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Development of Practical Rhodium Phosphine Catalysts for the Hydrogenation of β-Dehydroamino Acid Derivatives

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Abstract:

The rhodium-catalyzed asymmetric hydrogenation of various β-dehydroamino acid derivatives to give optically active β-amino acids has been examined. Chiral monodentate 4,5-dihydro-3*H*-dinaphthophosphepines, which are easily tuned and accessible in a multi-10-g scale, have been used as ligands. The enantioselectivity is largely dependent on the nature of the substituent at the phosphorous atom and on the structure of the substrate. Applying optimized conditions up to 94% ee was achieved.

Introduction

The discovery of new effective drugs is an important challenge for industrial and academic research. During the last decades an intense area of research in medicinal chemistry was the development of peptide-based therapeutics, mainly constructed by α-amino acids. More recently, significant attention was also directed to non-natural β-amino acids, which are interesting building blocks for the synthesis of biologically active compounds such as β-lactam antibiotics, the taxol derivatives, and β-peptides (Scheme 1).[1] In view of the growing demand of chiral β-amino acids, an increasing number of synthetic methods have been established for their preparation such as homologation of α-amino acids, conjugate addition of amines to carbonyl compounds, Mannich reaction, hydrogenation etc.[1c,2] Within these methodologies, asymmetric catalytic hydrogenation constitutes the most attractive and versatile technology as to industrial applications due to the remarkable improvements achieved in the past few years in the asymmetric hydrogenation of β-dehydroamino acid derivatives. Good-to-excellent enantioselectivities have been obtained in this reaction by applying rhodium- or ruthenium-catalysts with chiral diphosphines such as MeDuPhos, cat*AS*ium M, BINAP, BINAPO, BICP, TunaPhos, FerroTane, JosiPhos, DIOP, BPPM, P-Phos and others.[3]

A current trend in asymmetric catalysis is to switch from chiral bidentate to chiral monodentate phosphines because the latter are more easily accessible and tuneable than the bidentate counterparts.[4,5] Seminal contributions in this field have come from Feringa and de Vries et al.[6] (phosphoramidites), Reetz et al.[7] (phosphites), and Pringle and Claver et al.[8] (phosphonites). Furthermore, excellent enantioselectivities were reported by Zhou and co-workers applying monodentate spiro phosphoramidites (SIPHOS).[9,10]

Following the first report by Gladiali[11] and parallel to the work of Zhang,[12] we have focused in recent years on different monodentate phosphines based on a 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine framework (**5** and **6a**−**j**)

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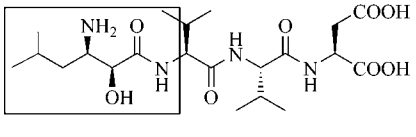
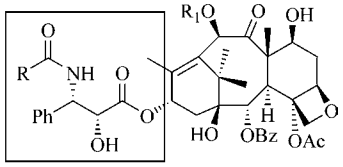
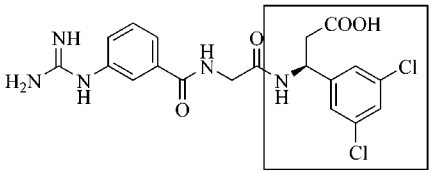
Scheme 1. **Selection of biologically active compounds containing β-amino acid units**



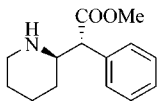
Amastatin (1)
Aminopeptidase A inhibitor



Taxol (2)
anti cancer drug



(3)
integrin antagonist



Methylphenidate (4)
anti attention-deficit disorder drug

(Scheme 3).[13] The first catalytic application of such a ligand (Ph-BINEPINE; **6a**) in the Rh-catalyzed asymmetric hydroformylation of styrene was reported by one of us (S.G.) in the early 1990s.[11a] In the following years, the Rostock group has expanded the structural diversity of the BINEPINE ligand family **6** into a library of ligands which has been screened with remarkable success (ee up to 95%) in the asymmetric hydrogenation with Rh- and Ru-catalysts of α-amino acid precursors, dimethyl itaconate, enamides and β-ketoesters.[13] In the meantime, the utility of Ph-BINEPINE **6a** has been demonstrated in a range of asymmetric reactions catalyzed by different transition metals such as the Pd-catalyzed umpoled-allylation of aldehydes and the Pt-catalyzed alkoxycyclization of 1,5-enynes. The ligand itself without any metal is an efficient chiral catalyst for the enantioselective acylation of diols, and for [3 + 2] cycloadditions and [4 + 2] annulations (Scheme 2).[11d,e,14] Quite recently excellent enantioselectivities have been scored in the Rh-catalyzed transfer hydrogenation of α-amino acid precursors and itaconic acid derivatives using formic acid as H-donor. Under these conditions β-dehydroamino acids derivatives have also been successfully hydrogenated, albeit in modest stereoselectivity.[11f]

Pursuing our ongoing research in hydrogenation chemistry, we report herein on the Rh-catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives. A multi-10-g scale synthesis of binaphthophosphepines is described, which allowed these ligands to be commercialized last year.[15]

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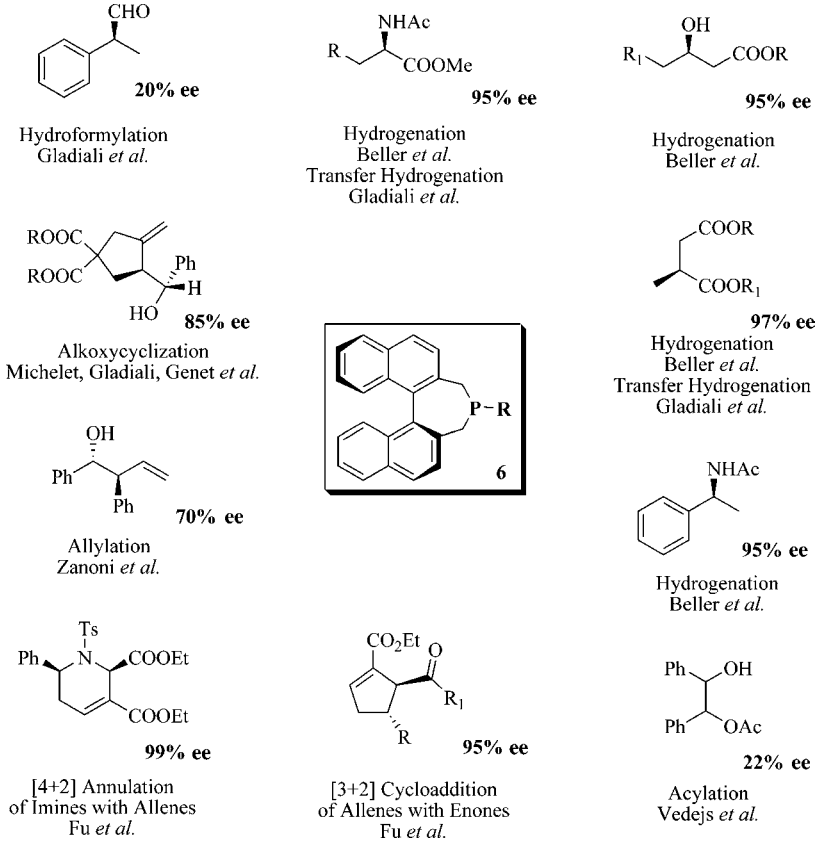
Scheme 2. **Applications of ligand class 6 in asymmetric synthesis**



Results and Discussion

The synthesis of binaphthophosphepines starts with diesterification of enantiomerically pure 2,2′-binaphthol[16] (98% ee) with trifluoromethanesulfonic acid anhydride in the presence of pyridine (Scheme 3). The corresponding diester was obtained in 99% yield, and subsequent nickel-catalyzed Kumada coupling with methyl magnesium bromide led to 2,2′-dimethylbinaphthyl in 95% yield.[13,17] Two different synthetic strategies were established to obtain 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands **6**. On the one hand, double metalation of 2,2′-dimethylbinaphthyl with *n*-butyl lithium in the presence of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) followed by quenching with commercially available dichlorophosphines gives ligands **6a** (P-phenyl) and **6i** (P-*tert*-butyl) in 60−83% yield. Both ligands have been synthesized on >10-g scale. In the second procedure the dilithiated dimethyl binaphthalene is quenched with diethylaminodichlorophosphine, giving the phosphepine **5** which, upon treatment with gaseous HCl, is converted into 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine in 80% yield. This enantiomerically pure chlorophosphine is easily coupled with various Grignard or lithium reagents to give a broad selection of ligand **6**. The limited number of commercially available dichlorophosphines and the large diversity of Grignard compounds make the access through 4-chloro-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]-phosphepine the route of choice to a library of ligands **6**.

The syntheses of β-acetamido acrylates **7**−**11** and **14** were carried out according to literature protocols by reaction of the corresponding β-ketoester with NH_4OAc followed by acylation of the β-amino acrylate intermediate.[3c,d] *E*/*Z*-Isomers were separated by crystallization and column chromatography. Ethyl 3-acetamido-3-phenyl-2-propenoate (**12**) and methyl 3-benzamido butenoate (**13**) were synthesized by reaction of the corresponding β-amino acrylate with acyl chloride or benzoyl chloride.[3l]

To compare the behaviour of the *Z*- and *E*-isomers, initial catalytic runs were carried out separately on the (*Z*)- and (*E*)-methyl 3-acetamido butenoates (*Z*-**7** and *E*-**7,** respectively) as substrates and 4-phenyl-4,5-dihydro-3*H*-dinaphtho-[2,1-*c*;1′,2′-*e*]phosphepine (**6a**) as our standard ligand.[13] Typically, we used an in situ precatalytic mixture of 1 mol % $[Rh(cod)_2]BF_4$ and 2.1 mol % of the corresponding ligand. All hydrogenation reactions were carried out in an 8-fold parallel reactor array with a reactor volume of 3.0 mL.[18]

We first focused our attention on the influence of the solvent and the hydrogen pressure. The first set of reactions was run at constant concentration in toluene, dichloromethane, methanol, ethanol,[19] and 2-propanol at three

(15) The ligands Ph-BINEPINE (**6a**) and *t*-Bu-BINEPINE (**6i**) are commercially available by Degussa DHC (Degussa Homogeneous Catalysis, Rodenbacher Chaussee 4, building 097, 63457 Haunau (Wolfgang), Germany, (www.creavis.com/site_dhc/de/default.cfm)) with the product names cat*A*Sium KPh (**6a**) and cat*A*Sium KtB (**6i**).

(16) Optically pure 2,2′-binaphthol is available on large scale from RCA (Reuter Chemische Apparatebau KG), Engesserstr. 4, 79108 Freiburg, Germany.

(17) The synthesis of 2,2′-bistriflate-1,1′-binaphthyl (1.2 mol, 615 g, 92%) and 2,2′-dimethyl-1,1′-binaphthyl (0.74 mol, 201 g, 96%) was carried out in large scale by the group of Zhang (See ref 11b).

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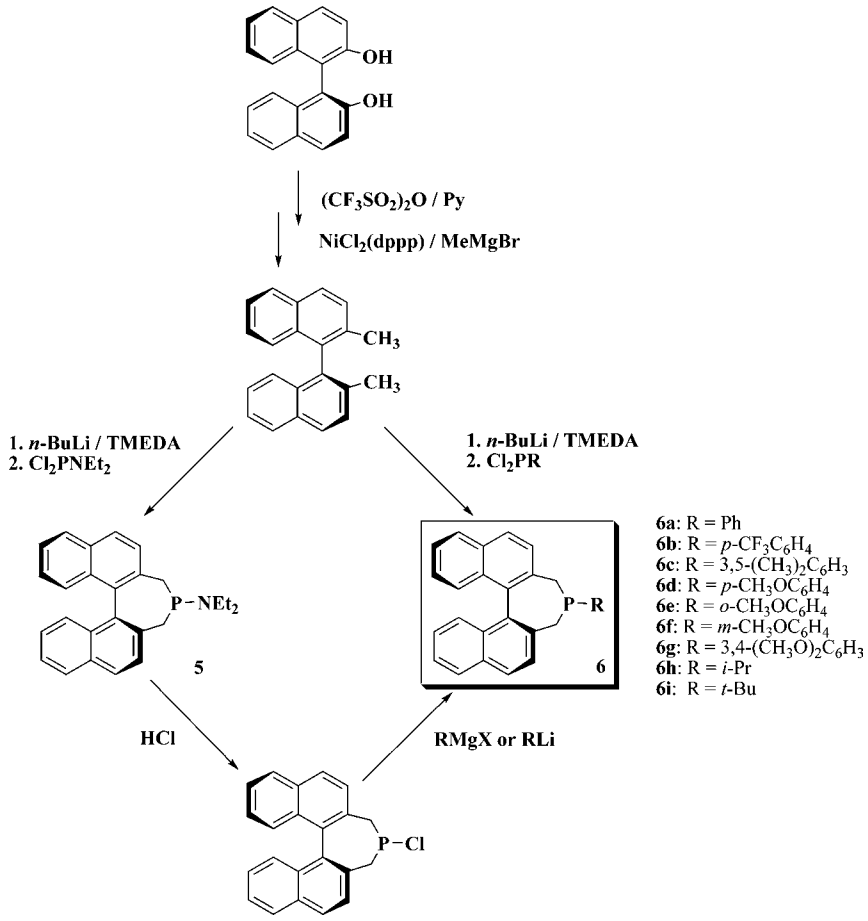
Scheme 3. **Synthetic approach to 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands 6**



different pressures (2.5, 10.0, and 50.0 bar). Selected results are presented in Figure 1.

In the case of hydrogenation of *E*-**7** the best enantioselectivity was consistently achieved at the lowest pressure (2.5 bar) and ranged between 42−79% ee, depending on the solvent. After 24 h the reaction was complete only in 2-propanol, whereas lower conversions were observed in ethanol, methanol, and toluene.[20] No reaction at all took place in dichloromethane. The stereoselectivity decreased upon increasing the pressure of hydrogen to 10.0 bar or 50.0 bar. From these results 2-propanol and 2.5 bar were selected as solvent and pressure of choice, respectively, for the hydrogenation of the *E*-isomer (conversion: >99%; enantioselectivity: 79%). The hydrogenation of *Z*-**7** resulted in higher enantioselectivities in all the solvents (up to 92% ee). Notably, compared to *E*-**7** the configuration of the prevailing enantiomer was always opposite. Furthermore, in ethanol and in methanol the enantioselectivity/pressure trend was reversed, the top value (92% ee) having been reached at the highest pressure (50.0 bar) compared to 86% ee at 2.5 bar. Full conversions were obtained in all the experiments, except in toluene (37%) and in dichloromethane (45%). These results indicated ethanol and methanol as the best solvents and 50.0 bar as the pressure of choice for the hydrogenation of the *Z*-isomer (conversion: >99%; enantioselectivity: 92%).

No incorporation of deuterium in the product was noticed upon running the reaction in methanol-d_4. This is in line with the absence in the reduction process of any interference of transfer hydrogenation as well as of protonolysis of the Rh−C bond of an alkyl rhodium intermediate.[21] Two facets deserving mention are (1) the *Z*-isomer gives higher ee's than the *E*-isomer, whereas in most cases the opposite behaviour has been reported[3] and (2) the configuration switches depending on the different geometry of the double bond, which has been scarcely reported.[3c,22]

Next, we investigated the influence of temperature on enantioselectivity and conversion as shown in Figure 2.[23] Applying our model ligand **6a** we found a pronounced negative effect on the enantioselectivity at higher temperatures for both isomers. Interestingly, the loss of enantioselectivity for the hydrogenation of *E*-**7** is higher than for *Z*-**7** (10 °C: *E*-**7** 79% ee (*R*) and *Z*-**7** 88% ee (*S*); 90 °C: *E*-**7** *rac* and *Z*-**7** 60% ee (*S*)).

(19) The hydrogenation performed in ethanol and 2-propanol led exclusively to product **7**. No transesterification was observed.

(20) In the case of toluene we assume an inhibition of the catalyst by the solvent, due to the formation of catalytical inactive rhodium−arene complexes. Heller, D.; Drexler, H.-J.; Spannenberg, A.; Heller, B.; You, J.; Baumann, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 777−780.

(21) Tsukamoto, M.; Yoshimura, M.; Tsuda, K.; Kitamura, M. *Tetrahedron* **2006**, *62*, 5448−5453.

(22) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419−422.

(23) Jerphagnon, T.; Renaud, J.-L.; Demonchaux, P.; Ferreira, A.; Bruneau, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1973−1977.

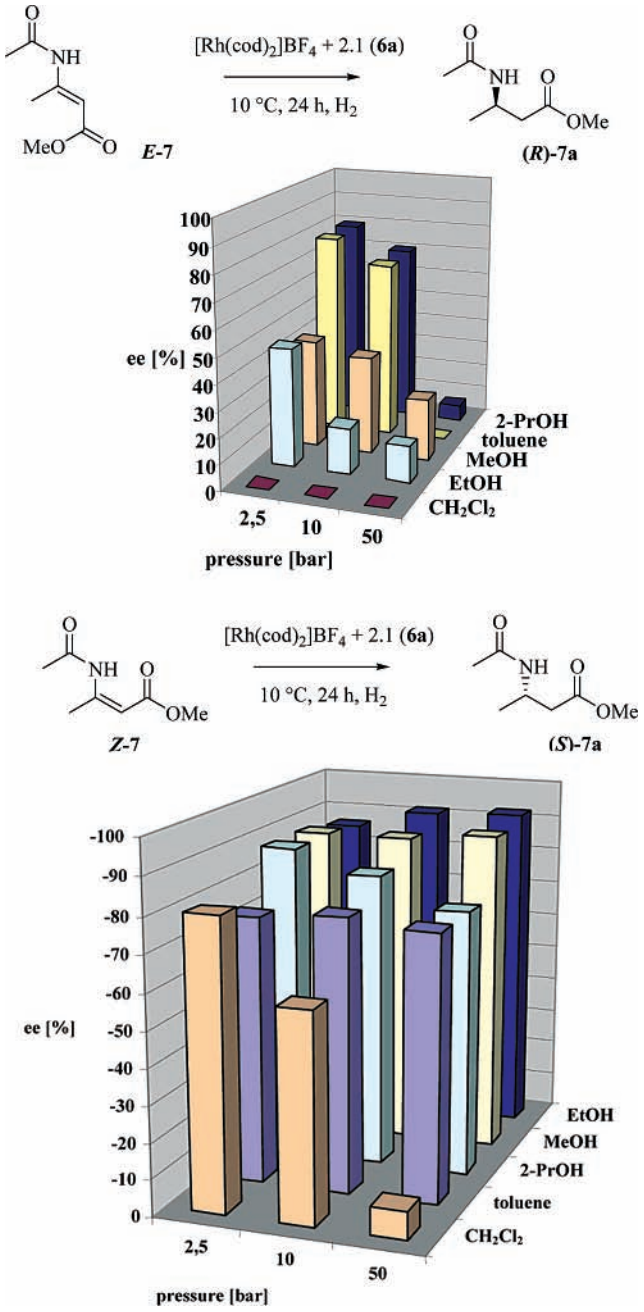


Figure 1. **Solvent and pressure variation. Reactions were carried out at 10 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of solvent. Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min). The absolute configuration was determined by comparison with reported data.[3l]**

For estimating the feasible enantioselectivity at lower temperature we analysed the corresponding Eyring plot[24] for both isomers. As a consequence we considered 10 °C as temperature of choice, because of good enantioselectivity and also acceptable reaction times.

The original protocol used for the synthesis of methyl 3-acetamido butenoate (**7**) gives a mixture of *E*- and *Z*-isomers whose composition depends on the reaction conditions.[1f] Although separation of the isomers by fractional

(24) Buschmann, H.; Scharf, H.-D.; Hoffmann, N.; Esser, P. *Angew. Chem.* **1991**, *103*, 480−518.

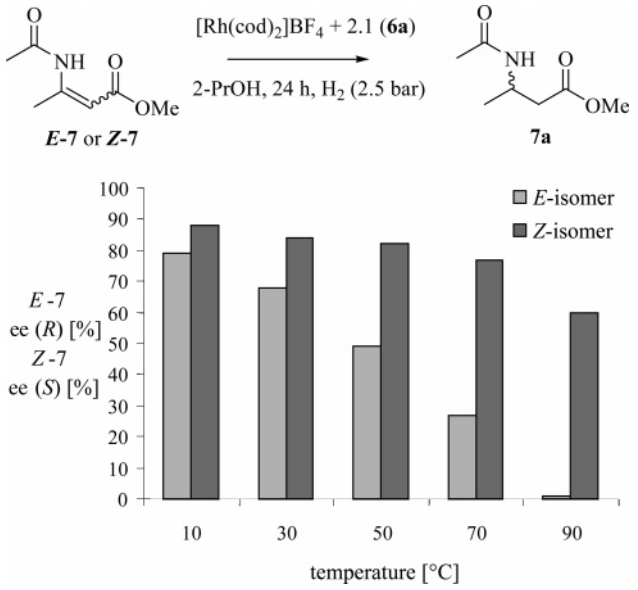


Figure 2. **Dependency of enantioselectivity versus temperature. Reactions were carried out at corresponding temperature for 1−24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of 2-propanol. Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

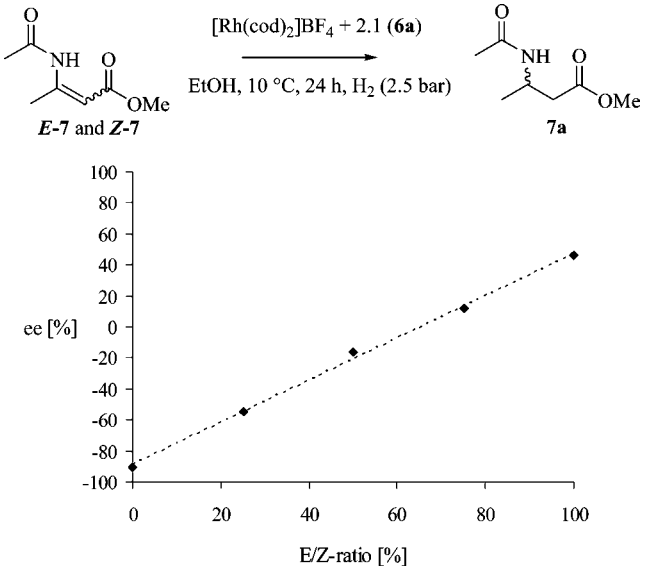


Figure 3. **Dependency of enantioselectivity versus *E*/*Z* ratio. Reactions were carried out at 10 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of ethanol. Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

crystallization is feasible, the selective hydrogenation of the mixture is clearly advantageous. This prompted us to explore the hydrogenation of different *E*/*Z* ratios including the mixture obtained from the synthesis (Figure 3). The results showed a linear decrease of enantioselectivity for all mixtures and demostrated that the hydrogenation of the single isomers led to highest enantioselectivity.

Recently, Heller and Börner have reported kinetics and mechanistic investigations for the hydrogenation of *E*-**7** and *Z*-**7** through the use of bidentate phosphine ligands. The mentioned results modified the existent declaration that the

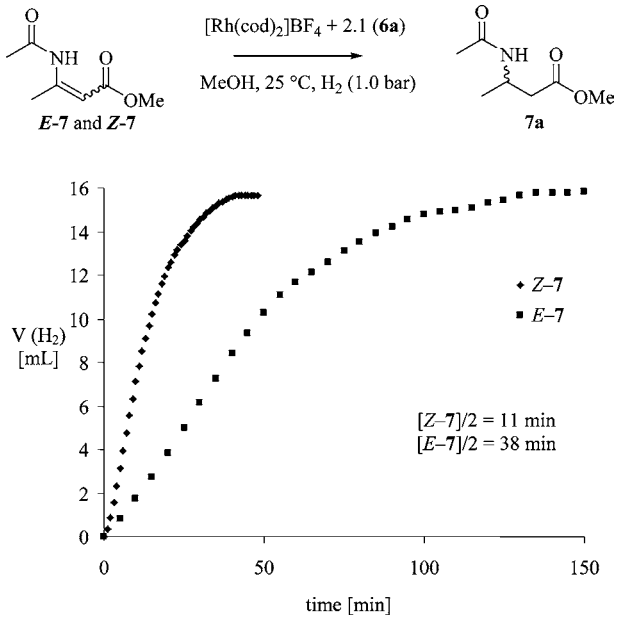


Figure 4. **Dependency of hydrogen consumption versus reaction time. Reactions were carried out under isobaric conditions (1.0 bar) at 25 °C. $[Rh(cod)_2]BF_4$ (0.0072 mmol) and 0.015 mmol ligand 6a were stirred for 10 min under hydrogen atmosphere in 10.0 mL of methanol. Afterwards the substrate (0.72 mmol) was added in 1.0 mL of methanol. The conversions and ee's were determined by GC (50 m Chiraldex *β*-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

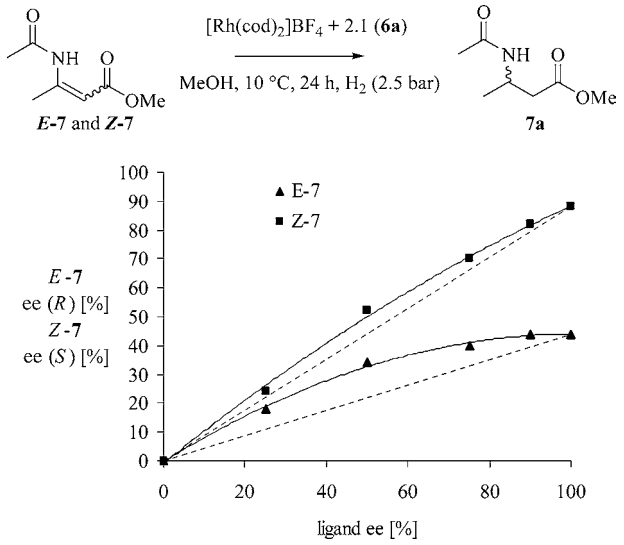


Figure 5. **Dependency of the optical purity of ligand 6a on product selectivity. Reactions were carried out at 10 °C for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand 6a and 0.24 mmol substrate in 2.0 mL of methanol. Conversions and ee's were determined by GC (50 m Chiraldex *β*-PM, 130 °C, (*S*)-7a 15.1 min, (*R*)-7a 16.4 min).**

reaction rate for hydrogenation of *E*-isomers is higher than that for the *Z*-isomers, because in some cases the opposite behaviour was observed.[3g]

To classify ligand **6a** we recorded the hydrogen uptake in relation to the reaction time for the asymmetric hydrogenation of *E*-**7** and *Z*-**7** with our catalyst in isobaric conditions and under normal pressure of hydrogen (Figure 4).

To minimize the interfering effect of cyclooctadiene (cod), the precatalyst was stirred for 10 min under hydrogen atmosphere before adding the substrate *E*-**7** or *Z*-**7**. We were surprised to see that, unlike the case of most bidentate ligands, in our case at 50% conversion it was the *Z*-isomer which was hydrogenated faster (about 3.5 times the *E*-isomer).

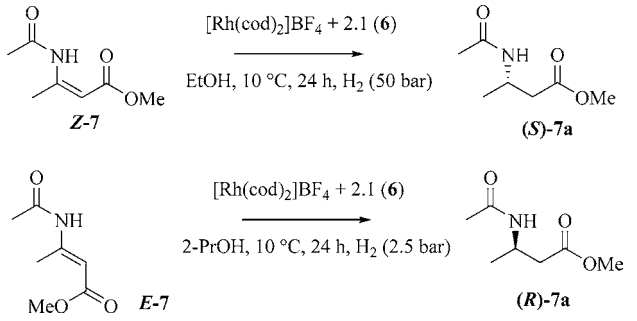
For gaining an insight into the structure of the catalyst, the hydrogenation of *Z*-**7** was perfomed using the preformed complex $[Rh(\mathbf{6a})_2(nbd)]^+CF_3SO_3^-$ as the catalyst. This cationic complex was prepared as previously reported by us,[11f] and the reaction was run in MeOH at 5 bar at 25 °C. Under these conditions, *Z*-**7** was completely hydrogenated in 12 h to give the (*S*)-enantiomer in 92% ee. This result is quite close to the one obtained with the catalysts prepared in situ by adding 2 equiv of the ligand **6a** either to $[Rh(nbd)_2]^+BF_4^-$ (89% ee) or to $[Rh(cod)_2]^+BF_4^-$ (88% ee). From this it follows that the catalytically active species most likely contain two monodentate P-ligands per Rh center and that the ancillary diolefin ligand has a negligible effect, if any, on the stereoselectivity, while the anion may exert some influence. Further support to the presence of two ligands around the metal comes from the search of nonlinear effect (NLE) in the model reaction.[25] A set of hydrogenations was performed on both the isomers using various samples of ligand **6a** of different enantiomeric purity, and the ee's observed have been plotted against the enantiomeric purity of the ligand (Figure 5). For both *Z*-**7** and *E*-**7** a positive nonlinear effect, which implies the bonding of at least two ligands to the rhodium, is clearly apparent. Similar results were reported by Reetz,[7i] Zhou,[9b] and Feringa[6f] for the asymmetric hydrogenation of itaconic esters or α-amino acid derivatives by the use of different monodentate P-donor ligands. To verify the positive nonlinear effect we decreased the amount of ligand to 1 equiv with respect to rhodium. Here, we observed a diminished reaction rate compared to the rate of hydrogenation with 2 equiv of ligand. In addition, the amount of ligand was increased to 4 equiv with respect to rhodium, but also in this case a reduced reaction rate was monitored.

In previous studies we have shown the pronounced effect that the substitution pattern at the P-centre of BINEPINE ligands has on the stereoselectivity of the asymmetric process.[13] In order to evaluate this substituent effect the asymmetric hydrogenation of *E*-**7** and *Z*-**7** was performed in the optimized conditions previously devised with nine different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines (**6a**−**6i**) (*E*−**7**: 2.5 bar hydrogen pressure, 2-propanol, 10 °C, 24 h; *Z*-**7**: 50.0 bar, ethanol, 10 °C, 24 h) (Table 1).

In the hydrogenation of *E*-**7** the best enantioselectivities up to 90, 88, and 87% ee, respectively, were achieved with ligands **6g**, **6d**, and much to our surprise, with **6i** (Table 1, entries 7, 4, and 9). The last one has always given quite poor results in the other benchmark tests where it has been screened. The presence of electron-donating groups on the P-aryl substituent has a positive effect on the stereoselectivity (Table 1, entries 4, 6, and 7), whereas the opposite occurs for electron-withdrawing groups (Table 1, entry 2). This trend

(25) (a) Girard, C.; Kagan, H. B.; *Angew. Chem.* **1998**, *110*, 3088−3127. (b) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804−805.

Table 1. **Hydrogenation of *E*-7 and *Z*-7 with different 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepines (6a−6i)**



entry	ligand	isomer[a]	conv. [%][b]	ee [%][b]	isomer[c]	conv. [%][b]	ee [%][b]
1	**6a**	*E*	>99	79 (*R*)	*Z*	>99	**92 (*S*)**
2	**6b**	*E*	91	40 (*R*)	*Z*	>99	32 (*S*)
3	**6c**	*E*	80	69 (*R*)	*Z*	>99	80 (*S*)
4	**6d**	*E*	>99	**88 (*R*)**	*Z*	>99	86 (*S*)
5	**6e**	*E*	>99	20 (*R*)	*Z*	>99	*rac*
6	**6f**	*E*	91	81 (*R*)	*Z*	90	40 (*S*)
7	**6g**	*E*	>99	**90 (*R*)**	*Z*	>99	**89 (*S*)**
8	**6h**	*E*	>99	76 (*R*)	*Z*	5	38 (*S*)
9	**6i**	*E*	>99	**87 (*R*)**	*Z*	3	60 (*S*)

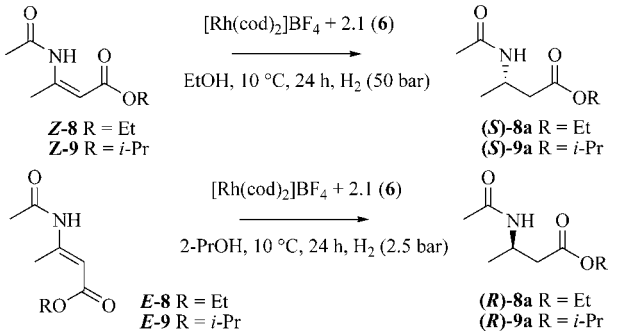
[a] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [b] Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-**7a** 15.1 min, (*R*)-**7a** 16.4 min). The absolute configuration was determined by comparing with reported data.[3l] [c] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL).

is similar to the one observed in the hydrogenation of *Z*-**7** although in that case the best ee was scored with the plain phenyl ligand **6a**. Alkyl-substituted phosphepines **6h** and **6i** produced catalysts of negligible activity in hydrogenation of this substrate (Table 1, entries 8 and 9).

To explore scope and limitation of our ligand toolbox, the asymmetric hydrogenation of a range of β-dehydroamino acids derivatives was performed under optimized conditions (Table 2). First the influence of the ester-group on the hydrogenation of both *Z*- and *E*-isomers was investigated in detail. For *E*-**7** changing from methyl to isopropyl ester resulted consistently in a slight decrease of stereoselectivity, whereas in the case of the *Z*-isomer no reliable correlation between ester functionality and enantioselectivity was detected. Notably, a diminished yield for all hydrogenations of *Z*-**9** was attained (Table 2).

Finally, the influence of β^3- and β^2-substitution was investigated on a set of seven different substrates (Scheme 4 and Table 3). While substitution of a methyl with an ethyl group has negligible effects, an increase in the branching of the alkyl group resulted in an improved selectivity with ligands **6g** and **6i**. Furthermore, we also carried out a substitution in the β^3-position by an aromatic group (compound *Z*-**12**). As a tendency, depletion of conversion and enantioselectivity was observed in comparison to *Z*-**8** (Table 1, entries 1−7 and Table 2, entries 15−21). A similar negative effect was found after substitution of the acyl protecting group by benzoyl and subjecting *Z*-**13** in the hydrogenation reaction (Table 3, entries 15−21).

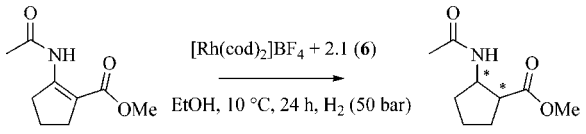
Table 2. **Influence of ester group on conversion and enantioselectivity**



entry	ligand	isomer[a]	conv. [%][b]	ee [%][b]	isomer[c]	conv. [%][b]	ee [%][b]
1	**6a**	*E*-**8**	98	83 (*R*)	*Z*-**8**	>99	**94 (*S*)**
2	**6b**	*E*-**8**	79	46 (*R*)	*Z*-**8**	>99	*rac*
3	**6c**	*E*-**8**	65	20 (*R*)	*Z*-**8**	>99	36 (*S*)
4	**6d**	*E*-**8**	98	84 (*R*)	*Z*-**8**	>99	83 (*S*)
5	**6g**	*E*-**8**	97	**84 (*R*)**	*Z*-**8**	>99	85 (*S*)
6	**6h**	*E*-**8**	>99	66 (*R*)	*Z*-**8**	>99	*rac*
7	**6i**	*E*-**8**	>99	80 (*R*)	*Z*-**8**	>99	*rac*
8	**6a**	*E*-**9**	>99	70 (*R*)	*Z*-**9**	52	78 (*S*)
9	**6b**	*E*-**9**	63	40 (*R*)	*Z*-**9**	23	46 (*S*)
10	**6c**	*E*-**9**	73	20 (*R*)	*Z*-**9**	61	24 (*S*)
11	**6d**	*E*-**9**	>99	**76 (*R*)**	*Z*-**9**	69	**91 (*S*)**
12	**6g**	*E*-**9**	92	72 (*R*)	*Z*-**9**	55	73 (*S*)
13	**6h**	*E*-**9**	>99	66 (*R*)	*Z*-**9**	34	*rac*
14	**6i**	*E*-**9**	>99	**76 (*R*)**	*Z*-**9**	32	6 (*S*)

[a] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [b] Conversions and ee's were determined by GC (**8** (25 m Lipodex E, 70/40-8-180, (*R*)-**8a** 33.2 min, (*S*)-**8a** 33.4 min), **9** (25 m Lipodex E, 70/25-10-180, (*R*)-**9a** 33.2 min, (*S*)-**9a** 33.4 min). The absolute configurations were determined by comparing the sign of specific rotation with reported data.[3d] [c] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL).

Scheme 4. **Asymmetric hydrogenation of methyl 2-acetamidocylopent-1-enecarboxylate (14)[a]**



6a: conv. 96%; >99% de; 76% ee
6b: conv. 52%; >99% de; 66% ee

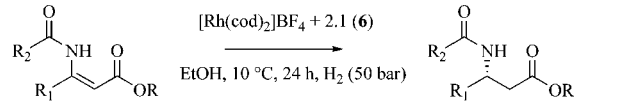
[a] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL). Conversion, de's and ee's were determined by GC (25 m Chirasil Val, 120 °C, **14a1** 26.8 min, **14a2** 27.6 min, **14a3** 52.1 min, **14a4** 53.0 min).

As an example for tetra-substituted β-dehydroamino acid precursor (β^3- and β^2-substitution) we tested methyl2-acetamidocyclopent-1-enecarboxylate (**14**)[26] under optimized conditions for *Z*-isomers (Scheme 4). In the majority of cases excellent diastereoselectivities up to >99% de were achieved, accompanied by good to moderate conversions. Best enantioselectivities up to 76% ee were obtained by utilizing ligands **6a** and **6b** (Scheme 4).

An additional possibility offered by monodentate ligands from which one can profit in asymmetric catalysis is the possibility to introduce in the coordination sphere of the

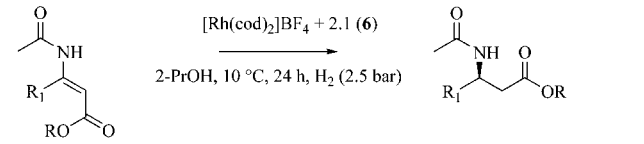
(26) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570−9571.

Table 3. **Influence of β^3-substitution on conversion and enantioselectivity**



***Z*-10** R = Me; R_1 = Et; R_2 = Me
***Z*-11** R = Me; R_1 = *i*-Pr; R_2 = Me
***Z*-12** R = Et; R_1 = Ph; R_2 = Me
***Z*-13** R = Me; R_1 = Me; R_2 = Ph

(*S*)-10a R = Me; R_1 = Et; R_2 = Me
(*S*)-11a R = Me; R_1 = *i*-Pr; R_2 = Me
(*S*)-12a R = Et; R_1 = Ph; R_2 = Me
(+/-)-13a R = Me; R_1 = Me; R_2 = Ph



***E*-10** R = Me; R_1 = Et
***E*-11** R = Me; R_1 = *i*-Pr

(*R*)-10a R = Me; R_1 = Et
(*R*)-11a R = Me; R_1 = *i*-Pr

entry	ligand	isomer[a]	conv. [%][b]	ee [%][b]	isomer[c]	conv. [%][b]	ee [%][b]
1	**6a**	*E*-**10**	>99	78 (*R*)	*Z*-**10**	98	86 (*S*)
2	**6b**	*E*-**10**	91	44 (*R*)	*Z*-**10**	96	58 (*S*)
3	**6c**	*E*-**10**	95	60 (*R*)	*Z*-**10**	>99	20 (*S*)
4	**6d**	*E*-**10**	>99	78 (*R*)	*Z*-**10**	97	50 (*S*)
5	**6g**	*E*-**10**	>99	75 (*R*)	*Z*-**10**	93	48 (*S*)
6	**6h**	*E*-**10**	>99	72 (*R*)	*Z*-**10**	97	rac
7	**6i**	*E*-**10**	>99	**84 (*R*)**	*Z*-**10**	47	24 (*R*)
8	**6a**	*E*-**11**	>99	26 (*R*)	*Z*-**11**	>99	78 (*S*)
9	**6b**	*E*-**11**	39	42 (*R*)	*Z*-**11**	99	68 (*S*)
10	**6c**	*E*-**11**	88	70 (*R*)	*Z*-**11**	99	28 (*S*)
11	**6d**	*E*-**11**	50	60 (*R*)	*Z*-**11**	94	26 (*S*)
12	**6g**	*E*-**11**	>99	88 (*R*)	*Z*-**11**	94	68 (*S*)
13	**6h**	*E*-**11**	98	34 (*R*)	*Z*-**11**	67	rac
14	**6i**	*E*-**11**	>99	**90 (*R*)**	*Z*-**11**	10	58 (*R*)
15	**6a**	*Z*-**12**	99	**70 (*R*)**	*Z*-**13**	19	70 (−)
16	**6b**	*Z*-**12**	46	26 (*R*)	*Z*-**13**	9	4 (−)
17	**6c**	*Z*-**12**	90	47 (*R*)	*Z*-**13**	7	46 (+)
18	**6d**	*Z*-**12**	95	52 (*R*)	*Z*-**13**	<1	n.d.
19	**6g**	*Z*-**12**	91	38 (*R*)	*Z*-**13**	11	48 (−)
20	**6h**	*Z*-**12**	25	54 (*R*)	*Z*-**13**	<1	n.d.
21	**6i**	*Z*-**12**	33	36 (*R*)	*Z*-**13**	10	40 (−)

[a] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [b] Conversion was determined by GC or ^{1}H NMR. The enantiomeric excess was determined by GC or HPLC (**10** (25 m Lipodex E, 120/30, (*R*)-**10a** 31.8 min, (*S*)-**10a** 32.2 min), **11** (25 m Lipodex E, 130/20, (*R*)-**11a** 33.2 min, (*S*)-**11a** 33.4 min), **12** (OD−H, *n*-hexane/ethanol 98:2, 1.3 mL/min, (*S*)-**12a** 27.8 min, (*R*)-**12a** 36.8 min), **13** (Chiralcel OB−H, *n*-hexane/2-propanol 90:10, 1.0 mL/min, (+)-**13a** 15.9 min, (−)-**13a** 18.8 min)). The absolute configuration was determined by comparing with reported data or by reported sign of specific rotation.[3d,l] [c] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL).

metal two different ligands and to play the game of matching−mismatching combinations of chiral elements. This opens the way to a combinatorial approach as developed by Reetz et al.[7d−f,27] and Feringa et al.[28] for different transition metal-catalyzed reactions.[29]

To foster this possibility, we have selected **6a** and **6i** as the pivotal ligands for the hydrogenation of *Z*-**7** and *E*-**7**, respectively, in combination with achiral phosphines and phosphites. The catalysts were prepared in situ using a ratio

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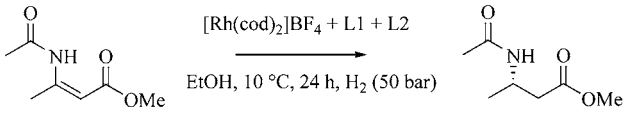
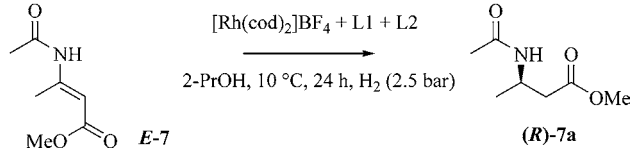
Table 4. **Application of ligand mixtures in the asymmetric hydrogenation of *Z*-7 and *E*-7**



***Z*-7** **(*S*)-7a**



***E*-7** **(*R*)-7a**

entry	L1	L2	isomer	conv. [%][c]	ee [%][c]
1	**6a**	**6a**	*Z*[a]	>99	92 (*S*)
2	**6a**	PPh_3	*Z*[a]	>99	76 (*S*)
3	**6a**	PCy_3	*Z*[a]	>99	78 (*S*)
4	**6i**	**6i**	*E*[b]	>99	87 (*R*)
5	**6i**	PPh_3	*E*[b]	>99	34 (*R*)
6	**6i**	PCy_3	*E*[b]	>99	88 (*R*)
7	**6i**	**15**[d]	*E*[b]	21	12 (*R*)

[a] All reactions were carried out at 10 °C under 50.0 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in ethanol (2.0 mL). [b] All reactions were carried out at 10 °C under 2.5 bar pressure of hydrogen for 24 h with 0.0024 mmol $[Rh(cod)_2]BF_4$, 0.005 mmol ligand and 0.24 mmol substrate in 2-propanol (2.0 mL). [c] Conversions and ee's were determined by GC (50 m Chiraldex β-PM, 130 °C, (*S*)-**7a** 15.1 min, (*R*)-**7a** 16.4 min). The absolute configuration was determined by comparing with reported data.[3l] [d] **15** = tris(2,4-di-*tert*-butylphenyl)phosphite.

of 1.05 to 1.05 equiv of the two ligands with respect to 1.0 equiv of $[Rh(cod)_2]BF_4$, and the reactions were carried out under the optimized conditions defined above. As a general trend, the heterocombination of monodentate ligands was always less stereoselective compared to the homocombination of the pivotal ligands (Table 4). There was just one notable exception for the system **6i**/tricyclohexylphosphine (Table 4, entry 6) which gave the same ee as obtained when **6i** was used alone. Even if these results do not permit to draw any substantial conclusion, we may infer that in these conditions the catalytic activity of the different complexes which are formed in solution lies in the same range and that they compete for the substrate.

Summary

In conclusion, we have shown that monodentate chiral 4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine ligands can be synthesized on multi-10-g scale from 2,2′-binaphthol. They can be tuned easily by variation of the substituent at the P-atom. This class of ligands can be used for various rhodium- and ruthenium-catalyzed hydrogenations. For the first time their application towards the synthesis of β-amino acid derivatives is shown, and enantioselectivities up to 94% ee were achieved.

Experimental Section

All manipulations were performed under argon atmosphere using standard Schlenk techniques. Toluene, *n*-hexane, and diethyl ether were distilled from sodium benzophenone ketyl under argon. Methanol was distilled from magnesium under argon. Ethanol and 2-propanol were

distilled from sodium under argon. Methylene chloride was distilled from CaH_2 under argon. Ligands **6** were synthesized according to our previously published protocols.[13] $[Rh(cod)_2]$-BF_4 (purchased from Fluka) was used without further purification. The synthesis of (*S*)-2,2′-dimethyl-1,1′-binaphthyl in a 200-g scale has been described in the literature.[12b]

Synthesis of 4-Phenyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (6a) and 4-*tert*-Butyl-4,5-dihydro-3*H*-dinaphtho[2,1-*c*;1′,2′-*e*]phosphepine (6i) on 10-g Scale. *Synthesis of the Dilithio Species.* A solution of *n*-BuLi (0.19 mol, 120 mL, 1.6 M in *n*-hexane) was concentrated under vacuum and the residual oil dissolved in diethyl ether (60 mL). After cooling the mixture to 0 °C a solution of (*S*)-2,2′-dimethyl-1,1′-binaphthyl (74.5 mmol, 21 g) in diethyl ether (140 mL) was added over a dropping funnel during 20 min to give a red solution. Afterwards TMEDA (192 mmol, 28.6 mL, distilled over CaH_2) was added slowly, and the resulting solution was kept for 24 h at room temperature, yielding deep red crystals. The supernatant solution was decanted via a tube. The crystals were washed two times with dry *n*-hexane (30 mL, removed by a tube) and dried under vacuum to give 60−80% yield (24.6−37.8 g).

*Synthesis of the 4-Phenyl-4,5-dihydro-3H-dinaphtho[2,1-c;1′,2′-e]phosphepine (**6a**).* Starting with the dilithium salt of (*S*)-2,2′-dimethyl-1,1′-binaphthyl (24.5 g, 44.4 mmol) in *n*-hexane (130 mL) a solution of phenyl dichlorophosphine (6.8 mL, 50.3 mmol) in *n*-hexane (55 mL) was added at 0 °C. After 2 h refluxing, the reaction mixture was quenched with water/toluene. The organic layer was separated and dried over $MgSO_4$. The ligand **6a** was purified by column chromatography in dry toluene and gave light-yellow foam (12.9 g; 75%).

*Synthesis of the 4-tert-Butyl-4,5-dihydro-3H-dinaphtho-[2,1-c;1′,2′-e]phosphepine (**6i**).* Starting with the dilithium salt of (*S*)-2,2′-dimethyl-1,1′-binaphthyl (24.5 g, 44.4 mmol) in *n*-hexane (130 mL) a solution of *tert*-butyl dichlorophosphine (8 g, 50.3 mmol) in *n*-hexane (55 mL) was added at 0 °C. After 3 h refluxing, the reaction mixture was quenched with water/toluene. The organic layer was separated and dried over $MgSO_4$. The ligand **6i** was purified by crystallization from toluene (13.2 g; 81%).

General Synthesis of β-Dehydroamino Acid Derivatives 7−11 and 14.[3c] To a solution of NH_4OAc (0.36 mol) in methanol, ethanol, or 2-propanol (depending on the ester-functionality (100 mL)) was added the corresponding β-ketoester (0.07 mol). After stirring for 60 h at room temperature the solvent was removed, and a mixture of $CHCl_3$ and water was added. The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, yielding the corresponding 3-amino-2-alkenoate. The 3-amino-2-alkenoate (0.07 mol), pyridine (0.13 mol), and acetic anhydride (0.32 mol) were dissolved in THF (50 mL) and stirred for 12 h at 70 °C (procedure A) or 95 °C (procedure B). The solution was reduced to half of the volume and ethylacetate was added. After washing with water, HCl, $NaHCO_3$, brine and drying over Na_2SO_4, the solvent was removed.

Procedure A (E-Isomer Enriched Residue). Dissolving the residue in ethylacetate/*n*-hexane (1:1) and storing the solution overnight at −20 °C yielded the *E*-isomers of β-dehydroamino acid derivatives **7**−**11**, which were recrystallized three times from ethylacetate/*n*-hexane (1:1) to give colorless crystals [yield of the main fraction referred to β-ketoester: *E*-**7**: 1.4 g (11%), *E*-**8**: 1.2 g (10%), *E*-**9**: 1.5 g (11%), *E*-**10**: 1.4 g (12%), *E*-**11**: 1.8 g (14%)].

Procedure B (Z-isomer Enriched Residue). The pure *Z*-isomer was obtained by column chromatography (eluent: ethylacetate/*n*-hexane, 1:1 or 1:2) [yield referred to β-ketoester: *Z*-**7**: 4.3 g (39%), *Z*-**8**: 1.2 g (35%) (0.035 mmol β-ketoester), *Z*-**9**: 6.0 g (46%), *Z*-**10**: 1.6 g (26%) (0.035 mmol β-ketoester), *Z*-**11**: 4.0 g (31%)]. In the case of methyl 2-acetamidocyclopent-1-enecarboxylate (**14**) purification was carried out by crystallization (3×) from ethylacetate/*n*-hexane (1:1), yielding brown crystals [yield of the main fraction: 4.1 g (32%)].

Synthesis of Ethyl 3-Acetamido-3-phenyl-2-propenoate (*Z*-12).[3l] To a solution of NH_4OAc (0.65 mol) in ethanol (100 mL) was added the corresponding β-ketoester (0.13 mol). After stirring for 60 h at room temperature the solvent was removed, and a mixture of $CHCl_3$ and water was added. The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, yielding the corresponding 3-amino-2-alkenoate. To a stirred solution of the corresponding 3-amino-2-alkenoate (0.026 mmol) and pyridine (0.046 mol) in toluene (50 mL) was added dropwise a solution of acetyl chloride (0.027 mol) in toluene (10 mL) at 0 °C. The mixture was stirred for 48 h at 25 °C. A further amount of acetylchloride (0.027 mol) in toluene (10 mL) was added at 0 °C, and the resulting mixture was stirred for 48 h. After quenching with aqueous $NH_4H_2PO_4$ solution the mixture was extracted with ethylacetate (3 × 50 mL). The organic layer was washed with water (2 × 50 mL) and dried over Na_2SO_4. The solvents were removed in vacuo, and the obtained yellow oil was purified by column chromatography (eluent: ethylacetate/*n*-hexane, 1:1), yielding yellow crystals [yield: *Z*-**12**: 0.59 g (10%)].

Synthesis of Methyl 3-Benzamido-2-butenoate (*Z*-13).[3l] To a solution of NH_4OAc (0.65 mol) in ethanol (100 mL) was added the corresponding β-ketoester (0.13 mol). After stirring for 60 h at room temperature the solvent was removed, and a mixture of $CHCl_3$ and water was added. The organic layer was washed with water (3 × 50 mL) and brine (50 mL) and was dried over Na_2SO_4. The solvent was evaporated under reduced pressure, yielding the corresponding 3-amino-2-alkenoate. To a stirred solution of the corresponding 3-amino-2-alkenoate (0.026 mmol) and pyridine (0.046 mol) in diethylether (70 mL) was added dropwise a solution of benzoyl chloride (0.027 mol) in toluene (10 mL) at −30 °C. The mixture was stirred for 12 h at −30 °C and for 24 h at room temperature. After quenching with aqueous water the mixture was extracted with ethylacetate (3 × 50 mL). The organic layer was washed with HCl (1 mol/L) and brine and dried over Na_2SO_4. The solvents were removed in vacuo, and the obtained yellow oil was purified by column chromatography (eluent: ethylacetate/*n*-hexane, 1:1), yielding crystals [yield: *Z*-**13**: 2.9 g (9%)].

General Procedure for the Catalytic Hydrogenation of β-Dehydroamino Acid Derivatives. A solution of the β-dehydroamino acid derivative (0.24 mmol) and 1.0 mL of solvent was transferred via syringe into an autoclave charged with argon. The catalyst was generated in situ by stirring $[Rh(cod)_2]BF_4$ (0.0024 mmol) and the corresponding 4,5-dihydro-3*H*-dinaphthophosphepine ligand (0.005 mmol) in 1.0 mL of solvent for a period of 10 min and afterwards transferring via syringe into the autoclave. The autoclave was then charged with hydrogen and stirred at the required temperature. After the predetermined time the hydrogen was released, and the reaction mixture passed through a short plug of silica gel. The conversion was measured by GC or ^{1}H NMR and the enantioselectivity by GC or HPLC.

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