**	92
2	4-CN	**8a**	H	*n*-Bu	12	**9b**	60
3	4-COOEt	**8b**	–$(CH_2)_4$–		2	**9c**	99
4	4-COOEt	**8b**	H	*n*-Bu	12	**9d**	76
5	H	**8c**	–$(CH_2)_4$–		24	**9e**	92
6	H	**8c**	H	*n*-Bu	12	**9f**	64
7	4-OMe	**8d**	–$(CH_2)_4$–		24	**9g**	93
8	4-OMe	**8d**	H	*n*-Bu	12	**9h**	93
9	2-COOMe	**8e**	–$(CH_2)_4$–		3.5	**9i**	68

[a] Isolated yield

Table 3



			Product distribution[a]			Yield (%)[b]	
Entry	"Pd"	Base	**7d**	**10**	**11**	**10**	**11**
1	$PdCl_2(C_3H_5)_2$, 2PPh_3	DBU	84	6	10	—	—
2	$PdCl_2(C_3H_5)_2$, 2PPh_3	DABCO	95	0	0	—	—
3	Pd(*t*-$Bu_3P)_2$	DBU	0	93	7	70	—
4	Pd(*t*-$Bu_3P)_2$	DABCO	0	11	89	—	67

[a] Estimated by ^{1}H-NMR. [b] Isolated yields

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Notes and references

‡ The double carbonylation of aryl bromides and aryl chlorides did not proceed under the same set of reaction conditions to recover the starting materials. Further studies on expanding the generality of double carbonylation reactions are under investigation.

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