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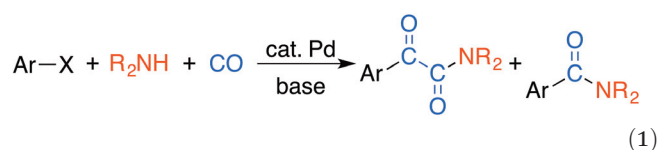
Double carbonylation of aryl iodides with amines under an atmospheric pressure of carbon monoxide using sulfur-modified Au-supported palladium†

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A double carbonylation of aryl iodides with amines proceeded smoothly under an atmospheric pressure of carbon monoxide by using palladium nanoparticles (Pd NPs) leached from a sulfur-modified Au-supported palladium material (SAPd), producing α -ketoamides in good to excellent yields.

In 1982, Yamamoto^{1a} and Tanaka^{1b} independently reported the first palladium-catalyzed double carbonylation of aryl halides with amines giving α -ketoamides, which are important fragments found in some biologically active molecules² as well as valuable synthons for the preparation of nitrogen-containing compounds³ (eqn (1)). Since then, various synthetic applications of double carbonylation have been demonstrated, and it is now widely utilized as a promising and indispensable methodology for the synthesis of α -ketoamides.^{4,5}

It is well known that Pd-catalyzed double carbonylation proceeds efficiently under a high pressure of carbon monoxide (CO). Recently, several examples of double carbonylation under an atmospheric pressure of CO have been reported.⁶ In these cases, however, the reaction proceeded only in the presence of some specific additives, such as a copper co-catalyst, nucleophilic amine base^{6b–e} or a bulky trialkylphosphine.^{6c} Ligand- and additive-free double carbonylations under such mild conditions have not been reported.⁷



We developed a sulfur-modified Au-supported Pd (SAPd) material, which immobilized 300–400 μg of palladium on the piranha-treated Au mesh (100 mesh, 12 mm \times 14 mm), and it showed remarkable reactivity for Suzuki–Miyaura coupling,^{8a,b,d,e} and Buchwald–Hartwig amination,^{8c,e} as well as C–H bond activation,^{8f,g} with low leaching and highly recyclable characteristics. Furthermore, recent studies in which the structure of the SAPd material was analyzed revealed that palladium nanoparticles (Pd NPs) of approximately 5 nm in size were immobilized on its surface.⁸ⁱ

During the course of further investigation of synthetic applications of the SAPd material, we found that double carbonylation of aryl iodides with amine proceeded under an atmospheric pressure of CO to afford an α -ketoamide with good chemoselectivity. Thus, a solution of *p*-iodoanisole (**1a**) and morpholine (**2a**) in DMF was heated at 80 $^\circ\text{C}$ for 24 hours in the presence of a sheet of SAPd, which was prepared by a 2nd-generation method,^{8e} under an atmospheric pressure of CO without stirring,⁹ giving α -ketoamide **3aa** in 40% yield accompanied by the formation of amide **4aa** in 9% yield and recovery of **1a** (Scheme 1). As mentioned above, there have been no reports on efficient double carbonylation under an atmospheric pressure of CO in the absence of any ligands or specific additives. We therefore decided to conduct further investigation of ligand-free double carbonylation of aryl iodides under an atmospheric pressure of CO by utilizing SAPd.

When the reaction in Scheme 1 was carried out, precipitation of Pd-black was observed in the reaction vessel, indicating that aggregation of Pd NPs occurs *via* exfoliation of Pd NPs from the surface of SAPd under the reaction conditions.¹⁰ This result also means that SAPd cannot be reused for further double carbonylations by this procedure. Therefore, we

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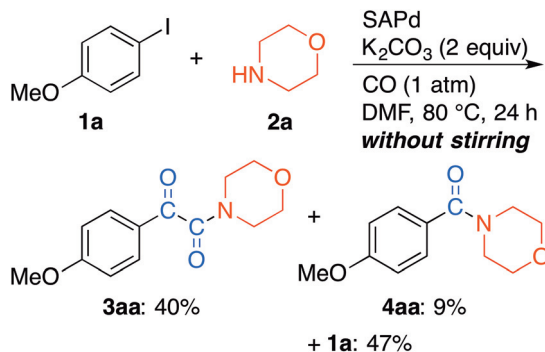
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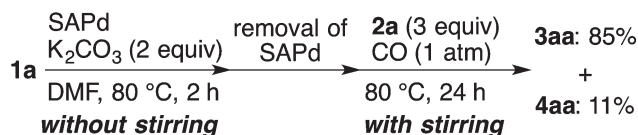
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Scheme 1 Reaction of *p*-iodoanisole (**1a**) and morpholine (**2a**) under a CO atmosphere (1 atm) in the presence of SAPd.



Scheme 2 Optimization of the reaction procedure.

decided to adopt a two-step protocol that was previously reported for C–H alkynylation using SAPd;^{8f} the first step is the leaching of a sufficient amount of Pd from SAPd by contact with *p*-iodoanisole and the second step is the carbonylation process. Thus, a solution of **1a** in the presence of K₂CO₃ and a sheet of SAPd in DMF were heated at 80 °C for 2 hours under an Ar atmosphere without stirring (1 atm). After removal of SAPd from the reaction vessel, **2a** was added to the reaction mixture and then the resulting mixture was stirred at 80 °C for 24 h under a CO atmosphere (1 atm). As a result, *p*-iodoanisole (**1a**) was completely consumed, and double carbonylation product **3aa** was produced in 85% yield along with amide derivative **4aa** in 11% yield (Scheme 2).

With the optimal procedure, studies on the scope and limitation of double carbonylation using SAPd were conducted. First, reactions of *p*-iodoanisole (**1a**) with various aliphatic amines were investigated (Table 1). Reactions of **1a** and secondary cyclic amines **2b–2f** gave the corresponding α-ketoamides **3ab–3af** in high yields (runs 1–5). Acyclic primary and secondary amines **2g–2j** were also applicable for double carbonylation, and the desired coupling products **3ag–3aj** were obtained in good yields (runs 6–9). On the other hand, the reaction using aniline (**2j**) gave only amide **4ak** in 55% yield, and α-ketoamide **3ak** was not obtained (run 10).

Next, the reactions of various aryl iodides and morpholine (**2a**) were investigated, and the results are summarized in Table 2. When *m*-iodoanisole (**1b**) was used, α-ketoamide **3ba** was obtained with good chemoselectivity (run 1). On the other hand, the reaction using *o*-iodoanisole (**1c**) as a substrate gave mono carbonylation product **4ca** as the major product (run 2). Reactions of **2a** with 3,5-dimethyliodobenzene (**1d**) and 3,4,5-trimethoxyiodobenzene (**1e**) afforded the corresponding double carbonylation products **3da** and **3ea**, respectively, in

Table 1 Reactions of *p*-iodoanisole (**1a**) and various amines

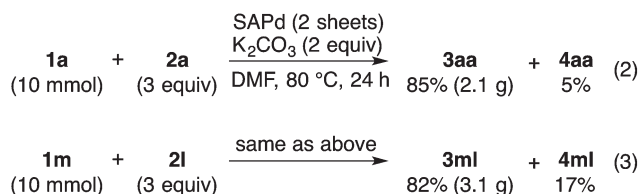
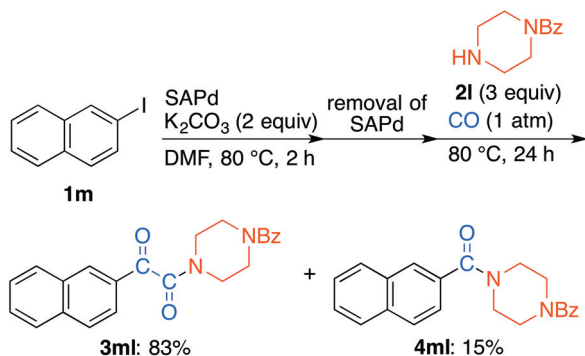
$\text{1a} \xrightarrow[\text{DMF, 80 } ^\circ\text{C, 2 h}]{\text{SAPd, K}_2\text{CO}_3 \text{ (2 equiv)}} \xrightarrow[\text{80 } ^\circ\text{C, 24 h, CO (1 atm)}]{\text{removal of SAPd, 2 (3 equiv)}}$			
Run	Amine 2	α-Ketoamide 3	Amide 4
1	2b (<i>n</i> = 0, X = CH ₂)	3ab : 82%	4ab : 10%
2	2c (<i>n</i> = 1, X = CH ₂)	3ac : 94%	4ac : 6%
3	2d (<i>n</i> = 1, X = NMe)	3ad : 86%	4ad : 11%
4	2e (<i>n</i> = 1, X =)	3ae : 87%	4ae : 9%
5	2f	3af : quant	4af :—
6	2g : ⁿ BuNH ₂	3ag : 74%	4ag : 22%
7	2h : ⁿ Pr ₂ NH	3ah : 75%	4ah : 20%
8	2i : Bn(Me)NH	3ai : 87%	4ai :—
9	2j : TBSOCH ₂ CH ₂ (Me)NH	3aj : 70%	4aj :—
10	2k : C ₆ H ₅ NH ₂	3ak :—	4ak : 55% ^a

^a NMR yield.

Table 2 Reactions of various aryl iodides and morpholine (**2a**)

$\text{1} \xrightarrow[\text{DMF, 80 } ^\circ\text{C, 2 h}]{\text{SAPd, K}_2\text{CO}_3 \text{ (2 equiv)}} \xrightarrow[\text{80 } ^\circ\text{C, 24 h, CO (1 atm)}]{\text{removal of SAPd, 2a (3 equiv)}}$			
Run	Aryl iodide 1	α-Ketoamide 3	Amide 4
1	1b 3-MeOC ₆ H ₄ I	3ba : 84%	4ba : 14%
2	1c 2-MeOC ₆ H ₄ I	3ca : 29% ^a	4ca : 55% ^a
3	1d 3,5-Me ₂ C ₆ H ₃ I	3da : 76%	4da : 4%
4	1e 3,4,5-(MeO) ₃ C ₆ H ₂ I	3ea : 84%	4ea : 4%
5	1f C ₆ H ₅ I	3fa : 69%	4fa : 21%
6	1g 4-ClC ₆ H ₄ I	3ga : 65%	4ga : 27%
7	1h 4-MeO ₂ CC ₆ H ₄ I	3ha : 46%	4ha : 42%
8	1i	3ia : 44%	4ia : 52%
9	1j	3ja : 84%	4ja : 16%
10	1k	3ka : 94%	4ka : 6%
11	1l	3la : 80%	4la : 17%

^a NMR yield.



high yields (runs 3 and 4). When iodobenzene (**1f**) was subjected to double carbonylation conditions, α -ketoamide **3fa** was obtained in 69% yield accompanied by the formation of benzamide derivative **4fa** in 21% yield (run 5). On the other hand, the reactions of aryl iodides **1g–1i** bearing an electron-withdrawing group on the aromatic ring resulted in increases in the formation of mono carbonylation products **4ga–4ia** compared to the amounts of products obtained from the reactions of aryl iodides having an electron-donating group (runs 6–8). Double carbonylation of heteroaromatic compounds **1j–1l** proceeded in a chemoselective manner, giving the corresponding α -ketoamides **3ja–3la** in high yields (runs 9–11).

It is noteworthy that the potent anti-HIV agent **3ml**¹¹ could be synthesized in one step *via* double carbonylation of 2-iodonaphthalene (**1m**) with *N*-benzoylpiperazine (**2l**) (Scheme 3).

Next, a large-scale reaction by using SAPd was investigated (Scheme 4). As a result, the reaction of 10 mmol of **1a** with **2a** gave **3aa** in 85% yield (2.1 g) with good chemoselectivity (eqn (2)). Furthermore, multi-gram synthesis of anti-HIV agent **3ml** was also achieved by using 10 mmol of **1m** (eqn (3)).

It was expected that a sufficient amount of Pd NPs remained on SAPd even after a sufficient amount of Pd NPs for the progress of double carbonylation had leached into the reaction mixture. Thus, we investigated the reusability of SAPd and also measured amounts of the leached palladium in the reaction mixtures (Table 3). After the solution of **1a** in DMF in the presence of K_2CO_3 and SAPd had been heated at 80 °C for 2 hours, SAPd was removed and reused in the next reaction. It was found that SAPd could be used for at least five reaction cycles without a significant loss of catalytic activity, and double carbonylated products were obtained in good yields and with good chemoselectivities in all cycles. Measurements

Table 3 Reusability of SAPd and catalyst loading^a

Cycle	Yields \pm SD ^{b,c} (%)		Amount of leached Pd \pm SD ^d (μ g)
	3aa	4aa	
1st	87 \pm 3	7 \pm 1	56 \pm 43
2nd	88 \pm 3	8 \pm 1	50 \pm 35
3rd	91 \pm 1	7 \pm 1	28 \pm 7
4th	91 \pm 2	8 \pm 1	30 \pm 16
5th	90 \pm 1	7 \pm 1	23 \pm 16
Average of 5 cycles	89	7	38

^a Conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), K_2CO_3 (1.0 mmol), DMF (3 mL). ^b Yield was determined by GC analysis using bibenzyl as an internal standard. ^c Yields are average values of 3 reactions. ^d Amounts of leached Pd were measured by ICP-MS analysis and are average values of three experiments.

of the amounts of leached palladium in the reaction mixtures were also conducted by inductively coupled plasma mass spectroscopy (ICP-MS) analysis, and the catalyst loading in each reaction was estimated to be 0.009–0.18 mol%.¹⁰

In summary, we demonstrated double carbonylation of aryl iodides and amines catalyzed by Pd nanoparticles leached from the SAPd material giving α -ketoamides with good chemoselectivities.¹² It is noteworthy that the reaction proceeded even under an atmospheric pressure of carbon monoxide without any specific additives or ligands. Further studies along this line are in progress.

Acknowledgements

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- 12 Since the reaction was carried out under ligand-free conditions, carbon monoxides could effectively coordinate to the surface of Pd nanoparticles. Therefore, insertion of CO into the Pd–C bond in the Ar–Pd–X intermediate and/or the nucleophilic attack of amines on the carbonyl moiety on Pd would proceed efficiently to give α -ketoamides with good chemoselectivities.