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Asymmetric catalysis. Part 128:[1] Diastereomeric rhodium(I) complexes in the enantioselective hydrogenation of ketopantolactone

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Abstract

In the hydrogenation of ketopantolactone, new rhodium complexes bearing (R,R)-diop and various bidentate chiral N,N′ co-ligands with (R)- or (S)-configuration were used. On the one hand, the N,N′ co-ligands consist of pyrroleimines, which derive from (R)- and (S)-1-phenylethylamine, (R)- and (S)-1-cyclohexylethylamine (and benzylamine), and on the other hand of pyrroleoxazolines and pyridineimines. Stereoselectivities of 31–33% ee for (R)-pantolactone were achieved using related compounds (RR-R) and (RR-S), respectively, with no double stereoselectivity being observed. It is assumed that during catalysis the pyrroleimines bind in a monodentate way at the sixth coordination site of the rhodium atom by the pyrrole nitrogen with the imine nitrogen carrying the different chiral substituents far away from the rhodium atom. Monodentate deltacyclane phosphanes, chloro ligands or solvent molecules, bound at the sixth coordination site of the catalyst, led to widely differing enantioselectivities in the ketopantolactone hydrogenation.

1. Introduction

The hydrogenation of ketopantolactone has become a standard reaction for the enantioselective reduction of carbonyl groups. In this transformation rhodium(I) complexes containing bidentate chiral phosphorus ligands proved to be efficient catalysts.[2–24] The aim is the synthesis of the (R)-(−)-enantiomer of pantolactone, which is part of pantothenic acid, a member of the vitamin B complex and a constituent of coenzyme A. With up to 87% ee, good results were achieved in the hydrogenation of ketopantolactone using the phosphine *bppm*.[18,21–24] The best result reported is 98.7% ee obtained with *oxoproNOP*.[6] In the present study rhodium(I) catalysts were used which contain (R,R)-(−)-diop [(4R,5R)-trans-4,5-bis(diphenylphosphanylmethyl)-2,2-dimethyl-1,3-dioxolane] and, in addition, (R)- and (S)-configured pyrrolealdimine, pyrroleketimine and pyrroleoxazoline ligands (see preceeding paper) were used in order

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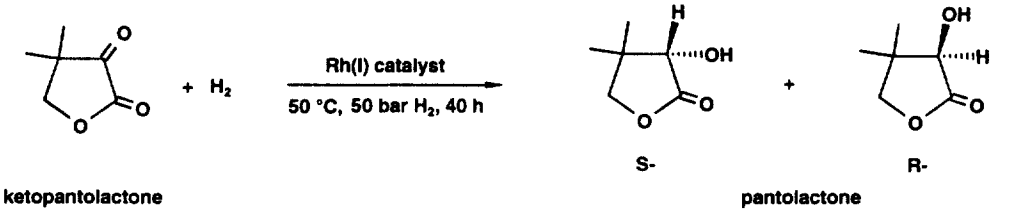
to study the effect of a chiral N,N′-ligand besides the phosphine (−)-diop on the stereoselectivity of the reduction of ketopantolactone. Provided the N,N′-ligand remains bound to Rh during the enantiodetermining step of the catalytic cycle, the (RR-R)-configured diop–N,N′–rhodium complex should give an enantiomeric excess different from the (RR-S)-configured complex. The matched combination should result in higher enantioselectivities, the mismatched combination in lower enantioselectivities (double stereoselection).[25–27]

2. The model system hydrogenation of ketopantolactone

Under standard conditions the enantioselective hydrogenation of ketopantolactone was carried out with rhodium(I) catalysts at 50°C in toluene using 50 bar hydrogen pressure (Scheme 1). The rhodium:substrate ratio was 1:200.



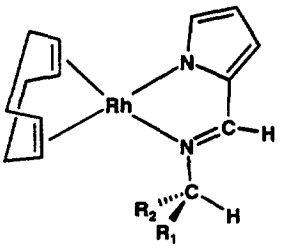
Scheme 1.

After 40 h the solvent was removed. The residue was distilled in a Kugelrohr apparatus (ketopantolactone and pantolactone have similar volatilities). The chemical yield was determined by weighing. It was constantly 90–95%, which means essentially quantitative taking into account the losses in the distillation process. This was confirmed by adding biphenyl as an internal standard to correlate the peak area and quantity of ketopantolactone and pantolactone. In the catalyses described here ketopantolactone was completely hydrogenated to pantolactone. Ketopantolactone as well as the isomers of (R,S)-pantolactone could be separated by gas chromatography without any derivatization in less than 6 min with a Chirasil-DEX-CB column allowing the accurate determination of the degree of hydrogenation and the enantiomeric excess of pantolactone.

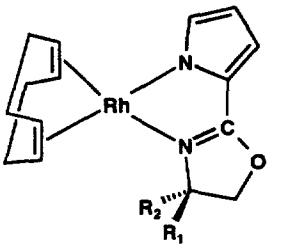
3. In situ catalysts

Neutral compounds of the type 1,5-cyclooctadiene-N,N′-rhodium(I) **1** and **2** do not catalyze the hydrogenation of ketopantolactone. However, used together with achiral or chiral phosphines, the systems become active in hydrogenation. Therefore, we studied the effect of the achiral phosphines triphenylphosphine and 1,4-diphos [1,4-bis(diphenylphosphanyl)ethane] in addition to the chiral phosphine (−)-diop in combination with the 1,5-cyclooctadiene–pyrrolylimine–rhodium(I) complexes **1** and the 1,5-cyclooctadiene–pyrrolyloxazoline–rhodium(I) complexes **2** (Scheme 2).

In combination with the achiral phosphines the compounds **1a** and **1b** give only racemic pantolactone (entries 1–4). When (−)-diop is used, enantiomeric excesses of 30–35% (pyrrolylimine complexes **1**) and 25–30% (pyrrolyloxazoline complexes **2**) are achieved (entries 5–8). The system $[Rh(cod)Cl]_2$/(−)-diop affords 54–55% ee (R)-pantolactone (entry 9). As the (RR-R)- as well as the (RR-S)-configured diop–N,N′–rhodium(I) complexes give almost identical enantioselectivities (entries **5/6** and **7/8**), there is no matched/mismatched effect. Together with the lack of enantioselectivity shown for the in situ catalysts



complex	R_1	R_2	configuration
1a	Ph	Me	R
1b	Me	Ph	S



complex	R_1	R_2	configuration
2a	Et	H	R
2b	H	Et	S

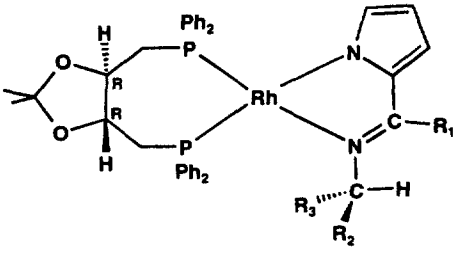
Scheme 2.

containing the achiral phosphines (entries 1–4) this could be taken as evidence for a loss of the optically active N,N′-ligands from the catalyst during the hydrogenation reaction. This, however, can be excluded, because the catalyst $[Rh(cod)Cl]_2$/(−)-diop definitely gives an enantioselectivity of 54–55% (entry 9), which is more than 20% higher than the enantioselectivities of **1**/(−)-diop and **2**/(−)-diop. Thus, it must be assumed that ligands such as N,N′ (and Cl) remain within the catalyst during the reaction (see later).

4. Catalyses with isolated complexes

The neutral diop–N,N′–rhodium(I) complexes described in the preceding paper are active in the hydrogenation of ketopantolactone. In addition to (R,R)-diop they contain chiral pyrrolylaldimines or pyrrolylketimines with either (R)- or (S)-configuration as N,N′-ligands. The diop–pyrrolylaldimine–rhodium(I) complexes **3–5** derive from 1-phenylethylamine, 1-cyclohexylethylamine and achiral benzylamine, respectively, the diop–pyrrolylketimine–rhodium(I) complexes **6** from 1-phenylethylamine. The complexes **3a** and **3b** correspond to the in situ catalysts consisting of complexes **1a** and **1b** combined with (R,R)-(−)-diop (Scheme 3).

complex	R_1	R_2	R_3	configuration
3a	H	Ph	Me	RR-R
3b	H	Me	Ph	RR-S
4a	H	Cyhex	Me	RR-R
4b	H	Me	Cyhex	RR-S
5	H	H	Ph	RR
6a	Me	Ph	Me	RR-R
6b	Me	Me	Ph	RR-S



Scheme 3.

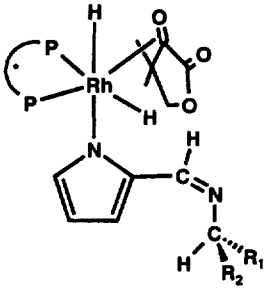
The results of several dozen hydrogenations with the complexes **3–6** fluctuate around 31–33% ee for (R)-pantolactone (Table 2, entries 10–16). The diop–pyrrolylaldimine–rhodium(I) complexes **3a**, **3b**, derived from 1-phenylethylamine, gave the same enantioselectivities as the in situ catalysts **1a**, **1b** with (−)-diop (entries 10, 11, Table 2 and entries 5, 6, Table 1).

Obviously, during the reactions, all the catalysts **3–6** form species, which give similar enantioselectivities, although they differ in the imine substituents (1-phenylethyl, 1-cyclohexylethyl and benzyl, respectively). Additionally, there are no matched/mismatched effects of the (RR-R)- and the (RR-S)-

Table 1
Enantioselective hydrogenation of ketopantolactone with in situ catalysts. Solvent toluene; pressure 50 bar; temperature 50°C; rhodium:substrate=1:200; rhodium:ligand=1:1.1 (chelate phosphines) or 1:2.2 (triphenylphosphine)

entry	compound	ligand	no. of runs	reaction time [h]	degree of hydrogenation [%]	%ee (R-pantolactone)
1	**1a**	PPh_3	4	47	98-100	racemate
2	**1b**	PPh_3	4	71	99-100	racemate
3	**1a**	1.4-diphos	4	42.5	100	racemate
4	**1b**	1.4-diphos	4	70	99-100	racemate
5	**1a**	(-)-diop	4	43	100	31.5, 31.5, 32.0, 33.9
6	**1b**	(-)-diop	4	42	100	29.0, 30.1, 33.3, 35.6
7	**2a**	(-)-diop	2	41.5	100	24.3, 29.1
8	**2b**	(-)-diop	2	41.5	100	29.1, 31.5
9	**$[Rh(cod)Cl]_2$**	(-)-diop	4	40	100	54.1, 54.4, 54.4, 54.6

configured catalysts. Thus, there is no contribution from the chirality of the N,N′-ligands. We explain these results in the following way. We assume that the N,N′-ligands remain in the catalyst during the reaction, but only bonded in a monodentate way by the anionic pyrrole nitrogen (Scheme 4). Then the 1-phenylethyl, 1-cyclohexylethyl and benzyl substituents bound at the free imine nitrogen are far away from the rhodium atom and do not affect the enantioselectivity of the hydrogenation reaction.



Scheme 4.

If an octahedral geometry of the rhodium complex is assumed after oxidative addition of hydrogen and bonding of the substrate ketopantolactone, five coordination sites will be required by the chelating phosphane, the two hydride ligands and the substrate. The sixth coordination site at the rhodium atom will be occupied by an additional ligand, a solvent molecule, another substrate molecule or a product molecule. Thus, coordination of a N,N′-ligand at the sixth position is only possible in a monodentate way.

In the hydrogenation of ketopantolactone the pyrrolylketimine containing catalysts **6a** and **6b** achieved, in most cases, enantioselectivities of about 31% (Table 2), similar to the complexes **3–5**. This can be rationalized on the basis of the same monodentate binding of the ketimine ligands via the pyrrole nitrogen as assumed for the aldimine ligands. However, in some cases, lower (about 25%) and higher enantioselectivities (up to 56%) were found. 56% ee was obtained by addition of 10 mol% (−)-diop to the catalyst in order to compensate for losses of diop by oxidation with traces of oxygen. In the catalyses with the pyrrolylaldimine complexes **3–5**, the addition of (−)-diop did not lead to varying enantioselectivities. No hydrogenation activity was left when (−)-diop was added to $[Rh(cod)Cl]_2$ in a 2,2-fold excess with respect to rhodium.

Table 2
Enantioselective hydrogenation of ketopantolactone with diop-N,N′-rhodium complexes. Solvent toluene; pressure 50 bar; temperature 50°C; reaction time 40–50 h; chemical yield 90–95% (after distillation); rhodium:substrate=1:200

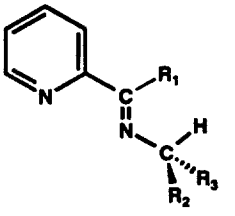
entry	10	11	12	13	14	15	16
catalyst	3a	3b	4a	4b	5	6a	6b
no. of runs	8	8	5	11	4	12	11
%ee R-pantolactone	33.3 ± 3.2	33.1 ± 2.6	32.7 ± 2.9	31.4 ± 3.0	32.4 ± 0.5	31.6 ± 6.3	31.3 ± 4.5

The scattering of the stereoselectivities with the catalysts **6a** and **6b** can be explained by a delicate balance of diverse species, the concentration of which is dependent on the conditions of the catalyses. As the result of the additional methyl group, the ketimine ligands in **6a** or **6b** should experience more steric hindrance than the aldimine ligands in **3–5**, resulting in an increased tendency for substitution by solvent, substrate, product or (−)-diop (eventually as the mono-oxidized species).

The air sensitivity of the catalysts **3–6** was studied by ^{31}P NMR spectroscopy. The complex **4a** exhibits an ABX system with 8 lines (see preceding paper). After short contact of its benzene-d_6 solution with air, the ^{31}P NMR spectrum shows a couple of new signals, which disappear within four days to give the signal of diop-oxide.[27] In addition, after the chromatography a sample of the complex **4b** shows another 8-line system besides its own ABX system. The mass spectrum contains the molecular ion of the pyrrolyl-1-cyclohexylethylimine–rhodium species with two diop-monoxide ligands besides the molecular ion of **4b**.[27] Obviously, complexes **4** react with traces of air to give species which are active in the hydrogenation reaction and contribute to the differing enantioselectivities.

In addition to the anionic pyrroleimines used as N,N′-ligands in the complexes **3–6**, the influence of neutral pyridineimine ligands **7** and **8**[28] (Scheme 5) together with the rhodium components [Rh(cod)(−)-diop]PF_6 and {Rh[(−)-diop]Cl}$_2$[26] in the hydrogenation of ketopantolactone was studied. The in situ combination of **7** and **8** with [Rh(cod)(−)-diop]PF_6 gave incomplete hydrogenation reactions and scattering enantioselectivities.[27]

ligand	R_1	R_2	R_3
7a	H	Ph	Me
7b	H	Me	Ph
8a	Me	Ph	Me
8b	Me	Me	Ph

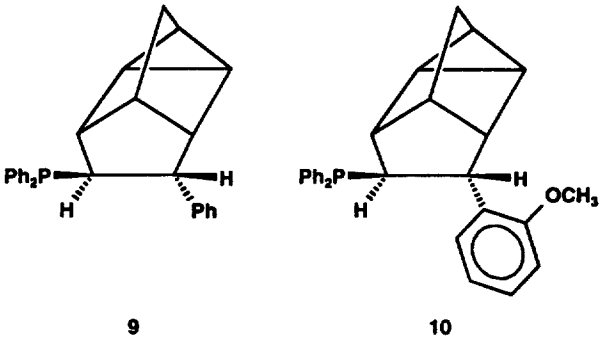


Scheme 5.

When the ligands **7** and **8** were combined with {Rh[(−)-diop]Cl}$_2$, the enantioselectivities were in the range of 51–56% ee (R)-pantolactone, and the hydrogenations were complete. {Rh[(−)-diop]Cl}$_2$ without any addition of pyridineimine achieved 56% ee (R)-pantolactone. Therefore, it is not possible to differentiate whether the added pyridineimines indeed coordinate at the sixth position of the rhodium atom causing identical enantioselectivities to the chloro systems or not. In contrast, the role of the chloro ligand at the sixth coordination site for the enantioselectivity is obvious from the fact that the complex [Rh(cod)(−)-diop]PF_6 gave only 8% ee (R)-pantolactone compared to 54–56% with {Rh[(−)-diop]Cl}$_2$ and the in situ system [Rh(cod)Cl]$_2$/(−)-diop (Table 1). All the catalyses were carried out in the solvent toluene.

Thus, modifications carried out at the sixth coordination position of the rhodium catalyst are expected

to change the enantioselectivity of the hydrogenation of ketopantolactone. In this respect the influence of the two optically active monodentate deltacyclane phosphane ligands **9** and **10**[29] (Scheme 6) in competition for the sixth position at the catalyst was investigated.



9 **10**

Scheme 6.

The phosphanes **9** and **10** were used as co-ligands in the hydrogenation of ketopantolactone together with the complex $\{Rh[(-)\text{-diop}]Cl\}_2$. The combination with **9** achieved 50–51% ee (R)-pantolactone and the combination with **10** gave 41–43% ee (R)-pantolactone (complete hydrogenation).

In addition, solvent effects in the hydrogenation of ketopantolactone can be traced back to the sixth coordination position in the rhodium catalyst. In pure tetrahydrofuran, $[Rh(cod)(-)\text{-diop}]PF_6$ gave 36% (S)-pantolactone, whereas in pure toluene, 8% ee (R)-pantolactone was obtained. Interestingly, mixtures of tetrahydrofuran/toluene did not show a linear dependence of the enantioselectivity on the solvent composition but led to a maximum of the enantioselectivity of 24% ee (R)-pantolactone (tetrahydrofuran:toluene=1.7:6.3 ml, Fig. 1).

The maximum can be attributed to a species with a tetrahydrofuran ligand coordinating at the sixth position of the rhodium atom, while the whole complex is solvated by toluene. This species induces a different enantioselectivity compared to the species formed in pure tetrahydrofuran or toluene.

We used the catalysts **4a** and **4b**, also in the standard hydrogenation of N-acetamidocinnamic acid,[26] which binds to the rhodium atom in a bidentate way. Thus, no further coordination of a co-ligand is possible. As expected, there was no additional effect of the pyrrolylimine in **4a** and **4b** compared to the standard system $[Rh(cod)Cl]_2/(-)\text{-diop}$.[30] In all cases, 80% ee (R)-N-acetylphenylalanine was obtained.[27] The catalysts **4a** and **4b** as well as $\{Rh[(-)\text{-diop}]Cl\}_2$ led to complete hydrogenation within 3–5 min, whereas the standard system $[Rh(cod)Cl]_2/(-)\text{-diop}$ required several hours because of the slow reductive elimination of the 1,5-cyclooctadiene ligand.

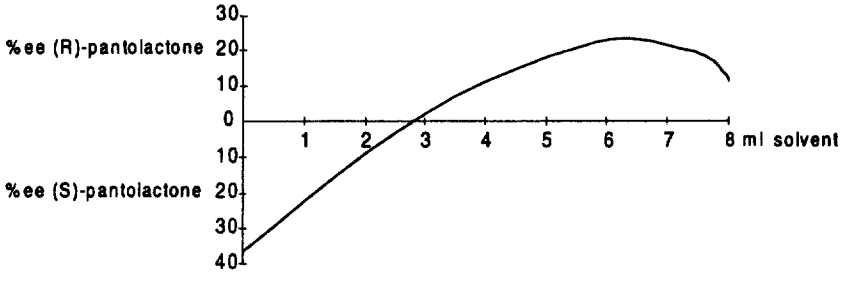


Figure 1. Enantioselectivity in the hydrogenation of ketopantolactone in a tetrahydrofuran/toluene mixture: share of toluene in 8 ml of solvent

5. Experimental

Under argon the catalyst {Rh[(−)-diop]pyrrolylimine} (0.025 mmol) was dissolved in 2 ml of toluene. The in situ catalysts were prepared from the corresponding precursor [Rh(cod)(N,N′-ligand)] (0.025 mmol) and (−)-diop (13.7 mg, 0.0275 mmol) in 2 ml of toluene and stirred at 20°C for 15 min (rhodium:ligand ratio 1:1.1). Ketopantolactone (0.64 g, 5 mmol) was dissolved in toluene (6 ml) and combined with the catalyst solution (rhodium:substrate ratio 1:200). A 100 ml steel autoclave was equipped with an empty glass vessel, closed, evacuated and flooded with argon several times. Then the manometer was removed. Through the opening, the substrate–catalyst solution was introduced, while the autoclave was flushed with argon. The manometer was reattached and the autoclave was pressurized with 50 bar hydrogen. The solution was stirred vigorously at 50°C for 40 h.

The solvent was removed. The residue was distilled in a Kugelrohr apparatus at 110°C/2 torr and the chemical yield was determined by weighing. The distillate was completely dissolved in methylene chloride and diluted to a concentration of about 20 mg within 2 ml of solution. The enantiomeric excess was determined by injecting 0.1 μl of the solution into a Fisons 8130 gas chromatograph (reproducibility±0.5%). Column Chrompack Chirasil-DEX CB (l=25 m, Ø=0.25 mm), integrator Varian 4290. Retention times (135°C): 3.0 min (ketopantolactone), 5.4 min [(S)-pantolactone], 5.9 min [(R)-pantolactone], 7.8 min (biphenyl).

For the catalyses with the complexes **3–6**, the following relations between the colour of the solution catalyst/ketopantolactone and the enantioselectivities were observed. Normally, the solution had an orange colour before hydrogenation. After the reaction, the orange brown solution became yellow when in contact with air. In these cases high enantioselectivities in the range of 33–39% ee were obtained. In some cases the solution became yellow before hydrogenation (probably due to air-oxidation). In these cases the colour of the solution was still yellow after the reaction and it remained yellow on contact with air. In this case, low enantioselectivities in the range of 10–20% ee were served. Obviously, unintentional contact with air of solutions containing small quantities of catalyst leads to scattering enantioselectivities and represents a crucial point in the hydrogenation of ketopantolactone with the catalysts **3–6**.

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References

1. Part 127: Brunner, H.; Prommesberger, M. *Tetrahedron: Asymmetry*, submitted for publication.
2. Pasquier, C.; Naili, S.; Pelinski, L.; Brocard, J.; Mortreux, A.; Agbossou, F. *Tetrahedron: Asymmetry* **1998**, *9*, 193.
3. Brunner, H.; Janura, M. *Synthesis* **1998**, 45.
4. Agbossou, F.; Carpentier, J.-F.; Hatat, C.; Kokel, N.; Mortreux, A.; Betz, P.; Goddard, R.; Krueger, C. *Organometallics* **1995**, *14*, 2480.
5. Morimoto, T.; Takahashi, H.; Achiwa, K. *Chem. Pharm. Bull.* **1994**, *42*, 481.
6. Roucoux, A.; Agbossou, F.; Mortreux, A.; Petit, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2279.
7. Morimoto, T.; Chiba, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 1149.
8. Brunner, H.; Forster, S. *Monatsh. Chem.* **1992**, *123*, 659.
9. Brunner, H.; Ziegler, J. *J. Organomet. Chem.* **1990**, *397*, C25.

10. Hatat, C.; Kokel, N.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1990**, *31*, 4139.
11. Tani, K.; Suwa, K.; Tanigawa, E.; Ise, T.; Yamagata, T.; Tatsuno, Y.; Otsuka, S. *J. Organomet. Chem.* **1989**, *370*, 203.
12. Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron Lett.* **1988**, *29*, 4755.
13. Hatat, C.; Karim, A.; Kokel, N.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1988**, *29*, 3675.
14. Chiba, M.; Takahashi, H.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1987**, *28*, 3675.
15. Karim, A.; Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G.; Siv, C. *J. Organomet. Chem.* **1986**, *317*, 93.
16. Morimoto, T.; Takahashi, H.; Fuji, K.; Chiba, M.; Achiwa, K. *Chem. Lett.* **1986**, 2061.
17. Takahashi, H.; Hattori, M.; Chiba, M.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4477.
18. Ojima, I.; Kogure, T.; Yoda, Y. *Org. Synth.* **1985**, *63*, 18.
19. Tani, K.; Ise, T.; Tatsuno, Y.; Saito, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1641.
20. Yamamoto, K.; Saeed-Ur-Rehmann *Chem. Lett.* **1984**, 1603.
21. Ojima, I.; Kogure, T. *J. Organomet. Chem.* **1980**, *195*, 239.
22. Ojima, I.; Kogure, T.; Terasaki, T.; Achiwa, K. *J. Org. Chem.* **1978**, *43*, 3444.
23. Achiwa, K.; Kogure, T.; Ojima, I. *Chem. Lett.* **1978**, 297.
24. Achiwa, K.; Kogure, T.; Ojima, I. *Tetrahedron Lett.* **1977**, 4431.
25. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem.* **1985**, *97*, 1; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
26. Brunner, H.; Wagenhuber, L. *J. Organomet. Chem.* **1996**, *525*, 259.
27. Tracht, T. Thesis, University of Regensburg, 1998.
28. Brunner, H.; Reiter, B.; Riepl, G. *Chem. Ber.* **1984**, *117*, 1330.
29. Brunner, H.; Reimer, A. *Chem. Ber./Recueil* **1997**, *130*, 1495.
30. Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.