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Rhodium-catalysed racemisation of *N*-acyl α-amino acids

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Abstract

The first transition metal-catalysed racemisation of *N*-acyl α-amino acids, which is of importance for kinetic resolution processes, is described. Enantiomerically pure *N*-acyl α-amino acids were efficiently racemised under mild conditions using various rhodium complexes as catalysts, e.g. $[Rh(cod)Cl]_2$, in the presence of phosphines.

Keywords: racemisation; rhodium; tricyclohexylphosphine; *N*-acyl α-amino acids.

Racemisation, that is the interconversion between enantiomers, is an important but overlooked reaction. Racemisation of enantiomerically pure compounds is often an unwanted side reaction. Nevertheless, the ability to racemise enantiomerically pure compounds under mild conditions is important as a part of the kinetic resolution process.[1] In industry a number of important enantiomerically pure compounds are still produced by kinetic resolution procedures,[2] despite major advances in stereoselective synthesis. In a classic kinetic resolution only one enantiomer is converted into product and thus the maximum obtainable yield is 50%.[3] Racemisation of the remaining enantiomer followed by further kinetic resolutions leads, after several repetitions, to a maximum obtainable yield approaching 100%.

Recently, we became interested in the racemisation of *N*-acyl α-amino acids since we developed a convenient one-step procedure (amidocarbonylation) for the synthesis of this class of compounds.[4] It has long been known that *N*-acyl α-amino acids can be racemised using acetic anhydride at high temperatures via azlactone formation;[5] however, we wanted to find a milder, catalytic alternative to this procedure. To the best of our knowledge we report here the first transition metal-catalysed racemisation of *N*-acyl α-amino acids.

In order to find an active catalyst we tested a variety of transition metal complexes which are known to be active in transfer hydrogenation[6] (Rh, Ru, Ir complexes), since we postulated that a possible racemisation pathway might proceed through dehydrogenation of the α-H and the NH of the amino acid derivative and subsequent hydrogenation of the resulting imine. The catalyst activities were assessed by dissolving the catalyst, enantiomerically pure (*S*)-*N*-acetyl phenylalanine, our test substrate, in the chosen solvent and heating the mixture in a pressure tube for a given period of time. The enantiomeric excess

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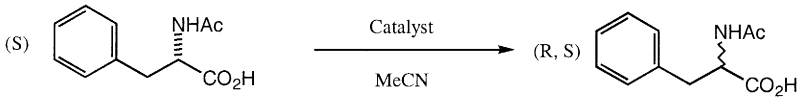
of the substrate was determined by GC analysis using a chiral column after derivatisation of the *N*-acyl α-amino acid using (trimethylsilyl)diazomethane in methanol.[7]

Interestingly, it was found that several rhodium complexes in acetonitrile catalysed the racemisation of (*S*)-*N*-acetyl phenylalanine (Table 1). The most efficient catalyst was found to be Wilkinsons' catalyst (entries 1–3), although both the cationic $Rh(cod)_2BF_4$ complex and the $[Rh(cod)Cl]_2$ complex exhibited some activity. Entries 1 to 3 show that significant racemisation already proceeds at 60°C. In addition, the catalyst seems to be very robust and does not appear to lose substantial activity after 24 h. With the exception of Rh(cod)acac all the complexes gave consistent results when the experiments were repeated. Entry 7 (Table 1) shows that when no catalyst is present only very little racemisation takes place at 60°C in the course of 48 h.

Table 1
Rhodium complex-catalysed racemisation of (*S*)-*N*-acetyl phenylalanine[8]



Entry	Catalyst	Solvent	Temp. [°C]	Time [h]	Enantiomeric excess [b]
1	$Rh(PPh_3)_3Cl$	MeCN	40	20	96 %
2	$Rh(PPh_3)_3Cl$	MeCN	60	24	87 %
3	$Rh(PPh_3)_3Cl$	MeCN	60	48	65 %
4	$[Rh(cod)Cl]_2$	MeCN	60	48	83 %
5	Rh(cod)acac	MeCN	60	48	32-86% [a]
6	$Rh(cod)_2BF_4$	MeCN	60	48	88 %
7	No Catalyst	MeCN	60	48	98 %

[a] These results were found not to be reproducible [b] The values in the table represent the average of at least two reactions

Since Wilkinsons' catalyst, a phosphino–rhodium complex, had proven to be the most active catalyst, the effect of the addition of a variety of phosphines was explored, in an attempt to form a more active phosphino–rhodium species in situ. Although a variety of phosphines were tested, (including *tris*(*o*-tolyl)phosphine, *tris*(*p*-trifluorophenyl)phosphine, *tris*-pyrolidinephosphine, *tris*(*t*-butyl)phosphine and the chelating phosphines DPPE and DPPB), it was found that tricyclohexylphosphine gave the best results (Table 2). The difference in the rate of racemisation between the systems using PPh_3 and PCy_3 is clearly visible in entries 6 to 9 (Table 2). With (*S*)-*N*-acetyl phenylalanine methyl ester as the substrate no racemisation was observed, indicating that the presence of a free carboxylic group is important. The addition of 1 equivalent of α-cinnamic acid or the presence of hydrogen led to a much reduced rate of racemisation, possibly due to the formation of inactive rhodium species.

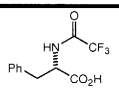
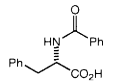
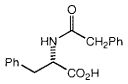
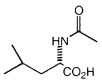
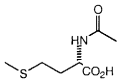
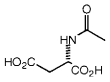
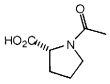
In order to see what effect the acyl moiety played on the racemisation we tested $[Rh(cod)Cl]_2$ in the presence of PPh_3 and PCy_3 for the racemisation of *N*-benzoyl, *N*-trifluoroacetyl and *N*-phenacetyl phenylalanine (Table 3). While the trifluoroacetyl derivative showed no racemisation and the *N*-benzoyl derivative did not racemise as well as the *N*-acetyl compound, the *N*-phenacetyl compound racemised at a comparable rate to the *N*-acetyl compound. In all cases the racemisation in the presence of PCy_3 was faster than in the presence of PPh_3. Next, the standard system was tested on a series of other *N*-acyl α-amino acids, with the enantiomeric excess of the substrate being measured at 24 and 48 h after the start

Table 2
Rhodium complex-catalysed racemisation of (*S*)-*N*-acetyl phenylalanine in the presence of phosphine ligands

Entry	Catalyst	Solvent	Temp. [°C]	Time [h]	Phosphine [mol%]	Enantiomeric excess
1	$[Rh(cod)Cl]_2$	MeCN	60	48	50 mol% PCy_3	0.4-10.3 %
2	$[Rh(nbd)Cl]_2$	MeCN	60	48	50 mol% PCy_3	18 %
3	$[Rh(cod)_2BF_4]$	MeCN	60	48	50 mol% PCy_3	50 %
4	$(CO)_2Rh(acac)$	MeCN	60	48	50 mol% PCy_3	74 %
5	$RhCl_3xH_2O$	MeCN	60	48	50 mol% PCy_3	70 %
6	$[Rh(cod)Cl]_2$	MeCN	60	20	50 mol% PCy_3	26 % [a]
7	$[Rh(cod)Cl]_2$	MeCN	60	20	50 mol% PCy_3	30 %
8	$[Rh(cod)Cl]_2$	MeCN	60	20	50mol% PPh_3	65 % [a]
9	$[Rh(cod)Cl]_2$	MeCN	60	20	50 mol% PPh_3	72 %

[a] Using (*R*)-*N*-acetyl phenylalanine

Table 3
Rhodium-catalysed racemisation of different *N*-acyl amino acids

Entry	Substrate	Catalyst [5 mol%]	Phosphine [mol%]	Temp. [°C]	Time [h]	Enantiomeric excess
1		$[Rh(cod)Cl]_2$	50 mol% PPh_3	60	48	100 %
2		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	100 %
3		$[Rh(cod)Cl]_2$	50 mol% PPh_3	60	48	73 %
4		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	26 %
5		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	6 %
6		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	50 %
7		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	25 %
8		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	93 %
9		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	[a]
10		$[Rh(cod)Cl]_2$	50 mol% PCy_3	60	48	> 1 %

[a] Racemisation was observed at 60 °C without the presence of the catalyst.

of the reaction (see Table 3). All the *N*-acetyl amino acids tested racemised, expect for *N*-acetyl aspartic acid. In all cases a control reaction was conducted with just the *N*-acetyl amino acid in acetonitrile and in each case no significant racemisation was observed (ee >95%).

In conclusion, we have demonstrated for the first time that *N*-acyl amino acids can be efficiently racemised using rhodium complexes under comparably mild condition. These results are not only of significance to kinetic resolution processes, but also of major importance to asymmetric hydrogenations of *N*-acylamido acrylic and cinnamic acids. It is possible that at low hydrogen pressure and at high conversion, small amounts of racemisation take place, thus decreasing the enantiomeric excess of the reaction.

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7. Ishida, T.; Inoue, M.; Harusawa, S.; Hamada, Y.; Shiori, T. *Chem. Pharm. Bull*. **1981**, *29*, 1475, 1495.
8. General procedure for racemisation experiments: A solution of PCy_3 was made up in absolute THF under argon and the appropriate amount was pipetted into an ACE pressure tube and the THF removed using a stream of argon. The residue was then dissolved in dry acetonitrile (10 mL) and the *N*-acyl α-amino acid (0.48 mmol) was added followed by the transition metal complex as either a solid or a solution in MeCN. The mixture was then heated for between 24 and 48 h at 40–60°C. A portion of the solution was then taken and derivatised using (trimethylsilyl)diazomethane (2 M in hexane) and methanol and the enantiomeric excess determined by GC or HPLC analysis.