DOI: 10.1002/ejoc.200800241

Iridium-Catalyzed Hydrogenation of β-Dehydroamino Acid Derivatives Using Monodentate Phosphoramidites

Stephan Enthaler,[a] Giulia Erre,[a] Kathrin Junge,[a] Kristin Schröder,[a] Daniele Addis,[a] Dirk Michalik,[a] Marko Hapke,[a] Dmitry Redkin,[a] and Matthias Beller*[a]

Keywords: Asymmetric catalysis / Homogeneous catalysis / Hydrogenation / P ligands / Amino acids / Iridium

The iridium-catalyzed asymmetric hydrogenation of 13 different β-dehydroamino acid derivatives to give optically active β-amino acid esters has been examined. Readily accessible monodentate octahydrobinaphthol-based phosphoramidites were used as chiral ligands. Good to excellent enantioselectivities and yields were obtained for the *E* isomers, whereas poorer catalyst performance was found for the *Z* isomers. Importantly, to obtain high enantioselectivity, substitution at the 3,3′-positions of the ligands was necessary. Enantioselectivities of up to 94% *ee* were achieved under optimized conditions.

Introduction

The discovery of novel peptide-based therapeutics is a major target of research in medicinal chemistry. More recently, significant attention has been devoted to non-natural β-amino acids, which are useful building blocks in the synthesis of biologically active compounds such as β-lactam antibiotics, taxol derivatives and β-peptides.[1] Over the years an increasing number of methods for the synthesis of β-amino acids has been established.[1c,2] In this respect, transition-metal-catalyzed asymmetric hydrogenation offers an efficient and versatile strategy and represents a key technology for the advancement of "green chemistry", specifically for waste prevention, achieving high atom efficiency and advantageous economics.[3] By using rhodium or ruthenium catalysts with chiral diphosphanes such as MeDuPhos, BINAP, BINAPO, BICP, TunaPhos, FerroTane, JosiPhos, DIOP, BPPM, P-Phos and others in the asymmetric hydrogenation of β-dehydroamino acid derivatives, good to excellent enantioselectivities have been accomplished.[4] Owing to the easier preparation and modification strategies that have been developed more recently, efforts have been dedicated to the application of systems based on monodentate phosphorus ligands[5] such as phosphoramidites, phosphites, phosphonites and phosphanes.[6] In the case of monodentate ligands, so far rhodium has been the transition metal of choice. As a result of our ongoing research in hydrogenation chemistry,[6j,7] we report herein for the first time on highly selective asymmetric hydrogenation reactions of β-dehydroamino acid derivatives with monodentate ligands in the presence of iridium as the central metal.

Previously, de Vries and co-workers described the iridium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives in the presence of monodentate phosphoramidites with enantioselectivities of up to 98% *ee*.[8] Following this work, we recently reported the improved synthesis and application of monodentate octahydrobinaphthol-based phosphoramidites **5** (Scheme 1).[9]

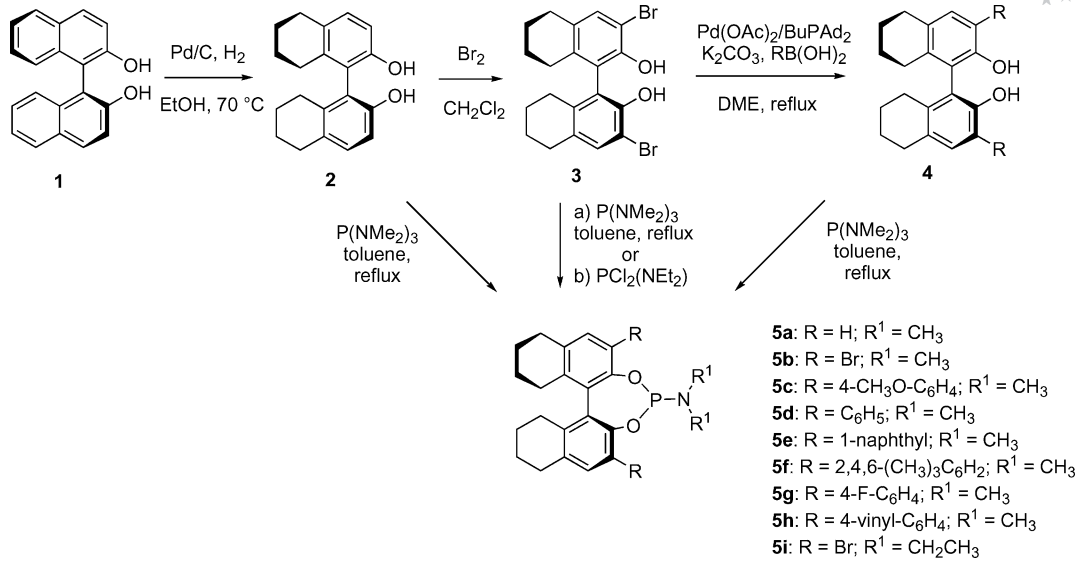
Results and Discussion

The synthesis of our phosphoramidite ligands **5** starts with the selective hydrogenation of enantiomerically pure 1,1′-bi-2-naphthol (**1**)[10] in the presence of catalytic amounts of Pd/C (Scheme 1).[11] The corresponding 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol (**2**) was obtained in excellent yield and subsequently selectively brominated at the 3,3′-positions with Br_2.[11a,11g,12] Compound **3** was subjected to palladium-catalyzed coupling reactions with several arylboronic acids.[13] The resulting diols **4** were treated with $P(NMe_2)_3$ in refluxing toluene to obtain ligands **5** in moderate to good yields.[14] Ligand **5i** was synthesized by treating diol **3** with $PCl_2(NEt_2)$ in the presence of triethylamine.

Initial studies on the effect of reaction conditions were carried out separately with ethyl (*E*)- and (*Z*)-3-acetamido-3-phenyl-2-propenoate (***E*-6** and ***Z*-6**) as model substrates. Typically, we used an in situ precatalytic mixture of 1 mol-% of $[Ir(cod)Cl]_2$ and 2 mol-% of the corresponding ligand. All hydrogenation reactions were carried out in an eightfold parallel reactor array with a 3.0 mL reactor volume.[15]

At first we focused our attention on the effect of different solvents such as dichloromethane, methanol, THF, toluene

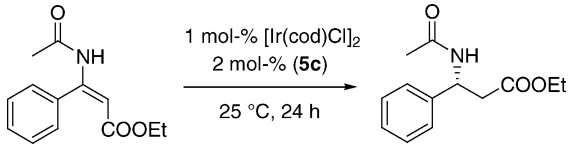
[a] Leibniz-Institut für Katalyse an der Universität Rostock e.V., Albert-Einstein-Str. 29a, 18059 Rostock, Germany
Fax: +49-381-12815000
E-mail: matthias.beller@catalysis.de



Scheme 1. Synthesis of octahydrobinaphthol-based phosphoramidites **5**.

and ethyl acetate combined with a variation of the initial hydrogen pressure (2.5, 10.0 and 25 bar). Selected results are presented in Tables 1 and 2. In the case of the hydrogenation of ***E*-6** the best enantioselectivity of 88% *ee* was achieved at a low hydrogen pressure (2.5 bar) in toluene, whereas other solvents led to a somewhat lower selectivity. By increasing the hydrogen pressure up to 50 bar slight decreases in the enantioselectivity (78% *ee*) and yield were observed. Next, the in situ system was compared with the analogous isolated complex. Here, no significant differences were observed (Table 1, Entries 8 and 9). By using standard

Table 1. Asymmetric hydrogenation of ethyl (*E*)-3-acetamido-3-phenyl-2-propenoate (***E*-6**) with variation of the solvent and pressure.[a]

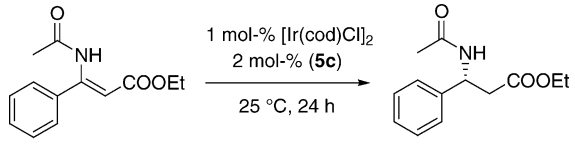


***E*-6** **(*S*)-6a**

Entry	Solvent	Pressure [bar]	Conv. [%]	*ee* [%]
1	MeOH	2.5	96	78 (*S*)
2	MeOH	10	86	78 (*S*)
3	MeOH	25	75	74 (*S*)
4	CH_2Cl_2	2.5	56	80 (*S*)
5	CH_2Cl_2	10	99	78 (*S*)
6	CH_2Cl_2	25	83	78 (*S*)
7[b]	toluene	1.0	>99	86 (*S*)
8	toluene	2.5	>99	88 (*S*)
9[c]	toluene	2.5	>99	86 (*S*)
10	toluene	10	>99	80 (*S*)
11	toluene	25	>99	84 (*S*)
12	THF	2.5	33	78 (*S*)
13	THF	25	39	74 (*S*)
14	ethyl acetate	2.5	>99	86 (*S*)
15	ethyl acetate	10	76	82 (*S*)
16	ethyl acetate	25	83	78 (*S*)

[a] Reactions were carried out at 25 °C for 24 h with 0.0012 mmol of $[Ir(cod)Cl]_2$, 0.0024 mmol of ligand **5c** and 0.12 mmol of substrate in 2.0 mL of solvent. The conversion was determined by GC (50 m Chiraldex β-PM, 110/30-4-180), and the *ee* was determined by HPLC (Chiralpak AD-H, *n*-hexane/ethanol, 95:5, 1.0 mL/min). [b] The reaction was carried out under isobaric conditions. [c] The isolated complex was used as the catalyst.

Table 2. Asymmetric hydrogenation of ethyl (*Z*)-3-acetamido-3-phenyl-2-propenoate (***Z*-6**) with variation of the solvent and pressure.[a]



***Z*-6** **(*S*)-6a**

Entry	Solvent	Pressure [bar]	Conv. [%]	*ee* [%]
1	MeOH	2.5	6	n.d.
2	MeOH	10	<1	n.d.
3	MeOH	25	2	n.d.
4	CH_2Cl_2	2.5	6	rac.
5	CH_2Cl_2	10	4	rac.
6	CH_2Cl_2	25	5	rac.
7	toluene	2.5	13	44 (*S*)
8	toluene	10	11	46 (*S*)
9	toluene	25	13	50 (*S*)
10	THF	2.5	62	40 (*S*)
11	THF	10	57	38 (*S*)
12	THF	25	51	37 (*S*)
13	ethyl acetate	2.5	48	36 (*S*)
14	ethyl acetate	10	48	32 (*S*)
15	ethyl acetate	25	41	18 (*S*)

[a] Reactions were carried out at 25 °C for 24 h with 0.0012 mmol of $[Ir(cod)Cl]_2$, 0.0024 mmol of ligand **5c** and 0.12 mmol of substrate in 2.0 mL of solvent. The conversions were determined by GC (50 m Chiraldex β-PM, 110/30-4-180) and the *ee*s by HPLC (Chiralpak AD-H, *n*-hexane/ethanol, 95:5, 1.0 mL/min).

chiral bidentate phosphorus ligands such as (–)-DIOP, (*S*)-BINAP, (*S*,*S*)-Ferrotane, (*R*,*S*)-JosiPhos and (*S*,*S*)-Me-DuPhos under these conditions (dichloromethane with 5 bar hydrogen), only a racemic mixture of **6a** was obtained.

After that, the effect of reaction temperature was investigated in more detail (Figure 1). In the presence of the model ligand **5c**, the hydrogenation of the *E* isomer was not appreciably influenced in the range of 10–110 °C (78–88% *ee*). However, at 110 °C a significant amount (ca. 10%) of the corresponding *Z* isomer was detected, probably caused by thermal *E*/*Z* isomerization. The best catalyst performance was found at 25 °C with an enantioselectivity of 88% *ee*.

On the other hand, the hydrogenation of ***Z*-6** with an iridium catalyst derived from $[Ir(cod)Cl]_2$ and ligand **5c** produced compound **6a** in poor yield and poor enantioselectivity in all solvents (Table 2). Only in toluene was the prevailing enantiomer isolated with selectivities of up to 50% *ee*, accompanied by moderate conversion (Table 2, Entries 7–9). Based on these results, toluene as the solvent and 2.5 bar hydrogen pressure were selected for the hydrogenation of the *E* isomer (conversion: >99%; enantioselectivity: 88%) for further investigations.

To improve the reaction rate and the enantioselectivity, we decided to exchange the halide ligand with weaker coordinating ligands, for example, BF_4^- and ClO_4^- (Table 3, Entries 3–7). However, addition of the corresponding silver salts led to diminished yields and selectivities, whereas the corresponding sodium salts showed only a slight effect compared with the chloride system. Notably a lower yield was observed in the presence of sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF). Since the addition of iodine proved to be beneficial in the iridium-catalyzed asymmetric hydrogenation of imines, we decided to study the effect of this additive as well.[16] However, the catalyst was completely inactive in the presence of iodine in this system (Table 3, Entry 2).

No pronounced effect was observed in the presence of sodium dodecylsulfonate (SDS)[7c] (Table 3, Entry 11). To stabilize the catalyst or mimic the Crabtree complex,[17] which is an excellent hydrogenation catalyst, pyridine was added to the precatalyst, but no product at all was obtained (Table 3, Entry 12). In addition, the effect of a second equivalent of phosphorus ligand was studied (Table 3, Entries 14 and 15); no improvement in selectivity or activity was observed in the presence of PPh_3 or MonoPhos. Finally, it was possible to reduce the catalyst loading to 0.1 mol-% iridium maintaining the high level of enantioselectivity.

Next we investigated the effect of different ligands on the selectivity of the model reaction. As shown in Table 4, substitution in the 3,3′-positions of the binaphthyl core is a prerequisite for obtaining reasonable enantioselectivity, as ligand **5a** gave a much lower selectivity (Table 4, Entry 1). The best enantioselectivity (88% *ee*) was achieved with

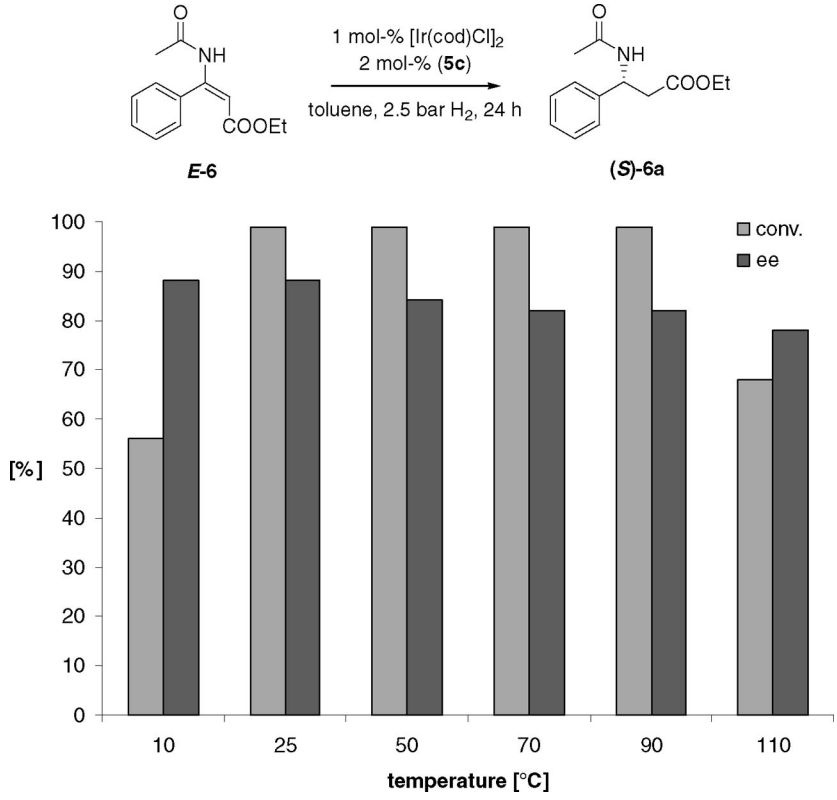
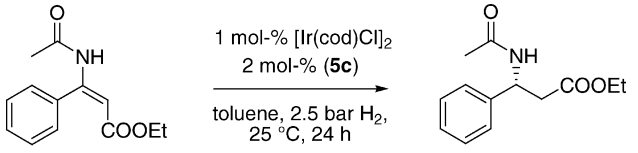


Figure 1. Temperature dependency of the hydrogenation reactions {reactions were carried out for 24 h with 0.0012 mmol of $[Ir(cod)Cl]_2$, 0.0024 mmol of ligand **5c** and 0.12 mmol of substrate in 2.0 mL of toluene under 2.5 bar of hydrogen; the conversions were determined by GC (50 m Chiraldex β-PM, 110/30-4-180) and the *ee*s by HPLC (Chiralpak AD-H, *n*-hexane/ethanol, 95:5, 1.0 mL/min); experiments carried out at 90 and 110 °C were run for 1 h}.

Table 3. Effect of additives and catalyst loading on the asymmetric hydrogenation of ***E*-6**.[a]

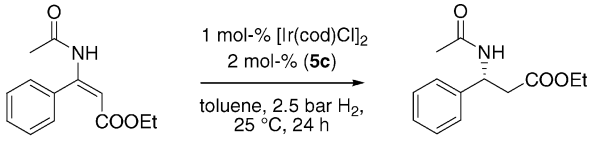


***E*-6** **(*S*)-6a**

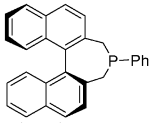
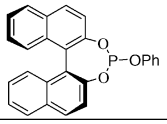
Entry	Additive	Cat. [mol-%]	Time [h]	Conv. [%]	*ee* [%]
1	–	2.0	6	95	88 (*S*)
2	I_2 [10 mol-%]	2.0	16	<1	n.d.
3	$AgBF_4$ [2 mol-%]	2.0	16	10	50 (*S*)
4	$AgClO_4$ [2 mol-%]	2.0	16	17	68 (*S*)
5	$NaBF_4$ [2 mol-%]	2.0	24	84	87 (*S*)
6	$NaClO_4$ [2 mol-%]	2.0	24	99	88 (*S*)
7	NaBARF [2 mol-%]	2.0	24	6	64 (*S*)
8	NH_4SO_4 [10 mol-%]	2.0	24	89	88 (*S*)
9	nBu_4Br [10 mol-%]	2.0	24	63	69 (*S*)
10	Me_3SI [10 mol-%]	2.0	24	48	82 (*S*)
11	SDS [10 mol-%]	2.0	16	97	88 (*S*)
12	pyridine [5 mol-%]	2.0	16	<1	n.d.
13	CF_3CH_2OH [10 mol-%]	2.0	16	>99	86 (*S*)
14	PPh_3 [2 mol-%]	2.0	24	70	28 (*S*)
15	(*S*)-MonoPhos [2 mol-%]	2.0	24	25	80 (*S*)
16	–	1.0	24	99	88 (*S*)
17	–	0.2	24	52	86 (*S*)
18	–	0.1	24	27	84 (*S*)
19	–	0.01	24	<1	n.d.

[a] Reactions were carried out with 0.0012 mmol of $[Ir(cod)Cl]_2$, 0.0024 mmol of ligand **5** and 0.12 mmol of substrate in 2.0 mL of toluene. The conversions were determined by GC (50 m Chiraldex β-PM, 110/30-4-180) and the *ee*s by HPLC (Chiralpak AD-H, *n*-hexane/ethanol, 95:5, 1.0 mL/min).

Table 4. Ligand screening in the asymmetric hydrogenation of **6**.[a]



***E*-6** **(*S*)-6a**

Entry	Ligand	Conv. [%]	*ee* [%]	^{31}P [ppm][b]	$J_{P\text{-}Se}$ [Hz][b]
1	**5a**	53	60 (*S*)	85.3	958.4
2	**5b**	55	84 (*S*)	81.3	990.0
3	**5c**	>99	88 (*S*)	79.9	965.4
4	**5d**	71	84 (*S*)	80.1	968.9
5	**5e**	>99	86 (*S*)	80.4	969.7
6	**5f**	99	74 (*S*)	84.6	952.9
7	**5g**	99	88 (*S*)	80.1	971.0
8	**5h**	>99	88 (*S*)	80.0	968.9
9	**5i**	99	84 (*S*)	80.4	981.0
10	(*S*)-MonoPhos[18]	14	44 (*S*)	88.1	971.0
11		35	rac.	51.0	728.3
12		5	rac.	73.3	1048.4

[a] Reactions were carried out at 25 °C for 24 h with 0.0012 mmol of $[Ir(cod)Cl]_2$, 0.0024 mmol of ligand and 0.12 mmol of substrate in 2.0 mL of toluene. The conversions were determined by GC (50 m Chiraldex β-PM, 110/30-4-180) and the *ee*s by HPLC (Chiralpak AD-H, *n*-hexane/ethanol, 95:5, 1.0 mL/min). [b] Values pertain to the selenide of the corresponding ligand.

para-substituted aryl groups in the 3,3′-positions, whereas phenyl and sterically demanding mesityl substituents gave 84 and 74% *ee*, respectively.

In order to obtain information on the electronic and steric properties of the presented ligands and to draw conclusions about possible structure–activity relationships, the corresponding selenides **12** were synthesized by reaction of the phosphoramidites with an excess of selenium powder in a sealed NMR tube. In most cases, the selenides were readily formed at room temperature, and rarely heating at 70°C for 2 h was necessary to obtain a sufficient amount of desired product. The samples were analyzed by ^{31}P NMR, and the chemical shifts and coupling constants are presented in Table 4. The ^{77}Se–^{31}P coupling constants represent a useful probe for the σ-donor properties and consequently for the metal–ligand interaction. The magnitude of the ^{77}Se–^{31}P coupling constants reveal the σ character of the phosphorus lone-pair orbital. High magnitudes are adjunct to high σ character, hence the basicity of the phosphorus atom is low.[19] In general, the values of the ^{77}Se–^{31}P coupling constants (952–990 Hz) are in agreement with the work of Murai et al., who reported values in the range of 960–980 Hz for MonoPhos-based phosphoramidites.[20] A comparison of the ^{77}Se–^{31}P coupling constants of MonoPhos and octahydro-MonoPhos showed a more basic phosphorus atom for the saturated MonoPhos. The introduction of bromo substituents at the 3,3′-positions significantly decreased the basicity, whereas aryl substituents led to lower coupling constants. Except for mesityl substituents, which strongly increase the basicity, no differences were detected for the various aryl substituents.

In Figure 2 the ^{77}Se–^{31}P coupling constants are correlated to the enantioselectivity observed for the asymmetric hydrogenation of ***E*-6** (Table 4). There is no clear trend observed: 3,3′-disubstituted ligands with a ^{77}Se–^{31}P coupling constant in the range of 965–971 Hz gave high enantiomeric excesses, whereas the electronically similar MonoPhos ligand (J = 971 Hz) gave a significantly lower enantioselectivity. Steric factors apparently determine the enantioselectivity in the iridium-catalyzed hydrogenation of β-amino acid derivatives.

To explore the scope and limitation of the presented ligands, the asymmetric hydrogenation of a selection of β-dehydroamino acid derivatives was performed (Table 5). The β-acetamido acrylates were synthesized according to literature protocols.[4] In the case of the alkyl β-acetamidoacrylates **13**–**17**, the *E*/*Z* isomers were separated by crystallization or column chromatography, whereas the syntheses of the aryl β-acetamidoacrylates and substrate **18** produced mainly the *Z* isomers. The corresponding *E* isomers were accessible according to the procedure of Knowles and co-workers by irradiation with light.[4b] A THF solution of the crude mixture obtained by the acylation protocol was stirred at room temperature and irradiated for

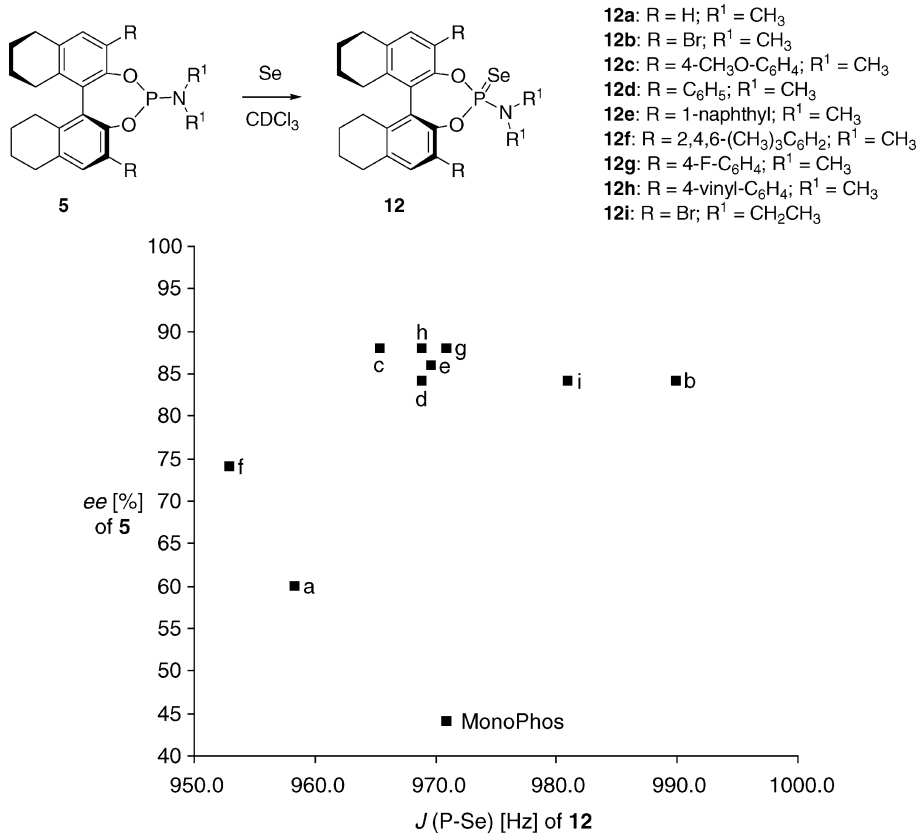


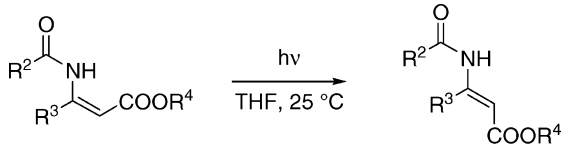
Figure 2. ^{77}Se–^{31}P coupling constants of **12** versus the enantiomeric excesses obtained with ligands **5**.

30–46 h and subsequently purified by crystallization or column chromatography (Table 5). The *E* isomers were obtained in good yields (60–83%). In the case of substrate **18**, separation of the isomers was unsuccessful either by crystallization or by column chromatography.

Asymmetric hydrogenation of those alkyl *E* substrates showed the following trends: Changing the ester group from a methyl to an isopropyl group resulted in a decrease in enantioselectivity, accompanied by a slight decrease in the yield (Table 6, Entries 1–3). The same tendency was observed for the asymmetric hydrogenation of ***E*-23**. The effect of R^3 substitution was investigated on a set of eight different substrates. Improved selectivity was observed when the bulkiness of the alkyl derivatives increased from methyl to isopropyl (Table 6, Entries 3 and 5). In the case of the aryl substituents, a slight negative effect on enantioselectivity was observed when an electron-withdrawing group (Table 6, Entry 8) was positioned at the 4-position, whereas an electron-donating group improved the enantioselectivity (Table 6, Entry 6). As good enantioselectivity was detected for the 4-methoxy-substituted substrate, we synthesized ***E*-20** bearing a 2-methoxy substituent, which allows for an additional coordination site to the metal atom. Here, 94% *ee* was obtained (Table 6, Entry 7).

Despite the fact that our initial attempts were unsuccessful (Table 2), we examined the potential of our catalysts in the asymmetric reduction of the corresponding *Z* derivatives (Table 7). By using a higher pressure (25 bar) and THF

Table 5. Synthesis of *E* substrates by the light-induced isomerization of *Z* substrates.

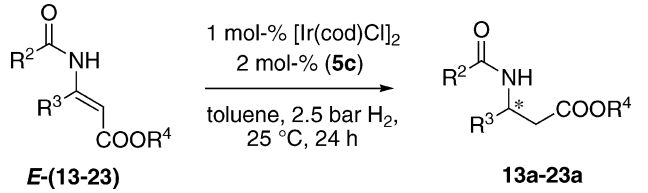


***Z*-(13-24)** ***E*-(13-24)**

Entry	Substrate	R^2	R^3	R^4	*t* [h]	Yield of *E* [%]	λ_{max} [nm][c]
1[a,b]	**13**	CH_3	CH_3	CH_3	–	11	312.0
2[a,b]	**14**	CH_3	CH_3	Et	–	10	312.5
3[a,b]	**15**	CH_3	CH_3	*n*Pr	–	11	323.5
4[a,b]	**16**	CH_3	Et	CH_3	–	12	311.5
5[a,b]	**17**	CH_3	*i*Pr	CH_3	–	14	327.0
6[d]	**18**	CH_3	*t*Bu	CH_3	30	29	–
7[d]	**6**	CH_3	C_6H_5	Et	30	80	352.9
8[c,d]	**19**	CH_3	4-$MeOC_6H_4$	Et	32	83	360.5
9[c,d]	**20**	CH_3	2-$MeOC_6H_4$	Et	30	67	354.7
10[d]	**21**	CH_3	4-FC_6H_4	Et	46	83	336.5
11[d]	**22**	CH_3	4-$CH_3C_6H_4$	Et	30	83	346.5
12[d]	**23**	CH_3	C_6H_5	CH_3	46	60	337.9

[a] Acceptable amounts of the *E* isomer were formed during the acylation process. [b] Separation of the *E*/*Z* mixture by crystallization (three times). [c] Separation of the *E*/*Z* mixture by column chromatography. [d] A 460 W Phillips HPM 12 lamp, $\lambda \approx 420$ nm, was used as the light source. The yield was determined on the crude mixture by ^1H NMR spectroscopy. [e] λ_{max} of the characteristic shoulder from the *Z* isomer, calculated from the unified UV/Vis spectra of the *Z* isomer minus the *E* isomer. All the measurements were carried out in ethanol at 25 °C. λ_{max} constitutes the energy of isomerization of the *Z* to the *E* isomer.

Table 6. Use of the octahydrobinaphthol-based phosphoramidites **5** in the asymmetric hydrogenation of various *E* substrates.[a]

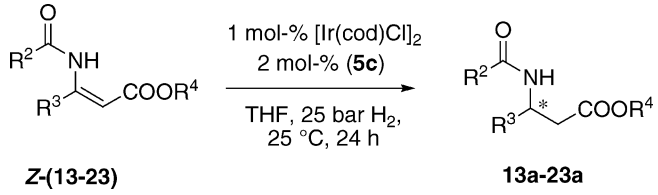


Entry	Ligand	Substrate	R^2	R^3	R^4	Conv. [%]	*ee* [%]
1[b]	**5c**	***E*-13**	CH_3	CH_3	CH_3	94	50 (*R*)
2[b]	**5c**	***E*-14**	CH_3	CH_3	Et	90	32 (*R*)
3[b]	**5c**	***E*-15**	CH_3	CH_3	*i*Pr	82	6 (*R*)
4[b]	**5c**	***E*-16**	CH_3	Et	CH_3	97	62 (*R*)
5[b]	**5c**	***E*-17**	CH_3	*i*Pr	CH_3	>99	80 (*R*)
6[c]	**5c**	***E*-19**	CH_3	4-$MeOC_6H_4$	Et	49	90 (–)
7[c]	**5c**	***E*-20**	CH_3	2-$MeOC_6H_4$	Et	62	94 (–)
8[c]	**5c**	***E*-21**	CH_3	4-FC_6H_4	Et	79	84 (–)
9[c]	**5c**	***E*-22**	CH_3	4-$CH_3C_6H_4$	Et	>99	88 (–)
10[c]	**5c**	***E*-23**	CH_3	C_6H_5	CH_3	>99	90 (*S*)

[a] Reactions were carried out at 25 °C for 24 h with 0.0012 mmol of $[Ir(cod)Cl]_2$, 0.0024 mmol of ligand **5** and 0.12 mmol of substrate in 2.0 mL of toluene under an initial hydrogen pressure of 2.5 bar. [b] Conversion determined by GC. [c] Conversion determined by ^1H NMR spectroscopy.

as the solvent, reasonable amounts of product were obtained with acceptable enantioselectivities. No detectable effect on the enantioselectivity of the ester functionality and R^3 substitution was observed as described for the corresponding *E*-amino acid precursors (Table 7, Entries 1–5). The best selectivity (75% *ee*) was observed with the bulky *tert*-butyl derivative (Table 7, Entry 6). For aryl substrates, in tendency lower enantioselectivities were achieved compared with the alkyl derivatives (Table 7, Entries 7–11).

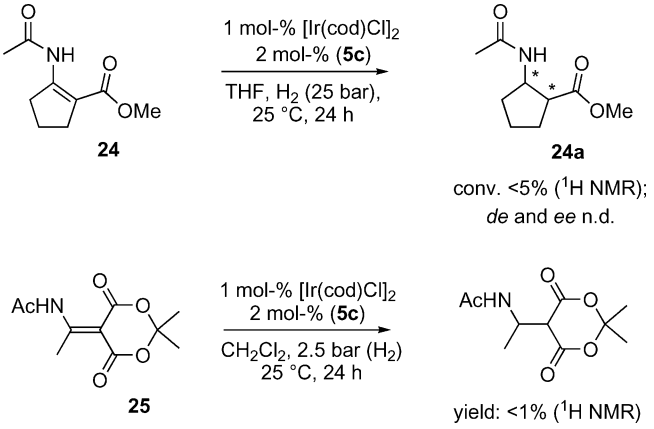
Table 7. Use of the octahydrobinaphthol-based phosphoramidites **5** in the asymmetric hydrogenation of various *Z* substrates.[a]



Entry	Ligand	Substrate	R^2	R^3	R^4	Conv. [%]	*ee* [%]
1[b]	**5c**	***Z*-13**	CH_3	CH_3	CH_3	58	58 (*R*)
2[b]	**5c**	***Z*-14**	CH_3	CH_3	Et	32	50 (*R*)
3[b]	**5c**	***Z*-15**	CH_3	CH_3	*i*Pr	37	62 (*R*)
4[b]	**5c**	***Z*-16**	CH_3	Et	CH_3	44	48 (*R*)
5[b]	**5c**	***Z*-17**	CH_3	*i*Pr	CH_3	53	60 (*R*)
6[b]	**5c**	***Z*-18**	CH_3	*t*Bu	CH_3	>99	75 (+)
7[c]	**5c**	***Z*-19**	CH_3	4-$MeOC_6H_4$	Et	59	46 (–)
8[c]	**5c**	***Z*-20**	CH_3	2-$MeOC_6H_4$	Et	10	–
9[c]	**5c**	***Z*-21**	CH_3	4-FC_6H_4	Et	78	37 (–)
10[c]	**5c**	***Z*-22**	CH_3	4-$CH_3C_6H_4$	Et	53	45 (–)
11[c]	**5c**	***Z*-23**	CH_3	C_6H_5	CH_3	70	67 (*S*)

[a] Reactions were carried out at 25 °C for 24 h with 0.0012 mmol of $[Ir(cod)Cl]_2$, 0.0024 mmol of ligand **5** and 0.12 mmol of substrate in 2.0 mL of THF under an initial hydrogen pressure of 25 bar. [b] Conversion determined by GC. [c] Conversion determined by ^1H NMR spectroscopy.

Finally, we tested two examples of tetrasubstituted β-dehydroamino acid precursors. Unfortunately, for both **24**[21] and **25** only traces of the products were found (Scheme 2).[22,23]



Scheme 2. Asymmetric hydrogenation of tetrasubstituted amino acid precursors.

Conclusion

For the first time the iridium-catalyzed asymmetric hydrogenation of several β-amino acid precursors has been examined in the presence of chiral monodentate octahydrobinaphthol-based phosphoramidites. Separate studies for the *E* and *Z* isomers showed crucial differences between the two hydrogenation reactions. After optimization of the reaction conditions, enantioselectivities of up to 94% *ee* were achieved for the *E* isomers. Importantly, to obtain high enantioselectivity, substitution at the 3,3′-positions of the ligands was found to be necessary.

Experimental Section

General: All manipulations with oxygen- and moisture-sensitive compounds were performed under argon using standard Schlenk techniques. Toluene and THF were distilled from sodium/benzophenone ketyl under argon. Methanol was distilled from Mg under argon. Dichloromethane was distilled from CaH_2 under argon. Ethyl acetate (purchased from Fluka on molecular sieves) was used without further manipulations. Ligands **5** were synthesized according to our previously published protocols.[9] $[Ir(cod)Cl]_2$ (Fluka and Strem Chemicals) was used without further purification. ^1H, ^{13}C and ^{31}P NMR spectra were recorded with Bruker Avance 500, 400 and 300 spectrometers (^1H: 500.13, 400.13 and 300.13 MHz; ^{13}C: 125.8, 100.6 and 75.5 MHz; ^{31}P: 121.5 MHz). Melting points were determined with a melting point apparatus Stuart SMP3. IR spectra were recorded with a Nicolet Magna 550 spectrometer. Mass spectra were recorded with an AMD 402 spectrometer.

General Synthesis of Alkyl β-Dehydroamino Acid Derivatives 13–17: The corresponding β-oxo ester (0.07 mol) was added to a solution of NH_4OAc (0.36 mol) in methanol, ethanol or 2-propanol, depending on the ester functionality (100 mL). After stirring at room temperature for 60 h, 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 with Na_2SO_4. The solvent was evaporated under reduced pressure to yield 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 the mixture was stirred at 70 (procedure A) or 95 °C (procedure B) for 12 h. The solution was reduced to half of the volume, and ethyl acetate was added. After washing with water, HCl, $NaHCO_3$ and brine and drying with Na_2SO_4, the solvent was removed.

Procedure A (*E* Isomer Enriched Residue): Dissolving the residue in ethyl acetate/*n*-hexane (1:1) and storing the solution overnight at –20 °C yielded the *E* isomers of β-dehydroamino acid derivatives **13**–**17**, which were recrystallized three times from ethyl acetate/*n*-hexane (1:1) to give colorless crystals [yield of the main fraction based on the β-oxo ester: ***E*-13**: 1.4 g (11%); ***E*-14**: 1.2 g (10%); ***E*-15**: 1.5 g (11%); ***E*-16**: 1.4 g (12%); ***E*-17**: 1.8 g (14%)].

Procedure B (*Z* Isomer Enriched Residue): The pure *Z* isomer was obtained by column chromatography (eluent: ethyl acetate/*n*-hexane, 1:1 or 1:2) [yield based on the β-oxo ester: ***Z*-13**: 4.3 g (39%); ***Z*-14**: 1.2 g (35%) (0.035 mmol of β-oxo ester); ***Z*-15**: 6.0 g (46%); ***Z*-16**: 1.6 g (26%) (0.035 mmol of β-oxo ester); ***Z*-17**: 4.0 g (31%)].

Methyl (*Z*)-3-Acetamido-4,4-dimethylpent-2-enoate (*Z*-18): Methyl (*Z*)-3-acetamido-4,4-dimethylpent-2-enoate was synthesized according to the general procedure A (see above), but the *Z* isomer was exclusively formed. M.p. 60–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (br., 1 H, NH), 5.46 (s, 1 H, =CH), 3.71 (s, 3 H, OCH_3), 2.16 [s, 3 H, C(=O)CH_3], 1.27 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.9, 167.9, 162.5, 101.1, 51.4, 36.7, 28.5, 25.0 ppm. IR (ATR): $\tilde{\nu}$ = 3244 (w), 3156 (w), 3014 (w), 2964 (w), 2909 (w), 2873 (w), 1724 (s), 1672 (m), 1650 (m), 1519 (m), 1480 (m), 1438 (m), 1393 (w), 1371 (m), 1348 (m), 1278 (m), 1260 (m), 1195 (s), 1174 (s), 1121 (m), 1035 (m), 1006 (m), 960 (w), 928 (w), 890 (w), 850 (m), 799 (w), 732 (m), 696 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 199 (4) [M]$^+$, 184 (2), 168 (6), 152 (8), 140 (100), 126 (18), 115 (14), 110 (30), 100 (18), 84 (12), 68 (30), 57 (10), 43 (62), 29 (6). HRMS: calcd. for $C_{10}H_{17}NO_3$ 199.12029; found 199.120440.

General Synthesis of Aryl β-Dehydroamino Acid Derivatives: The corresponding β-oxo ester (0.07 mol) was added to a solution of NH_4OAc (0.36 mol) in methanol or ethanol (100 mL), depending on the ester group. After stirring at room temperature for 60 h, 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 with Na_2SO_4. The solvent was evaporated under reduced pressure to yield the corresponding 3-amino-2-phenylacrylate. The 3-amino-2-phenylacrylate (0.07 mol), pyridine (0.13 mol) and acetic anhydride (0.32 mol) were dissolved in THF (50 mL), and the mixture was stirred at 90 °C for 12 h. The solution was reduced to half of the volume, and ethyl acetate was added. After washing with water, HCl, $NaHCO_3$ and brine and drying with Na_2SO_4, the solvent was removed. The oily residue was purified by column chromatography (eluent: ethyl acetate/*n*-hexane) to yield the corresponding (*Z*)-3-acetamido-3-phenylacrylate. The *E* isomers were accessible by subjecting a solution of the *Z* isomer in THF to light irradiation (460 W Phillips HPM 12 lamp, $\lambda \approx$ 420 nm) at room temperature for 2–3 d (Table 5).

Ethyl (*E*)-3-Acetamido-3-(4-methoxyphenyl)acrylate (*E*-19): M.p. 144–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.25 (m, 2 H, Ar), 7.01 (br., 1 H, CH), 6.94–6.90 (m, 2 H, Ar), 6.69 (br., 1 H, NH), 4.01 (q, *J* = 7.2 Hz, 2 H, CH_2CH$_3$), 3.83 (s, 3 H), 2.11 (s, 3 H), 1.14 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.8, 167.2, 160.5, 148.5, 129.6, 128.6, 113.8, 104.0, 59.7, 55.3, 25.0, 14.2 ppm. MS (ES, 70 eV): *m*/*z* (%) = 263 (28) [M]$^+$, 218 (5), 202 (3), 190 (100), 176 (23), 160 (3), 149 (45), 134 (30), 121 (4), 104 (3), 91 (4), 77 (6), 63 (3), 51 (2), 43 (15). HRMS: calcd. for $C_{14}H_{17}NO_4$ 263.11521; found 163.115110. Crystallization from ethanol.

Ethyl (*Z*)-3-Acetamido-3-(4-methoxyphenyl)acrylate (*Z*-19): M.p. 94–96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.59 (br., 1 H, NH), 7.32–7.29 (m, 2 H, Ar), 6.90–6.83 (m, 2 H, Ar), 5.25 (s, 1 H, =CH), 4.20 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 3.81 (s, 3 H, OCH_3), 2.16 (s, 3 H, $COCH_3$), 1.30 (t, *J* = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.7, 168.6, 160.8, 154.2, 128.6, 127.9, 113.5, 100.0, 60.1, 55.3, 24.9, 14.3 ppm. IR (ATR): $\tilde{\nu}$ = 3261 (w), 3103 (w), 3040 (w), 3020 (w), 2994 (w), 2950 (w), 2935 (w), 2910 (w), 2833 (w), 1724 (m), 1656 (m), 1607 (s), 1509 (m), 1486 (m), 1461 (m), 1369 (m), 1282 (s), 1241 (m), 1169 (s), 1101 (s), 1027 (s), 1003 (m), 994 (m), 967 (m), 876 (w), 837 (m), 824 (s), 777 (m), 740 (m), 729 (m), 702 (w), 681 (m) cm^{-1}. MS (ES, 70 eV): *m*/*z* (%) = 263 (27) [M]$^+$, 190 (100), 176 (23), 149 (44), 134 (30). HRMS: calcd. for $C_{14}H_{17}NO_4$ 263.11521; found 263.115321. R_f = 0.48 (ethyl acetate/*n*-hexane, 1:2).

Ethyl (*E*)-3-Acetamido-3-(2-methoxyphenyl)acrylate (*E*-20): M.p. 130–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.36 (m, 1 H, Ar), 7.22–7.18 (m, 1 H, Ar), 7.15 (br., 1 H, CH), 7.03–6.93 (m, 2 H, Ar), 6.78 (br., 1 H, NH), 3.98 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 3.82 (s, 3 H, OCH_3), 2.09 (s, 3 H, $COCH_3$), 1.10 (t, *J* = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.8, 167.0, 156.2, 145.7, 130.7, 130.0, 125.3, 120.6, 111.1, 105.2, 59.4, 55.7, 25.0, 14.1 ppm. MS (ES, 70 eV): *m*/*z* (%) = 263 (30) [M]$^+$, 190 (100), 176 (24), 149 (46), 134 (30) ppm. R_f = 0.1 (ethyl acetate/*n*-hexane, 1:2).

Ethyl (*Z*)-3-Acetamido-3-(2-methoxyphenyl)acrylate (*Z*-20): M.p. 59–62 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.95 (br., 1 H, NH), 7.37–7.30 (m, 1 H, Ar), 7.19–7.14 (m, 1 H, Ar), 6.98–6.90 (m, 1 H, Ar), 6.86–6.81 (m, 1 H, Ar), 5.06 (s, 1 H, =CH), 4.20 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 3.70 (s, 3 H, OCH_3), 2.09 (s, 3 H, $COCH_3$), 1.29 (t, *J* = 7.1 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 169.0, 167.4, 156.6, 152.4, 130.4, 128.7, 125.6, 120.3, 110.1, 99.2, 60.1, 55.5, 24.6, 14.2 ppm. IR (ATR): $\tilde{\nu}$ = 3254 (w), 3228 (w), 3072 (w), 3033 (w), 3004 (w), 2986 (w), 2975 (w), 2936 (w), 2837 (w), 1723 (m), 1661 (m), 1619 (s), 1597 (m), 1491 (m), 1458 (m), 1435 (m), 1389 (w), 1368 (m), 1357 (m), 1294 (s), 1273 (s), 1247 (s), 1228 (m), 1172 (s), 1128 (m), 1090 (m), 1046 (m), 1017 (s), 983 (m), 951 (m), 937 (w), 866 (w), 854 (w), 838 (m), 810 (m), 780 (m), 754 (s), 731 (m), 681 (m) cm^{-1}. MS (ES, 70 eV): *m*/*z* (%) = 263 (14) [M]$^+$, 190 (100), 176 (11), 134 (31). HRMS: calcd. for $C_{14}H_{17}NO_4$ 263.11521; found 163.115075. R_f = 0.25 (ethyl acetate/*n*-hexane, 1:2).

Ethyl (*E*)-3-Acetamido-3-(4-fluorophenyl)acrylate (*E*-21): M.p. 91–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 2 H, Ar), 7.12–7.06 (m, 2 H, Ar), 7.04 (br., 1 H, CH), 6.84 (br., 1 H, NH), 3.98 (q, *J* = 7.2 Hz, 2 H, CH_2CH$_3$), 2.10 (s, 3 H, $COCH_3$), 1.12 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.9, 167.1, 163.2 (d, *J* = 249.5 Hz), 147.7, 132.4 (d, *J* = 3.5 Hz), 130.2 (d, *J* = 8.4 Hz), 115.4 (d, *J* = 21.8 Hz), 104.6, 59.8, 25.0, 14.1 ppm. MS (ES, 70 eV): *m*/*z* (%) = 251 (14) [M]$^+$, 206 (5), 178 (100), 164 (37), 137 (56), 122 (26), 109 (8), 95 (6), 43 (20). HRMS: calcd. for $C_{13}H_{14}FNO_3$ 251.09522; found 251.095163. R_f = 0.15 (ethyl acetate/*n*-hexane, 1:2).

Ethyl (*Z*)-3-Acetamido-3-(4-fluorophenyl)acrylate (*Z*-21): M.p. 81–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.66 (br., 1 H, NH), 7.40–7.33 (m, 2 H, Ar), 7.09–7.05 (m, 2 H, Ar), 5.25 (s, 1 H, =CH), 4.23 (q, *J* = 7.1 Hz, 2 H, CH_2CH$_3$), 2.18 (s, 3 H, $COCH_3$), 1.33 (t,

J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.6, 168.5, 163.5 (d, J = 249 Hz), 153.4, 131.9 (d, J = 3.3 Hz), 129.0 (d, J = 8.5 Hz), 115.2 (d, J = 21.9 Hz), 101.0, 60.4, 24.8, 14.2 ppm. IR (ATR): $\tilde{\nu}$ = 3304 (w), 3060 (w), 2983 (w), 2935 (w), 2909 (w), 2871 (w), 1687 (m), 1622 (m), 1606 (s), 1592 (m), 1505 (s), 1470 (w), 1449 (w), 1418 (w), 1365 (m), 1290 (m), 1279 (m), 1225 (m), 1158 (s), 1116 (m), 1103 (m), 1093 (m), 1034 (m), 1016 (m), 985 (m), 959 (m), 881 (w), 854 (m), 831 (s), 819 (m), 790 (m), 748 (w), 721 (w), 672 (m) cm^{-1}. MS (ES, 70 eV): m/z (%) = 251 (16) $[M]^+$, 206 (5), 178 (100), 164 (38), 137 (57), 122 (26), 109 (8), 95 (6), 43 (20). HRMS: calcd. for $C_{13}H_{14}FNO_3$ 251.09522; found 251.095593. R_f = 0.32 (ethyl acetate/*n*-hexane, 1:3).

Ethyl (*E*)-3-Acetamido-3-(4-methylphenyl)acrylate (*E*-22): M.p. 97–100 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (m, 4 H), 7.01 (s, 1 H, C=CH), 6.88 (br., 1 H, NH), 3.95 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 2.37 (s, 3 H), 2.04 (s, 3 H), 1.11 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.9, 167.2, 148.9, 139.4, 133.5, 129.0, 128.0, 103.8, 59.6, 24.9, 21.4, 14.1 ppm. MS (ES, 70 eV): m/z (%) = 247 (15) $[M]^+$, 174 (100), 160 (26), 133 (47), 118 (25).

Ethyl (*Z*)-3-Acetamido-3-(4-methylphenyl)acrylate (*Z*-22): M.p. 40–43 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 10.53 (br., 1 H, NH), 7.23–7.06 (m, 2 H, Ar), 7.11–7.06 (m, 2 H, Ar), 5.20 (s, 1 H, C=CH), 4.14 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 2.29 (s, 3 H), 2.08 (s, 3 H), 1.24 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 168.6, 168.4, 154.5, 139.7, 132.9, 128.7, 127.0, 100.5, 60.2, 24.8, 21.3, 14.3 ppm. IR (ATR): $\tilde{\nu}$ = 3293 (w), 3208 (w), 3136 (w), 3054 (w), 3028 (w), 3005 (w), 2979 (w), 2934 (w), 2872 (w), 1903 (w), 1707 (m), 1686 (s), 1618 (s), 1568 (m), 1511 (m), 1470 (m), 1448 (m), 1412 (w), 1365 (m), 1290 (s), 1273 (s), 1219 (m), 1170 (s), 1115 (m), 1091 (m), 1033 (m), 1018 (m), 984 (m), 960 (w), 881 (w), 846 (m), 830 (m), 809 (s), 785 (w), 718 (m), 675 (m) cm^{-1}. MS (ES, 70 eV): m/z (%) = 247 (16) $[M]^+$, 174 (100), 160 (26), 133 (46), 118 (26). HRMS: calcd. for $C_{14}H_{17}NO_3$ 247.12029; found 247.119734. R_f = 0.48 (ethyl acetate/*n*-hexane, 1:2).

Synthesis of *N*-[1-(2,2-Dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-ethyl]acetamide (25): A mixture of acetonitrile (18 mmol) and methanol (18 mmol) was cooled to 0 °C, and a solution of HCl in diethyl ether (c = 2 mol/L, 30 mmol, 15 mL) was added under argon. Colourless crystals were obtained at –30 °C after 2 d. The crystals of methyl acetimidate hydrochloride were washed with diethyl ether and dried in vacuo. Triethylamine (18.5 mmol) was added to a well-stirred suspension of methyl acetimidate hydrochloride (9.12 mmol) in CH_2Cl_2 (20 mL) at room temperature. The mixture was cooled to –15 °C, and acetyl chloride (9.12 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The solution was stirred at room temperature for 20 h, then charged with an additional amount of triethylamine (10 mmol) and cooled to 0 °C. A solution of Meldrum's acid (9.12 mmol) in CH_2Cl_2 (10 mL) was added, and the mixture was heated at reflux for 20 h. The solution was washed with water and brine, dried with Na_2SO_4, and the crude product was purified by column chromatography (eluent: ethyl acetate/*n*-hexane, 1:1 to 4:1). M.p. 119–120 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 12.79 (br., 1 H, NH), 3.06 (s, 3 H), 2.30 (s, 3 H), 1.71 (s, 6 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 173.1, 169.7, 166.0, 161.4, 103.5, 93.6, 26.8, 26.3, 19.6 ppm. IR (KBr): $\tilde{\nu}$ = 3432 (m), 3008 (m), 2994 (m), 2328 (w), 1750 (s), 1720 (s), 1677 (s), 1590 (s), 1458 (m), 1394 (m), 1385 (m), 1366 (m), 1349 (s), 1278 (s), 1246 (s), 1193 (s), 1146 (m), 1072 (m), 1031 (m), 1009 (m), 945 (w), 927 (m), 897 (m), 862 (m), 799 (m), 728 (m), 650 (m), 614 (w), 600 (w), 572 (w), 496 (m), 449 (m), 433 (m) cm^{-1}. MS (ES, 70 eV): m/z (%) = 227 (2) $[M]^+$, 169 (80), 151 (20), 141 (24), 128 (43), 97 (45), 83 (47), 59 (12), 43 (100). HRMS: calcd. for $C_{10}H_{13}NO_5$ 227.07882; found 227.079149. Retention time (GC): 19.0 min (30 m HP 50-8-260/5-8-280/5-8-300/5).

General Procedure for the Catalytic Hydrogenation of β-Dehydroamino Acid Derivatives: A solution of the β-dehydroamino acid derivative (0.12 mmol) and the solvent (1.0 mL) was transferred by syringe into an autoclave charged with argon. The catalyst was generated in situ by stirring $[Ir(cod)Cl]_2$ (0.0012 mmol) and the corresponding ligand (0.0024 mmol) in solvent (1.0 mL) for a period of 10 min and afterwards transferring the solution by syringe into the autoclave. Then the autoclave was charged with hydrogen and the mixture 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 ^1H NMR spectroscopy and the enantioselectivity by GC or HPLC.

Ethyl 3-Acetamido-3-phenylpropanoate (6a): Chiralpak AD-H; *n*-hexane/ethanol, 95:5; flow rate 1.0 mL/min; retention time: (*R*)-**6a** 27.6 min, (*S*)-**6a** 29.3 min.

Methyl 3-Acetamidobutanoate (13a): 50 m Chiraldex β-PM; 130 °C; retention time: (*S*)-**13a** 15.1 min, (*R*)-**13a** 16.4 min.

Ethyl 3-Acetamidobutanoate (14a): 25 m Lipodex E, 70/40-8-180; retention time: (*R*)-**14a** 33.2 min, (*S*)-**14a** 33.4 min.

Isopropyl 3-Acetamidobutanoate (15a): 25 m Lipodex E, 70/25-10-180; retention time: (*R*)-**15a** 33.2 min, (*S*)-**15a** 33.4 min.

Methyl 3-Acetamidopentanoate (16a): 25 m Lipodex E, 120/30; retention time: (*R*)-**16a** 31.8 min, (*S*)-**16a** 32.2 min.

Methyl 3-Acetamido-4-methylpentanoate (17a): 25 m Lipodex E, 130/20, retention time: (*R*)-**17a** 33.2 min, (*S*)-**17a** 33.4 min.

Methyl 3-Acetamido-4,4-dimethylpentanoate (18a): 25 m Lipodex E, 70/40-8-200; retention time: (+)-**17a** 16.6 min, (–)-**17a** 18.9 min.

Ethyl 3-Acetamido-3-(4-methoxyphenyl)propanoate (19a): ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.10 (m, 2 H, Ar), 6.86–6.71 (m, 3 H, Ar and NH), 5.37–5.25 (m, 1 H, $CHCH_2$), 3.94 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.22 (s, 3 H, OCH_3), 2.90–2.64 (m, 2 H, $CHCH_2$), 1.92 (s, 3 H), 1.17 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.0, 169.0, 158.8, 132.6, 127.4, 113.8, 60.5, 55.1, 49.1, 40.1, 23.1, 13.9 ppm. IR (ATR): $\tilde{\nu}$ = 3277 (w), 3066 (w), 2981 (w), 2936 (w), 2837 (w), 1731 (m), 1646 (m), 1612 (m), 1586 (w), 1543 (m), 1512 (s), 1464 (w), 1443 (w), 1371 (m), 1296 (m), 1245 (s), 1176 (s), 1113 (m), 1094 (m), 1029 (s), 960 (w), 831 (m), 733 (w) cm^{-1}. MS (ES, 70 eV): m/z (%) = 265 (3) $[M]^+$, 222 (100), 178 (25), 136 (78), 132 (12), 91 (10). HRMS: calcd. for $C_{14}H_{19}NO_4$ 265.13086; found 265.131602. Chiralpak AD-H; eluent: *n*-heptane/ethanol, 90:10; flow rate 0.8 mL/min; retention time: (+)-**19a** 13.4 min, (–)-**19a** 17.0 min.

Ethyl 3-Acetamido-3-(2-methoxyphenyl)propanoate (20a): M.p. 90–96 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.23–7.11 (m, 2 H, Ar), 6.88–6.78 (m, 2 H, Ar), 6.74 (d, J = 8.8 Hz, 1 H, NH), 5.57–5.46 (m, 1 H, $CHCH_3$), 3.92 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.81 (s, 3 H, OCH_3), 2.90–2.67 (m, 2 H, $CHCH_2$), 1.92 (s, 3 H, $COCH_3$), 1.07 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.2, 168.8, 156.8, 128.8, 128.6, 127.9, 120.6, 101.7, 60.4, 55.3, 47.7, 39.3, 23.5, 14.0 ppm. IR (KBr): $\tilde{\nu}$ = 3285 (m), 3081 (w), 2988 (w), 2963 (w), 2842 (w), 2160 (w), 2026 (w), 1976 (w), 1732 (s), 1647 (s), 1601 (w), 1589 (w), 1553 (m), 1489 (m), 1466 (m), 1440 (m), 1390 (m), 1372 (m), 1298 (m), 1263 (m), 1239 (s), 1225 (m), 1175 (s), 1163 (s), 1134 (m), 1100 (m), 1072 (m), 1052 (m), 1025 (s), 967 (w), 928 (w), 868 (m), 800 (m), 779 (m), 767 (s), 754 (m), 707 (m), 657 (m) cm^{-1}. MS (ES, 70 eV): m/z (%) = 265 (7)

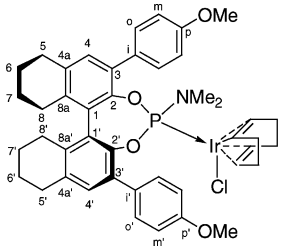
$[M]^+$, 222 (100), 178 (16), 136 (62). HRMS: calcd. for $C_{14}H_{19}NO_4$ 265.13086; found 265.131285. Chiralpak AD-H; eluent: *n*-heptane/ethanol, 95:5; flow rate 1.0 mL/min; retention time: (+)-**20a** 30.2 min, (–)-**20a** 41.3 min.

Ethyl 3-Acetamido-3-(4-fluorophenyl)propanoate (21a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H, Ar), 7.06–7.02 (m, 2 H, Ar), 6.74 (d, J = 8.2 Hz, 1 H, NH), 5.44 (m, 1 H, CH), 4.11 (q, J = 7.2 Hz, 2 H, CH_2CH_3), 2.87 (m, 2 H, $CHCH_2$), 2.05 (s, 3 H, $COCH_3$), 1.21 (t, J = 7.2 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.1, 169.5, 162.1 (d, J = 246 Hz), 136.5 (d, J = 3.2 Hz), 128.1 (d, J = 8.0 Hz), 115.4 (d, J = 21.5 Hz), 60.8, 49.1, 40.1, 23.3, 14.0 ppm. IR (capillary film): $\tilde{\nu}$ = 3279 (s), 3069 (m), 2983 (m), 2936 (m), 2873 (w), 1892 (w), 1732 (s), 1651 (s), 1606 (m), 1548 (s), 1512 (s), 1434 (m), 1373 (s), 1301 (s), 1225 (s), 1160 (s), 1097 (m), 1026 (m), 964 (w), 838 (s), 749 (w), 727 (m), 654 (w), 604 (m), 555 (m), 474 (m) cm^{-1}. MS (ES, 70 eV): *m*/*z* (%) = 253 (4) $[M]^+$, 210 (100), 179 (10), 166 (17), 149 (20), 137 (23), 124 (65), 97 (7), 75 (5), 43 (20), 29 (7). HRMS: calcd. for $C_{13}H_{16}FNO_3$ 253.11087; found 253.111388. Chiralpak AD-H; eluent: *n*-hexane/ethanol, 95:5; flow rate 1.0 mL/min; retention time: (+)-**21a** 32.8 min, (–)-**21a** 36.7 min.

Ethyl 3-Acetamido-3-(4-methylphenyl)propanoate (22a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.07 (m, 4 H, Ar), 6.55 (d, J = 8.1 Hz, 1 H, NH), 5.37 (m, 1 H, CH), 4.19 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 2.95 (m, 2 H, $CHCH_2$), 2.30 (s, 3 H, $ArCH_3$), 1.99 (s, 3 H, $COCH_3$), 1.16 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.3, 169.2, 137.5, 137.2, 129.3, 128.6, 126.2, 60.7, 49.3, 39.9, 23.4, 21.0 ppm. IR (ATR): $\tilde{\nu}$ = 3276 (w), 3056 (w), 2981 (w), 2930 (w), 2871 (w), 1733 (s), 1648 (s), 1542 (m), 1515 (m), 1444 (w), 1370 (m), 1293 (m), 1263 (m), 1162 (s), 1115 (m), 1095 (m), 1023 (m), 964 (w), 845 (w), 817 (m), 722 (m) cm^{-1}. MS (ES, 70 eV): *m*/*z* (%) = 249 (4) $[M]^+$, 206 (100), 160 (14), 145 (10), 133 (17), 120 (52), 91 (15). HRMS: calcd. for $C_{14}H_{19}NO_3$ 249.13594; found 249.136208. Chiralpak AD-H; eluent: *n*-heptane/ethanol, 92:8, flow rate 0.5 mL/min; retention time: (+)-**22a** 19.5 min, (–)-**22a** 23.9 min.

Methyl 3-Acetamido-3-phenylpropanoate (23a): Chiralcel OD-H; *n*-heptane/ethanol, 95:5; flow rate 1.0 mL/min; retention time: (*R*)-**23a** 15.5 min, (*S*)-**23a** 23.9 min.

Iridium Complex of Ligand 5c: $[Ir(cod)Cl]_2$ (0.15 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and the mixture stirred at room temperature for 10 min. The solvent and all volatiles were removed in vacuo. A solution of (*S*)-4-(dimethylamino)-2,6-bis(4-methoxyphenyl)-8,9,10,11,13,14,15-octahydrodinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]-dioxaphosphepine (**5c**) (0.15 mmol) was added, and the orange mixture was stirred overnight. The solution was filtered, and the solvent was removed in vacuo to afford an orange residue. Yield: 94%. $[\alpha]_D^{22}$ = 329.8 (c = 0.2, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68 (m, 2 H, *o*-C_6H_4), 7.47 (m, 2 H, *o*-C_6H_4), 7.26 (br. s, 1 H, 4-H), 7.13 (br. s, 1 H, 4′-H), 6.97–6.89 (m, 4 H, *m*,*m*′-C_6H_4), 4.99 (m, 1 H, cod-CH), 4.90 (m, 1 H, cod-CH), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.37 (m, 1 H, cod-CH), 2.86 (m, 4 H, 5,5′-H), 2.70–2.66 (m, 2 H, 8,8′-H), 2.46–2.27 (m, 2 H, 8,8′-H; m, 1 H, cod-CH), 2.12 [d, J = 10.8 Hz, 6 H, $N(CH_3)_2$], 2.12–2.00 (m, 3 H, cod-CH_2), 1.95–1.75 (m, 6 H, 6,6′,7,7′-H; m, 2 H, cod-CH_2), 1.70–1.55 (m, 2 H, 6,6′,7,7′-H; m, 2 H, cod-CH_2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 159.2 (*p*,*p*′), 158.8 (*p*,*p*′), 144.3 (d, J = 11.5 Hz, C-2,2′), 144.1 (d, J = 5.0 Hz, C-2,2′), 136.8 (d, J = 1.5 Hz, C-8a,8a′), 136.23 (d, J = 1.8 Hz, C-8a,8a′), 134.3 (d, J = 1.5 Hz, C-4a,4a′), 134.3 (d, J = 1.5 Hz, C-4a,4a′), 132.2 (C-1,1′ or 3,3′ or *i*,*i*′), 132.2 (C-1,1′ or 3,3′ or *i*,*i*′), 131.1 (*o*,*o*′), 130.5 (*o*,*o*′), 130.1 (C-1,1′ or 3,3′ or *i*,*i*′), 130.0 (d, J = 1.2 Hz, C-4,4′), 129.8 (d, J = 1.5 Hz, C-4,4′), 129.8 (C-1,1′ or 3,3′ or *i*,*i*′), 129.1 (C-1,1′ or 3,3′ or *i*,*i*′), 129.1 (d, J = 1.5 Hz, C-1,1′ or 3,3′ or *i*,*i*′), 113.7 (*m*,*m*′), 113.4 (*m*,*m*′), 101.5 (d, J = 19.0 Hz, cod-CH), 101.3 (d, J = 19.3 Hz, cod-CH), 55.4 (OCH_3), 55.3 (OCH_3), 52.5 (d, J = 1.9 Hz, cod-CH), 52.0 (d, J = 2.2 Hz, cod-CH), 36.3 [d, J = 9.3 Hz, $N(CH_3)_2$], 33.7 (d, J = 3.8 Hz, cod-CH_2), 33.6 (d, J = 3.2 Hz, cod-CH_2), 29.3 (C-5,5′), 29.2 (C-5,5′), 28.7 ("t", J = 2.5 Hz, cod-CH_2), 27.6 (C-8,8′), 27.5 (C-8,8′), 22.9, 22.8, 22.8, 22.7 (C-6,6′,7,7′) ppm. ^{31}P NMR (121.5 MHz, $CDCl_3$): δ = 110.3 ppm. IR (ATR): $\tilde{\nu}$ = 3033 (w), 3001 (w), 2930 (w), 2879 (w), 2833 (w), 1609 (m), 1514 (m), 1433 (m), 1399 (w), 1287 (m), 1245 (s), 1223 (m), 1176 (s), 1156 (m), 1135 (m), 1110 (w), 1063 (m), 1034 (m), 991 (s), 945 (s), 913 (w), 873 (w), 828 (s), 803 (s), 780 (m), 738 (m), 723 (m), 667 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 915 (8) $[M]^+$, 807 (16), 579 (100), 536 (29), 518 (11), 267 (17), 246 (22), 97 (14), 83 (15), 69 (24), 57 (26). HRMS: calcd. for $C_{44}H_{50}ClIrNO_4P$ 915.27897; found 915.276327.



Acknowledgments

We thank Dr. R. Jackstell, Mrs. M. Heyken, Mrs. S. Buchholz, Mrs. K. Reincke, Mrs. S. Schareina, Mrs. B. Friedrich and Dr. C. Fischer (all Leibniz-Institut für Katalyse e.V. an der Universität Rostock) for excellent technical and analytical assistance. In addition, we thank Dr. A. Köckritz, Dr. A. Pews-Davtyan and Dr. N. Nemati (all Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Außenstelle Berlin) for general discussions. Generous financial support from the state of Mecklenburg-Western Pomerania and the Bundesministerium für Bildung und Forschung (BMBF) as well as the Deutsche Forschungsgemeinschaft (Leibniz prize) is gratefully acknowledged.

[1] a) D. Guénard, R. Guritte-Voegelein, P. Potier, *Acc. Chem. Res.* **1993**, *26*, 160–167; b) D. C. Cole, *Tetrahedron* **1994**, *50*, 9517–9582; c) E. Juaristi, V. Soloshonok, *Enantioselective Synthesis of β-Amino Acids*, 2nd ed., Wiley-Interscience, New Jersey, **2005**; d) M. Lui, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; e) H.-J. Drexler, J. You, S. Zhang, C. Fischer, W. Baumann, A. Spannenberg, D. Heller, *Org. Process Res. Dev.* **2003**, *7*, 355–361; f) J. Ma, *Angew. Chem.* **2003**, *115*, 4426–4435; *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; g) R. P. Cheng, S. H. Gellman, W. F. DeGrado, *Chem. Rev.* **2001**, *101*, 3219–3232; h) D. Kubota, M. Ishikawa, M. Yamamoto, S. Murakami, M. Hachisu, K. Katano, K. Ajito, *Bioorg. Med. Chem.* **2006**, *7*, 2089–2108.

[2] a) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173–180; b) D. Seebach, J. L. Matthews, *Chem. Commun.* **1997**, 2015–2022.

[3] a) P. T. Anastas, M. M. Kirchhoff, *Acc. Chem. Res.* **2002**, *35*, 686–694; b) P. T. Anastas, M. M. Kirchhoff, T. C. Williamson, *Appl. Catal., A* **2001**, *221*, 3–13.

[4] a) C. Bruneau, J.-L. Renaud, T. Jerphagnon, *Coord. Chem. Rev.* **2008**, *252*, 532–544; see also: b) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952; c) K. Achiwa, T. Soga, *Tetrahedron*

Lett. **1978**, *13*, 1119–1120; d) W. D. Lubell, M. Kitamura, R. Noyori, *Tetrahedron: Asymmetry* **1991**, *2*, 543–554; e) G. Zhu, Z. Chen, X. Zhang, *J. Org. Chem.* **1999**, *64*, 6907–6910; f) D. Heller, J. Holz, H.-J. Drexler, J. Lang, K. Drauz, H.-P. Krimmer, A. Börner, *J. Org. Chem.* **2001**, *66*, 6816–6817; g) M. Yasutake, I. D. Gridnev, N. Higashi, T. Imamoto, *Org. Lett.* **2001**, *3*, 1701–1704; h) D. Heller, H.-J. Drexler, J. You, W. Baumann, K. Drauz, H.-P. Krimmer, A. Börner, *Chem. Eur. J.* **2002**, *8*, 5196–5203; i) Y.-G. Zhou, W. Tang, W.-B. Wang, W. Li, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 4952–4953; j) W. Yang, S. Wu, X. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571; k) I. V. Komarov, A. Monsees, A. Spannenberg, W. Baumann, U. Schmidt, C. Fischer, A. Börner, *Eur. J. Org. Chem.* **2003**, 138–150; l) J. You, H.-J. Drexler, S. Zhang, C. Fischer, D. Heller, *Angew. Chem.* **2003**, *115*, 942–945; *Angew. Chem. Int. Ed.* **2003**, *42*, 913–916; m) J. Holz, A. Monsees, H. Jiao, J. You, I. V. Komarov, C. Fischer, K. Drauz, A. Börner, *J. Org. Chem.* **2003**, *68*, 1701–1707; n) J. Wu, X. Chen, R. Guo, C.-h. Yeung, A. S. C. Chan, *J. Org. Chem.* **2003**, *68*, 2490–2493; o) H.-P. Wu, G. Hoge, *Org. Lett.* **2004**, *6*, 3645–3647; p) Y. Hsiao, N. R. Rivera, T. Rosner, S. W. Krska, E. Njolito, F. Wang, Y. Sun, J. D. Armstrong III, E. J. J. Grabowski, R. D. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919; q) Q. Dai, W. Yang, X. Zhang, *Org. Lett.* **2005**, *7*, 5343–5345.

[5] a) F. Lagasse, H. B. Kagan, *Chem. Pharm. Bull.* **2000**, *48*, 315–324; b) I. V. Komarov, A. Börner, *Angew. Chem.* **2001**, *113*, 1237–1240; *Angew. Chem. Int. Ed.* **2001**, *40*, 1197–1200; c) M. van den Berg, B. L. Feringa, A. J. Minnaard in *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 995–1027; d) G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *Coord. Chem. Rev.* **2008**, *252*, 471–491.

[6] a) D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553; b) D. Peña, A. J. Minnaard, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Lett.* **2003**, *5*, 475–478; c) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087–1089; d) H. Huang, Z. Zheng, H. Luo, C. Bai, X. Hu, H. Chen, *J. Org. Chem.* **2004**, *69*, 2355–2361; e) Y. Fu, X.-X. Guo, S.-F. Zhu, A.-G. Hu, J.-H. Xie, Q.-L. Zhou, *J. Org. Chem.* **2004**, *69*, 4648–4655; f) Y. Fu, G.-H. Hou, J.-H. Xie, L. Xing, L.-X. Wang, Q.-L. Zhou, *J. Org. Chem.* **2004**, *69*, 8157–8160; g) T. Jerphagnon, J.-L. Renaud, P. Demonchaux, A. Ferreira, C. Bruneau, *Adv. Synth. Catal.* **2004**, *346*, 33–36; h) M. T. Reetz, X. Li, *Angew. Chem.* **2005**, *117*, 3019–3021; *Angew. Chem. Int. Ed.* **2005**, *44*, 2959–2962; i) C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries, L. Lefort, *Chem. Eur. J.* **2005**, *11*, 6701–6717; j) S. Enthaler, G. Erre, K. Junge, J. Holz, A. Börner, E. Alberico, I. Nieddu, S. Gladiali, M. Beller, *Org. Process Res. Dev.* **2007**, *11*, 568–577; k) V. Bilenko, A. Spannenberg, W. Baumann, I. Komarov, A. Börner, *Tetrahedron: Asymmetry* **2006**, *17*, 2082–2087.

[7] a) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Tetrahedron Lett.* **2002**, *43*, 4977–4980; b) K. Junge, G. Oehme, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *J. Organomet. Chem.* **2003**, *675*, 91–96; c) K. Junge, B. Hagemann, S. Enthaler, A. Spannenberg, M. Michalik, G. Oehme, A. Monsees, T. Riermeier, M. Beller, *Tetrahedron: Asymmetry* **2004**, *15*, 2621–2631; d) K. Junge, B. Hagemann, S. Enthaler, G. Oehme, M. Michalik, A. Monsees, T. Riermeier, U. Dingerdissen, M. Beller, *Angew. Chem.* **2004**, *116*, 5176–5179; *Angew. Chem. Int. Ed.* **2004**, *43*, 5066–5069; e) B. Hagemann, K. Junge, S. Enthaler, M. Michalik, T. Riermeier, A. Monsees, M. Beller, *Adv. Synth. Catal.* **2005**, *347*, 1978–1986; f) S. Enthaler, B. Hagemann, K. Junge, G. Erre, M. Beller, *Eur. J. Org. Chem.* **2006**, 2912–2917; g) S. Enthaler, B. Hagemann, S. Bhor, G. Anilkumar, M. K. Tse, B. Bitterlich, K. Junge, G. Erre, M. Beller, *Adv. Synth. Catal.* **2007**, *349*, 853–860; h) S. Enthaler, G. Erre, K. Junge, D. Michalik, A. Spannenberg, F. Marras, S. Gladiali, M. Beller, *Tetrahedron: Asymmetry* **2007**, *18*, 1288–1298; S. Enthaler, B. Hagemann, G. Erre, K. Junge, M. Beller, *Chem. Asian J.* **2006**, *1*, 598–604; i) S. Enthaler, G. Erre, M. K. Tse, K. Junge, M. Beller, *Tetrahedron Lett.* **2006**, *47*, 8095–8099; j) S. Enthaler, R. Jackstell, B. Hagemann, K. Junge, G. Erre, M. Beller, *J. Organomet. Chem.* **2006**, *691*, 4652–4659; k) K. Junge, B. Hagemann, S. Enthaler, G. Erre, M. Beller, *ARKIVOC* **2007**, *5*, 50–66; l) G. Erre, S. Enthaler, K. Junge, S. Gladiali, M. Beller, *J. Mol. Catal. A* **2008**, *280*, 148–155.

[8] F. Giacomina, A. Meetsma, L. Panella, L. Lefort, A. H. M. de Vries, J. G. de Vries, *Angew. Chem.* **2007**, *119*, 1519–1522; *Angew. Chem. Int. Ed.* **2007**, *46*, 1497–1500.

[9] G. Erre, K. Junge, S. Enthaler, D. Addis, D. Michalik, A. Spannenberg, M. Beller, *Chem. Asian. J.* **2008**, *3*, 887–894.

[10] Optically pure 1,1′-bi-2-naphthol is available on a large scale from RCA (Reuter Chemische Apparatebau KG), Engesser Str. 4, 79108 Freiburg, Germany.

[11] a) A. Korostylev, V. I. Tararov, C. Fischer, A. Monsees, A. Börner, *J. Org. Chem.* **2004**, *69*, 3220–3221; b) T. Sugimura, H. Yamada, S. Inoue, A. Tai, *Tetrahedron: Asymmetry* **1997**, *8*, 649–655; c) M. T. Reetz, C. Merk, G. Naberfeld, J. Rudolph, N. Griebenow, R. Goddard, *Tetrahedron Lett.* **1997**, *38*, 5273–5276; d) H. Guo, K. Ding, *Tetrahedron Lett.* **2000**, *41*, 10061–10064; e) S. L. Aeilts, D. R. Cefalo, P. J. Bonitatebus Jr, J. H. Houser, A. H. Hoveyda, R. R. Schrock, *Angew. Chem.* **2001**, *113*, 1500–1504; *Angew. Chem. Int. Ed.* **2001**, *40*, 1452–1456; f) O. Karam, A. Martin-Mingot, M.-P. Jouannetaud, J.-C. Jacquesy, A. Cousson, *Tetrahedron* **2004**, *60*, 6629–6638; g) N. T. McDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman, S. E. Schaus, *Adv. Synth. Catal.* **2004**, *346*, 1231–1240.

[12] a) D. J. Cram, R. C. Helgeson, S. C. Peacock, L. J. Kaplan, L. A. Domeier, P. Moreau, K. Koga, J. M. Mayer, Y. Chao, *J. Org. Chem.* **1978**, *43*, 1930–1946; b) N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095.

[13] C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743–4748.

[14] R. Hulst, N. K. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 699–708.

[15] Institute of Automation (IAT), Richard Wagner Str. 31/H. 8, 18119 Rostock-Warnemünde, Germany.

[16] F. Spindler, H.-U. Blaser in *Handbook of Homogeneous Hydrogenation* (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, **2007**, pp. 1193–1214.

[17] a) R. H. Crabtree, H. Felkin, G. E. Morris, *J. Organomet. Chem.* **1977**, *141*, 205–215; b) R. H. Crabtree, *Acc. Chem. Res.* **1979**, *12*, 331–338.

[18] (*S*)-MonoPhos was also tested in the hydrogenation of α-acetamidocinnamate. Use of 1.0 mol-% $[Ir(cod)Cl]_2$ and 2.0 mol-% (*S*)-MonoPhos in toluene under 2.5 bar hydrogen pressure at 25 °C for 24 h yields 5% of the product with 40% *ee*.

[19] a) R. D. Kroshefsky, R. Webs, J. G. Yerkade, *Inorg. Chem.* **1979**, *18*, 469–472; b) D. W. Allen, B. F. Taylor, *J. Chem. Soc., Dalton Trans.* **1982**, 51–54; c) D. E. Schiff, J. W. Richardson Jr, R. A. Jacobson, A. H. Cowley, J. Lasch, J. G. Verkade, *Inorg. Chem.* **1984**, *23*, 3373–3377; d) A. Suárez, M. A. Méndez-Rojas, A. Pizzano, *Organometallics* **2002**, *21*, 4611–4621; e) S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion, P. Dellis, *Angew. Chem.* **2004**, *116*, 324–329; *Angew. Chem. Int. Ed.* **2004**, *43*, 320–325; f) S. Otto, A. Ionescu, A. Roodt, *J. Organomet. Chem.* **2005**, *690*, 4337–4342; g) T. Kimura, T. Murai, *Chem. Lett.* **2004**, *33*, 878–879; h) J. Holz, O. Zayas, H. Jiao, W. Baumann, A. Spannenberg, A. Monsees, T. H. Riermeier, J. Almena, R. Kadyrov, A. Börner, *Chem. Eur. J.* **2006**, *12*, 5001–5013.

[20] T. Murai, S. Inaji, K. Morishita, F. Shibahara, M. Tokunaga, Y. Obora, Y. Tsuji, *Chem. Lett.* **2006**, *35*, 1424–1425.

[21] W. Tang, S. Wu, X. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 9570–9571.

[22] Y. Yamamoto, Y. Morita, K. Minami, *Chem. Pharm. Bull.* **1986**, *34*, 1980–1986.
[23] Other bidentate ligands were tested in the hydrogenation of **26**. Use of 1.0 mol-% of $[Ir(cod)Cl]_2$ and 2.0 mol-% of ligand (for example: Me-DuPhos, BINAP, DIOP, BPPM, catASium M, Ferrotane, ChiraPhos or Ph-Binepine) in CH_2Cl_2 (2.0 mL) under a hydrogen pressure of 2.5 bar at 25 °C for 24 h showed no activity. Also no reactivity was observed with rhodium or ruthenium catalysts. Here, 1.0 mol-% of Me-DuPhos, BINAP, DIOP or Ph-Binepine (2.0 mol-%) was utilized with 1.0 mol-% of $[Rh(cod)_2BF_4]$ in CH_2Cl_2 or MeOH (2.0 mL) at 2.5 or 50 bar at 25 °C for 24 h. In the case of the ruthenium catalyst 1.0 mol-% of BINAP was used in combination with 1.0 mol-% of $[Ru(cod)methylallyl_2]$ under a hydrogen pressure of 50 bar at 25 °C for 24 h.

Received: March 3, 2008
Published Online: May 13, 2008

