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Versatile Palladium-Catalyzed Double Carbonylation of Aryl Bromides

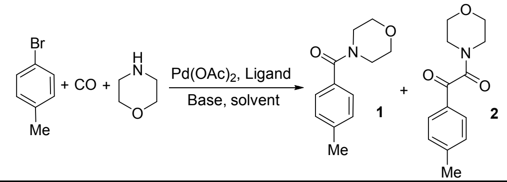
Chaoren Shen,[a] Cornel Fink,[b] Gabor Laurenczy,[b] Paul J. Dyson,[b] and Xiao-Feng Wu*[a]

Abstract: A versatile palladium-catalyzed double carbonylation of aryl bromides has been developed. With $Pd(OAc)_2$/$BuPAd_2$ as the catalyst system and DBU as the base, under relatively low CO pressure, various *α*-ketoamides were produced in good yields. In order to get insight into the reaction pathway, real time NMR studies were performed as well and a correlated reaction mechanism is been given.

α-Ketoamides and their derivatives are key constituents of natural products, biologically active molecules, functional materials, and various synthetic intermediates. Due to their importance, numerous synthetic approaches have been established for their synthesis.[1] Among the known procedures, palladium-catalyzed double carbonylation of aryl halides with carbon monoxide as the C_1 building block is considered to be a direct and efficient route.[1] Since the original report by Yamamoto et al. in 1982,[2] various homogeneous and heterogeneous palladium catalytic systems have been developed for the double carbonylative synthesis of *α*-ketoamides.[3] However, the CO pressure required is usually high (>50 bar) and the substrates are confined to aryl iodides. Compared to aryl iodides, the corresponding aryl bromides are more readily-available, but less reactive and therefore their use remains challenging. To the best of our knowledge, there is only one example of palladium-catalyzed double carbonylation of aryl bromides reported: Buchwald, Jensen and co-workers achieved the double carbonylation of 4-bromobenzonitrile employing a continuous-flow microreactor with palladium as the catalyst.[4] However, the reaction efficiency and selectivity were not optimum. Based on our on-going research on carbonylations,[5] we set out to establish a versatile and efficient catalyst for the double carbonylation of aryl bromides.

Initially, we selected 4-bromotoluene and morpholine as model substrates with $Pd(OAc)_2$ (2 mol%) and $BuPAd_2$ (6 mol%) as the catalyst system, under 5 bar of CO in toluene at 90 °C for 24 hours with DiPEA (diisopropylethylamine) as the base. Here, the $BuPAd_2$ applied has properties including strong electron donating, bulky and stable, and have been proven a powerful phosphine ligand in cross-coupling transformations. Morpholino(*p*-tolyl)methanone and 1-morpholino-2-(*p*-tolyl)ethane-1,2-dione were obtained from 4-bromotoluene following single and double CO insertion reactions, with a moderate conversion (Table 1, entry 1). The conversion was improved by increasing the reaction temperature and CO pressure, but the selectivity of the double carbonylation product remained unchanged (Table 1, entries 2 and 3). Different solvents were evaluated under 10 bar of CO at 90 °C. Although the conversion varies, but the selectivity does not improve (Table 1, entries 4-8). Interestingly, the selectivity to the double CO insertion product increases substantially in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (Table 1, entry 9). The desired 1-morpholino-2-(*p*-tolyl)ethane-1,2-dione product was isolated in 57% yield with a conversion of 4-bromotoluene of 73%. However, the other tested bases (K_2CO_3, Na_2CO_3, Cs_2CO_3) provided similar results as DiPEA. The yield can be further improved by increasing the temperature to 100 °C (Table 1, entry 10). Under these conditions, 71% of the double carbonylation product was isolated with conversion of 95%.

Table 1. Influence of solvent and base on the double carbonylation reaction.[a]



Entry	Solvent	CO (bar)	Base	Temp. (°C)	Selec. (1:2)[b]	Conv.[b]
1	Toluene	5	DiPEA	90	91:9	53
2	Toluene	10	DiPEA	90	88:12	94
3	Toluene	10	DiPEA	105	>99:1	>99
4	DMSO	10	DiPEA	90	91:9	47
5	DMAc	10	DiPEA	90	85:15	64
6	Dioxane	10	DiPEA	90	85:15	72
7	DMF	10	DiPEA	90	1:1	32
8	*p*-Xylene	10	DiPEA	90	81:19	89
9	Toluene	10	DBU	90	6:94	73 (57)[c]
10	Toluene	10	DBU	100	8:92	95 (71)[c]

[a] 4-Bromotoluene (0.5 mmol), morpholine (0.55 mmol, 1.1 equiv.), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), base (1.5 equiv.), CO, solvent, 24 h. [b] Conversion of 4-bromotoluene and the ratio of 1 and 2 were determined by GC using hexadecane as the internal standard based on calibrations. [c] Isolated yield.

Subsequent optimisation of the catalytic system was carried out with DBU as the base. The ratio of $Pd(OAc)_2$:phosphine ligand was crucial, with lower amounts of $BuPAd_2$ resulting in much reduced conversions of 4-bromotoluene (Table 2, entries 1-3). Evaluation of other

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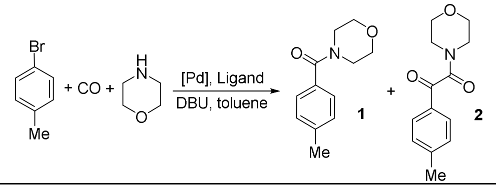
palladium precursors, ligands and bases did not improve the catalytic system (Table 2, entries 4-6). Notably, with PPh_3 and $P(2,4,6\text{-}(MeO)_3C_6H_3)_3$ no product was detected and with $P(tBu)_3$ the conversion was significantly reduced (Table 2, entries 7-9). Notably, improved yields can be achieved with lower amounts of DBU with 75% of desired *α*-ketoamide obtained (Table 2, entry 10). Decreased the loading of the catalyst dramatically decreased the conversion of substrates (Table 2, entry 11).

Table 2. Optimization of the reaction conditions.[a]

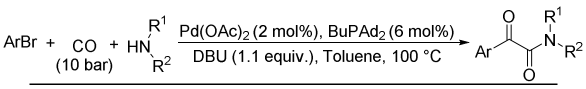


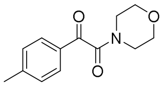
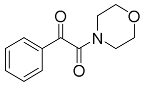
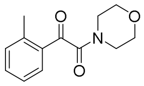
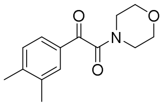
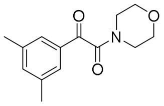
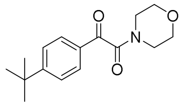
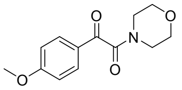
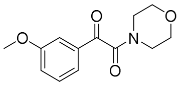
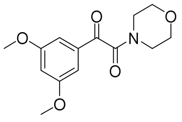
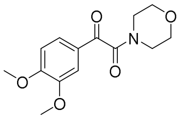
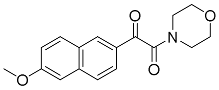
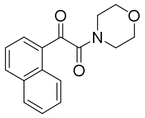
Entry	[Pd]	Ligand	Selec.(1:2)[b]	Conv.[b]
1	$Pd(OAc)_2$	$BuPAd_2$ (4 mol%)	14:86	76
2	$Pd(OAc)_2$	$BuPAd_2$ (2 mol%)	1:99	9
3	$Pd(OAc)_2$	$BuPAd_2$ (8 mol%)	5:95	97/(74)[c]
4	$PdCl_2$	$BuPAd_2$ (6 mol%)	8:92	94/(72)[c]
5	$Pd_2(dba)_3$	$BuPAd_2$ (6 mol%)	8:92	97/(75)[c]
6	$Pd(OAc)_2$	$BuPAd_2$ (6 mol%)	6:94	75[d]/(59)[c]
7	$Pd(OAc)_2$	PPh_3 (6 mol%)	/	<5
8	$Pd(OAc)_2$	$P(2,4,6\text{-}(MeO)_3C_6H_3)_3$ (6 mol%)	/	<5
9	$Pd(OAc)_2$	$tBu_3P\cdot HBF_4$ (6 mol%)	10:90	85
10	$Pd(OAc)_2$	$BuPAd_2$ (6 mol%)	7:93	100[e]/(75)[c]
11	$Pd(OAc)_2$ (1 mol%)	$BuPAd_2$ (3 mol%)	5:95	12

[a] 4-Bromotoluene (0.5 mmol), morpholine (0.55 mmol, 1.1 equiv.), palladium (2 mol%), ligand, DBU (1.5 equiv.), CO (10 bar), toluene, 100 °C, 24 h. [b] Conversion of 4-bromotoluene and the ratio of 1 and 2 were determined by GC using hexadecane as the internal standard based on calibrations. [c] Isolated yield. [d] DBN (1.5 equiv.). [e] DBU (1.1 equiv).

Using the optimized reaction conditions, we evaluated various aryl bromides and amines to verify the scope of our procedure (Table 3). In general, good yields of the desired *α*-ketoamides were obtained. A double, double carbonylation can be obtained when piperazine was used as the coupling partner with the product isolated in 53% yield. It is important to note that only the mono-carbonylation product was formed when aniline, *N*-methylaniline or *n*-butylamine was used as the reaction partners. In the case of aryl bromides with electron-withdrawing substituents or heterocyclic aryl bromides as the substrates, a mixture of mono- and double-carbonylation products was formed (1:1-2:1). Chlorobenzene was tested as the substrate under standard conditions as well, but not reaction could be detected.

Table 3. Synthesis of *α*-ketoamides.[a]



Entry	α -Ketoamides	Yield
1		75%
2		72%
3		68%
4		71%
5		66%
6		70%
7		61%
8		64%
9		62%
10		62%
11		76%
12		67%

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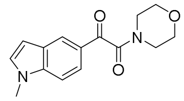
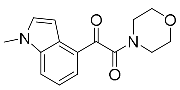
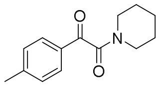
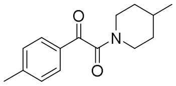
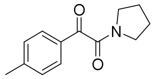
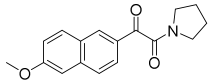
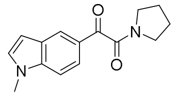
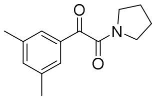
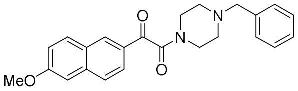
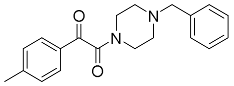
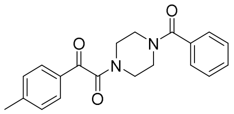
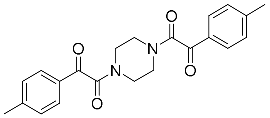
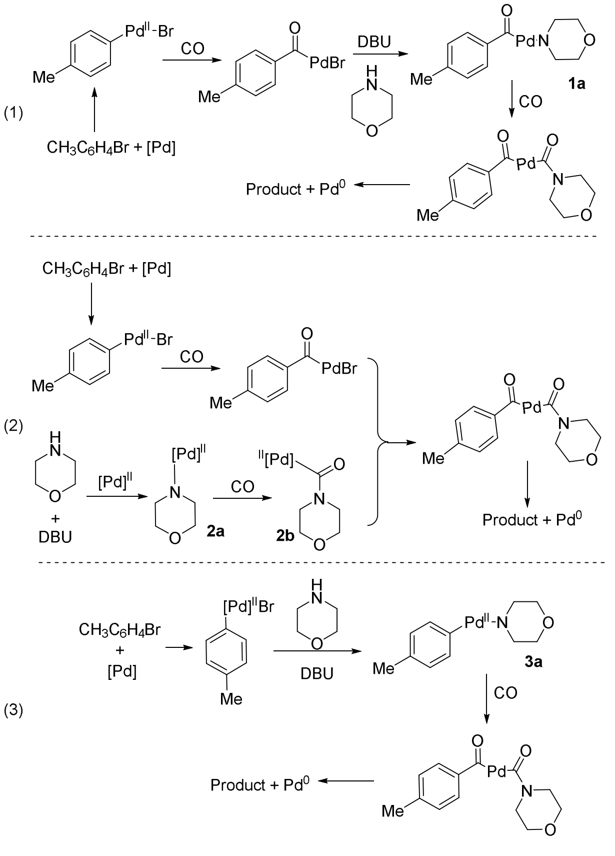
13		71%
14		69%
15		70%
16		66%
17		68%
18		63%
19		78%
20		61%
21		74%
22		61%
23		54%
24		53%[b]

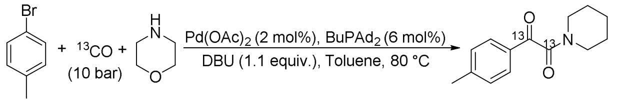
[a] Reaction conditions: 0.5 mmol of aryl bromides, 0.55 mmol of amines, 2 mol % of Pd(OAc)$_2$, 6 mol% of BuPAd$_2$ and 0.55 mmol of DBU in toluene (2.0 mL), CO (10 bar), 100 °C, 24 h. [b] 0.5 mmol of 4-bromotoluene, 0.25 mmol of piperazine.

Concerning the reaction pathway, based on literature and our understandings, three possibilities have been proposed and all through amido acylpalladium complex as the key intermediate (Scheme 1). One pathway is through amino acylpalladium intermediate **1a**, reductive elimination occurred after another CO inserted into the Pd-N bond (Scheme 1, eq.1). However, complex **1a** is prone to reductive elimination, which will lead to formation of the amide as the main product. Hence, pathway 1 is more likely predominant under high CO pressure (>50 bar). Another possibility is via **2b** as the intermediate, then transmetalation with acylpalladium complex to give the key complex (Scheme 1, eq.2). Real-NMR studies were performed for this pathway. In toluene^{D8} under ^{13}CO pressure, started with morpholine and Pd(OAc)$_2$, no **2b** could be detected with or without DBU, or DBU + BuPAd$_2$ in ^{13}C NMR. Hence, pathway 2 can be excluded as well. The third possibility is through **3a** as the intermediate (Scheme 1, eq.3). This pathway can explain the relative low CO pressure of this system and also the role of base.



Scheme 1. Proposed reaction mechanism.

Additionally, our model system was performed under ^{13}CO pressure as well (Scheme 2). The reaction proceeds smoothly at 80 °C and gave the same range of yield.



Scheme 2. ^{13}CO experiment.

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In conclusion, a versatile palladium-catalyzed double carbonylation of aryl bromides has been developed. With $Pd(OAc)_2$/$BuPAd_2$ as the catalyst system and DBU as the base, under relatively low CO pressure, various α-ketoamides were produced in good yields.

Acknowledgement

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[5] (a) Y. Li, K. Dong, F. Zhu, Z. Wang, X.-F. Wu, *Angew. Chem. Int. Ed.* 2016, **55**, 7227-7230; (b) F. Zhu, Y. Li, Z. Wang, X.-F. Wu, *Angew. Chem. Int. Ed.* 2016, **55**, 14151-14154; (c) Y. Li, F. Zhu, Z. Wang, X.-F. Wu, *ACS Catal.* 2016, **6**, 5561-5564; (d) C. Shen, X.-F. Wu, *Chem. Eur. J.* 2017, **23**, 2973-2987.

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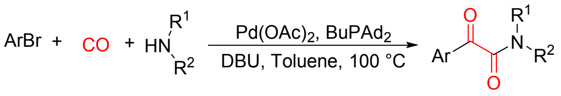

24 examples
up to 78% yield