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Safe Removal of the Allyl Protecting Groups of Allyl Esters using a Recyclable, Low-Leaching and Ligand-Free Palladium Nanoparticle Catalyst

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Abstract: A safe, facile and low-leaching (up to 0.04 ppm) method has been developed for the removal of allyl, prenyl and benzyl protecting groups from the corresponding esters, using a sulfur-modified gold-supported palladium (SAPd) nanoparticle catalyst, which is known to be non-flammable. The catalyst itself was found to be recyclable and the reaction appeared to proceed on the surface of the SAPd.

Keywords: allyl ester; allyl protecting group; cleavage; deprotection; ester; nanoparticle; palladium

Introduction

The allyl group is one of the most commonly used protecting groups in organic chemistry, especially for the protection of carboxylic acids as the corresponding allyl esters.[1] The key feature of this protecting group is its stability towards both acidic and basic conditions, and allyl protecting groups are commonly removed using transition metal-catalyzed methods, including palladium catalysis.[1,2] Despite these available methods, there remains a need to develop more efficient, milder and safer protocols for the general cleavage of allyl groups as there are several limitations to the existing procedures described above. One of the biggest limitations of the palladium-mediated cleavage of allyl groups is the removal of residual palladium species from the product material and/or the reaction mixture,[3] because this material can have an adverse impact on subsequent reactions and can also pose a serious risk to human health if it is not removed to a suitably low level from pharmaceutical products.

Supported transition-metal nanoparticles (NPs) provide catalytic systems under low catalyst loading and ligand-free conditions, and they are recyclable. These benefits are attributed to the very large surface areas and quantum size effects of metal NPs.[4]

Herein, we wish to report our development of a new method for the removal of allyl protecting groups from allyl esters using a safe, low-leaching, recyclable and ligand-free palladium nanoparticles catalyst. We recently described the development of a sulfur-modified Au-supported Pd (SAPd) material,[5] which is essentially an immobilized Pd catalyst bearing Pd nanoparticles (Pd-NPs) of approximately 5 nm in size on its surface. This material was prepared via the mixing of piranha treated Au with $Pd(OAc)_2$ in xylene (Figure 1). SAPd can repeatedly catalyze ligand-free Suzuki–Miyaura cross coupling, ligand-free Buchwald–Hartwig cross coupling, and carbon (sp^3 and sp^2)-hydrogen bond activation reactions, with no more than 1 ppm of Pd ever leaching into the reaction mixture.[5]

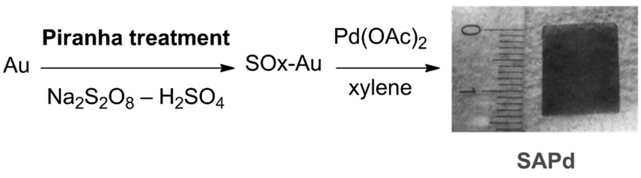
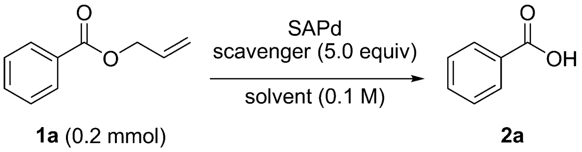


Figure 1. Preparation of SAPd.

Table 1. Optimization of the reaction conditions for the removal of the allyl-protecting group of allyl benzoate (**1a**) using SAPd as a catalyst.



Entry	Scavenger	Solvent	Temp [°C]	Time [h]	Yield [%][a] **2a**	**1a**
1	*N*-methylaniline	CH_3CN	80	6	NR	–
2	*N*,*N*-dimethylbarbituric acid	CH_3CN	80	6	NR	–
3	Ph_3SiH	CH_3CN	80	6	trace	–
4	formic acid and Et_3N	CH_3CN	80	2	96[e]	–
5	formic acid and Et_3N	dioxane	80	1	80[e]	–
6	formic acid and Et_3N	EtOH	80	2	62[e]	–
7	formic acid and Et_3N	DMF	80	2	85[e]	–
8	formic acid and Et_3N	CH_3CN	60	3	90	6
9	formic acid and Et_3N	CH_3CN	40	24	63	25
10	formic acid and Et_3N[b]	CH_3CN	80	2	2	82
11	formic acid and Et_3N[c]	CH_3CN	80	2	2	82
12	formic acid and Et_3N[d]	CH_3CN	r.t.	3	82	–

[a] HPLC yield.
[b] Without SAPd.
[c] Au-mesh was used instead of SAPd.
[d] 10% w/w of 10% Pd/C was used instead of SAPd.
[e] Isolated yield.

Results and Discussion

To achieve the Pd-NP-catalyzed removal of allyl protecting group on allyl esters, we initially examined the deprotection of benzoic acid allyl ester (**1a**) by treating a solution of this material (0.2 mmol) in acetonitrile (0.1 M) with SAPd (Au 100 mesh, 12 × 14 mm^2)[5,6] under conventional conditions instead of a homogeneous Pd catalyst[1,2] (Table 1). Under some typical conventional conditions, no reaction proceeded or only trace amount of **2a** was yielded (entries 1–3). When the reaction was performed with a combination of formic acid and Et_3N as scavenger agents at 80 °C for 2 h, the desired benzoic acid product **2a** was obtained in 96% yield (Table 1, entry 4). To determine the appropriate conditions for the reaction, we then screened a variety of solvents, temperatures and reaction times. Several different solvents were screened for the reaction, including acetonitrile, dioxane, EtOH and *N*,*N*-dimethylformamide; the desired product **2a** was isolated in good to excellent yield in all cases, but acetonitrile gave the best result and was selected for further optimization work (Table 1, entries 4–7). The reaction was then conducted at lower temperatures such as 60 and 40 °C, which give **2a** in 90 and 63% yields, respectively (Table 1, entries 8 and 9). It is noteworthy, however, that the starting material **1a** was recovered in 6 and 25% yields from these reactions, respectively. Control experiments were performed in the absence of SAPd and in the presence of Au-mesh instead of SAPd (Table 1, entries 10 and 11), both of which gave only a trace of **2a** even when the reaction was conducted for a longer time. Entry 12 shows that the conventional reaction conditions using Pd/C[7] gave the desired product **2a** in 82% yield. The amounts of Pd leached into the reaction mixture by SAPd and an Pd/C were determined by inductively coupled plasma resonance spectroscopy, and the results of these experiments will be described later in this article. Figure 2 shows a proposed reaction mechanism for the removal of the allyl-protecting group of allyl ester using a combination of a Pd catalyst and formic acid.

With the optimized conditions in hand (Table 1, entry 4), we proceeded to examine the scope and generality of this SAPd-catalyzed method for the removal of the protecting groups of esters using a series of different benzoic acid esters **1b–i** (Table 2). Prenyl and benzyl protecting groups were readily cleaved from the corresponding ester under the optimized conditions (Table 2, entries 2 and 3), whereas *n*-propyl and propargyl groups remained intact (Table 2, entries 4 and 5). Pleasingly, all of the allyl groups on allyl esters **1f–o**, including an amino acid (entry 13), were

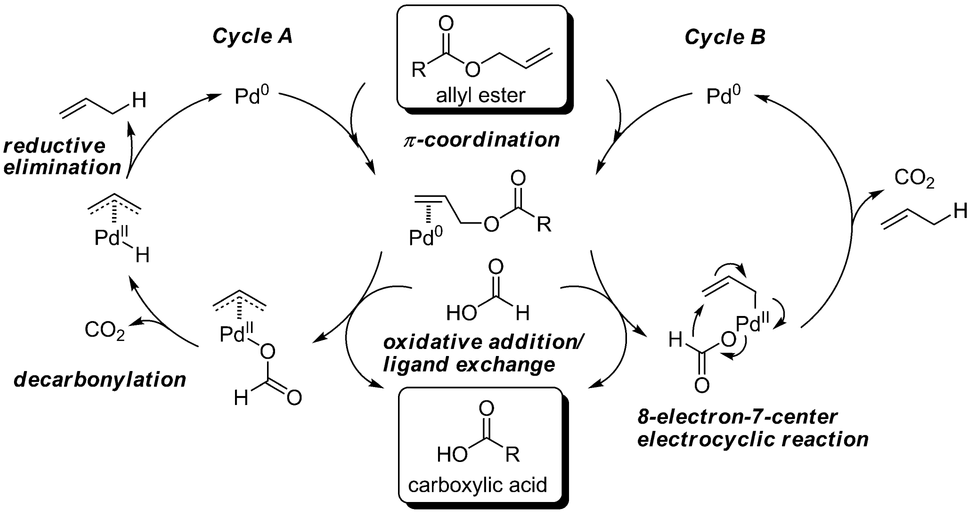
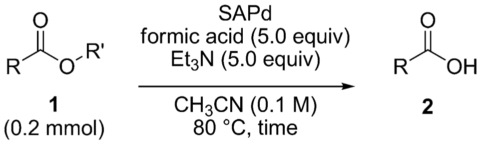
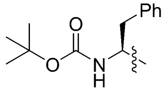


Figure 2. A proposed reaction mechanism for the removal of the allyl-protecting group of allyl ester using a combination of a Pd catalyst and a formic acid.

Table 2. Removal of the allyl protecting groups of different esters using SAPd as a catalyst.



Entry		Substrate **1** R	R′	Time [h]	Product yield [%][a]
1	**1a**	Ph	$CH_2CH=CH_2$	2	**2a** (96)[b]
2	**1b**	Ph	$CH_2CH=CMe_2$	2	**2a** (96)[b]
3	**1c**	Ph	CH_2Ph	1	**2a** (93)[b]
4	**1d**	Ph	$CH_2CH_2CH_3$	3	NR
5	**1e**	Ph	propargyl	3	NR
6	**1f**	4-$MeOC_6H_4$	$CH_2CH=CH_2$	1	**2f** (quant.)
7	**1g**	4-ClC_6H_4	$CH_2CH=CH_2$	1	**2g** (quant.)
8	**1h**	*c*-Hex	$CH_2CH=CH_2$	3	**2h** (90)
9	**1i**	$TBDPSO(CH_2)_3$	$CH_2CH=CH_2$	2.5	**2i** (44)[c]
10	**1j**	$BnO(CH_2)_3$	$CH_2CH=CH_2$	3	**2j** (75)
11	**1k**	$Ph(CH_2)_2$	$CH_2CH=CH_2$	0.5	**2k** (quant.)
12	**1l**	$PhOCH_2$	$CH_2CH=CH_2$	2.5	**2l** (86)
13	**1m**		$CH_2CH=CH_2$	4	**2m** (82)
14	**1n**	*Z* $CH_3(CH_2)_7CH=CH(CH_2)_7$	$CH_2CH=CH_2$	1.5	**2n** (92)
15	**1o**	Ph	$CH_2C_6H_4$ *p*NO_2	4	**2a** (96)[b]

[a] Isolated yield

[b] HPLC yield.

[c] Temp.: 60 °C.

converted to the corresponding carboxylic acids in good to excellent yields,[8] except **1i**, which gave a much lower yield. This was because the *tert*-butyldiphenylsilyl group on the alcohol of this substrate was partially cleaved under these reaction conditions, even at a lower reaction temperature of 60 °C.

It was expected that a sufficient amount of Pd NPs would remain on the SAPd even after deallylation, and the reusability of the SAPd material was therefore evaluated together with the amount of palladium that leached into the reaction mixtures (Table 3). After a solution of **1a** (0.2 mmol) in acetonitrile

Table 3. Removal of the allyl protecting group from an allyl ester using SAPd as a catalyst, repeated use of SAPd and analysis of the amount of Pd leaching into the reaction mixture.

Cycle	Yield [%][a,b,c]	Amount of Pd [μg] leached into the reaction mixture[a,c,e,f]
1	93 ± 0.9	0.92 ± 0.91 (0.46)
2	93 ± 2.2	0.41 ± 0.39 (0.21)
3	95 ± 1.4	0.15 ± 0.02 (0.07)
4	94 ± 1.2	0.25 ± 0.08 (0.13)
5	92 ± 1.7	0.12 ± 0.03 (0.06)
6	92 ± 1.7	0.11 ± 0.04 (0.05)
7	92 ± 0.8	0.09 ± 0.01 (0.05)
8	93 ± 3.3	0.09 ± 0.0.2 (0.05)
9	92 ± 0.5	0.09 ± 0.02 (0.05)
10	92 ± 0.5	0.09 ± 0.01 (0.04)
Average	93 ± 1.5	0.12 ± 0.08 (0.06)
Pd/C[d]	81 ± 0.9	1.50 ± 0.37 (0.75)

[a] Reaction conditions: $PhCO_2allyl$ (0.20 mmol), SAPd (100 mesh, $12 \times 14\ mm^2$), formic acid (5.0 equiv) and Et_3N (5.0 equiv) in CH_3CN (0.1 M) at 80 °C for 2 h.

[b] The HPLC yield.

[c] The standard deviation was calculated from the results of three independent samples.

[d] Reaction conditions: $PhCO_2allyl$ (0.20 mmol), Pd/C (10% w/w of 10%), formic acid (5.0 equiv) and Et_3N (5.0 equiv) in CH_3CN (0.1 M) at r.t. for 3 h.

[e] The entire reaction mixture was analyzed directly by inductively coupled plasma mass spectroscopy.

[f] Numbers in parentheses indicate the amount of Pd in ppm.

(0.1 M) had been heated at 80 °C for 2 h in the presence of formic acid (5 equiv), Et_3N (5 equiv) and SAPd, the SAPd was removed and reused in the next reaction. It was found that SAPd could be used for at least ten reaction cycles without any significant loss in its catalytic activity, and the deallylated products were obtained in excellent yields in all cycles. Measurements for the amount of palladium leached into the reaction mixtures were also conducted by inductively coupled plasma mass spectroscopy (ICP-MS) analysis, which revealed that 0.09–0.92 μg of Pd were present in the reaction mixture. This small amount of palladium was estimated to be 0.04–0.46 ppm in the whole mixture.[9] In a similar reaction using Pd/C instead of SAPd (Table 1, entry 12), a much larger amount of Pd was leached into the reaction mixture (1.50 ± 0.37 μg).

Kinetic studies/filtration tests were conducted on three different reactions and the time conversion plots of these reactions were compared to develop a deeper understanding of the nature of the catalytic species involved in this SAPd-catalyzed process. These investigations were conducted to confirm whether the leached Pd-species exhibited any catalytic activity towards the removal of the allyl group (Figure 3). The reaction with SAPd was performed under the optimized conditions described in Table 1 (entry 4) to give the deprotected product **2a** in 93% yield after 40 min. Another reaction was also performed under the same conditions, except that the SAPd was removed from the mixture 10 min after starting the reaction. In this particular case, the yield of product **2a** was determined to be only 49% after 10 min and the chemical conversion stopped completely following the removal of SAPd, with the yield of **2a** remaining at 49% after 120 min. These results therefore indicate quite strongly that the active Pd species involved in the removal of the allyl-protecting group from the allyl ester **1a** using SAPd as a catalyst is indeed the Pd-NPs on the SAPd surface, even though some Pd was released from the SAPd during the course of this reaction (Table 3). This result was particularly interesting when compared with the result of our previous experiments,[5] where Pd-catalyzed Suzuki–Miyaura cross coupling, Buchwald–Hartwig cross coupling and carbon (sp^3 and sp^2)-hydrogen bond activation reactions using halogen compounds were catalyzed by an active Pd species that was leached from SAPd.

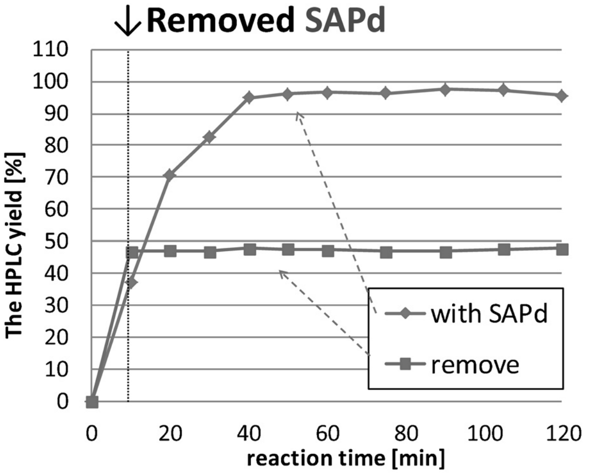


Figure 3. Removal of protecting group on ester **1a** using SAPd as a catalyst, filtration test.

Conclusion

In summary, we have developed a new safe method for the removal of allyl protecting groups of allyl esters using SAPd as a Pd-NP catalyst, where the reaction proceeded on the SAPd surface. It is noteworthy that SAPd could be recovered and reused at least 10 times without any discernible decrease in its activity and that much less Pd leached from the catalyst into the reaction mixture than that observed in conventional methods using Pd/C. Further studies towards developing a better understanding of the scope and utility of this system are currently underway in our laboratory.

Experimental Section

General considerations

Unless otherwise indicated, all of the reactions were carried out with magnetic stirring under an argon atmosphere. Reactions were monitored by thin layer chromatography (TLC).

Preparation of Sulfur-Modified Au-Supported Pd Material (SAPd)

SAPd was prepared according to a previously published literature procedure.[5d] Briefly, Au (100 mesh, 14×12 mm^2, 100.7 mg) was placed in a piranha solution for 5 min and then washed sequentially with H_2O (10×3.0 mL) and EtOH (6×3.0 mL). The resulting Au mesh was placed in a round-bottomed flask and dried for 10 min under reduced pressure (6 mmHg). The sulfur-modified Au mesh was placed in a solution of $Pd(OAc)_2$ (5.3 mg, 0.023 mmol) in xylene (3.0 mL) and stirred at 100 °C for 12 h. The mesh was then rinsed with xylene (50×3.0 mL) and dried under vacuum before being placed in xylene (3.0 mL) and heated at 135 °C for 12 h. The material was then rinsed with xylene (50×3.0 mL) and dried under vacuum for 10 min to give SAPd (100.8 mg), and this was the only source of SAPd used throughout this research.

General procedure for the SAPd-catalyzed deallylation of allyl esters

Formic acid (37.7 μL, 1.00 mmol, 5.0 equiv), triethylamine (139 μL, 1.00 mmol, 5.0 equiv) and SAPd were added to a solution of allyl ester (0.20 mmol, 1.0 equiv) in dry CH_3CN (2.0 mL, 0.1 M), and the resulting mixture was slowly stirred at 80 °C. Upon completion of the reaction, as determined by TLC, the reaction mixture was cooled to room temperature. The SAPd was removed from the mixture by a pair of tweezers (the SAPd was washed sequentially with CH_2Cl_2 [3×3 mL] and EtOH [3×3 mL] before being stored for the next cycle). The reaction mixture was diluted by CH_2Cl_2 and concentrated under reduced pressure to give the crude product as a residue, which was purified by silica gel chromatography eluting with a 1:1 (v/v) mixture of hexane and EtOAc containing 0.5% (v/v) AcOH.[10]

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[6] Piranha treatment; $Na_2S_2O_8$ (4.0 g) was added in small portions to ice-cooled 98% H_2SO_4 (4.7 g) with continuous stirring, and then crushed ice (13.0 g) and water (4.0 g) were added to the solution while the temperature was maintained below 15 °C. When all the salt dissolved to a homogeneous solution at room temperature, the Au (100 mesh-12×14 mm^2, 100.7 mg) was placed in the solution (3.0 mL) for 5 min and washed first with H_2O (3.0 mL × 10) and then with EtOH (3.0 mL × 6). The resulting Au-mesh was placed in a round bottom flask and dried for 10 min under reduced pressure (ca. 6 mmHg).

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[8] For compound **1n**, we did not observe migration or/and isomerization of the alkene moiety in the R group.

[9] Immobilized Pd on SAPd itself both before and after use from 3 sets of samples were analyzed by ICP-Mass and 2167 ± 411 µg and 1867 ± 125 µg of Pd was detected, respectively, which means that loaded Pd in the reaction mixture is 0.10 mol% and 0.09 mol% in maximum, respectively. Leaching of Pd in Table 3 gradually decreases each cycle. This means that there is a possibility that we can optimize our heated washing conditions, the last step in SAPd preparation, much more in detail.

[10] The stored SAPd was used for the next cycles in the same manner as for the previous reaction.