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Efficient synthesis of *N*-acyl-α-amino acids via polymer incarcerated palladium-catalyzed amidocarbonylation

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Abstract

A novel polymer incarcerated Pd catalyst (PI Pd **7c**) was synthesized from amide-containing polymer **6b**, and this catalyst was shown to be effective in amidocarbonylation, which is a versatile one-pot method for the preparation of *N*-acyl-α-amino acids. The reactions proceeded smoothly with a wide variety of substrates, and no leaching of the Pd metal to the reaction mixture was detected.

Keywords: Amino acid; Polymer-supported catalyst; Amidocarbonylation

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Amidocarbonylation has a great potential for the synthesis of *N*-acylamino acids due to a wide substrate scope and from an atom-economical point of view. *N*-Acyl-α-amino acids are formed in one step from the reaction of an aldehyde, an amide, and carbon monoxide in the presence of a transition metal [1]. Cobalt catalysts were first discovered by Wakamatsu et al. [2] in the early 1970s, while Pd catalysts were recently disclosed by Beller et al. [3]. The latter group also reported catalytic activities of rhodium, iridium, and ruthenium complexes in this amidocarbonylation in a patent [4]. Moreover, very recently, we have reported the first example of platinum-catalyzed amidocarbonylation [5]. Among these transition metals, the most active metal so far is Pd, and TON reaches 60,000 now in certain cases, although Pd catalysts are expensive, air-sensitive, and unrecoverable in many cases. To solve these problems, several polymer-supported Pd catalysts have been developed [6]; however, recovery and reuse of polymer catalysts have not been satisfactory. On the other hand, we have recently developed a polymer incarcerated (PI) method for immobilizing Pd catalysts onto polymers [7]. In the PI method, a Pd catalyst is first microencapsulated [8] and the microcapsules formed are then cross-linked. This method can create recoverable, reusable, and highly active heterogeneous Pd catalysts (PI Pd) for hydrogenation [7a,b], carbon–carbon and carbon–oxygen bond-forming reactions [7a], and Suzuki–Miyaura coupling [7c]. In this paper, we describe an application of this new technology to Pd-catalyzed amidocarbonylation.

In our initial studies, we intended to apply PI Pd (**2**), which was prepared from copolymer (**1**) and was successfully used in several reactions (Fig. 1), to the Pd-catalyzed amidocarbonylation (Table 1). In the presence of **2** (5 mol%), LiBr (35 mol%), and H_2SO_4 (100 mol%), cyclohexanecarboxaldehyde (**3**, 1.0 mmol) were combined with acetamide (**4**, 1.0 mmol) in 1-methyl-2-pyrrolidinone (NMP, 2 mL) at 120 °C for 15 h under carbon monoxide atmosphere (initial pressure: 60 atm) to afford the desired *N*-acyl-α-amino acid (**5**) in low yield (entry 1). To improve the chemical yield, we examined other solvents (entries 2–10). While the reaction proceeded in

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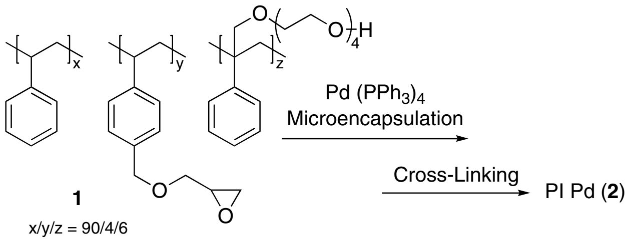
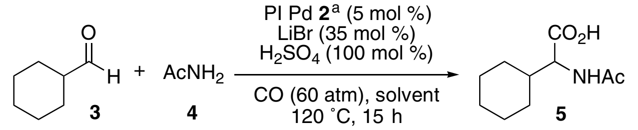


Fig. 1. Preparation of polymer incarcerated palladium (PI Pd) (**2**).

low yields in dioxane and methyl isobutyl ketone (MIBK) (entries 2 and 7), the yields were somewhat improved in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and 1,3-dimethyl-2-imidazolidinone (DMI) (entries 5 and 6). Next, we examined mixed-solvent systems based on DMI (Table 2). In general, the yields of the desired product were further improved, although leaching of the Pd, which was detected by X-ray fluorescence (XRF) analysis, was found to be a serious issue. It was revealed that the Pd-leaching was decreased without lose of chemical yields by using a DMI-1,2,3,4-tetrahydronaphthalene (THN) system. Thus, when two equivalents of **3** were used in DMI–THN (3/1), the yield of the desired adduct was increased to 94% (entry 7). Further, when the reaction was conducted at 90 °C using 1.5 equivalents of **3**, the desired product was obtained in 73% yield, and more importantly, no leaching of the Pd was detected (entry 8). However, after several trials, it was found that the reproducibility of the level of leaching of the Pd varied in the DMI–THN system due to an unknown reason.

Table 1
Effect of solvents in PI Pd-catalyzed amidocarbonylation (**1**)



Entry	Solvent	Yield of **5** (%)[b]
1	NMP[c]	9
2	Dioxane	3
3	$ClCH_2CH_2Cl$	0
4	PrCN	0
5	DMPU[d]	20
6	DMI[e]	44
7	MIBK[f]	4
8	Bu_2O	0
9	DMF	0
10	DMSO	0

[a] The loading level of the palladium was 0.156 mmol/g.

[b] Yield was determined by HPLC analysis using an internal standard technique.

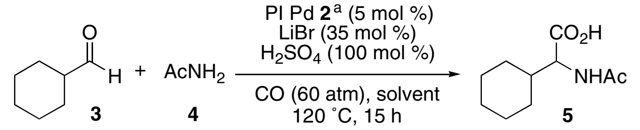
[c] 1-Methyl-2-pyrrolidinone.

[d] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

[e] 1,3-Dimethyl-2-imidazolidinone.

[f] Methyl isobutyl ketone.

Table 2
Effect of solvents in PI Pd-catalyzed amidocarbonylation (**2**)



Entry	Solvent	Yield of **5** (%)[b]	Pd leaching (%)[c]
1	DMI–DMA[d] (1/1)	12	77
2	DMI–TAA[e] (1/1)	30	18
3	DMI–PrCN(1/1)	46	30
4	DMI–Bu_2O(1/1)	48	4
5	DMI–MIBK(1/1)	56	18
6	DMI–THN[f](1/3)	73	9
7[g]	DMI–THN(3/1)	94	6
8[h]	DMI–THN(3/1)	73	nd[i]

[a] The loading level of the palladium was 0.156 mmol/g.

[b] Yield was determined by HPLC analysis using an internal standard technique.

[c] Leaching of palladium was determined by XRF analysis.

[d] Dimethyl acetamide.

[e] *tert*-Amyl alcohol.

[f] 1,2,3,4-Tetrahydronaphthalene.

[g] Aldehyde (2.0 eq.) was used.

[h] Aldehyde (1.5 eq.) was used. The reaction was performed at 90 °C.

[i] No peaks corresponding to Pd were observed (detection limit = 5 ppm).

While coordination solvents such as NMP, DMPU and DMI accelerated the amidocarbonylation, these solvents were prone to induce the leaching of the Pd from polymer-supports. Considering that polymers that contain amide moieties might have a similar solvent effect in this amidocarbonylation, we then designed new copolymers **6** (Fig. 2). Copolymers **6** were synthesized

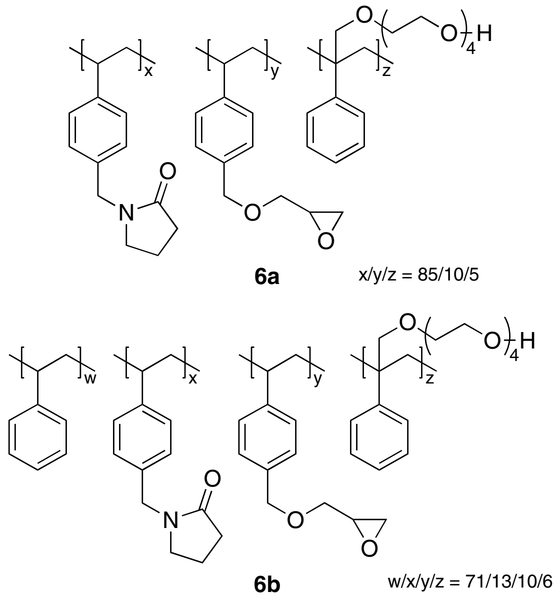
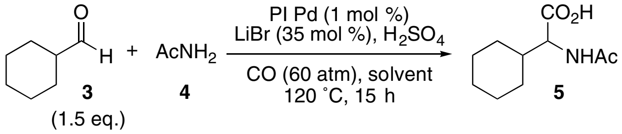


Fig. 2. Amino-containing polymers.

Table 3
Effect of the amounts of sulfuric acid



Entry	PI Pd	H_2SO_4 (mol%)	Solvent	Yield of **5** (%)[a]	Pd leaching (%)[b]
1	**7a**[c]	10	Dioxane	51	13
2	**7b**[d]	10	Dioxane	82	10
3	**2**[e]	100	DMI–THN(3/1)	84	29
4	**2**[e]	10	DMI–THN(3/1)	85	6

[a] Yield was determined by HPLC analysis using an internal standard technique.

[b] Leaching of palladium was determined by XRF analysis.

[c] PI Pd (**7a**) was prepared from copolymer **6a**. The loading level of the palladium was 0.088 mmol/g.

[d] PI Pd (**7b**) was prepared from copolymer **6b**. The loading level of the palladium was 0.091 mmol/g.

[e] The loading level of the palladium was 0.075 mmol/g.

by radical copolymerization of styrene derivatives, and PI Pd (**7**) was prepared from $Pd(PPh_3)_4$ and polymers **6** according to the standard method. We were delighted to find that PI Pd (**7b**) prepared using copolymer **6b** gave a promising result; thus, the desired amidocarbonylation product was obtained in 82% yield in the presence of **7b** (1 mol%), LiBr (35 mol%), and H_2SO_4 (10 mol%) (Table 3, entry 2). It is noted that the reaction proceeds smoothly using 1 mol% of the catalyst and 10 mol% of H_2SO_4 in a single solvent (dioxane), and that the former amide-solvent effect was also observed here by using the amide-containing polymer. As for the amount of H_2SO_4, the use of 10 mol% gave better results than that of 100 mol% even in the reactions using PI Pd (**2**) (entries 3 and 4). We assumed that the excess acid might affect the ether moiety of the polymers to change the polymer structure. For the amounts of the amide moiety in the polymers, PI Pd (**7b**) having a lower level of the amide moiety gave a better result than PI Pd (**7a**) did. It seemed that a large amount of the amide moiety might trap the proton (a co-catalyst in amidocarbonylation) during the reaction course. Thus, high chemical yield was attained using the novel PI Pd (**7b**) under milder reaction conditions; however, leaching of the Pd still remains a problem to be solved.

Previously, we have found that PI Pd is formed by aggregation of nanocapsules consisting of metal-containing polymer micelles [9]. If Pd is located around the benzene rings of the polymer in the PI catalyst, the structure of micelles would affect the activity and the leaching of Pd. Therefore, we prepared PI Pd (**7c**) using a different solvent system in the coacervation stage (Fig. 3), and examined the effect of halide sources using **7c** (Table 4). When LiBr was used as a halogen source, no improvement was observed (entries 1 and 2). On the other hand, leaching of the Pd was suppressed when Bu_4NBr was used as a halogen source (entry 3). Beller et al. [10] also reported the use of Bu_4NBr in amidocarbonylation. In their case, however, low chemical yield was obtained in dioxane. After further investigations on loading amounts of **7c** and the structure of ammonium bromides, the best result was obtained when the higher loading catalyst and $BnEt_3NBr$ were used (entry 6).

Several examples of PI Pd-catalyzed amidocarbonylation using PI Pd (1 mol%), $BnEt_3NBr$ (35 mol%), and H_2SO_4 (10 mol%) are summarized in Table 5. In most cases, the desired *N*-acyl-α-amino acids were obtained in moderate to high yields. It is noted that aromatic aldehydes as well as several types of aliphatic aldehydes could be applicable to this reaction, though reaction conditions have not yet been optimized.

In summary, we have prepared a novel type of PI Pd (**7c**) from $Pd(PPh_3)_4$ and copolymer **6b**. This catalyst could be applied to amidocarbonylation to give *N*-acyl-α-amino acids in moderate to high yields. Moreover, it is noteworthy that no leaching of Pd to the reaction mixture was detected by XRF analysis. Further investigations on scale-up synthesis of α-amino acids using this reaction are now in progress.

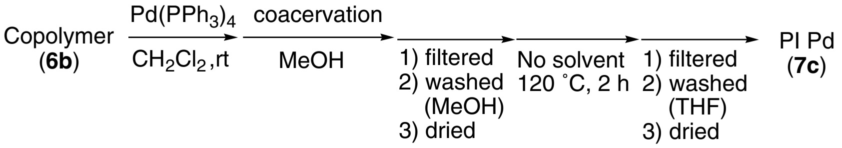
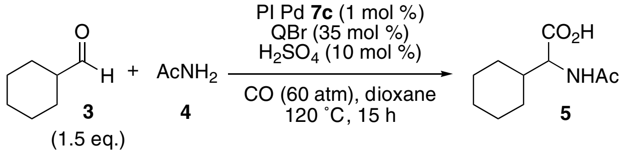


Fig. 3. Preparation of PI Pd (**7c**) from copolymer **6b**.

Table 4
Effect of bromide sources in amidocarbonylation



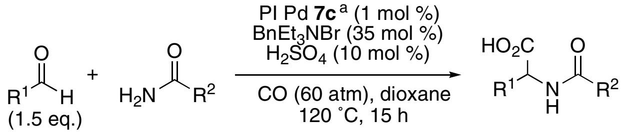
Entry	Loading (mmol/g)	QBr	Yield of **5** (%)[a]	Pd leaching (%)[b]
1	0.118	LiBr	84	13
2	0.820	LiBr	85	20
3	0.113	Bu_4NBr	83	nd[c]
4	0.820	Bu_4NBr	98	23
5	0.113	$BnEt_3NBr$	56	nd[c]
6	0.820	$BnEt_3NBr$	96	nd[c]
7	1.04	Et_4NBr	72	nd[c]

[a] Yield was determined by HPLC analysis using an internal standard technique.

[b] Leaching of palladium was determined by XRF analysis.

[c] No peaks corresponding to Pd were observed (detection limit = 5 ppm).

Table 5
PI Pd catalyzed amidocarbonylation



Entry	R^1	R^2	Yield (%)[b]
1	*c*-Hex	Me	Quant (96)[c,d]
2	*c*-Hex	$(CH_2)_4Me$	75[c]
3	*c*-Hex	Ph	20[c]
4	*c*-Hex	NHMe	20[c,e]
5	$PhCH_2CH_2$	Me	49[c,f]
6	*i*-Pr	Me	67
7	*t*-Bu	Me	55
8	Ph	Me	78
9	*p*-$CF_3C_6H_4$	Me	46[g]
10	*p*-$MeOC_6H_4$	Me	38
11	α-Naph	Me	58[g]
12	β-Naph	Me	44[h]

[a] Unless otherwise noted, the loading level of the palladium was 1.04 mmol/g.

[b] Isolated yields.

[c] Yield was determined by HPLC analysis.

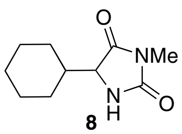
[d] The loading level of the palladium was 0.820 mmol/g.

[e] The product was identified as **8** [11].

[f] The reaction mixture was stirred at rt for 6 h before introducing CO.

[g] The loading level of the palladium was 0.629 mmol/g.

[h] The reaction was performed for 24 h.



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