Enantioselective synthesis of β²-amino acids using rhodium-catalyzed hydrogenation

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A series of protected β²-dehydroamino acids has been prepared in three steps from commercially available starting materials in good yields. These were used as substrates in rhodium-catalyzed asymmetric hydrogenation applying a mixed ligand system of monodentate phosphoramidites and phosphines. Optimization of the catalyst structure was achieved by high throughput experimentation. High enantioselectivities were obtained (up to 91%) with full conversion for a number of β-amino acids.

Introduction

Since the seminal reports on the use of monodentate ligands in the highly enantioselective rhodium-catalyzed asymmetric hydrogenation by the groups of Pringle,[1a] Feringa, De Vries, Minnaard[1b] and Reetz,[1c] the number of studies on the use of monodentate ligands increased spectacularly.[2] Furthermore, the fact that two monodentate ligands coordinate to the metal-centre in the catalytically active species, was exploited by Reetz and coworkers[3] and our own group[4] to show that mixtures of monodentate ligands can be used in the hydrogenation to enhance selectivities and reactivity.[5]

In recent years, we have focused on the development of new catalytic systems for asymmetric hydrogenations,[6] and considerable effort has been directed towards the exploration of new substrate classes.[7]

β-Peptides have attracted considerable interest in the last decade.[8] Interesting features of these molecules are that they can fold in a predictable way to form secondary structures in solution, they show resistance to cleavage by peptidases and other metabolic transformations and mimic α-peptides in protein–protein and peptide–protein interactions. The building blocks for β-peptides are β-amino acids which can be subdivided in three categories, *i.e.* β²-, β³- and β²,³-amino acids (Fig. 1).

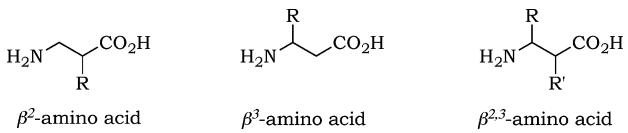

Fig. 1 β-Amino acids.

A wide variety of methods are available to prepare enantiomerically pure β-amino acids.[9] The synthesis of β³-amino acids has received most attention although a number of studies have focused on β²-amino acids. Approaches taken include[10] stereoselective alkylation of β-homoglycine derivatives,[11] addition of chiral enolates to acyliminium salts,[12] Curtius rearrangement of enantiomerically pure succinates,[13] resolution of racemic β²-amino acids[14] and enantioselective organocatalytic aminomethylation of aldehydes.[15] Limited effort has been devoted to the synthesis of β²-amino acids by transition metal catalysis. Examples are Pd-catalyzed allylic substitution,[16] Rh-catalyzed CH activation,[17] Cu-catalyzed conjugate addition[18] and Rh-catalyzed hydrogenation.[19]

In contrast to the asymmetric hydrogenation of β³-dehydroamino acid esters,[20] the asymmetric hydrogenation of the corresponding β²-amino acid precursors is still less developed. Robinson and co-workers[19] have reported the asymmetric hydrogenation of β²-amino acid precursors. Phthalimido nitriles were hydrogenated, which form β²-amino acids after simultaneous hydrolysis of the phthalimido and the nitrile functional groups. Promising enantioselectivities (78%) were obtained with Rh–DuPHOS or Rh–BPE complexes. The substrates, however, are prepared by Ni-catalyzed addition of the toxic hydrogen cyanide to alkynes. The same group recently described an alternative preparation of β²-amino acids in three steps with modest ee's (67%).[19c]

Very recently, Zheng and co-workers reported a short synthesis of β²-amino acids *via* rhodium-catalyzed asymmetric hydrogenation of β²-dehydroamino acids using monodentate phosphites as ligands.[21] Excellent enantioselectivities were obtained with precursors containing 1,1-disubstituted olefinic bonds. For the trisubstituted analogues good ee's were accompanied by incomplete conversions even after 12 h at 85 atm of hydrogen pressure.

This paper prompted us to report our results on the synthesis of β²-amino acids *via* asymmetric rhodium-catalyzed hydrogenation reactions employing a mixed ligand system consisting of chiral monodentate phosphoramidites and achiral phosphines.

Results and discussion

The synthesis of the substrates was executed on a multi-gram scale, in three steps starting from benzaldehydes **1–8** and methyl acrylate **9** (Scheme 1).

The synthesis starts with a Baylis–Hillman reaction that is well documented[22] and proceeds smoothly with good yields (77–87%) for substrates **1** and **5–8**. The methyl-substituted products

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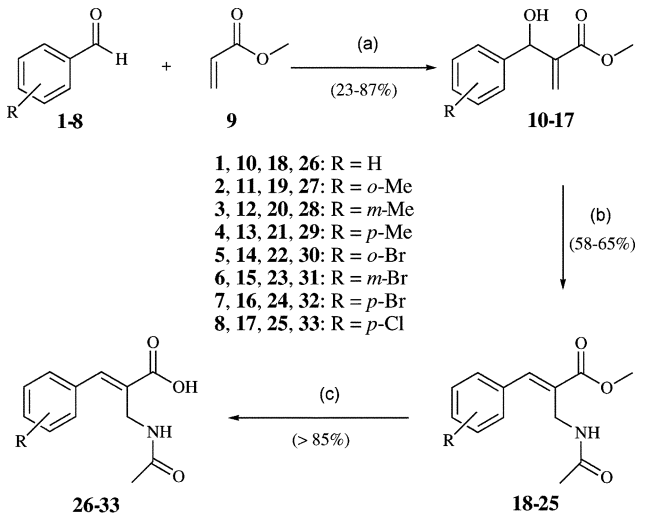


(a) Me_3N, or DABCO, MeOH (b) CH_3SO_3H, 110°C, CH_3CN
(c) LiOH, MeOH / H_2O

Scheme 1 Synthesis of substrates **26–33**.

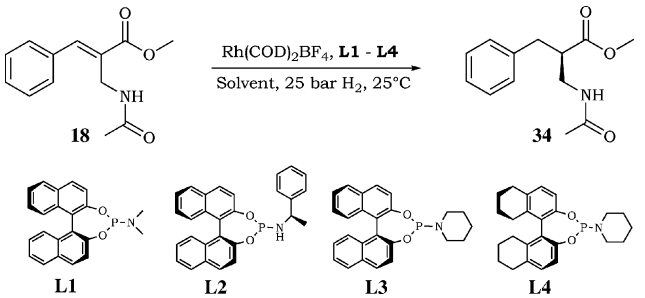
11–13 were obtained in low yield, due to incomplete conversions, even after 10 d reaction time. The second step, recently reported by Basavaiah *et al.*,[23] is a Ritter-type reaction. This reaction proceeded in good yields with exclusive formation of the *E*-isomer. Subsequently, the dehydroamino acids **26–33** could be obtained in high yield after straightforward hydrolysis of **18–25**.

Initially, we attempted the asymmetric hydrogenation of substrate **18**, applying the conditions developed previously[24] for the hydrogenation of β[3]-dehydroamino acids using phosphoramidite ligands **L1–L4** (Table 1). Surprisingly, when these reactions were performed with Rh–**L*x*** in CH_2Cl_2 and 25 bar of hydrogen pressure no conversion was seen at 25 °C. Reactions performed with Rh–**L*x*** in *i*-PrOH gave in some cases low conversions, but the enantioselectivities obtained were poor. Ee determination was carried out by RP-HPLC using an acetonitrile–NaH_2PO_4 buffer (see Experimental section).[25]

Recently, we described the successful rhodium-catalyzed asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[4b] In this study, the combination of an achiral phosphine and a chiral phosphoramidite increased the rate of the reaction and enantioselectivity dramatically. The presence of a carboxylic acid instead of the corresponding methyl ester appeared to be important. Since the structure of **26** bears some relationship to the substrates used in our previous study, hydrogenations were studied under similar conditions (Table 2).

Employing a Rh–**L*x*** catalyst, increasing the temperature to 60 °C, adding 20% water[4b] and using carboxylic acid **26** led to full conversion, although a racemic mixture was obtained (Table 2). *Addition of an equivalent of triphenylphosphine increased the ee dramatically*, *however.* The largest increase was observed in combination with **L6**. The homo-combination of **L6** induced no selectivity, whereas the hetero-combination of **L6** with PPh_3 led to an ee of 83% (entries 5 and 6). As observed previously, phosphoramidites substituted with two methyl groups at the 3 and 3′ positions of the BINOL moiety, led to higher enantioselectivities than the unsubstituted BINOL based phosphoramidites (entries 2 and 6).

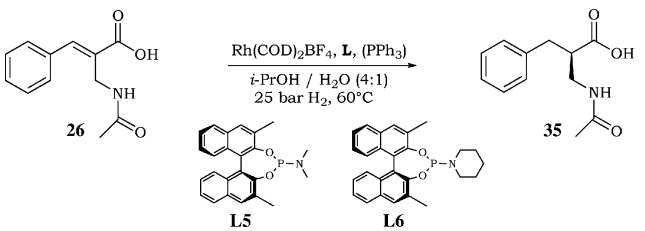
Table 1 Screening of **L1–L4** on the hydrogenation of **18** in *i*-PrOH and CH_2Cl_2[a,b,c]



Entry	Solvent	Ligand	Conversion	Ee[d,e]
1	CH_2Cl_2	**L1**	0	—
2	CH_2Cl_2	**L2**	0	—
3	CH_2Cl_2	**L3**	0	—
4	CH_2Cl_2	**L4**	0	—
5	*i*-PrOH	**L1**	20	46
6	*i*-PrOH	**L2**	< 10	ND
7	*i*-PrOH	**L3**	0	—
8	*i*-PrOH	**L4**	15	10

[a] Reaction conditions: 0.2 mmol of substrate in 4 ml of solvent with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidite. [b] 16 h at rt and 25 bar H_2. [c] Conditions are reported in ref. 1*b*, 20*a* and 24. [d] Ee's were determined by chiral RP-HPLC, see Experimental section. [e] Absolute configuration of product is unknown.

Table 2 Influence of PPh_3 on the hydrogenation of **26**[a,b]



Entry	Ligand	Conversion	Ee[c,d]
1	**L3**	100	0
2	**L3** + PPh_3	100	66
3	**L5**	100	0
4	**L5** + PPh_3	100	75
5	**L6**	100	0
6	**L6** + PPh_3	100	83

[a] Reaction conditions: 0.2 mmol of substrate in 4 ml of an *i*-PrOH–H_2O (4 : 1) mixture with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidites and possibly 0.002 mmol of PPh_3. [b] 16 h at 60 °C and 25 bar H_2. [c] Ee's were determined by chiral RP-HPLC after conversion of product to the corresponding methyl ester (for details see experimental section). [d] Absolute configuration of product is unknown.

One of the major advantages of monodentate phosphoramidite ligands is their straightforward synthesis, which makes structural variation easy. This has been exploited by the development of an automated method for the parallel solution phase synthesis of monodentate phosphoramidite ligands and their corresponding catalyst libraries.[26] This approach allows the screening of a large number of structurally diverse phosphoramidites over a short period of time. We have used this method to optimize the catalyst in terms of conversion and enantioselectivity.

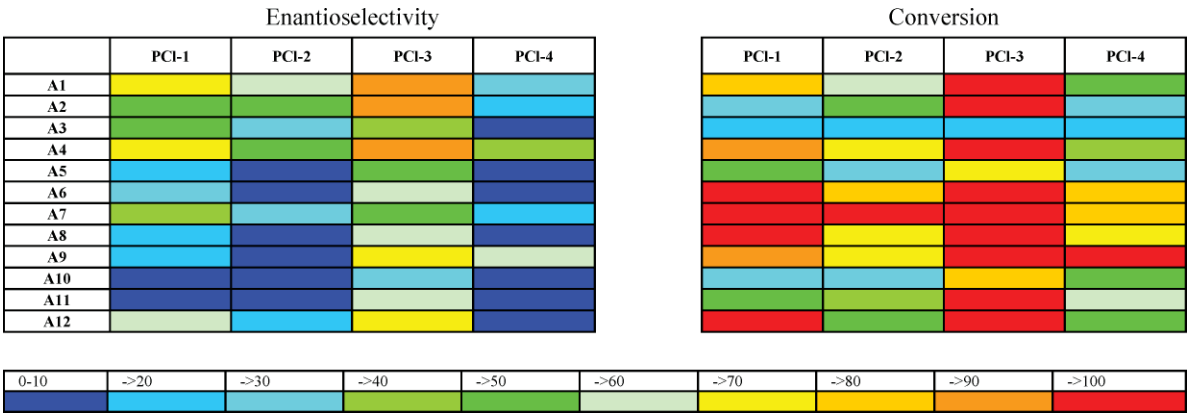
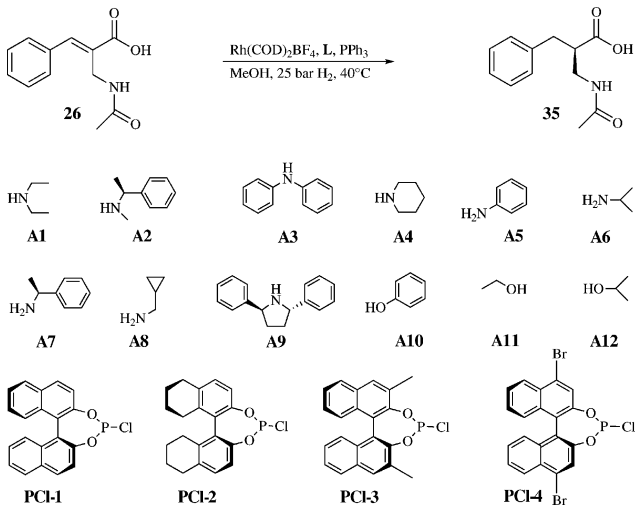


Fig. 2 Hydrogenation results with first library.

A first library of 48 monodentate ligands, based on 4 phosphorochloridites and 12 different amines and alcohols, was used in the hydrogenation of substrate **26** at 25 bar of H_2 and 40 °C using one equivalent of PPh_3 as the co-ligand (Scheme 2). The results are depicted in Fig. 2.

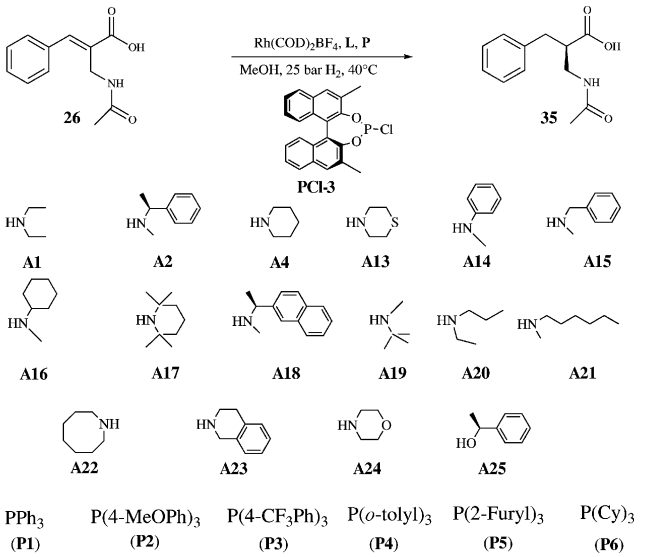


Scheme 2 Setup of first library of phosphoramidites and phosphites.

Ligands based on a 3,3′-dimethyl BINOL (**PCl-3**) induced in most cases full conversion and modest to good ee's. By contrast, ligands based on BINOL (**PCl-1**), 8H BINOL (**PCl-2**) and 4,4′-dibromo BINOL (**PCl-4**) led to relatively low active catalysts with, in general, decreased ee's. The enantioselectivities induced by ligands based on primary amines **A5–A8** and alcohols **A10–A12** were poor. The best results were obtained with ligands based on combinations of **PCl-3** with secondary amines **A1**, **A2** and **A4** (full conversion and 89% ee).

Following on from these results, a second library with 16 different phosphoramidites based on 3,3′-dimethyl BINOL and 16 different secondary amines was designed. Each phosphoramidite was combined with 6 different achiral phosphines (Scheme 3) to afford in total 96 Rh-catalysts.

The results of the screening of the hydrogenation of substrate **26** of the second library are depicted in Fig. 3. In general, most of the ligands performed well. Good to full conversions were



Scheme 3 Setup of second library of phosphoramidites and phosphites.

obtained, with some exceptions, mostly phosphoramidites based on fully aliphatic amines and phosphites. With most ligands, enantioselectivities of >80% were obtained using PPh_3 (**P1**) as an achiral co-ligand. The use of other phosphines did not show any improvements. Although modest to good ee's were obtained with **P5**, the conversions were incomplete in all cases. Contrarily use of **P6** resulted in good to excellent conversions, but the enantioselectivities remained low.

The results of the library screenings showed that **L6** (a combination of **PCl-3** and **A4**) in combination with PPh_3 (**P1**) or P(*o*-tolyl)$_3$ (**P4**) led to the best results in terms of conversion and enantioselectivity (full conversion and 90% ee).

It has been observed previously that small alterations in the phosphine structure can have large effects on the selectivity and conversion in the hydrogenation reactions. Table 3 represents the results obtained from a screening of structural different phosphines on the hydrogenation of substrate **26** under optimized conditions, *i.e.* $Rh(COD)_2BF_4$, **L6** and PR_3 (2 : 1 ratio of **L6** : PR_3), MeOH, 30 °C, 25 bar H_2. Although the variation in enantioselectivity is not as large as for the hydrogenation of

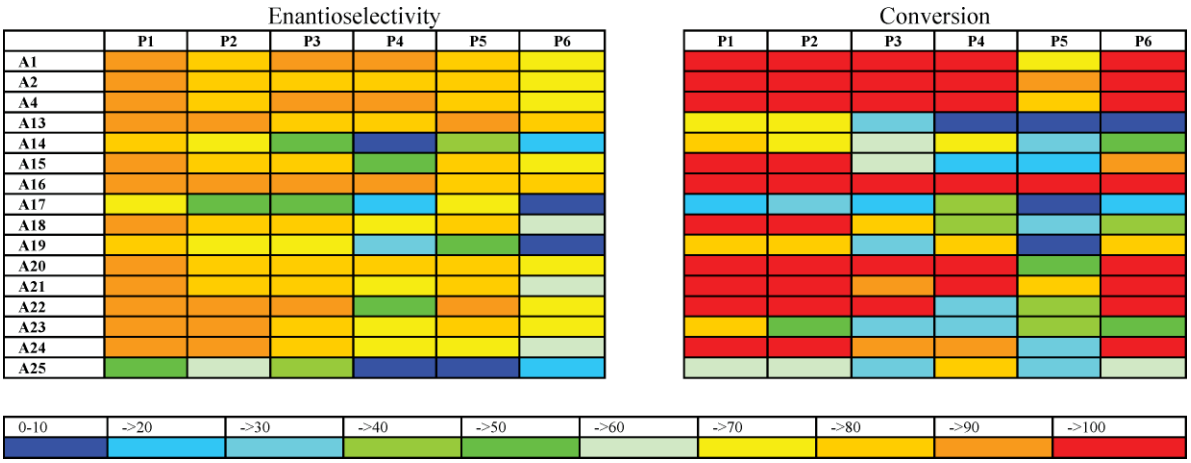
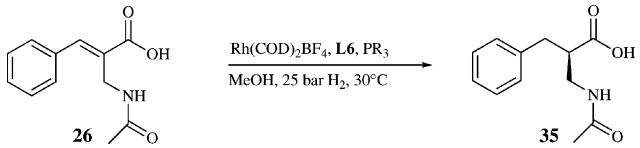


Fig. 3 Hydrogenation results with first library.

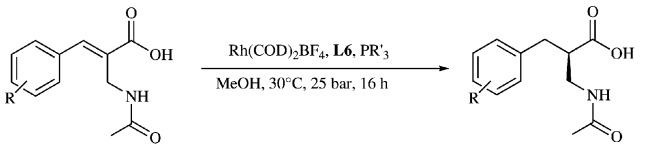
Table 3 Screening of phosphines[a,b]



Entry	R	Ee[c,d,e]
1	Ph (**P1**)	89
2	*o*-Tolyl (**P4**)	91
3	*m*-Tolyl (**P7**)	89
4	*p*-Tolyl (**P8**)	85
5	Xylyl (**P9**)	85
6	Mesityl (**P10**)	33 (53)
7	*m*-ClPh (**P11**)	89
8	*p*-ClPh (**P12**)	88
9	*p*-FPh (**P13**)	87
10	1,2,3,4,5-FPh (**P14**)	0 (12)
11	1-Naphthyl (**P15**)	91
12	*p*-MeOPh (**P2**)	66 (88)
13	Cyclohexyl (**P6**)	62 (86)
14	*tert*-Butyl (**P16**)	0 (29)

[a] Reaction conditions: 0.2 mmol of substrate in 4 ml of MeOH with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidite and 0.002 mmol of PR_3; [b] 16 h, 25 bar H_2 and 30 °C; [c] Ee's were determined by chiral RP-HPLC after conversion of product to the corresponding methyl ester (for details see experimental section). [d] Conversion is depicted in brackets in case no full conversion is reached; [e] Absolute configuration of product is unknown.

Table 4 Expanding the scope of substrates[a,b]



		Phosphines[c,d,e]				
Entry	Substrate	**P1**	**P4**	**P7**	**P8**	**P15**
1	**27**	82	90	82	77	—(< 5)
2	**28**	83	86	84	84	91
3	**29**	78	89	81	85	91
4	**33**	85	80 (65)	79 (90)	78	56 (86)

[a] Reaction conditions: 0.2 mmol of substrate in 4 ml of MeOH with 0.002 mmol of $Rh(COD)_2BF_4$, 0.004 mmol of phosphoramidites and 0.002 mmol of PR_3. [b] 16 h at 25 bar H_2 and 30 °C. [c] Ee's were determined by chiral RP-HPLC after conversion of the products to their corresponding methyl ester (for details see Experimental section). [d] Conversion is depicted in brackets in cases where full conversion is not reached. [e] Absolute configuration of products is unknown.

α,β-unsaturated carboxylic acids,[4b] substantial effects were also observed in this case.

Substitution of the phenyl at the *ortho* position in the triarylphosphine increased the ee slightly (compare entries 1, 2 and 11). Substitution on other positions had no effect. Introduction of electron withdrawing groups had no influence on the enantioselectivity (entries 7–9). On the other hand, introduction of an electron donating methoxy group decreased the ee and the rate of the reaction (entry 12). Sterically crowded phosphines induced low reactivity and low selectivity (entries 6 and 14). Furthermore, alkyl phosphines led to poorer results than aryl phosphines (entries 1, 13 and 14). This screening showed that an optimal ligand system consists of **L6** and an *ortho*-substituted phenylphosphine *e.g.* **P4** and **P15**.

To broaden the substrate scope, the hydrogenation of a series of substituted β^2-phenyl alanine precursors was performed. **L6** was used as ligand in combination with phosphines **P1**, **P4**, **P7**, **P8** and **P15**. The results are depicted in Table 4. The highest enantioselectivities in the hydrogenation of substrates **27–29** were obtained using *ortho*-substituted phosphines **P4** and **P15** (up to 91% ee). While for substrates **28** and **29** the best results were obtained with phosphine **P15**, substrate **27** with an *o*-methyl group, was not converted using this phosphine as co-ligand, probably due to steric hindrance. The enantioselectivity obtained with chloro-substituted substrate **33** was in general lower than for those obtained with the methyl substituted derivatives. In addition to the lower ee, a drop in reaction rate was observed, which can be seen from the incomplete conversions obtained with phosphines **P4**, **P7** and **P15**. Whereas in the hydrogenation

of **27–29** use of the *ortho*-substituted phosphines gave the best results, with **33** the less hindered phosphine **P1** induced the highest ee (85%).†

Conclusions

β^2-Amino acids have been prepared in high enantiomeric excess employing rhodium-catayzed hydrogenation using a mix-ligand approach comprising chiral and achiral ligands. The substrates are synthesized in a 3-step procedure with reasonable yields (up to 50% over 3 steps), starting from commercially available aryl aldehydes and methyl acrylate (**9**). Optimization of the catalytic system was performed using library screening. The results obtained in the hydrogenations are the best so far for this class of substrate, and comparable to the results reported by Zheng and co-workers,[21] with an ee up to 91% obtained for several compounds at full conversion.

Experimental

General remarks

^{1}H-NMR, ^{13}C-NMR and ^{31}P-NMR spectra were recorded on a Varian Gemini-200, Varian VXR-300 or a Varian Mercuri Plus. Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signals of $CHCl_3$ (^{1}H-NMR: δ 7.26; ^{13}C-NMR: δ 77.0); DMSO (^{1}H-NMR: δ 2.49; ^{13}C-NMR: δ 39.5) or relative to an external standard for ^{31}P (H_3PO_4 at δ 0.0). The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), b (broad). Optical rotations were measured with a Schmidt + Haensch Polartronic MH8. Column chromatography was performed using silica gel (Aldrich 60, 230–400 mesh). Mass spectra (HRMS) were recorded on an AEI MS-902. Phosphoramidites **L1–L6** were commercially available or made by literature procedures.[24] (*S*)-3,3′-Dimethylbinol and phosphoramidite **L5** were donated by DSM. Phosphines **P1–P13** were purchased from Aldrich or Strem Chemicals.

2-(Hydroxy-phenyl-methyl)-acrylic acid methyl ester (10)[27]. To 4.06 ml (40 mmol) of benzaldehyde (**1**) and 10 ml of a 33% (w/v) aqueous solution of Me_3N in 40 ml of MeOH was added 120 mmol of methyl acrylate. The solution was stirred for 48 h and 400 ml of $CHCl_3$ and 100 ml H_2O were added. The layers were separated and the aqueous layer was extracted twice with 100 ml $CHCl_3$. The organic layers were dried on Na_2SO_4, filtered and concentrated. The product was purified by column chromatography (SiO_2; heptane : EtOAc 5 : 1) to yield 5.9 g (30.7 mmol; 77%) of a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.30–7.21 (m, 5H), 6.26 (d, J = 6.0 Hz, 1H), 5.83 (s, 1H), 5.48 (d, J = 6.0 Hz, 1H), 3.62 (s, 1H), 3.60 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 166.3 (s), 141.9 (s), 141.2 (s), 128.1 (d), 127.4 (d), 126.4 (d), 125.4 (t), 72.4 (d), 51.6 (q); HRMS calcd. for $C_{11}H_{11}O_3$ 191.071 found 191.070.

† Attempts to hydrogenate the bromo-substituted substrates **30–32** met with failure. In all cases incomplete conversion was obtained. In addition to the desired hydrogenation product, the formation of the dehalogenated product **35** was observed, in combination with other unidentified side-products.

General method for Baylis–Hillman preparation of 11–17

A mixture of 100 mmol of aldehyde, 150 mmol of methyl acrylate and 10 mmol of DABCO in 50 ml of MeOH was stirred at RT until the reaction was complete (monitored by TLC). The mixture was diluted with 150 ml of Et_2O. The organic layer was washed with water (2 × 150 ml), brine (150 ml), dried on Na_2SO_4, filtered and concentrated. Products **11–17** were purified by column chromatography. (SiO_2; heptane : EtOAc 5 : 1) Products **11–17** were used as obtained.

2-(Hydroxy-*o*-tolyl-methyl)-acrylic acid methyl ester (11). 4.65 g (22.6 mmol; 23%) of a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.73–7.35 (m, 1H), 7.18–7.10 (m, 3H), 6.27 (s, 1H), 5.76 (s, 1H), 5.57 (s, 1H), 3.71 (s, 3H), 2.85 (bs, 1H), 2.28 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 167.1 (s), 141.2 (s), 138.7 (s), 135.6 (s), 130.4 (d), 127.4 (d), 126.2 (d), 126.2 (t), 126.1 (d), 69.2 (d), 52.0 (q), 19.1 (q); HRMS calcd for $C_{12}H_{14}O_3$ 206.094 found 206.095.

2-(Hydroxy-*m*-tolyl-methyl)-acrylic acid methyl ester (12). 3.17 g (15.4 mmol; 31%) of a colorless oil.[28] ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.21–7.09 (m, 3H), 7.04 (d, J = 7.3 Hz, 1H), 6.29 (d, J = 1.1 Hz, 1H), 5.81 (d, J = 1.1 Hz, 1H), 5.46 (s, 1H), 3.65 (s, 3H), 3.21 (bs, 1H), 2.30 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 166.6 (s), 141.9 (s), 141.1 (s), 137.9 (s), 128.4 (d), 128.2 (d), 127.2 (d), 125.8 (t), 123.6 (d), 72.9 (d), 51.8 (q), 21.3 (q); HRMS calcd for $C_{12}H_{14}O_3$ 206.094 found 206.095.

2-(Hydroxy-*p*-tolyl-methyl)-acrylic acid methyl ester (13)[27]. 3.64 g (17.7 mmol; 35%) of a colorless oil.[28] ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.21 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 7.7 Hz, 2H), 6.28 (d, J = 0.9 Hz, 2H), 5.82 (d, J = 0.9 Hz, 2H), 5.47 (s, 1H), 3.66 (s, 3H), 3.03 (bs, 1H), 2.29 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 166.7 (s), 142.0 (s), 138.3 (s), 137.4 (s), 129.0 (d), 126.5 (d), 125.7 (t), 72.9 (d), 51.8 (q), 21.0 (q); HRMS calcd for $C_{12}H_{14}O_3$ 206.094 found 206.094.

2-[(2-Bromo-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (14)[27]. 23.6 g (87 mmol; 87%) of a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.44–7.40 (m, 2H), 7.21 (dd, J = 7.7 Hz, 7.0 Hz, 1H), 7.04 (dt, J = 7.7 Hz, 1.5 Hz, 1H), 6.23 (s, 1H), 5.84 (d, J = 4.4 Hz, 1H), 5.51 (s, 1H), 3.80 (d, J = 4.4 Hz, 1H), 3.62 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 166.5 (s), 140.6 (s), 139.4 (s), 132.4 (d), 129.0 (d), 128.1 (d), 127.3 (d), 126.7 (t), 122.9 (s), 70.8 (d), 51.8 (q); HRMS calcd for $C_{11}H_{11}BrO_3$ 270.979 found 270.981.

2-[(3-Bromo-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (15)[27]. 9.62 g (35.5 mmol; 86%) of a colorless oil.[29] ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.44 (d, J = 1.5, 1H), 7.32 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 7.12 (dt, J = 7.7 Hz, 1.8 Hz, 1H), 6.27 (s, 1H), 5.80 (s, 1H), 5.40 (d, J = 4.4 Hz, 1H), 3.63 (s, 3H), 3.50 (bs, 1H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 166.3 (s), 143.6 (s), 141.2 (s), 130.7 (d), 129.8 (d), 129.5 (d), 126.4 (t), 125.1 (d), 122.3 (s), 72.2 (d), 51.9 (q); HRMS calcd. for $C_{11}H_{11}BrO_3$ 271.987 found 271.987.

2-[(4-Bromo-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (16). 23.1 g (85 mmol; 85%) of a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.38 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.26 (s, 1H), 5.78 (s, 1H), 5.41 (s, 1H), 3.63 (s, 1H),

3.39 (bs, 1H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 166.4$ (s), 141.5 (s), 140.3 (s), 131.3 (d), 128.3 (d), 126.1 (t), 121.6 (s), 72.3 (d), 51.9 (q); HRMS calcd. for $C_{11}H_{11}BrO_3$ 271.987 found 271.987.

2-[(4-Chloro-phenyl)-hydroxy-methyl]-acrylic acid methyl ester (17)[27]. 19.5 g (86 mmol; 86%) of a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.24$ (s, 4H), 6.27 (s, 1H), 5.78 (s, 1H), 5.44 (s, 1H), 3.65 (s, 1H), 3.21 (bs, 1H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 166.5$ (s), 141.5 (s), 139.7 (s), 133.4 (s), 128.4 (d), 127.9 (d), 126.2 (t), 72.4 (d), 51.9 (q); HRMS calcd. for $C_{11}H_{11}ClO_3$ 226.040 found 226.041.

General procedure for the synthesis of 18–25

A solution of 80 mmol of Baylis–Hillman adduct in 350 ml of CH_3CN was heated to 60 °C. To this mixture was added 215 ml of CH_3SO_3H. The resulting solution was warmed to 110 °C and stirred for 6 h. After cooling, the mixture was poured into 150 ml of H_2O. The solution was neutralized with K_2CO_3(s) (pH paper). The resulting solution was extracted with Et_2O (2 × 400 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. To the remaining yellow solid was added 100 ml of Et_2O. The pure product precipitated as a white solid and was collected (58–65% yield).

(*E*)-2-(Acetylamino-methyl)-3-phenyl-acrylic acid methyl ester (18)[23]. ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.78$ (s, 1H), 7.50 (d, $J =$ 7.3 Hz, 2H), 7.42–7.34 (m, 3H), 6.18 (bs, 1H), 4.32 (d, $J = 5.9$ Hz, 2H), 3.83 (s, 3H), 1.96 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.6$ (s), 168.2 (s), 142.4 (d), 134.0 (s), 129.5 (d), 129.2 (d), 128.6 (d), 127.7 (s), 52.1 (q), 36.7 (t), 23.2 (q); HRMS calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106; Anal. Calc. for $C_{13}H_{15}NO_3$: C, 66.92%; H, 6.49%; N, 6.01%, found: C, 66.65%; H, 6.44%; N, 5.98%.

(*E*)-2-(Acetylamino-methyl)-3-*o*-tolyl-acrylic acid methyl ester (19). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.82$ (s, 1H), 7.29–7.14 (m, 4H), 6.05 (bs, 1H), 4.14 (d, $J = 5.5$ Hz, 2H), 3.81 (s, 3H), 2.23 (s, 3H), 1.89 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.3$ (s), 168.1 (s), 141.9 (d), 136.7 (s), 133.5 (s), 130.1 (d), 129.1 (d), 128.8 (d), 128.6 (s), 126.0 (d), 52.2 (q), 36.8 (t), 23.3 (q), 19.9 (q); HRMS calcd. for $C_{14}H_{17}NO_3$ 247.121 found 247.122.

(*E*)-2-(Acetylamino-methyl)-3-*m*-tolyl-acrylic acid methyl ester (20). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.71$ (s, 1H), 7.21 (m, 3H), 7.12 (d, $J = 5.1$ Hz, 1H), 6.01 (bs, 1H), 4.28 (d, $J = 5.5$ Hz, 2H), 3.78 (s, 3H), 2.32 (s, 3H), 1.92 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.5$ (s), 168.3 (s), 142.7 (d), 138.3 (s), 134.0 (s), 130.3 (d), 130.1 (d), 128.6 (d), 127.5 (s), 126.6 (d), 52.2 (q), 36.8 (t), 23.3 (q), 21.3 (q); HRMS calcd. for $C_{14}H_{17}NO_3$ 247.121 found 247.122.

(*E*)-2-(Acetylamino-methyl)-3-*p*-tolyl-acrylic acid methyl ester (21)[23]. ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.74$ (s, 1H), 7.37 (d, $J = 8.1$ Hz, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 6.27 (bs, 1H), 4.31 (d, $J = 5.5$ Hz, 2H), 3.80 (s, 3H), 2.33 (s, 3H), 1.95 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.7$ (s), 168.3 (s), 142.6 (d), 139.6 (s), 131.1 (s), 129.6 (d), 129.3 (d), 126.6 (s), 52.1 (q), 36.7 (t), 23.1 (q), 21.3 (q); HRMS calcd. for $C_{14}H_{17}NO_3$ 247.121 found 247.121.

(*E*)-2-(Acetylamino-methyl)-3-(2-bromo-phenyl)-acrylic acid methyl ester (22). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.78$ (s, 1H), 7.59 (t, $J = 7.7$ Hz, 2H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.19 (t, $J = 7.7$ Hz, 1H), 6.22 (bs, 1H), 4.16 (d, $J = 5.5$ Hz, 2H), 3.83 (s, 3H), 1.91 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.3$ (s), 167.6 (s), 141.2 (d), 134.6 (s), 132.5 (d), 130.6 (d), 130.3 (d), 129.5 (s), 127.5 (d), 123.8 (s), 52.3 (q), 36.7 (t), 23.2 (q); HRMS calcd. for $C_{13}H_{14}BrNO_3$ 313.014 found 313.013; Anal. Calc. for $C_{13}H_{14}BrNO_3$: C, 50.16%; H, 4.54%; N, 4.50%, found: C, 50.25%; H, 4.52%; N, 4.45%.

(*E*)-2-(Acetylamino-methyl)-3-(3-bromo-phenyl)-acrylic acid methyl ester (23). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.58$ (s, 2H); 7.39 (dd, $J = 7.3$ Hz, 7.0 Hz, 2H), 7.18 (t, $J = 8.1$ Hz, 1H), 6.22 (bs, 1H), 4.19 (d, $J = 5.9$ Hz, 2H), 3.74 (s, 3H), 1.87 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.6$ (s), 167.8 (s), 140.4 (d), 136.1 (s), 132.3 (d), 132.0 (d), 130.1 (d), 129.2 (s), 127.9 (d), 122.6 (s), 52.2 (q), 36.6 (t), 23.1 (q); HRMS calcd. for $C_{13}H_{14}BrNO_3$ 313.014 found 313.014; Anal. Calc. for $C_{13}H_{14}BrNO_3$: C, 50.16%; H, 4.54%; N, 4.50%, found: C, 50.30%; H, 4.53%; N, 4.48%.

(*E*)-2-(Acetylamino-methyl)-3-(4-bromo-phenyl)-acrylic acid methyl ester (24). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.64$ (s, 1H), 7.48 (d, $J = 8.4$, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 6.30 (bs, 1H), 4.23 (d, $J = 5.5$ Hz, 2H), 3.79 (s, 3H), 1.92 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.6$ (s), 167.8 (s), 140.8 (d), 132.8 (s), 131.7 (d), 131.0 (d), 128.4 (s), 123.5 (s), 52.1 (q), 36.5 (t), 23.1 (q); HRMS calcd. for $C_{13}H_{14}BrNO_3$ 313.014 found 313.013; Anal. Calc. for $C_{13}H_{14}BrNO_3$: C, 50.16%; H, 4.54%; N, 4.50%, found: C, 50.15%; H, 4.51%; N, 4.48%.

(*E*)-2-(Acetylamino-methyl)-3-(4-chloro-phenyl)-acrylic acid methyl ester (25). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.72$ (s, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 6.12 (bs, 1H), 4.31 (d, $J = 5.9$ Hz, 2H), 3.85 (s, 3H), 1.99 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.6$ (s), 168.0 (s), 140.9 (d), 135.3 (s), 132.5 (s), 130.9 (d), 128.9 (d), 128.3 (s), 52.2 (q), 36.6 (t), 23.2 (q); HRMS calcd. for $C_{13}H_{14}ClNO_3$ 267.066 found 267.066; Anal. Calc. for $C_{13}H_{14}ClNO_3$: C, 58.41%; H, 5.28%; N, 5.24%, found: C, 58.45%; H, 5.22%; N, 5.21%.

General procedure for the synthesis of 26–33

The ester (25.8 mmol) and LiOH (250 mmol) in 160 ml of a 1 : 1 mixture of H_2O and MeOH were stirred overnight at RT. The mixture was diluted with 100 ml of H_2O, washed with CH_2Cl_2 and acidified with 2 M HCl (aq) to pH = 1. The white precipitate was collected and dried *in vacuo.* The products were obtained as white solids in >85% yield.

(*E*)-2-(Acetylamino-methyl)-3-phenyl-acrylic acid (26). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 12.68$ (bs, 1H), 7.98 (bs, 1H), 7.72 (s, 1H), 7.48–7.38 (m, 5H), 4.01 (d, $J = 4.2$ Hz, 2H), 1.82 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.1$ (s), 168.3 (s), 141.0 (d), 134.5 (s), 129.5 (d), 129.2 (s), 129.1 (d), 128.6 (d), 36.3 (t), 22.3 (q); HRMS calcd. for $C_{12}H_{13}NO_3$ 219.090 found 219.089; Anal. Calc. for $C_{12}H_{13}NO_3$: C, 65.74%; H, 5.98%; N, 6.39%, found: C, 65.35%; H, 5.95%; N, 6.40%.

(*E*)-2-(Acetylamino-methyl)-3-*o*-tolyl-acrylic acid (27). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.90$ (bs, 1H), 7.76 (s, 1H), 7.29–7.20 (m, 4H), 3.85 (d, $J = 4.4$ Hz, 2H), 2.23 (s, 3H), 1.78 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 168.8$ (s), 168.1 (s), 140.1 (d), 136.6 (s), 134.0 (s), 130.1 (s), 129.9 (d), 128.7 (d), 128.5 (d), 125.7 (d),

36.4 (t), 22.4 (q), 19.6 (q); HRMS calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106.

(*E*)-2-(Acetylamino-methyl)-3-*m*-tolyl-acrylic acid (28). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.97$ (bs, 1H), 7.68 (s, 1H), 7.33–7.26 (m, 3H), 7.20 (d, $J = 6.2$ Hz, 1H), 4.01 (d, $J = 4.0$ Hz, 2H), 2.30 (s, 3H), 1.83 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.0$ (s), 168.5 (s), 141.2 (d), 137.8 (s), 134.4 (s), 130.2 (d), 129.8 (d), 129.0 (s), 128.5 (d), 126.6 (d), 36.3 (t), 22.4 (q), 21.0 (q); HRMS calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106; Anal. Calc. for $C_{13}H_{15}NO_3$: C, 66.92%; H, 6.49%; N, 6.01%, found: C, 67.00%; H, 6.56%; N, 5.84%.

(*E*)-2-(Acetylamino-methyl)-3-*p*-tolyl-acrylic acid (29). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.96$ (bs, 1H), 7.68 (s, 1H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 4.01 (d, $J = 4.4$ Hz, 2H), 2.32 (s, 3H), 1.82 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta =$ 169.1 (s), 168.5 (s), 141.2 (d), 138.9 (s), 131.6 (s), 129.6 (d), 129.3 (d), 128.3 (s), 126.0 (d), 36.4 (t), 22.4 (q), 20.9 (q); HRMS calcd. for $C_{13}H_{15}NO_3$ 233.105 found 233.106; Anal. Calc. for $C_{13}H_{15}NO_3$: C, 66.92%; H, 6.49%; N, 6.01%, found: C, 66.75%; H, 6.49%; N, 5.84%.

(*E*)-2-(Acetylamino-methyl)-3-(2-bromo-phenyl)-acrylic acid (30). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.95$ (bs, 1H), 7.70 (d, $J = 8.1$ Hz, 1H), 7.65 (s, 1H), 7.53 (d, $J = 5.9$ Hz, 1H), 7.43 (dd, $J = 7.7$ Hz, 7.3 Hz, 1H), 7.32 (dd, $J = 7.7$ Hz, 7.3 Hz, 1H), 3.87 (d, $J = 4.0$ Hz, 2H), 1.78 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.0$ (s), 167.8 (s), 139.4 (d), 134.7 (s), 132.6 (d), 131.3 (s), 130.7 (d), 130.6 (d), 127.8 (d), 123.6 (s), 36.2 (t), 22.4 (q); HRMS calcd. for $C_{12}H_{12}BrNO_3$ 297.000 found 296.999; Anal. Calc. for $C_{12}H_{12}BrNO_3$: C, 48.34%; H, 4.06%; N, 4.70%, found: C, 48.40%; H, 4.03%; N, 4.67%.

(*E*)-2-(Acetylamino-methyl)-3-(3-bromo-phenyl)-acrylic acid (31). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 7.99$ (bs, 1H), 7.72 (s, 2H); 7.65 (s, 1H), 7.57 (d, $J = 8.1$ Hz, 1H), 7.49 (d, $J = 7.7$ Hz, 1H), 7.38 (t, $J = 7.7$ Hz, 1H), 3.97 (d, $J = 4.4$ Hz, 2H), 1.81 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.1$ (s), 168.1 (s), 139.2 (d), 137.0 (s), 131.9 (d), 131.6 (d), 130.9 (s), 130.6 (d), 128.4 (d), 121.9 (s), 36.2 (t), 22.4 (q); HRMS calcd. for $C_{12}H_{12}BrNO_3$ 297.000 found 296.998; Anal. Calc. for $C_{12}H_{12}BrNO_3$: C, 48.34%; H, 4.06%; N, 4.70%, found: C, 48.35%; H, 4.00%; N, 4.65%.

(*E*)-2-(Acetylamino-methyl)-3-(4-bromo-phenyl)-acrylic acid (32). ^{1}H-NMR (400 MHz, $CDCl_3$) $\delta = 8.00$ (bs, 1H), 7.64 (s, 1H), 7.61 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 3.97 (d, $J = 4.0$ Hz, 2H), 1.81 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta = 169.2$ (s), 168.2 (s), 139.7 (d), 133.8 (s), 131.6 (d) (4×), 130.1 (s), 122.5 (s), 36.2 (t), 22.4 (q); HRMS calcd. for $C_{12}H_{12}BrNO_3$ 297.000 found 296.999.

(*E*)-2-(Acetylamino-methyl)-3-(4-chloro-phenyl)-acrylic acid (33). ^{1}H-NMR (400 MHz, DMSO-d_6) $\delta = 8.00$ (bs, 1H), 7.67 (s, 1H), 7.52 (d, $J = 8.8$ Hz, 2H), 7.48 (d, $J = 8.8$ Hz, 2H), 3.98 (d, $J = 4.4$ Hz, 2H), 1.81 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) $\delta =$ 169.1 (s), 168.2 (s), 139.6 (d), 133.7 (s), 133.4 (s), 131.3 (d), 131.0 (s), 128.6 (d), 36.2 (t), 22.4 (q); HRMS calcd. for $C_{12}H_{12}ClNO_3$ 253.051 found 253.050; Anal. Calc. for $C_{12}H_{12}ClNO_3$: C, 56.82%; H, 4.77%; N, 5.52%, found: C, 56.50%; H, 4.74%; N, 5.50%.

General procedure for the synthesis of solution phase phosphoramidite ligand libraries[26a]

Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in anhydrous toluene (all by weight). For the phosphorochloridites a concentration of 0.150 M was used, for the amines 0.158 M, and for the triethylamine 0.538 M. Using the liquid handling robot in a glovebox 0.333 ml (1.00 eq.) of each of the phosphorochloridites was transferred into one of the 3 corresponding 32 wells of the Whatman PKP filter plate. The triethylamine solution, 0.100 ml (1.00 eq.) was added to each of the 96 wells. Next 0.333 ml (1.05 eq.) of each of the amines was added to one of the 3 corresponding 32 wells of one of the 3 plates. The microplate was placed on an orbital shaker and vortexed for 2 h at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of vacuum. The filtrates, *i.e.* the solutions of different phosphoramidites in dry toluene (0.766 ml; 0.065 M) were collected and stored into a 96-well polypropylene microplate.

General procedure for the screening of solution phase phosphoramidite ligand libraries in rhodium-catalyzed hydrogenation of 26[26a]

Using the liquid handling robot 0.100 ml (2.0 eq.) of the ligand solution was transferred from the microplate into 96 vials, equipped with stirring bars. Then 0.1 ml (1.0 eq.) of a 0.0329 M PPh_3 stock solution in DCM, 0.25 ml (0.1 eq.) of a 0.0131 M $Rh(COD)_2BF_4$ stock solution in DCM and 2.25 ml of a 0.073 M (50 eq.) substrate stock solution in MeOH was added. The mixtures were capped under inert atmosphere and transferred to a parallel hydrogenation reactor. The vials were purged with nitrogen and then with hydrogen (25 bar) and heated to 40 °C. The reaction mixtures were left stirring for 16 h. Samples of the mixtures were analyzed by chiral HPLC to determine the conversion and the ee (see Table 5).

Table 5 Ee determination of **35–39**[a,b]

		Retention times[c]		
Entry	Product	Enantiomer 1	Enantiomer 2	Starting material
1	**35**	19.5	21.7	33.0
2	**36**	26.8	31.5	39.9
3	**37**	31.5	35.1	64.1
4	**38**	35.4	40.3	75.5
5	**39**	52.7	59.3	96.6

[a] Products were analyzed as their corresponding Me-esters. [b] All products were analyzed by the same method: RP-HPLC, AD-RH Chiralpak; acetonitrile–NaH_2PO_4 buffer (pH 2.7) 20 : 80 (flow 0.5 ml min^{-1}). [c] Retention times in min.

General procedure for hydrogenation reactions in Endeavor™[30]

In a glass tube, 0.81 mg (2 μmol) of $Rh(COD)_2BF_4$, 4 μmol of ligand, 0.2 μmol of phosphine, 0.2 mmol of the substrate and 4 ml of solvent, was added. The small glass tube was placed in a semi-automated autoclave with eight reactors (Endeavor™)[30] that was purged 4 times with nitrogen and once with hydrogen

and heated if necessary. Then, the autoclave was pressurized with hydrogen. The reaction was stirred for 16 h. A sample of the resulting mixture was converted into the corresponding methyl ester by 2 M solution of trimethylsilyl diazomethane in ether until the yellow color persisted. MeOH was added to the sample in those cases where the reaction was performed in another solvent than MeOH. This sample was filtered over a silica plug and subjected to conversion (^{1}H NMR) and ee determination (HPLC).

2-(Acetylamino-methyl)-3-phenyl-propionic acid (35). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.12 (bs, 1H), 7.25–7.07 (m, 5H), 6.56 (s, 1H), 3.58–3.42 (m, 1H), 3.32–3.22 (m, 1H), 2.98–2.84 (m, 2H), 2.77–2.67 (m, 1H), 1.85 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 177.4 (s), 171.7 (s), 138.0 (s), 128.8 (d), 128.5 (d), 126.6 (d), 46.5 (d), 40.4 (t), 35.7 (t), 22.7 (q); HRMS calcd. for $C_{12}H_{15}NO_3$ 221.105 found 221.106.

2-(Acetylamino-methyl)-3-*o*-tolyl-propionic acid (36). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.21 (bs, 1H), 7.15–7.08 (m, 4H), 6.38 (bs, 1H), 3.51–3.38 (m, 2H), 3.06–3.01 (m, 1H), 2.93–2.88 (m, 1H), 2.77–2.72 (m, 1H), 2.31 (s, 3H), 1.92 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 178.1 (s), 171.5 (s), 136.3 (s), 136.2 (s), 130.5 (d), 129.4 (d), 126.8 (d), 126.1 (d), 45.4 (d), 40.7 (t), 33.1 (t), 22.9 (q), 19.4 (q); HRMS calcd. for $C_{13}H_{15}NO_3$ 235.121 found 235.122.

2-(Acetylamino-methyl)-3-*m*-tolyl-propionic acid (37). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.19 (bs, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.03–6.97 (m, 3H), 6.33 (bs, 1H), 3.54–3.49 (m, 1H), 3.36–3.32 (m, 1H), 3.01–2.90 (m, 2H), 2.78–2.73 (m, 1H), 2.30 (s, 3H), 1.92 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 177.9 (s), 171.4 (s), 138.1 (s), 137.9 (s), 129.6 (d), 128.4 (d), 127.4 (d), 125.8 (d), 46.6 (d), 40.5 (t), 35.7 (t), 22.9 (q), 21.3 (q); HRMS calcd. for $C_{13}H_{15}NO_3$ 235.121 found 235.122.

2-(Acetylamino-methyl)-3-*p*-tolyl-propionic acid (38). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.12 (bs, 1H), 7.07 (s, 4H), 6.32 (bs, 1H), 3.53–3.48 (m, 1H), 3.36–3.30 (m, 1H), 3.00–2.89 (m, 2H), 2.79–2.72 (m, 1H), 2.30 (s, 3H), 1.92 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 178.0 (s), 171.4 (s), 136.2 (s), 134.8 (s), 129.2 (d), 128.7 (d), 46.7 (d), 40.4 (t), 35.3 (t), 22.9 (q), 21.0 (q); HRMS calcd. for $C_{13}H_{15}NO_3$ 235.121 found 235.122.

2-(Acetylamino-methyl)-3-(4-chloro-phenyl)-propionic acid (39). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.22 (bs, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.43 (bs, 1H), 3.52–3.47 (m, 1H), 3.37–3.30 (m, 1H), 2.99–2.88 (m, 2H), 2.78–2.74 (m, 1H), 1.93 (s, 3H); ^{13}C-NMR (101.0 MHz, $CDCl_3$) δ = 177.4 (s), 171.6 (s), 136.5 (s), 132.5 (s), 130.2 (d), 128.7 (d), 46.6 (d), 40.5 (t), 35.0 (t), 22.9 (q); HRMS calcd. for $C_{12}H_{12}ClNO_3$ 255.066 found 255.066.

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