Rhodium-Catalyzed Asymmetric Hydrogenation using Phosphoramidite Ligands

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Chapter 3

Asymmetric Hydrogenation of 3,3-Disubstituted Dehydroamino Acids[1]

Abstract

The synthesis of several prochiral methyl 3,3-disubstituted 2-acetamido acrylates and methyl 3,3-disubstituted 2-benzyloxycarbonylamino acrylates is described. A study of the asymmetric hydrogenation of these compounds using a cationic rhodium(I) complex $[RhL_2(COD)]BF_4$ with chiral phosphoramidites acting as ligands is reported. The products were obtained with various degrees of enantioselectivity up to 89 % e.e.

3.1 Introduction

3.1.1 3,3-Disubstituted 2-acetamido acrylates

Opposite to the 3-monosubstituted 2-acetamido acrylates described in Chapter 2, methyl 3,3-disubstituted 2-acetamidoacrylates (Figure 3.1) are by no means benchmark substrates for homogeneous hydrogenations. There are several reports in the literature describing their application in asymmetric hydrogenation.[2,3,4,5,6,7,8,9,10,11] The hydrogenation of methyl 3-monosubstituted 2-acetamido acrylates (Figure 3.1, **1** R=H) described in Chapter 2 of this thesis and have been described extensively in the literature.[12]

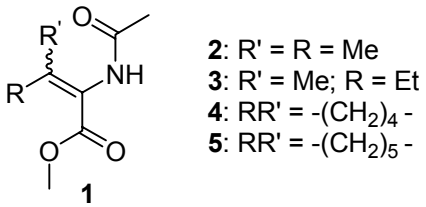
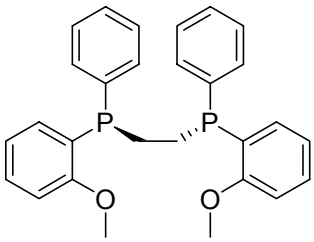


Figure 3.1 *Methyl 3,3-disubstituted 2-acetamidoacrylates.*

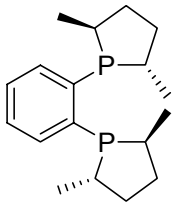
In the first application of an asymmetric hydrogenation of tetra-substituted alkenes the bidentate phosphine (*R*,*R*)-DiPAMP was used.[2] With methyl 2-acetamido-3-methylbut-2-enoate (**2**) as a substrate, an e.e. of 55% was obtained. In most cases, C_2 symmetric diphosphine ligands like DuPHOS,[4,5] Me-BPE,[4] MiniPHOS,[7,10] (*S*,*S*)-1,2-bis(isopropylmethylphosphino)benzene[8] or BisP*[11] have been employed. The selectivities reached with these ligands are compiled in Table 3.1. Apart from these ligands, the more elaborate diferrocene system TRAP[6,9] has been used. Most of these ligands facilitate full conversion within 12 – 24 h when applied as ligands in the Rh-catalyzed hydrogenation. TOF's of 20 - 40 h^{-1} are obtained either at atmospheric pressures or at elevated pressures up to 20 bar.

Drawbacks of these ligands are their long and complicated methods of preparation, their sensitivity toward oxidation and low reaction rate. The application of phosphoramidites as ligands in the asymmetric hydrogenation of 3,3-disubstituted dehydroamino acids has, until now, never been reported. In the disubstituted acrylate substrates the 3,3-substituents R and R' usually are alkyl and/or aryl groups, although heterocyclic substituents and a keto enamide have been examined.[4] Solvents usually employed are MeOH,[2,7,10,11] 2-PrOH,[6,9] CH_2Cl_2[6,9] and benzene.[4,10] A less common approach, which provides results comparable to those obtained in traditional solvents, is based on the use of supercritical CO_2 as a solvent in these hydrogenations.[5]

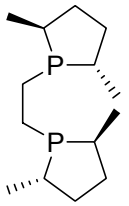
Table 3.1 *Reported enantioselectivities in the Rh-catalyzed hydrogenation of 3,3-disubstituted 2-acetamido acrylates using different ligands.*



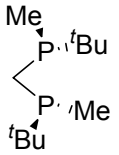
DiPAMP



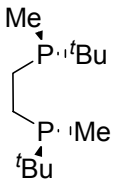
Me-DuPHOS



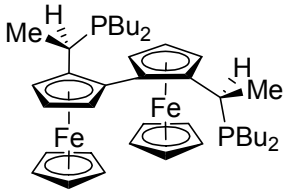
Me-BPE



MiniPHOS



BisP*



TRAP

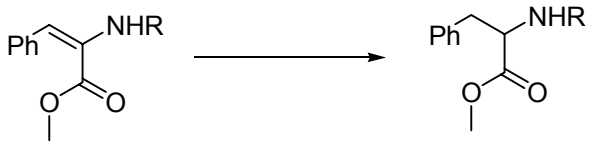
ligand	substrate		
	2 (e.e. %)	**4 (e.e. %)**	**5 (e.e. %)**
Me-DuPHOS[4,5]	96	96.8	96.2
Me-BPE[4]	98.2	97.2	98.6
Bu-TRAP[6,9]	88		78
*t*Bu-MiniPHOS[7,10]		94	
BisP*[11]	91		95

The aim of our investigation was to examine whether the catalytic system of rhodium and the monodentate phosphoramidite ligand MonoPhos™ (**L1**, Figure 3.4) or related phosphoramidite ligands, so successfully employed on benchmark substrates,[13] would show equally good results in the asymmetric hydrogenations of the more demanding tetra-substituted alkenes.

3.1.2 Methyl 3,3-disubstituted 2-benzyloxycarbonylamino acrylates

Enamides with an *N*-acetyl protecting group, for instance the ones described in Chapters 2 and 4 of this thesis, constitute one of the most extensively investigated classes of substrates in asymmetric hydrogenation. These substrates however do have a drawback, which consists of the fact that the *N*-acetyl protecting group requires fairly harsh conditions in order to be removed after hydrogenation of the substrate. A synthetically more convenient class of protecting groups are carbamates. Probably the best-known protecting groups of this type are

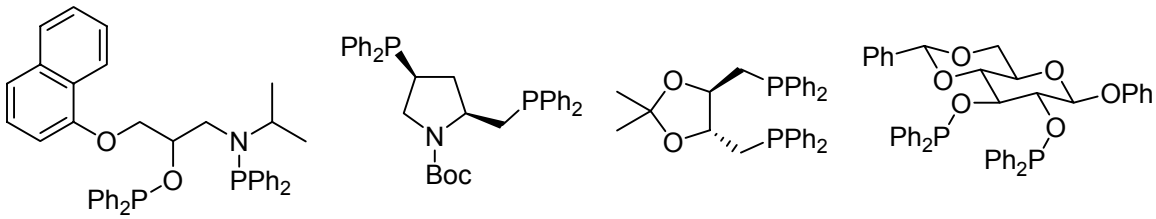
the *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz or simply Z) groups. They are easily applied and removed, for example in the case of Cbz by simple heterogeneous hydrogenolysis. Yet, they have received relatively scant attention as protecting groups for substrates used in the rhodium-catalysed asymmetric hydrogenation. In one publication, the rhodium catalysed asymmetric hydrogenations of *N*-acetyl and *N*-Cbz protected dehydrophenylalanine methyl ester have been compared in terms of enantioselectivity.[14] The use of acetyl protecting groups prevails due to the ease of comparing new ligands with published results. Another aspect is that the substrates are more easily accessible. Moreover the deprotection of the benchmark substrates does not pose any problems.



6: R = Ac
7: R = Cbz

Scheme 3.1 *N-Cbz versus N-Ac protected substrates.*

Using a ferrocenyl diphosphine ligand, the e.e. in the hydrogenation of the Cbz-protected substrate was 85.3% *versus* 97.6% in the hydrogenation of the acyl-protected analog.[14] The solvent was methanol in case of the Cbz protected substrate, whereas for the acetyl protected substrate ethanol has been used. Therefore a solvent effect might have affected the results. However, since methanol and ethanol are very similar solvents, this difference by itself does not fully explain the much lower enantioselectivity in the hydrogenation of Cbz protected substrate compared to the acetyl protected one.

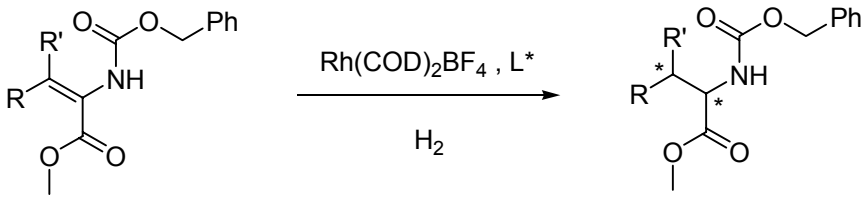


PROPRAPHOS BPPM DIOP Ph-ß-GLUP

Figure 3.2 *Bidentate ligands used in the Rh-catalyzed hydrogenation of dehydrophenylalanine methyl ester with various protecting groups.*

In another report, the *N*-protecting groups Ac, Bz, Cbz and Boc have been compared in asymmetric hydrogenation of dehydrophenylalanine methyl ester.[15] Four different ligands were tested: (*S*)-PROPRAPHOS, (2*S*,4*S*)-BPPM, (4*R*,5*R*)-DIOP and (*R*)-Ph-β-GLUP (Figure 3.2). The *N*-carbamate protected substrates required prolonged reaction times compared to the *N*-acyl protected ones for all ligands tested. On the contrary, the highest

enantioselectivities are obtained using the *N*-acetyl protecting group, except for (*S*)-PROPRAPHOS, which showed the best e.e. using the *N*-Boc protected substrate.



8 **9**

Scheme 3.2 *Asymmetric hydrogenation of methyl 3,3-disubstituted 2-benzyloxycarbonylamino acrylates.*

Carbamate protecting groups have also been employed in the synthesis of a peptidomimetic.[16] One of the key steps in this synthesis is a rhodium-catalysed asymmetric hydrogenation reaction using (*R*,*R*)-Me-DuPHOS as the ligand. To the best of our knowledge, methyl 3,3-disubstituted 2-benzyloxycarbonylamino acrylates have never before been reported in the literature as substrates in asymmetric hydrogenation reactions. Therefore, the hydrogenation of this class of compounds (Scheme 3.2) seemed to be a challenging enterprise, as well as to offer a lot of potential.

3.2 Results and Discussion

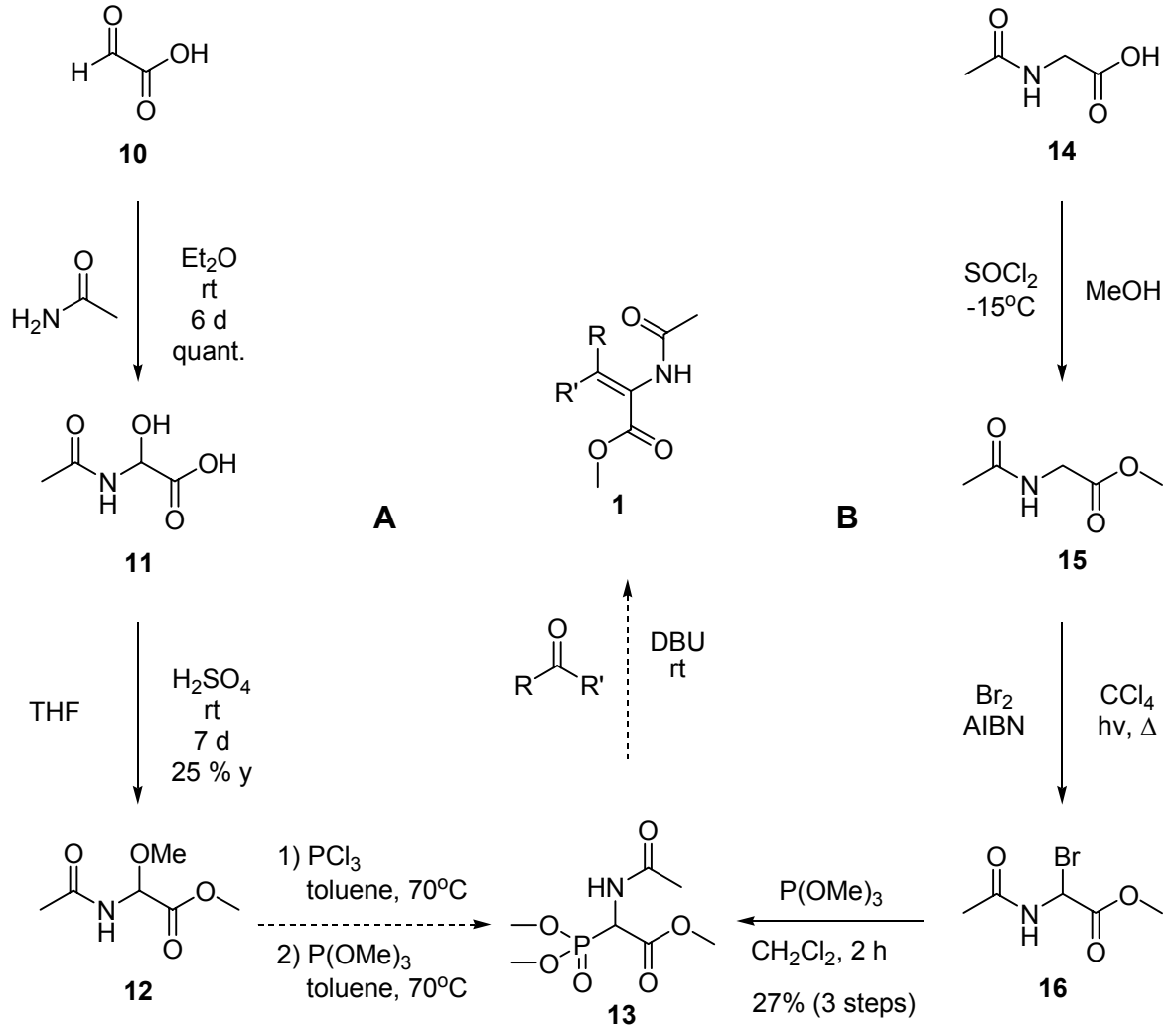
3.2.1 Substrate synthesis

3.2.1.1 Synthesis of methyl 3,3-disubstituted 2-acetamido acrylates

Methods reported in literature to obtain methyl 3,3-disubstituted 2-amidoacrylates include dehydrochlorination of *N*-chloroacetamido esters,[17] acetamide condensation of α-ketoesters,[4,18] Horner-Wadsworth-Emmons olefinations,[4,19] aldol condensation of methyl isocyanoacetate with a ketone followed by deprotonation, rearrangement to the *N*-formamide, acylation and deformylation[20] or, if one of the substituents is aromatic or vinylic in nature, a Suzuki reaction.[4,21]

3.2.1.1.1 Synthesis using Horner-Wadsworth-Emmons olefinations

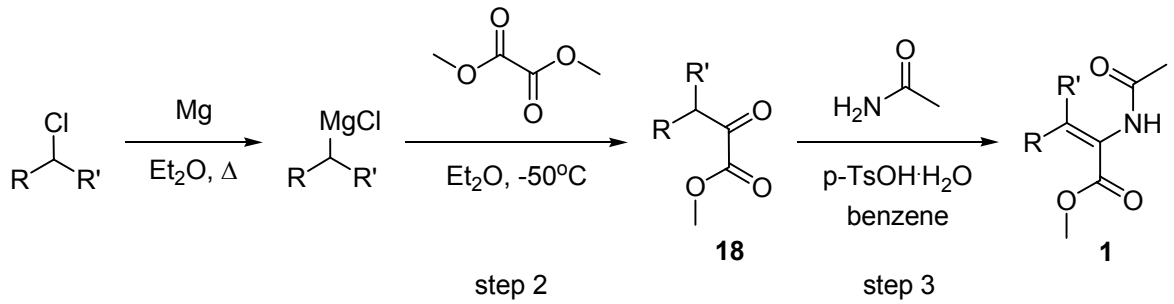
To synthesize the substrate precursor **13** two routes were explored (Scheme 3.3, A). The first route, a modified procedure of the one given by Schmidt *et al.*[19] to make various *N*-Cbz protected olefins, starts with a condensation of glyoxylic acid (**10)** and acetamide to **11**. Although the reaction takes a long time to go to completion the product is obtained in quantitative yield. The next step on the other hand was not as straightforward as described in literature.[22] Following the literature procedure the reaction yielded **12** in only mediocre amounts. Due to this fact another route was used to synthesise **13**. This route[23] (Scheme 3.3, **B**) starts with the esterification of 2-acetamidoacetic acid (**14**) into **15**. This molecule is subsequently brominated at the α-position to form compound **16**. The bromine atom acts as a leaving group in a Michaelis-Arbusov reaction to give methyl 2-acetamido-2-(dimethoxyphosphoryl)acetate (**13**) in good yield (27% over three steps). From this precursor various substrates can be synthesized in a Horner-Wadsworth-Emmons reaction with a ketone or aldehyde using DBU as a base.



Scheme 3.3 *Horner-Wadsworth-Emmons route towards substrates **1**.*

3.2.1.1.2 Acetamide condensation of α-ketoesters

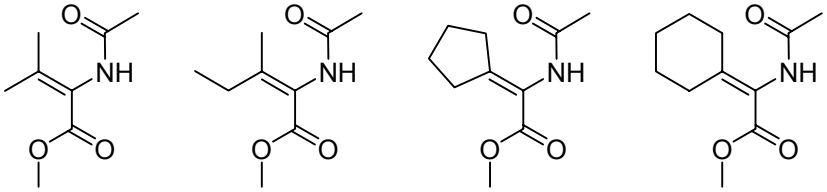
Another route towards the substrates **1** is via a condensation of a ketoester with acetamide; a method used by Burk *et al.*[4] and depicted in Scheme 3.4.



Scheme 3.4 *Synthesis of methyl 3,3-disubstituted 2-acetamidoacrylates.*

The route starts with a secondary chloride that eventually provides the two β-alkyl substituents of the substrate. This chloride is converted to the corresponding Grignard reagent using standard procedures after which the Grignard reagent is added to dimethyl oxalate. In the literature procedure,[4] the reaction was performed at a temperature of -20 °C and two equivalents of dimethyl oxalate were used, presumably to avoid double addition of the Grignard reagent. Extensive side product formation was observed. However, this was not the anticipated di-substituted product. This result led to the use of a slightly modified literature procedure. When one equivalent of dimethyl oxalate was used and the reaction was performed at -50 °C yields improved and workup was more convenient compared to the original procedure. The final step in this synthetic route comprises of an acid catalyzed condensation reaction of **18** with acetamide under Dean-Stark conditions to provide acetamidoacrylates **2** - **5**.

Table 3.2 *Methyl 3,3-disubstituted N-acetyl dehydroamino esters.*



2 **3** **4** **5**

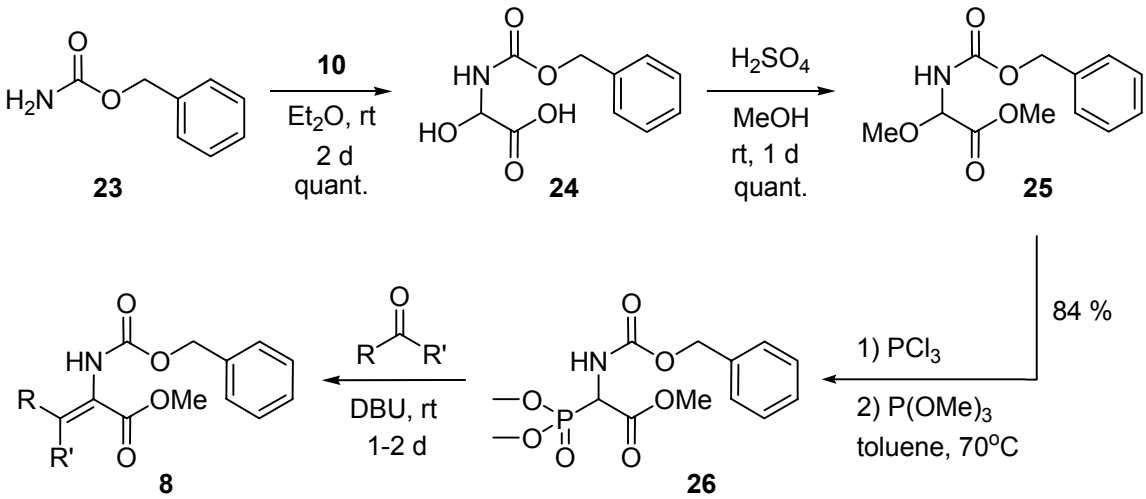
entry	substrate	R	R'	yield step 2	yield step 3
1	**2**	Me	Me	64 %	35 %
2	**3**[a]	Et	Me	70 %	19 %
3	**4**	-$(CH_2)_4$-		85 %	56 %
4	**5**	-$(CH_2)_5$-		79 %	45 %

[a] E / Z mixture 1.5:1.

This reaction had been described by Burk and co-workers using benzene as a solvent. For obvious reasons, we tried to avoid the use of benzene and investigated the possibility of using toluene as a solvent. However, this led to extensive formation of side-products and very poor yields, probably due to the higher reaction temperature. Furthermore, problems with water removal led to moderate to poor yields, urging us to seek ways of removing the water formed in this reaction more efficiently than with the Dean-Stark apparatus employed thus far. Using methylpyruvate as a model substrate, the use of various drying agents, like $MgSO_4$ and molecular sieves, either in solution or in a Soxhlet apparatus, was investigated with disappointing results. Eventually, performing the reaction in benzene and using Dean-Stark conditions as described by Burk *et al.*, led to the moderate but satisfying results depicted in Table 3.2.
Considering these results, the potentially facile route of obtaining various 3,3-disubstituted enamides via the route described in 3.2.1.1.1 was abandoned.

3.2.1.2 Synthesis of methyl 3,3-disubstituted 2-benzyloxycarbonyl-amino acrylates

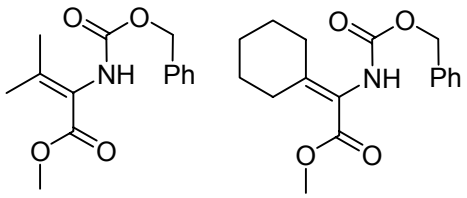
For the synthesis of these substrates an existing method was used (Scheme 3.5).[19] This procedure starts with the formation of **26** from benzyl carbamate and glyoxylic acid[24] in four steps. The substrates **8** are subsequently formed from this precursor via a Horner-Wadsworth-Emmons reaction.



Scheme 3.5 *Synthetic route toward the N-Cbz protected substrates.*

The first step comprises of addition of benzyl carbamate to glyoxylic acid to form compound **24** in quantitative yield. This also holds for the esterification and etherification of compound **24** to yield **25**. Conversion to compound **26** is then achieved via a two-step one-pot synthesis of which the second step is a Michaelis-Arbusov reaction, yielding **26** in excellent yield

(84% based on **25**). The dehydroamino acid derivatives **8** can be readily formed from this precursor by allowing it to react with a ketone under the influence of a base.



27 55 %

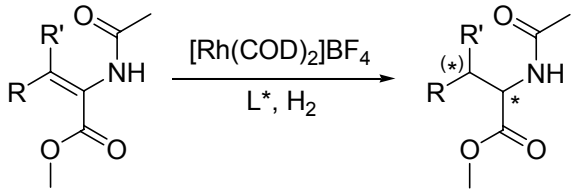
28 88 %

Figure 3.3 *Methyl 3,3-disubstituted 2-benzyloxycarbonyl-dehydroamino acids.*

In a variant of this original[19] procedure, Burk *et al.*[4] used 1,1,3,3-tetramethylguanidine (TMG) as a base in the Horner-Wadsworth-Emmons reaction instead of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In our case, application of TMG gave no conversion at all when applied to cyclohexanone and **26**. Employing DBU instead gave our substrates in yields ranging from moderate to good.

3.2.2 Hydrogenation

3.2.2.1 Hydrogenation of methyl 3,3-disubstituted 2-acetamido acrylates



1 **29**

Scheme 3.6 *Asymmetric hydrogenations of methyl 3,3-disubstituted 2-acetamido acrylates.*

The use of phosphoramidite ligands in the asymmetric hydrogenation of methyl 3,3-disubstituted 2-acetamido acrylates was examined on different substrates under various conditions. The ligands used for the transformation of the substrates are depicted in Figure 3.4. Both monodentate and bidentate ligands have been used, derived from TADDOL and BINOL. For the reactions the catalyst precursor $[Rh(COD)_2]BF_4$ was used. In the studies described earlier (Chapter 2) it was shown that in general the ligands that gave the best results had relatively small substituents on the nitrogen atom of the ligand. This improved the reactivity as well as the enantioselectivity. Because of the lower reactivity generally associated with the sterically more hindered substrates described in this section,[4] reducing

steric hindrance on nitrogen in the ligand was thought to be especially crucial. We therefore also tested some ligands derived from primary amines, **L4**, **L5** and **L6**, besides the ligands derived from secondary amines.

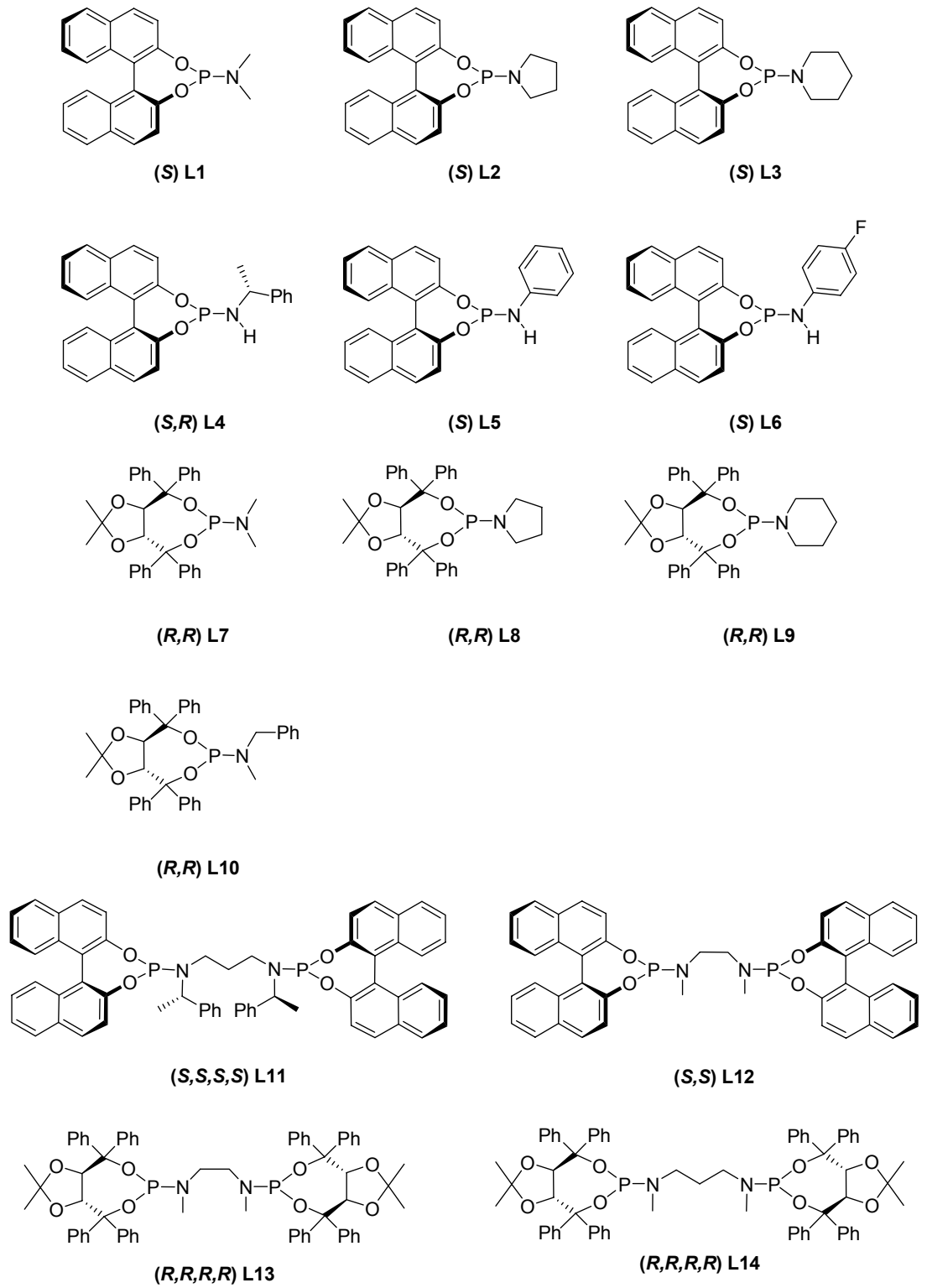
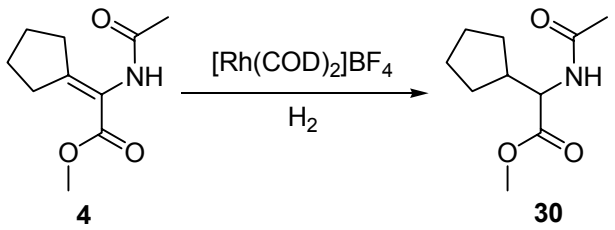


Figure 3.4 *Ligands tested in the asymmetric hydrogenation of methyl 3,3-disubstituted amidoacrylates.*

Table 3.3 *Asymmetric hydrogenation of **4** with various ligands in dichloromethane.*



4 **30**

entry	ligand	t (h)	conversion[b] (%)	e.e.[c] (%)	conf.[25]
1	**L1**	22	98	40	*R*
2	**L2**	90	100	47	*R*
3	**L3**	90	100	67	*R*
4	**L4**	18	100	65	*R*
5	**L5**	90	100	58	*R*
6	**L6**	90	100	62	*R*
7	**L7**	16	4	56	*S*
8	**L11**	16	100	68	*R*
9	**L13**	16	28	89	*S*
10	**L14**	16	32	64	*S*

[a] Conditions used: $[Rh(COD)_2]BF_4$ (5 mol%), ligand (11 mol%, monodentate; 5.5 mol% bidentate), 5 bar H_2. [b] Conversion was determined by means of 1H NMR. [c] The e.e. was determined by means of chiral GC.

For the hydrogenation of these substrates we started using the standard conditions used in Chapter 2 of this thesis. The solvent first tested was dichloromethane at a hydrogen pressure of 5 bar and with 5 mol% of catalyst. Under these conditions we obtained promising preliminary results as can be noted from Table 3.3. Except for ligand **L7** all of the monodentate ligands gave full conversions. Although it should be mentioned that the time of hydrogenation in some cases is long, this is due to the fact that we wanted to be sure that the reactions went to completion. As can be seen from other entries in Table 3.3 the actual time required for full conversion is often shorter. An interesting feature is the rate of the reaction when ligands are used which are derived from TADDOL. These reaction rates are much lower compared to the rates when ligands derived from BINOL are used. The enantioselectivities are moderate, however. When ligand **L13** is used (entry 9) a good e.e. is obtained, albeit with a low conversion. The use of ligands derived from primary amines like **L4**, **L5** and **L6** give higher e.e.'s compared to MonoPhos™ (**L1**). The results are in the same range as those obtained using **L3**. The change from a phenyl (**L5**, **L6**) substituent to a benzyl (**L4**) substituent does not seem to have much influence on the enantioselectivity (entries 4 – 6). Substrate **4** is hydrogenated with higher selectivity's when bidentate ligands are used. This in contrast to the results described in Chapter 2. The absolute configuration of the products is dictated by the configuration of the chiral backbone in the ligand.

The use of ligands with *S*-chirality in the backbone leads to products with *R*-chirality. This holds for both the TADDOL and the BINOL backbone, even if there are other stereogenic centers in the ligand (**L4** and **L11**).[26]

Table 3.4 *Asymmetric hydrogenation of **4** with various ligands in ethyl acetate.*

entry	ligand	t (h)	conversion[b] (%)	e.e.[c] (%)	conf.[25]
1	**L1**	18	24	12	*R*
2	**L2**	18	16	12	*R*
3	**L7**	18	45	67	*S*
4	**L8**	18	71	84	*S*
5	**L9**	17.5	22	57	*S*
6	**L10**	16.5	89	43	*S*
7	**L11**	17.5	17	45	*R*
8	**L12**	17.5	0	-	
9	**L13**	16.5	100	79	*S*
10	**L14**	17.5	100	84	*S*

[a] Conditions used: $[Rh(COD)_2]BF_4$ (5 mol%), ligand (11 mol%, monodentate; 5.5 mol% bidentate), 5 bar H_2. [b] Conversion was determined by means of 1H NMR. [c] The e.e. was determined by means of chiral GC.

These results prompted us to further test the conditions, see Chapter 2, which also was a useful tool to improve the results in the hydrogenation of dehydrophenylalanine and dehydroalanine. We replaced dichloromethane for ethyl acetate, keeping the other conditions the same. This led to some surprising results (Table 3.4). The use of BINOL derived bidentate ligands in the rhodium-catalyzed asymmetric hydrogenation in ethyl acetate at 5 bar hydrogen pressure gives rise to low conversions. Interestingly TADDOL derived ligands give higher reaction rates and enantioselectivities compared to the ligands derived from BINOL (entries 1, 2, 7, 8). Again the use of bidentate TADDOL derived ligands give the highest e.e.'s, albeit that in ethyl acetate ligand **L14** slightly outperforms ligand **L13**. With the notion that a hydrogen pressure of 5 bar is sufficient in most cases to get full conversion and the existence of a large solvent effect on the e.e., we screened several solvents to determine the optimal solvent for this type of substrates. The results are presented in Table 3.5. Using ligand **L1** (entries 1 – 4) clearly dichloromethane gives the best performance. In this solvent full conversion is reached and the e.e. is the highest. This trend, with a few exceptions, repeats itself for the other ligands with a BINOL backbone. The ligands with a TADDOL backbone, on the other hand, show the best performance in ethyl acetate. The performance is judged by both the rate of the reaction and the enantioselectivity. Using the bidentate TADDOL derived ligands **L13** and **L14** for the hydrogenation of **4** with ethyl acetate gave full conversions and high e.e.'s (Table 3.5, entries 26 and 30). The reaction in dichloromethane using ligand **L13** did give a higher e.e. in the product, however the conversion was low (entry 27). Using ligand **L14** in dichloromethane to hydrogenate **4**

resulted in both a lower conversion as well as a lower e.e. Using **L5** (entry 14) showed that with toluene as the solvent results comparable to those obtained using dichloromethane (entry 15) are reached.

Table 3.5 *Solvent and ligand screening in the hydrogenation of **4**.*

entry	ligand	solvent	t (h)	conversion[b] (%)	e.e.[c] (%)	conf.[25]
1	**L1**	MeOH	16	5	10	*R*
2	**L1**	2-PrOH	17	38	13	*R*
3	**L1**	EtOAc	18	24	12	*R*
4	**L1**	CH_2Cl_2	22	98	40	*R*
5	**L2**	MeOH	16	18	6	*R*
6	**L2**	2-PrOH	17	39	7	*R*
7	**L2**	α,α,α-trifluorotoluene	17.5	12	33	*R*
8	**L2**	EtOAc	18	16	12	*R*
9	**L2**	CH_2Cl_2	90	100	47	*R*
10	**L3**	α,α,α-trifluorotoluene	17.5	18	47	*R*
11	**L3**	CH_2Cl_2	90	100	67	*R*
12	**L4**	2-PrOH	17	100	44	*R*
13	**L4**	CH_2Cl_2	18	100	65	*R*
14	**L5**	toluene	24	78	58	*R*
15	**L5**	CH_2Cl_2	90	100	58	*R*
16	**L7**	EtOAc	18	45	67	*S*
17	**L7**	CH_2Cl_2	16	4	56	*S*
18	**L8**	2-PrOH	17	4	57	*S*
19	**L8**	α,α,α-trifluorotoluene	17.5	4	54	*S*
20	**L8**	EtOAc	18	71	84	*S*
21	**L9**	α,α,α-trifluorotoluene	17.5	9	76	*S*
22	**L9**	EtOAc	17.5	22	57	*S*
23	**L11**	2-PrOH	18.5	28	50	*R*
24	**L11**	EtOAc	17.5	17	45	*R*
25	**L11**	CH_2Cl_2	16	100	68	*R*
26	**L13**	EtOAc	16.5	100	79	*S*
27	**L13**	CH_2Cl_2	16	28	89	*S*
28	**L14**	MeOH	16	35	18	*S*
29	**L14**	2-PrOH	18.5	77	78	*S*
30	**L14**	EtOAc	17.5	100	84	*S*
31	**L14**	CH_2Cl_2	16	32	64	*S*

[a] Conditions used: $[Rh(COD)_2]BF_4$ (5 mol%), ligand (11 mol%, monodentate; 5.5 mol% bidentate), 5 bar H_2. [b] Conversion was determined by means of 1H NMR. [c] The e.e. was determined by means of chiral GC.

In order to improve those results we tested α,α,α-trifluorotoluene as a solvent with several ligands, only to find out that this strategy actually did not give better results. Generally methanol is the worst solvent we tested in this hydrogenation whereas isopropanol gave mixed results. Clearly dichloromethane and ethyl acetate gave the best results depending on the ligand used.

The lack of reactivity of the BINOL derived ligands was studied to some extend by varying the hydrogen pressure. From the results in Table 3.6 it can be noted that using **L1** at least 5 bar of hydrogen is required. At atmospheric pressure no reaction occurred within 22 hours. Increasing the pressure to 60 bar did give full conversion but did not affect the enantioselectivity. Substituting **L1** for **L4** gives rise to a faster reaction as well as a higher enantioselectivity. Another feature is the effect of hydrogen pressure. In this case the e.e. increases with increasing hydrogen pressure, which is in contrast to observations generally reported in the literature on the asymmetric hydrogenation of dehydroamino acids using a number of bidentate ligands.[13]

Table 3.6 *Pressure effects on the hydrogenation reaction of **4**.*

entry	ligand	pH_2 (bar)	t (h)	conversion[b] (%)	e.e.[c] (%)	conf.[25]
1	**L1**	1	22	0	-	
2	**L1**	5	22	98	40	*R*
3	**L1**	60	65	100	42	*R*
4	**L4**	1	88	90	29	*R*
5	**L4**	5	18	100	65	*R*
6	**L4**	60	20	100	70	*R*

[a] Conditions used: $[Rh(COD)_2]BF_4$ (5 mol%), ligand (11 mol%), 5 bar H_2. [b] Conversion was determined by means of 1H NMR. [c] The e.e. was determined by means of chiral GC.

This unusual observation can probably be ascribed to the formation of rhodium(0) after a certain amount of time.[27] This rhodium(0) species might, after formation of colloidal particles, also be catalytically active, however, this species will give rise to racemic product. This will, of course, lower the overall enantioselectivity of the product.[28] Upon applying a higher pressure the rate of hydrogenation increases and the substrate is hydrogenated before the formation of colloidal particles can occur.

After having established the best solvents we started testing the other substrates at various pressures (Table 3.7). As expected, the same features encountered in the hydrogenation of **4** were also observed in the hydrogenation of the other substrates. For instance, the reactivity and enantioselectivity observed when trying to convert **2** was low using **L1** in dichloromethane (entry 1), but increased dramatically upon switching to **L4** (entry 2). The enantioselectivity increased even more when the bidentate TADDOL-based ligand **L13** in ethyl acetate was used (entry 3), establishing an impressive 87 % e.e. and almost complete

conversion in a reaction done overnight. Hydrogenation of the *E*/*Z* mixture of substrate **3** gave results comparable to the hydrogenation of **2** with ligand **L13** (entry 4). The *Z*-isomer had a conversion of 95 % while the *E*-isomer had a conversion of only 76 %. The e.e.'s show that the hydrogenation of the *Z*-isomer is more selective compared to the hydrogenation of the *E*-isomer. This contrasts with the results described in the literature as both the *E*- and *Z*-isomer yielded diastereomeric products with the same enantioselectivity.[4] Substrate **5** was hydrogenated using **L1** at three different pressures and improved conversion with increasing pressure was observed. At atmospheric pressure the rate of hydrogenation is very low. This can be overcome already at a pressure of 5 bar. Increasing the pressure to 50 bar only slightly improved the outcome. The enantioselectivity only varied marginally with increasing pressure.

Table 3.7 *Hydrogenation of various methyl 3,3-disubstituted 2-acetamido acrylates.*

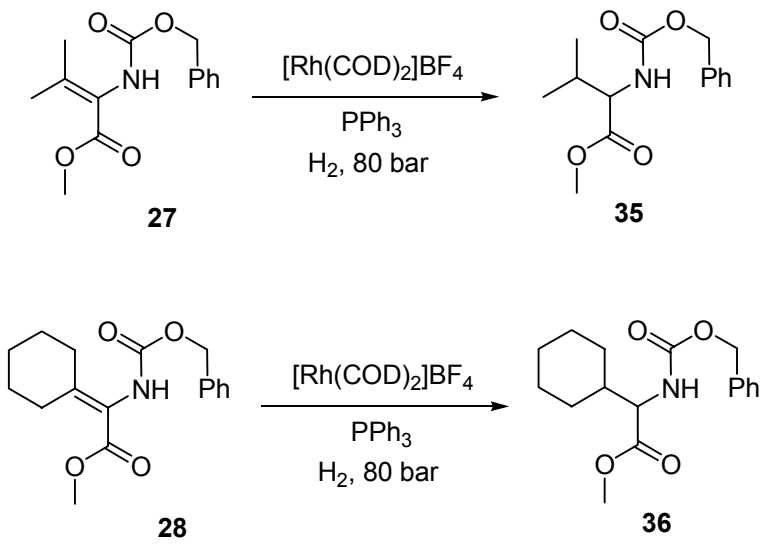
entry	sub.	ligand	solvent	pH_2 (bar)	t (h)	conv.[d] (%)	e.e.[e] (%)	conf.[25]
1	**2**	**L1**	CH_2Cl_2	60	15.5	6	12	*R*
2	**2**	**L4**	CH_2Cl_2	60	15.5	100	67	*R*
3	**2**	**L13**	EtOAc	5	16	99	87	*S*
4	**3**[b]	**L13**	EtOAc	5	16	70	85 / 70[c]	*S* / *S*
5	**5**	**L1**	CH_2Cl_2	1	120	27	14	*R*
6	**5**	**L1**	CH_2Cl_2	5	21	95	17	*R*
7	**5**	**L1**	CH_2Cl_2	50	16	100	21	*R*
8	**5**	**L4**	CH_2Cl_2	1	45	28	31	*R*
9	**5**	**L4**	CH_2Cl_2	60	20	97	46	*R*
10	**5**	**L13**	EtOAc	5	16	34	71	*S*

[a] Conditions used: $[Rh(COD)_2]BF_4$ (5 mol%), ligand (11 mol%, monodentate; 5.5 mol% bidentate). [b] *E* / *Z* mixture 1.5:1 [c] 85 % e.e. for (2*R*,3*S*) and 70 % for (2*R*,3*R*). [d] Conversion was determined by means of 1H NMR. [e] The e.e. was determined by means of chiral GC.

Substituting **L1** for **L4** again resulted in a higher reaction rate, indicating that the ligand derived from a primary amine indeed provides a rhodium complex which is able to reach higher rates of hydrogenation compared to the ligands derived from secondary amines. For all four substrates (**2** – **5**) ligand **L13** gives the best results when used in combination with the solvent ethyl acetate. The rate of the reaction is a bit lower compared to those with the catalyst based on the other ligands used; however the enantioselectivity is often 20-30 % higher.

3.2.2.2 Hydrogenation of methyl 3,3-disubstituted 2-Cbz-amino acrylates

Substrates with an *N*-Cbz protecting group have not been used frequently in the rhodium-catalyzed asymmetric hydrogenation (*vide supra)*. This may be partly related to a low reactivity in the hydrogenation of these substrates. This became apparent in the attempt to make racemic mixtures for the determination of a suitable GC analysis. Wilkinson's[29] catalyst $[Rh(PPh_3)_3Cl]$ did not give any conversion, not even at a hydrogen pressure of 80 bar. To overcome this problem a catalyst with the non-coordinating counter ion BF_4^- was tested. This catalyst was made *in situ* from $[Rh(COD)_2]BF_4$ and 3 equivalents of triphenyl phosphine. This catalyst yielded the racemates of products **35** and **36** under otherwise the same conditions. In this elegant manner Wilkinson's catalyst has been modified to a more active cationic version.



Scheme 3.7 *Synthesis of racemates of **35** and **36** using a modified Wilkinson catalyst.*

A number of screening experiments were performed using (*S*)-MonoPhos™ (**L1**) in the hydrogenation of methyl 2-(benzyloxycarbonylamino)-3-methylbut-2-enoate (**27**) and methyl 2-(benzyloxycarbonylamino)-2-cyclohexylideneacetate (**28**). The results are summarized in Table 3.8. In spite of the high pressure and sometimes long reaction times used, conversions were often very low. Only when allowing reactions to run for several days it was possible to obtain reasonable conversions (entries 1 and 5). Striking is the absence of any conversion at all when the hydrogenation of substrate **28** was attempted at a hydrogen pressure of 5 bar, even after prolonged reaction time (entry 3).

Table 3.8 *Hydrogenation of methyl 3,3-disubstituted 2-benzyloxycarbonylamino acrylates.*

entry	substrate	ligand	pH_2 (bar)	t (h)	conversion[b] (%)	e.e.[c] (%)
1	**27**	**L1**	60	41	75	22[30]
2	**27**	**L4**	60	15.5	1.5	nd[d]
3	**28**	**L1**	5	112	-	nd[d]
4	**28**	**L1**	60	1	5	nd[d]
5	**28**	**L1**	60	44	35	3[30]

[a] Conditions used: $[Rh(COD)_2]BF_4$ (5 mol%), ligand (11 mol%), dichloromethane. [b] Conversion was determined by means of ^1H NMR. [c] The e.e. was determined by means of chiral GC. [d] not determined.

In the small number of cases where reliable enantiomer separation was possible,[31] the e.e.'s (up to 22 %) turned out to be very disappointing. Striking is the low reactivity of substrate **27** toward hydrogenation using ligand **L4**. In the asymmetric hydrogenation of the corresponding *N*-acetyl substrate (*vide supra)* use of **L4** resulted in one of the most active catalysts.

The explanation for the low reactivity of Cbz protected substrates compared to acetyl protected substrates is not trivial. Increased steric hindrance due to the size of the Cbz protecting group could hamper the formation of the catalyst substrate complex. However, hydrogenation of *N*-Boc protected dehydroalanine proceeds at a higher rate than *N*-acetyl protected dehydroalanine.[32] The Boc protecting group is a carbamate as well and poses even more steric hindrance than a Cbz group. We can therefore rule out the possibility that only the size of the protecting group is responsible for the low reactivity of the substrate. A second possibility is that the substrate more or less blocks the catalyst via a tridentate coordination.[33] Next to the olefinic double bond and the oxygen of the Cbz group, the phenyl group can coordinate to the rhodium,[34] effectively blocking a large area of the space around the Rh atom making the oxidative addition of hydrogen more difficult.

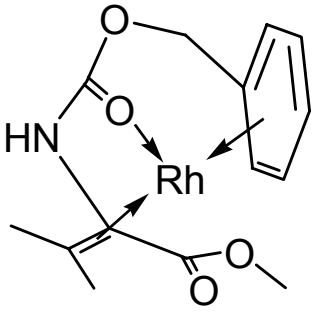


Figure 3.5 *Possible tridentate coordination of N-Cbz protected dehydro amino acids, the ligands are omitted for clarity.*

3.3 Conclusions

The asymmetric hydrogenation of 3,3-disubstituted 2-acetamido acrylates using a rhodium catalyst with phosphoramidite ligands has thus far not been able to match the enantioselectivities and reaction rates reported in the literature. However, the enantioselectivity has been increased from 42% to 89% in the case of substrate **4** by tuning of the ligands and solvents. This also holds for the other substrates, like **2**, which is hydrogenated with a high e.e. of 87%. Substrate **5** also showed an increase in e.e. (21 % to 71 %) upon modifying the ligand and changing the conditions used in the hydrogenation. The rates of the hydrogenation reactions are dependant on the ligands used. Full conversions within 24 h at 1 – 5 bar are reached with several ligands. The actual TOF still needs to be determined however.
Bidentate ligands derived from TADDOL and ethyl acetate as the solvent seems be the most promising combination for future research. In contrast to the findings described in Chapter 2 of this thesis, the 3,3-disubstituted dehydroamino acids are most effective hydrogenated using bidentate phosphoramidite ligands instead of monodentate ones. A drawback of this ligand class, phosphoramidites, is the low reactivity of the corresponding rhodium complexes in hydrogenation reaction, as shown by the disappointing results obtained after decreasing the amount of catalyst. Improvement of the reactivity is likely to become a major challenge, for both the mono- as well as the bidentate ligands. However, there are still a lot of possibilities to improve the ligands used. The only two backbones tested thus far are TADDOL and BINOL which can also be changed. Changing both steric and electronic properties can facilitate the right combination in order to find the most effective ligand to be used in the hydrogenation of tetra-substituted carbon-carbon double bonds.

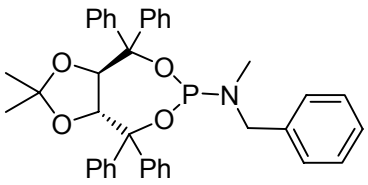
Asymmetric hydrogenation of 3,3-disubstituted *N*-Cbz protected amino acrylates would offer a lot of potential as a facile method to obtain a large variety of non-natural amino acids. Although high hydrogen pressures are required to obtain conversion we were able to reach a conversion of 75 % within reasonable reaction times. The highest enantiomeric excess obtained in the first hydrogenation (to the best of our knowledge) of two 3,3-disubstituted *N*-Cbz protected amino acrylates, **27** and **28**, was 22 %. This result is promising for further research into the asymmetric hydrogenation of this type of substrates. Thus far we were able to improve the conversion by increasing the hydrogen pressure. This high pressure could be responsible for the low enantioselectivity. The primary variable to look into would therefore be the solvent. Using a solvent that suppresses the possible tridentate coordination of the substrate could make the hydrogenation possible at lower hydrogen pressures. Besides the solvent a lot more ligands can be tested as well, which are known to be able to influence to great extend the Rh-catalyzed asymmetric hydrogenation.

3.4 Experimental

General remarks:
For general information, see Chapter 2. GC measurements were performed either on a HP 5890 A, HP 5890 series II or a HP 6890 gas chromatograph using a flame ionization detector.

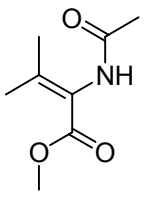
Ligands **L1**, **L2**, **L3**, **L4**, **L11**, **L12**, **L13** and **L14** have been described in Chapter 2. The other ligands were synthesized according to literature procedures: **L7**[35]

(*R*,*R*)-Benzyl-(2,2-dimethyl-4,4,8,8-tetraphenyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-methyl-amine (L10)



A 100 ml 2-neck flask fitted with a magnetic stirrer was flame dried under a nitrogen atmosphere before it was charged with (*R*,*R*)-TADDOL (**5.5**; 2.049g; 4.30 mmol), anhydrous THF (10 ml) and triethylamine (1.8 ml; 1.314 g; 13.00 mmol). After stirring at 0°C for 1h phosphorus trichloride (0.41 ml; 0.644 g; 4.70 mmol) was added, and stirring at 0°C was continued for another 2h. The formed precipitate was filtered off under nitrogen and washed with a small amount of THF. Meanwhile, a Schlenk tube was flame dried under a nitrogen atmosphere and charged with THF (5 ml), *N*-benzylmethylamine (0.56 ml; 0.53 g; 4.34 mmol) and *n*-butyllithium (1.6M in hexane; 2.7 ml). This mixture was stirred for 1h at 0°C before it was added to the previously collected filtrate using a syringe. The resulting mixture was stirred for 1d, during which the reaction mixture was allowed to slowly warm to r.t. After filtration the volatiles were removed *in vacuo*. The crude product was dissolved in EtOAc, and washed with 0.5M NaOH, followed by recrystallization from a CH_2Cl_2 / heptane mixture to give 0.264 g (0.43 mmol; 10%) of an off white solid.
^{1}H NMR δ 0.30 (s, 3H), 1.30 (s, 3H), 2.66 (d, ^{3}J = 8.8 Hz, 3H), 4.21 (d, ^{2}J = 4.6 Hz, 1H), 4.25 (d, ^{2}J = 4.6 Hz, 1H), 4.84 (d, ^{3}J = 8.6 Hz, 1H), 5.22-5.28 (dd, ^{3}J = 8.5 Hz, ^{4}J = 3.4 Hz, 1H), 7.15-7.55 (m, 21H), 7.60-7.70 (m, 2H), 7.75-7.85(m, 2H); ^{31}P NMR δ 138.12; ^{13}C NMR ($CDCl_3$) δ 25.35 (q), 27.53 (q), 31.78 (q, ^{2}J = 15.1 Hz), 52.64 (t, ^{2}J = 27.5 Hz), 81.50 (s, ^{2}J = 10.1 Hz), 82.38 (d), 82.47 (d), 111.74 (s), 126.93 (d), 127.11 (d), 127.29 (d), 127.51 (d), 127.68 (d), 128.10 (d), 128.17 (d), 128.26 (d), 128.74 (d), 128.83 (d), 129.03 (d), 139.09 (s, ^{3}J = 7.0 Hz), 141.68 (s), 142.24 (s), 146.47 (s), 146.88 (s).

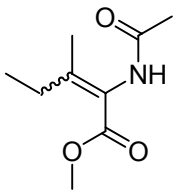
Methyl 2-acetamido-3-methylbut-2-enoate (2)



A 250 mL 2-necked flask equipped with a magnetic stirrer, Dean Stark apparatus, reflux condenser and a $CaCl_2$-tube, was charged with acetamide (5.02 g; 85.1 mmol), *p*-toluenesulphonic acid monohydrate (3.91 g; 20.6 mmol) and benzene (250 mL). This mixture was heated at reflux for 1 h to remove water. 3-Methyl-2-oxo-butyric acid methyl ester (**19**; 7.5 g; 51.9 mmol) was added and heated at reflux was continued for 24 h, while following the reaction by TLC (eluent

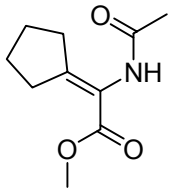
hexane:EtOAc 1:3). The reaction mixture was allowed to cool to room temperature before aq. $NaHCO_3$ (sat., 75 mL) was added. The aqueous layer was extracted with EtOAc (4 x 50 mL), washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent the product was purified by column chromatography using silica with hexane:EtOAc 1:4 as the eluent. 2-Acetylamino-3-methyl-but-2-enoic acid methyl ester (**2**) was isolated with a yield of 3.07 g (17.93 mmol; 35%). Spectroscopic data were in good agreement with the data in the literature.[4]

(E / Z)-Methyl 2-acetamido-3-methylpent-2-enoate (3)



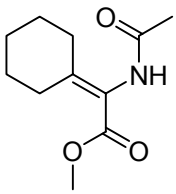
The procedure employed for making this substrate is analogous to the one described for **2**. The amounts of starting material used were: 3-methyl-2-oxo-pentanoic acid methyl ester (17.61 g; 120 mmol), acetamide (11.29 g; 191.4 mmol), *p*-toluenesulphonic acid monohydrate (9.17 g; 48.3 mmol) and benzene (300 mL). The mixture was heated at reflux for 48 h. Workup was as described previously, followed by purification by column chromatography using silica, with hexane:EtOAc 4:1 as an eluent. Total yield 4.16 g (22.5 mmol; 19%). ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[4]

Methyl 2-acetamido-2-cyclopentylideneacetate (4)



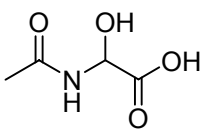
The procedure employed for making this substrate is analogous to the one described for **2**, using cyclopentyl-oxo-acetic acid methyl ester (9.94 g; 63.7 mmol), acetamide (6.10 g; 103.3 mmol), *p*-toluenesulphonic acid monohydrate (4.81 g; 25.3 mmol) and benzene (250 mL). This mixture was heated at reflux under Dean-Stark conditions for 24 h. Workup was done as described previously and purification by column chromatography using silica, with hexane:EtOAc 4:1 as an eluent. The yield was 6.98 g (35.4 mmol; 56%). ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[4]

Methyl 2-acetamido-2-cyclohexylideneacetate (5)



The procedure employed for making this substrate is analogous to the one described for **2**, using cyclohexyl-oxo-acetic acid methyl ester (9.76 g; 57.4 mmol), acetamide (5.51 g; 93.4 mmol), *p*-toluenesulphonic acid monohydrate (4.32 g; 22.7 mmol) and 250 mL of benzene. The mixture was heated at reflux for 28 h followed by a work up as described previously. Because not all starting material had been converted, despite the long reaction time, the remainder was deployed in a second reaction. The total amount isolated was 5.5 g (26.1 mmol; 45%). ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[4]

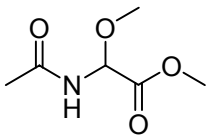
2-Acetamido-2-hydroxyacetic acid (11)



A mixture of acetamide (2.78 g; 47.1 mmol) and glyoxylic acid monohydrate (4.54 g; 49.3 mmol) in THF (75 mL) was gently heated until a clear solution was obtained. This solution was stirred for 3 d at room

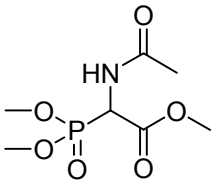
temperature. The solvent was removed *in vacuo* giving compound **11** in quantitative yield. This product was used in the next synthesis step without any purification.

Methyl 2-acetamido-2-methoxyacetate (12)



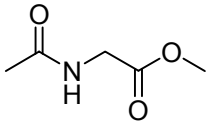
To an ice-cooled solution of **11** (3.0 g, 13.3 mmol) in anhydrous methanol (50 mL) was added concentrated sulphuric acid (0.5 mL). The mixture was allowed to warm to room temperature and stirred for 48 h. At this point the reaction mixture was quenched by being poured into ice-saturated aq. $NaHCO_3$ (sat. 100 mL). The product was extracted with ethyl acetate (5 × 50 mL) and the organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* yielding a mixture with **12** present in only 25 % according to ^{1}H NMR.

Methyl 2-acetamido-2-(dimethoxyphosphoryl)acetate (13)



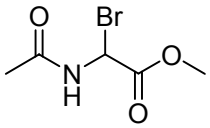
To a solution of crude acetylamino-bromo-acetic acid methyl ester (**16**) in CH_2Cl_2 (50 mL) was added trimethylphosphite (5.33 g, 43.0 mmol). This mixture was stirred for 2 h, the dichloromethane was evaporated and the remaining oil solidified. The solids were filtered and washed with a mixture of ethyl acetate and hexane. The solvent was evaporated *in vacuo*, after which the second crop of product could be isolated The combined crystalline fractions were recrystallized from THF. The resulting crystals were filtered off and washed with a small amount of cold THF. Yield 3.31 g (13.85 mmol; 27% over 3 steps). ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[36]

Methyl 2-acetamidoacetate (15)



To a stirred suspension of *N*-acetylglycine (6.04 g; 51.6 mmol) in MeOH (16 mL) at -18 ^{o}C was added dropwise thionyl chloride (11.62 g; 97.6 mmol) over a period of 45 min. Stirring was continued at room temperature for 3 h, after which the reaction mixture was evaporated, providing the product in quantitative yield. The crude product thus obtained was used in the next step without purification.

Methyl 2-acetamido-2-bromoacetic acid (16)

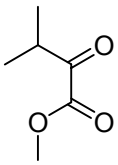


A mixture of acetylamino-acetic acid methyl ester (**15**), (50 mmol), AIBN (0.17 g; 1.06 mmol) and tetrachloromethane (100 mL) was heated to reflux, before a solution of Br_2 (4 mL; 78 mmol) in tetrachloromethane (70 mL) was added dropwise over a period of 30 min under irradiation with a Tungsten lamp forming a precipitate. Heating at reflux was continued for another 1.75 h, while conversion was followed by TLC. While still hot, the solution was decanted. The remaining oily residue was extracted with hot ethyl acetate. The resulting organic solution was combined with the decanted reaction mixture and the solvents were evaporated *in vacuo*. The crude product thus obtained was deployed in the next step without purification.

Isopropylmagnesium chloride (17)

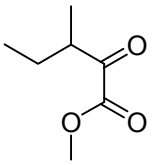
A 250 mL 3-necked flask was fitted with a magnetic stirrer, a pressure-equalising dropping funnel and a reflux condenser. This setup was thoroughly flame-dried and placed under a nitrogen atmosphere. It was then charged with magnesium turnings (2.1 g, 87.5 mmol), that had been activated with a mortar and pestle. A solution of isopropyl chloride (6.0 mL, 66 mmol) in anhydrous diethyl ether (35 mL) was placed in the dropping funnel. The reaction was initiated by dropping a small quantity of the isopropyl chloride solution to the magnesium turnings and heating it with a hotgun. Once initiated the remainder of the solution was added at such a rate as to keep the mixture under gentle reflux. After complete addition the reaction mixture was allowed to reflux for another 1.5 h and finally allowed to cool to room temperature. The obtained solution was directly used in the next step, without purification or analysis.

Methyl 3-methyl-2-oxobutanoate (19)



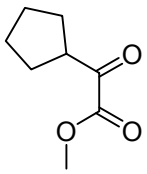
A 1L 2-necked flask was fitted with a pressure-equalising dropping funnel, thoroughly flame-dried and placed under a nitrogen atmosphere. Subsequently, it was charged with a solution of dimethyl oxalate (15.42 g, 130 mmol) in anhydrous diethyl ether (250 mL), and the solution cooled to –50 ^{o}C. The solution of isopropyl magnesium chloride was transferred to the dropping funnel using a glass syringe and added dropwise to the mixture in about 1 h. The reaction mixture was allowed to stir for another hour. After replacing the cooling bath for an ice bath, aqueous HCl (10%, 150 mL) was added and stirring was continued for 1 h. After separation of layers the aqueous layer was extracted with diethyl ether (3 x 100 mL), the combined organic layers were washed with brine and dried over Na_2SO_4, filtered and evaporated *in vacuo*. Residual dimethyl oxalate was removed by dissolving the crude product in hexane, cooling with liquid nitrogen to facilitate precipitation before filtrating over a glass filter. Finally, the solvent was evaporated, yielding 5.50 g (42.3 mmol, 64% based on isopropyl chloride) of a pale yellow oil (**19**). ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[37]

Methyl 3-methyl-2-oxopentanoate (20)



Synthesis of the Grignard reagent was performed analogous to **17** using 4.90 g (200 mmol) of magnesium turnings, *s*-butyl chloride (19.5 mL, 184 mmol) and 65 mL of Et_2O. Synthesis of **20** was analogous to **19**, using 21.67 g (183.6 mmol) of dimethyl oxalate in 400 mL of diethyl ether at a temperature of -55 ^{o}C, yielding 21.45 g (130 mmol, 70 % from s-butyl chloride) of **20**. ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[38]

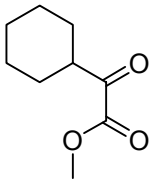
Methyl 2-cyclopentyl-2-oxoacetate (21)



Synthesis of the Grignard reagent was analogous to **17** using 3.16 g (130 mmol) of magnesium turnings, cyclopentyl chloride (11.9 g, 113 mmol) and 75 mL of Et_2O. Synthesis of **21** was analogous to **19**, using 12.14 g (102.9 mmol) of dimethyl oxalate at a temperature of -55 ^{o}C, yielding 13.68 g (87.7 mmol, 85%

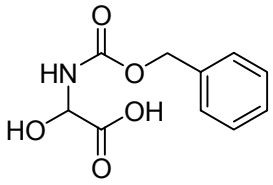
from cyclopentyl chloride) of **20**. [39]

Methyl 2-cyclohexyl-2-oxoacetate (22)



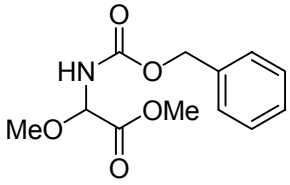
Synthesis of the Grignard reagent was analogous to **19** using 3.16 g (130 mmol) of magnesium turnings, cyclohexyl chloride (11.9 g; 100 mmol) and 75 mL of Et_2O. Synthesis of **22** was analogous to **19** using 12.12 g (102.7 mmol) of dimethyl oxalate at a temperature of -55 °C, yielding 13.50 g (79.4 mmol, 79% from cyclohexyl chloride) of **22**. ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[39]

2-(Benzyloxycarbonylamino)-2-hydroxyacetic acid (24)



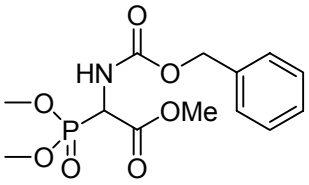
Benzyl carbamate (37.91 g; 251 mmol) and glyoxylic acid monohydrate (25.02 g; 272 mmol) were dissolved in 400 mL of dry diethyl ether. The mixture was stirred for 20 h, after which the Et_2O was evaporated *in vacuo*, giving the product in quantitative yield. ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[40]

Methyl 2-(benzyloxycarbonylamino)-2-methoxyacetate (25)



The crude product obtained in the previous step was dissolved in anhydrous methanol (500 mL) and placed in an ice bath. While stirring, concentrated sulphuric acid (10 mL) was added. The reaction mixture was allowed to warm to room temperature and stirring was continued for 3 d. The mixture was then poured into ice-cooled $NaHCO_3$ (sat., 1 L) and stirred, after which the aqueous layer was extracted with EtOAc (5 x 500 mL). The combined organic layers were dried over Na_2SO_4, filtrated and the solvents evaporated *in vacuo*, providing a white solid in quantitative yield. ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[22,41]

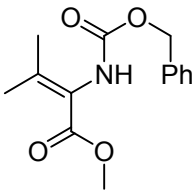
Methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl) acetate (26)



The solid obtained in the previous step was dissolved in toluene (300 mL) and heated to 70 °C, followed by addition of PCl_3 (22 mL; 252 mmol). After stirring the mixture at 70 °C for 45 h, $P(OMe)_3$ (29.5 mL; 250 mmol) was added and stirring was continued for another 2.75 h. The mixture was then allowed to cool to room temperature and the solvent was evaporated *in vacuo*, after which the residue was dissolved in EtOAc (100 mL). This solution was washed with aq. $NaHCO_3$ (sat., 3 x 50 mL), dried over Na_2SO_4, filtrated and the solvents evaporated *in vacuo*. After adding a small amount of a mixture of hexane:EtOAc 1:1 and shaking vigorously, white crystals appeared that were washed with a small amount of hexane. From the filtrate other fractions were isolated, that were combined and recrystallized from *t*-butyl methyl ether. Total yield 70 g (210 mmol; 84% from benzyl carbamate).

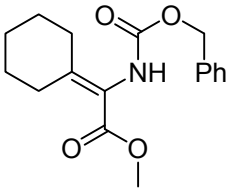
^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.80-3.84 (m, 6H), 4.86-5.01 (dd, ^{2}J = 22.5 Hz, ^{3}J = 9.3 Hz, 1H), 5.14 (s, 2H), 5.65 (br d, ^{3}J = 7.7 Hz, 1H), 7.35 (s, 5H); ^{31}P NMR ($CDCl_3$) δ 17.99; ^{13}C NMR ($CDCl_3$) δ 51.76 (d, ^{1}J = 136 Hz), 53.62 (q, ^{2}J = 26 Hz), 53.87 (q, ^{4}J = 13 Hz), 67.37 (t), 127.92 (d), 128.10 (d), 128.33(d), 135.70 (s), 155.59 (s), 167.00 (s); EI-MS *m/z* = 65, 91, 109, 138, 165, 182, 196, 224, 254, 272, 299, 331[M]$^{+\cdot}$; HRMS (EI^{+}) calculated for $C_{13}H_{18}NO_7P$: 331.0821, found: 331.0813.

Methyl 2-(benzyloxycarbonylamino)-3-methylbut-2-enoate (27)



A 250 ml 3-neck flask was flame-dried, placed under a nitrogen atmosphere and charged with methyl benzyloxycarbonylamino-(dimethoxy-phosphoryl)-acetate (**26**; 6.73 g; 20.3 mmol), anhydrous acetone (50 mL) and DBU (3 mL; 20.1 mmol). The mixture was left stirring for 5 d, while the conversion was followed by TLC (SiO_2, hexane:EtOAc 1:1). Then ethyl acetate (250 mL) was added and the mixture was washed with 1N H_2SO_4 (125 mL). After separation, the organic layer was dried over $MgSO_4$, the solvents evaporated *in vacuo* and the crude product filtrated over silica 60Å (eluent hexane:EtOAc 1:1). The product was recrystallized from *t*-butyl methyl ether. Yield 2.90 g (11.02 mmol; 55%). ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[19]

Methyl 2-(benzyloxycarbonylamino)-2-cyclohexylideneacetate (28)



Analogous to **27**, using **26** (0.81 g; 2.46 mmol), cyclohexanone (10 mL) and DBU (0.35 mL; 2.41 mmol). The mixture was stirred for 3 d, while the conversion was checked by TLC (SiO_2, hexane:EtOAc 1:1). Ethyl acetate (100 mL) was added and the mixture was washed with 1N aq. H_2SO_4 (25 mL). After separation the organic layer was dried over $MgSO_4$, the solvents evaporated *in vacuo* and the crude product filtered over silica 60Å (eluent hexane:EtOAc 1:1). The product was recrystallized from hexane:EtOAc 1:3 and washed with hexane. A second fraction was isolated from the filtrate, giving a total yield of 0.65 g (2.13 mmol; 88%). ^{1}H NMR and ^{13}C NMR data were in good agreement with those in the literature.[19]

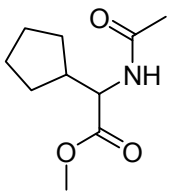
Asymmetric Hydrogenations

Standard Schlenk-type techniques were used. Most hydrogenation reactions were performed in a Parr autoclave mini reactor series 4560 (Hastelloy C) equipped with 7 glass reaction vessels (5 mL).[42] In a typical experiment in the metal autoclave, a 5 mL oven dried glass tube with a small stirring bar, was charged with substrate (200 μmol), $[Rh(COD)_2]BF_4$ (10 μmol) and ligand (22 μmol if monodentate, 11 μmol if bidentate) and degassed solvent (3.5 mL). The autoclave was then closed, purged with nitrogen, the appropriate pressure of hydrogen was applied, and stirring was started. After a certain time, the autoclave was opened and samples of 0.2 mL were taken from the reaction mixture. These samples were run over a plug of silica with 2 mL of hexane:EtOAc 1:4 as the eluent to make a GC sample. From the

remaining of the reaction mixture the solvent was evaporated and the product analysed by ^{1}H NMR.
For reactions performed at 1 bar, a 10 mL Schlenk tube was used in combination with a hydrogen balloon.

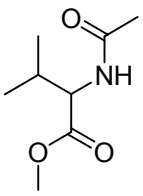
The racemic mixtures were prepared using 5 mol% $[Rh(COD)_2]BF_4$ with 3 equivalents of PPh_3 using dichloromethane as a solvent at 80 bar of hydrogen pressure.

Methyl 2-acetamido-2-cyclopentylacetate (30)



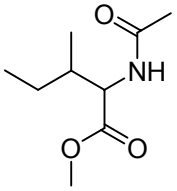
This product was obtained after hydrogenation of substrate **4**. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m, 250 µm, 0.12 µm), N_2-flow: 1.3 mL/min., 140 °C isothermal, T_r = 7.2 min. (*R*), T_r = 8.1 min. (*S*), T_r = 13.4 min. (sm).[25]

Methyl 2-acetamido-3-methylbutanoate (32)



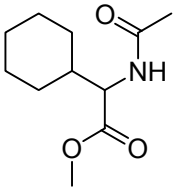
This product was obtained after hydrogenation of substrate **2**. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m, 250 µm, 0.12 µm), N_2-flow: 1.3 mL/min., 140 °C isothermal, T_r = 2.5 min. (*R*), T_r = 2.6 min. (*S*), T_r = 4.5 min. (sm).[25]

Methyl 2-acetamido-3-methylpentanoate (33)



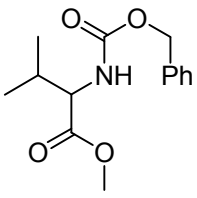
This product was obtained after hydrogenation of substrate **3**. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m, 250 µm, 0.12 µm), N_2-flow: 1.3 mL/min., 140 °C isothermal, T_r = 3.0 min. (*R*, *R*), T_r = 3.2 min. (*R*, *S*), T_r = 3.3 min. (*S*, *S*), T_r = 3.5 min. (*S*, *R*), T_r = 5.8 min. (sm, E), T_r = 6.7 min. (sm, Z).[25]

Methyl 2-acetamido-2-cyclohexylacetate (34)



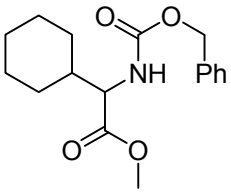
This product was obtained after hydrogenation of substrate **5**. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m, 250 µm, 0.12 µm), N_2-flow: 1.3 mL/min., 140 °C isothermal, T_r = 10.7 min. (*R*), T_r = 12.3 min. (*S*), T_r = 19.2 min. (sm).[25]

Methyl 2-(benzyloxycarbonylamino)-3-methylbutanoate (35)



This product was obtained after hydrogenation of substrate **27**. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m, 250 µm, 0.12 µm), N_2-flow: 1.3 mL/min., 140 °C isothermal, T_r = 19.4 min. (*R*), T_r = 19.6 min. (*S*), T_r = 22.4 min. (sm).[30]

Methyl 2-(benzyloxycarbonylamino)-2-cyclohexylacetate (36)



This product was obtained after hydrogenation of substrate **28**. E.e. determination by GC analysis: CP Chirasil-L-Val (25 m, 250 μm, 0.12 μm), N_2-flow: 1.3 mL/min., 140 °C isothermal, T_r = 19.9 min. (*R*), T_r = 20.6 min. (*S*), T_r = 23.4 min. (sm).[30]

3.5 References and Notes

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[25] Absolute configurations were assigned by analogy (GC elution order) with the results reported by Burk *et al*, see ref 4.
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[30] Absolute configurations were not assigned. Absolute configurations could not be assigned by analogy (GC elution order) with any results reported in literature. Due to the poor results obtained no effort was made to determine the absolute configuration.
[31] Because of the low conversions, it often proved impossible to determine reliable e.e. values. Even when conversion was higher than a few percent, we often experienced difficulties in determining the enantioselectivity. We noticed that the *N*-Cbz protected products were much less volatile than their *N*-acetyl protected analogues and that their response on the detector was low for unknown reasons. Perhaps chiral HPLC would be a more suitable separation method for these products.
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