Platinum-catalyzed Amidocarbonylation

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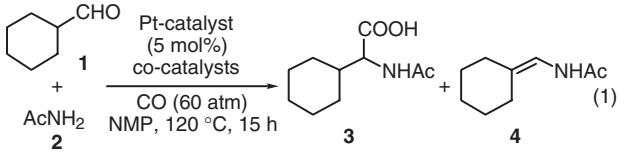
The first example of platinum-catalyzed amidocarbonylation of aldehydes with amides and carbon monoxide is described. In contrast to precedent palladium catalysis, a remarkable ligand acceleration by phosphines was observed. Furthermore, an optically active *N*-acetyl amino acid was partially epimerized under the platinum-catalyzed conditions, while faster racemization was observed under the palladium catalysis.

The transition metal-catalyzed three-component coupling reaction of aldehydes, amides, and carbon monoxide, so-called amidocarbonylation or Wakamatsu reaction, is a versatile one-pot method for the preparation of *N*-acylated α-amino acids.[1] Cobalt-catalysts were first discovered by Wakamatsu et al. in early 1970's[2] and palladium-catalysts were recently revealed by Beller et al.[3] The latter group also reported the catalytic activities of rhodium, iridium, and ruthenium complexes in a patent.[4] Among these transition metals, the most active metal so far is palladium, and now TON reaches 60000 in a certain case. However, despite the importance of optically active α-amino acid derivatives, asymmetric amidocarbonylation (either diastereoselective or enantioselective) has not been accomplished yet.[5] During the course of our study to address this issue, we have found that platinum catalysts were also effective for the reaction. Herein, we describe preliminary results of our study on the platinum-catalyzed amidocarbonylation.

Initially, we have examined the catalytic activity of various transition metals for the reaction of cyclohexanecarboxaldehyde (**1**) with acetamide (**2**) under the Beller's conditions [LiBr (35 mol%), conc. H_2SO_4 (cat.), and CO (60 atm) at 120 °C in *N*-methylpyrrolidone (NMP)]. After many trials, an interesting ligand effect was observed when platinum complexes were employed (Eq 1).[6] While $PtCl_2(PPh_3)_2$ showed a moderate catalytic activity (**3**: 15%), this was vanished in the presence of DPPE. A Pt(0) complex, $Pt(PPh_3)_4$, exhibited similar activity to $PtCl_2(PPh_3)_2$ (**3**: 13%). On the other hand, the absence of any phosphine ligand, that is, use of $PtCl_2$(cod) resulted in loss of the activity (**3**: trace), while the activity was dramatically enhanced on the addition of 2-(di-*tert*-butylphosphino)biphenyl (biphP*t*-Bu_2)[7] (**3**: 67%). In good contrast, the phosphorous ligand is not essential for the catalytic activity of palladium catalysis. It has been reported that palladium on carbon is the most effective catalyst in palladium-catalyzed amidocarbonylation.[8]



Thus, we have examined various combinations of platinum sources and phosphine ligands for the reactions of **1** with **2** under the similar conditions. With $PtCl_2$(cod) (5 mol%), sterically hindered monophosphines (10 mol%), 2-(dicyclohexylphosphino)biphenyl (biphPCy_2),[9] PCy_3, and P*t*-Bu_3 were less effective than biphP*t*-Bu_2 (**3**: 22%, 7%, and 13%, respectively). However, simple PPh_3 afforded **3** in good yield (45%). On the other hand, bidentate ligands, DPPE and BINAP suppressed the reaction completely. With PtX_2(cod)/biphP*t*-Bu_2 (X = Br or I), the catalytic activity was decreased (**3**: 59% and 12%, respectively). This suggests that the halide anion coordinated to the metal was not replaced by the added LiBr. The combination of $PtCl_2$ with biphP*t*-Bu_2 showed comparable activity to that with $PtCl_2$(cod) (**3**: 58–75%). Therefore, the effect of triarylphosphines was extensively investigated using $PtCl_2$. It was found that (1) biaryldiphenylphosphines, 2-(diphenylphosphino)biphenyl and 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl (MOP),[10] were ineffective (**3**: 0%), (2) *para*-substituted triarylphosphines, P(*p*-$MeC_6H_4)_3$ and P(*p*-$ClC_6H_4)_3$, were effective regardless of their electronic nature (**3**: 45% and 54%, respectively), (3) mono-*ortho*-substitution or di-*metha* and *para*-substitutions on triarylphosphines, P(*o*-$MeC_6H_4)_3$, P[3,5-Me_2-4-(MeO)$C_6H_3]_3$, and P(3,5-$Me_2C_6H_3)_3$, were effective (**3**: 62%, 43%, and 61%, respectively), and (4) bis-*ortho*-substitution, P(2,4,6-$Me_3C_6H_2)_3$ and P[2,6-$(MeO)_2C_6H_3]_3$, decreased the catalytic activity significantly (**3**: 8% and 0%, respectively). Consequently, it was concluded that the platinum catalyst system tended to depend on steric factors of the triarylphosphines rather than electronic ones.

Further investigations of the platinum catalysts revealed that $PtCl_2$/biphP*t*-Bu_2 system promoted the reaction even without the addition of H_2SO_4 co-catalyst or both of H_2SO_4 and LiBr, though the yields were decreased (**3**: 50% and 45%, respectively). Under these conditions, *N*-cyclohexylidenemethylacetamide (**4**) was obtained as a by-product in moderate yields (ca. 20%). It was suggested that HCl was formed from $PtCl_2$ under the reaction conditions. Accordingly, the effect of HCl as well as platinum sources on the reaction was further studied. In the absence of any acids, $Pt(PPh_3)_4$ did not catalyze the reaction, while in the addition of anhydrous HCl/dioxane, $Pt(PPh_3)_4$ exhibited the catalytic activity (**3**: 40%, **4**: 25%). On the other hand, other acids, TFA and TfOH, were ineffective regardless of the acid strength. In these cases, only formation of enamide **4** was observed (43–45%). Similar acid effect was observed when $Pt(dba)_2$ was used. Interestingly, (*R*)-MOP served as an effective ligand in combination with $Pt(dba)_2$ (**3**: 35%, **4**: 17%), while $PtCl_2$/MOP system resulted in no formation of the desired product (*vide supra*).

In sharper contrast to $PtCl_2$/phosphine system, K_2PtCl_4/phosphine system showed higher catalytic activity when (*R*)-MOP was employed as a ligand instead of biphP*t*-Bu_2 (Table 1, run 2 vs. 4 or run 3 vs. 5). Combinations of K_2PtCl_4 and triarylphosphines also afforded the desired adduct in good yields (runs 6 and 7). The coordination geometry (*cis* vs. *trans*) of the plausible platinum halide phosphine complex might attribute to this phenomena. Disappointingly, however, no chiral induction

Table 1. Effect of K_2PtCl_4/Phosphine/Acid catalysts[a]

Run	Conditions		Yield/%	
	Phosphine	Acid	**3**	**4**
1	—	—	0	nd[b]
2	biphP*t*-Bu_2	—	15	37
3	biphP*t*-Bu_2	HCl	28	24
4	(*R*)-MOP	—	56	20
5	(*R*)-MOP	HCl	77	4
6	PPh_3	HCl	63	13
7	P(*o*-$MeC_6H_3)_3$	HCl	63	2

[a]All reactions were performed using **1** (1 mmol) and **2** (1 mmol) in the presence of K_2PtCl_4 (5 mol%), a ligand (10 mol%), and an acid (10 mol%) in NMP under CO (60 atm) at 120 °C for 15 h. [b]nd = not determined.

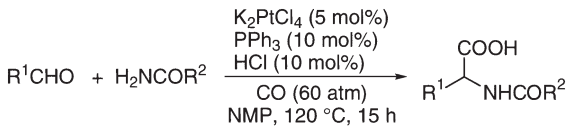
was observed when (*R*)-MOP was used as a chiral ligand.

Enamide **4** is not a dead end but one of the intermediates of the platinum-catalyzed reaction. Thus, K_2PtCl_4/(*R*)-MOP or *trans*-$PtCl_2(CH_3CN)_2$/(*R*)-MOP (5 mol%/10 mol%) was found to catalyze carbonylation of **4** with water (1 equiv.) to give the desired product **3** even in the absence of the acid co-catalyst (**3**: 64% and 65%, respectively).[11]

Furthermore, racemization experiments of (*S*)-*N*-acetylphenylalanine (**5**) (98% *ee*) were performed under either platinum- or palladium-catalyzed conditions [under CO (60 atm) in NMP at 120 °C for 15 h]. Almost no racemization of **5** was observed by treatment of K_2PtCl_4/(*R*)-MOP catalyst (recovery of **5**: 99%, 96% *ee*), while $PdBr_2(PPh_3)_2$/LiBr/H_2SO_4 catalyst[3] promoted the complete racemization (recovery of **5**: 89%, 0% *ee*).[12] In order to ensure the formation of the catalytically active species, racemization experiments of **5** were also performed in the presence of **1** and **2** (**5**/**1**/**2** = 0.5/1/1). With K_2PtCl_4/PPh_3 catalyst (5 mol%/10 mol%), partial racemization of **5** was observed (recovery of **5**: quant., 80% *ee*) as well as formation of amino acid **3** (35%) and enamide **4** (30%). On the other hand, $PdBr_2(PPh_3)_2$ (5 mol%) without co-catalysts resulted in faster racemization of **5** (recovery of **5**: 87%, 28% *ee*), though a higher catalytic activity was observed (**3**: 79%, **4**: 5%). Towards asymmetric catalysis of amidocarbonylation, this racemization problem is one of the major obstacles to be overcome. The milder conditions of the platinum catalysis could contribute to this issue.

Finally, substrate scope of the platinum-catalyzed reaction was surveyed (Table 2). All reactions were performed in a 5 mmol scale of aldehydes using K_2PtCl_4/PPh_3/HCl catalyst under CO (60 atm) at 120 °C for 15 h.[13] It was found that the desired amidocarbonylation products were obtained in moderate to good yields, though reaction conditions were not optimized yet.

Table 2. Pt-catalyzed amidocarbonylation (see Ref. 13)



Run	R^1	R^2	Yield/%[a]
1	*c*-C_6H_{11}	Me	53 (70)
2	*c*-C_6H_{11}	Ph	60 (69)
3	$PhCH_2CH_2$	Me	28 (29)
4	Me_2CHCH_2	Me	44 (47)
5	*i*-Pr	Me	46
6	Ph	Me	32

[a]Isolated yields. Yields determined by HPLC analyses are in parentheses.

In summary, we have disclosed that platinum/phosphine catalysts exhibited a good catalytic activity for amidocarbonylation, and that a remarkable ligand acceleration by phosphines was observed. It was also revealed that the undesired racemization of the product, which would be a major obstacle for asymmetric synthesis, could be retarded under the conditions. Further investigations on the asymmetric amidocarbonylation are now under way.

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References and Notes

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5 It was described in a review (ref. 1) that a low enantioselectivity (10% *ee*) was attained by using 1-diphenylphosphanylethylbenzene as a chiral ligand in palladium-catalyzed amidocarbonylation.
6 To avoid the contamination of palladium as possible, the platinum complexes or salts with high purity were employed in this study: PtX_2(cod) (Strem, X = Cl and I, 99%; X = Br, 98%), $PtCl_2$ (Strem, 99.9%, Pd 5 ppm%), $Pt(PPh_3)_4$ (Aldrich, 97%), K_2PtCl_4 (Aldrich, 99.99%), $PtCl_2(CH_3CN)_2$ and $Pt(dba)_2$ (prepared from K_2PtCl_4).
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12 It was confirmed that an acid such as H_2SO_4 itself promoted the racemization under the reaction conditions. On the other hand, Beller et al. reported that rhodium or palladium complexes catalyzed the racemization of *N*-acyl α-amino acids, see: a) M. J. Hateley, D. A. Schichl, H. Kreusfeld, and M. Beller, *Tetrahedron Lett.*, **41**, 3821 (2000). b) M. J. Hateley, D. A. Schichl, C. Fischer, and M. Beller, *Synlett*, **2001**, 25.
13 General experimental procedure: In a 50 mL stainless steel autoclave with a glass liner and a magnetic stirring bar, a mixture of an aldehyde (5 mmol), an amide (5 mmol), K_2PtCl_4 (5 mol%), triphenylphosphine (10 mol%), and HCl/dioxane (4 M, 10 mol%) in *N*-methylpyrrolidone (NMP) (5 mL) was heated at 120 °C for 15 h under carbon monoxide (an initial pressure: 60 atm). The reaction was terminated by cooling to rt. After releasing carbon monoxide, the deep green reaction mixture was collected with NMP and analyzed by a reverse phase HPLC using 2,6-dimethylphenol as an internal standard (YMC-pack ODS-A, 250 × 4.6 mm I.D.; CH_3CN/H_2O = 3/7 phosphate buffer solution). After removal of NMP at 80–100 °C under a reduced pressure, dichloromethane (30 mL) and sat. aqueous $NaHCO_3$ (30 mL) were added to the residue. The mixture was stirred well and filtered through a Celite pad. The aqueous layer was separated, washed with dichloromethane (3 × 30 mL), acidified with 85% phosphoric acid to ca. pH 2, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crystalline residue was washed with diethyl ether, collected by filtration, and dried under vacuum to give an analytically pure *N*-acyl amino acid.