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Palladium-Catalyzed Alkynylcarbonylation of Aryl Iodides with the Use of $Mo(CO)_6$ in the Presence of tBu_3P Ligand

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Palladium-catalyzed alkynylcarbonylation of aryl iodides was accomplished by using $Mo(CO)_6$ as a CO source. The reaction was conducted at room temperature with the use of tBu_3P as a ligand, which was found to be essential for smooth carbonylation. One-pot construction of pyrazoles by using aryl iodides with electron-withdrawing groups was also accomplished under these reaction conditions in the presence of methylhydrazine.

Introduction

The palladium-catalyzed carbonylation of aryl halides in the presence of carbon monoxide is an important method for the preparation of carbonyl-containing derivatives.[1] The carbonylation usually tolerates a wide range of functionalities and has been employed for the synthesis of many biologically active molecules. In the study of the palladium-catalyzed double carbonylation of aryl halides, it was suggested that the smooth formation of an aroylpalladium intermediate is key for the successful reaction.[2] We recently reported that tBu_3P is effective in the double carbonylation of aryl halides possessing electron-withdrawing groups.[3] The role of tBu_3P is still unclear, but its assistance in the formation of an aroylpalladium intermediate is one possible speculation. tBu_3P has been shown to exhibit unique reactivity in a variety of palladium-catalyzed coupling reactions.[4] The use of tBu_3P has mainly focused on the coupling reaction of aryl chlorides and bromides, and the lower reactivity towards bromides has been commented on in some palladium-catalyzed coupling reactions.[5] Although tBu_3P was employed in carbonylation reactions in some recent papers, significant ligand effects were not demonstrated for the carbonylation of aryl iodides before our work.[3,6] Because the presence of tBu_3P in the carbonylation of aryl halides was found to be essential for successful double carbonylation, our next interest was focused on the alkynylcarbonylation of aryl iodides. Alkynylcarbonylation is also an important process for the formation of alkynyl ketones, which play important roles as intermediates or target molecules in organic synthesis.[7] In the carbonylation process, the most important step is considered to be the formation of aroylpalladium intermediate **2** as well as the double carbonylation process (Figure 1).

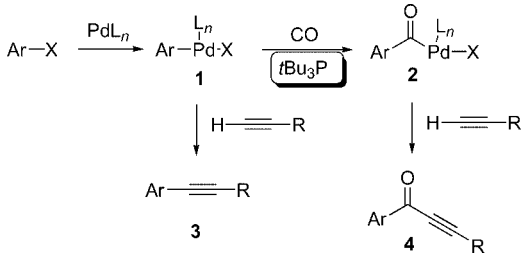

Figure 1. Palladium-catalyzed carbonylaton with tBu_3P.

Some improved reaction conditions were reported for alkynylcarbonylation, but in the case of aryl halides with electron-withdrawing substituents, direct Sonogashira coupling usually proceeds competitively.[8] Here the facilitated formation of **2** by the presence of tBu_3P is also considered to be advantageous in the alkynylcarbonylation process to give alkynyl ketone **4** by suppressing the formation of Sonogashira product **3**.

Results and Discussion

Recently, the in situ generation of CO was investigated; $Mo(CO)_6$ is regarded as an excellent CO generator, and we recently reported that CH_3CN is effective in releasing CO from $Mo(CO)_6$.[3,9] First, the alkynylcarbonylation of iodoacetophenone (**5**) was examined by using phenylacetylene and $Mo(CO)_6$ in the presence of palladium catalysts, and the reaction conditions were optimized. When Pd(dppf)Cl_2 was used as a catalyst and the reaction was carried out at room temperature, the progress of the reaction was slow and Sonogashira product **7** was produced together

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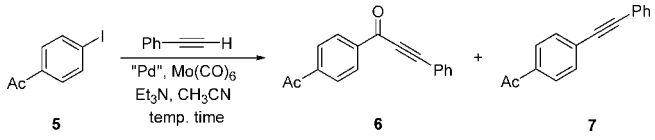
with desired alkynyl ketone **6** (Table 1, Entry 1). The reaction was then carried out at 80 °C, but the reaction was incomplete and starting material **5** was left unchanged with the formation of **7** (Table 1, Entry 2). The catalyst $Pd(PPh_3)_2Cl_2$ was also examined for the reaction at 80 °C and in this case significant formation of Sonogashira product **7** was observed (Table 1, Entry 3). When $Pd(tBu_3P)_2$ was used as a catalyst, the performance of the reaction surprisingly changed. The reaction proceeded smoothly at room temperature and alkynyl ketone **6** was formed exclusively; **7** was not observed. Ketone **6** was isolated in 76% yield (Table 1, Entry 4).

Table 1. Alkynylcarbonylation of iodoacetophenone.



5 6 7

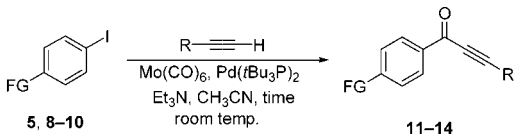
Entry	"Pd"	Temp. [°C]	Time [h]	Product distribution[a] 5	6	7	Yield of 6 [%][b]
1	$Pd(dppf)Cl_2$	room temp.	13.5	42	34	21	–
2	$Pd(dppf)Cl_2$	80	3	4	58	38	–
3	$Pd(PPh_3)_2Cl_2$	80	3	0	42	58	–
4	$Pd(tBu_3P)_2$	room temp.	12	0	100	0	76

[a] Estimated by ^1H NMR spectroscopy. [b] Isolated yields.

The use of $Pd(tBu_3P)_2$ was found to be effective, and the alkynylcarbonylation of other substrates was examined by using this protocol.

4-Iodonitrobenzene (**8**) was treated with phenylacetylene and $Mo(CO)_6$ in the presence of $Pd(tBu_3P)_2$ at room temperature, and ketone **11** was obtained in 68% yield (Table 2, Entry 1). The alkynylcarbonylation of ethyl iodobenzoate **9** also proceeded at room temperature to give ketone **12** in 92% yield (Table 2, Entry 2). The reaction of 4-iodoanisole required a long reaction time of 48 h, but the desired ketone was obtained in 85% yield (Table 2, Entry 3). As a terminal acetylene, trimethylsilylacetylene can be used, and the reaction of **5** gave ketone **14** in 81% yield (Table 2, Entry 4).

Table 2. Alkynylcarbonylation of aryl iodides.



5, 8–10 11–14

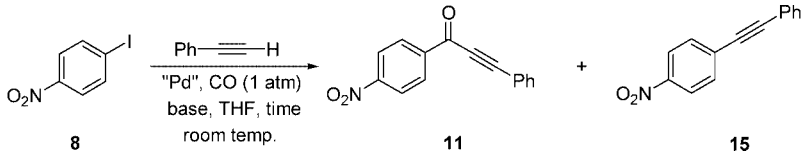
Entry	FG	Substrate	R	Time[h]	Product	Yield [%][a]
1	NO_2	**8**	Ph	12	**11**	68
2	COOEt	**9**	Ph	12	**12**	92
3	OMe	**10**	Ph	48	**13**	85
4	Ac	**5**	$SiMe_3$	12	**14**	81

[a] Isolated yield.

The usefulness of the $Pd(tBu_3P)_2$ catalyst was also examined in the alkynylcarbonylation reaction with the use of gaseous CO from a cylinder. First, as a control experiment, the reaction of **8** with phenylacetylene was carried out in the presence of PPh_3 and significant formation of Sonogashira product **15** was observed (Table 3, Entry 1). When $Pd_2(dba)_3/2tBu_3P$ or $Pd(tBu_3P)_2$ was used in the alkynylcarbonylation reaction, the formation of **15** was not detected and alkynyl ketone **11** was obtained in 76 or 64% yield, respectively (Table 3, Entries 2 and 3). In this case, DABCO was found to be a suitable base, whereas DBU was ineffective (Table 3, Entry 4). The reaction was found to be slow when Et_3N was used in combination with gaseous CO (Table 3, Entry 5).

We next focused on the one-pot construction of pyrazole by the four-component-coupling reaction.[10] Our reaction conditions for alkynylcarbonylation in the presence of $Mo(CO)_6$ allowed us to employ aryl iodides with electron-withdrawing groups. First, 4-iodonitrobenzene was treated with phenylacetylene, methylhydrazine, and $Mo(CO)_6$ in the presence of the palladium catalyst in acetonitrile at room temperature, and pyrazole **16** was obtained in 58% yield (Table 4, Entry 1). The addition of LiCl was found to improve the yield. Similarly, 4-iodobenzoate (**9**), 4-iodoanisole (**10**), and 4-iodoacetophenone (**5**) were converted into corresponding pyrazoles **17**–**20** in excellent yields.

Table 3. Alkynylcarbonylation with the use of gaseous CO.

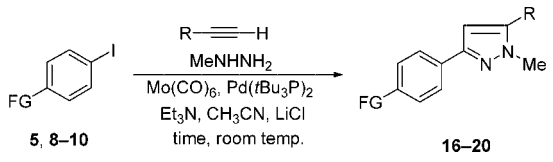


8 11 15

Entry	"Pd"	Base	Time [h]	Product distribution[a] 8	11	15	Yield of 11 [%][b]
1	$Pd_2(dba)_3/2PPh_3$	DABCO	6	47	21	32	–
2	$Pd_2(dba)_3/2tBu_3P$[a]	DABCO	6	0	100	0	76
3	$Pd(tBu_3P)_2$	DABCO	6	0	100	0	64
4	$Pd(tBu_3P)_2$	DBU	24	100	0	0	–
5	$Pd(tBu_3P)_2$	Et_3N	24	44	56	0	–

[a] Estimated by ^1H NMR spectroscopy. [b] Isolated yields.

Table 4. Pyrazole formation by using alkynylcarbonylation.



5, 8–10 16–20

Entry	FG	Substrate	R	Time[h]	Product	Yield [%][a]
1	NO_2	**8**	Ph	14	**16**	58
2	COOEt	**9**	Ph	13.5	**17**	94
3	COOEt	**9**	*n*Bu	13.5	**18**	75
4	OMe	**10**	Ph	26.5	**19**	75
5	Ac	**5**	Ph	14	**20**	83

[a] Isolated yield.

Conclusions

The use of tBu$_3$P as a ligand dramatically improved the generality of the alkynylcarbonylation of aryl iodides. The facilitated formation of the aroylpalladium species is considered to be the presumed factor for the selectivity, but further careful investigations are necessary to understand the real effect of tBu$_3$P in this carbonylation reaction. The one-pot formation of pyrazole in the presence of methylhydrazine was also successful and aryl iodides with electron withdrawing groups were easily converted into pyrazoles. Further investigation on the scope and limitations of the tBu$_3$P-assisted alkynylcarbonylation reaction, and the mechanistic aspects, are also underway.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data of the synthesized compounds.

Acknowledgments

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