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Synthesis of a New Chiral Bisphospholane Ligand for the Rh(I)-Catalyzed Enantioselective Hydrogenation of Isomeric β-Acylamido Acrylates

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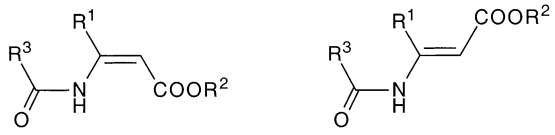
The highly stereoselective synthesis of a chiral silylphospholane has been described, which can be advantageously used as a building block under base-free conditions for the construction of diphosphines related to DuPHOS. The utility of silylphospholane is shown in the synthesis of a new bisphospholane ligand **1** (MalPHOS), which is characterized by a maleic anhydride backbone. The ligand forms with Rh(I) a complex with a larger bite angle P−Rh−P than the analogue Me−DuPHOS complex. Both complexes have been tested in the asymmetric hydrogenation of unsaturated α- and β-amino acid precursors of pharmaceutical relevance. In several cases, the new catalyst was superior in comparison to the Me−DuPHOS complex, in particular when (*Z*)-configured β-acylamido acrylates were used as substrates.

Introduction

Although being less abundant than α-amino acids, enantiopure β-amino acids represent compounds of broad natural and pharmaceutical importance.[1] In nature, they are produced in different organisms either in a free form or as part of peptides and depsipeptides. As components of natural and unnatural compounds with interesting antibiotic, antifungal, and cytotoxic properties,[2] their enantioselective synthesis is of increasing importance, in particular for pharmaceutical chemistry.[3]

One of the most promising methods for the large-scale preparation of enantiopure β-amino acids seems to be the asymmetric hydrogenation of substituted β-acylamido acrylates with Rh(I) catalysts bearing easily available chiral phosphorus compounds as ancillary ligands. The requisite prochiral substrates can be conveniently synthesized by reaction of β-keto carboxylates with ammonium salts and subsequent *N*-acylation. Interestingly, although the preparation of α-amino acids by catalytic hydrogenation is a well established procedure, even on an industrial scale, only a few investigations have been concerned with the Rh(I)-catalyzed enantioselective hydrogenation of prochiral β-acylamido acrylates.[4,5] The reason for this is probably the different behavior of isomeric β-acylamido acrylates in the asymmetric hydrogenation. Both isomers are produced simultaneously in common synthetic protocols, and their individual hydrogenation demands prior separation.



Z *E*

In recent reports, we gave evidence that the asymmetric hydrogenation of (*E*)- and (*Z*)-methyl 3-acetamidobutenoate employing a Rh(I) precatalyst with Me−DuPHOS[6] as a chiral ligand proceeds very fast and

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(5) Recently, excellent enantioselectivities were achieved with a chiral Ru-catalyst: Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952.

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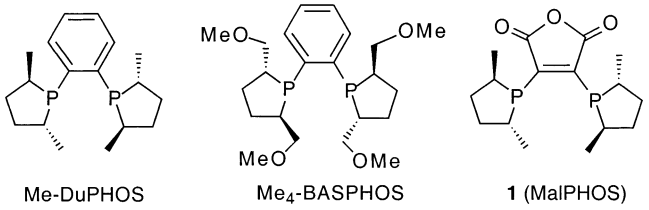
produces the product with the same configuration.[7] Under optimized conditions, methyl-β-acetamido butyrate was obtained in quantitative yield and by up to 98% ee. Such excellent enantioselectivities were preferentially achieved when the (*E*)-configured substrate was employed. In contrast, results attained in the hydrogenation of the relevant (*Z*)-enamide, usually formed in a large excess in synthetic protocols, were inferior. Since the exchange of Me−DuPHOS by Et−DuPHOS only slightly affected the enantioselectivity, we also tested oxyfunctionalized analogues of DuPHOS such as Me_4−BASPHOS.[8] Also, this alteration in the structure of the phospholane moiety was not beneficial for the hydrogenation of the (*Z*)-substrate.



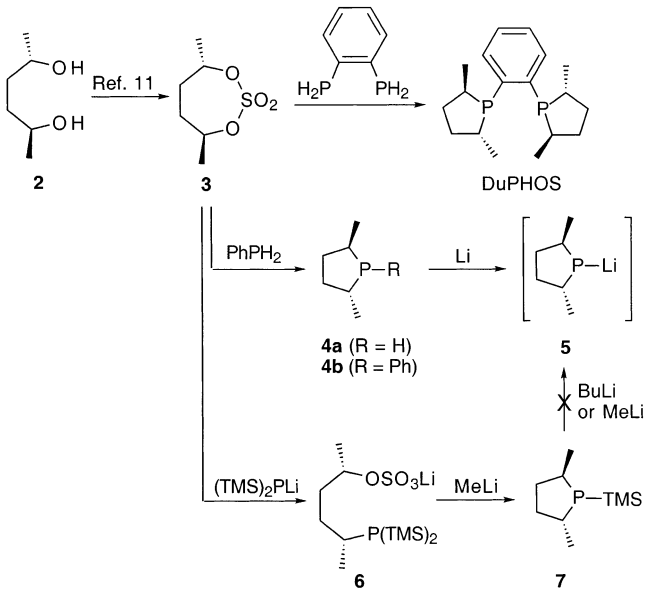
Perusal of the literature in terms of homogeneous Rh(I)-catalysis indicates that fine-tuning of a catalyst may also be achieved by variation of the bite angle of the diphosphine ligand.[9] A recent report by Orpen and Pringle et al. showed that replacement of the phenylene backbone in a DuPHOS−Rh-catalyst by 1,2-cyclopentane changed significantly the enantioselectivity in the hydrogenation of unsaturated α-amino acid precursors.[10]

On the basis of this finding we envisaged the synthesis of a new bisphospholane **1** (MalPHOS) bearing a maleic anhydride backbone. The new ligand was prepared via a new synthetic pathway and subsequently tested in the enantioselective hydrogenation of several β-amino acid precursors.

Results and Discussion

Bisphospholanes of the DuPHOS type are commonly synthesized by double nucleophilic substitution of an appropriately substituted chiral cyclic 1,4-sulfate such as **3** with *o*-phenylenediphosphine (Scheme 1).[11] This methodology originally disclosed by Burk is superior to the use of corresponding 1,4-bissulfonates[12] suffering frequently by the formation of byproducts. In the past decade, this straightforward method, which can be even

SCHEME 1



scaled up to industrial needs, has seen application in the synthesis of several other C_2-symmetric nonfunctionalized and functionalized bisphospholanes[13] and related bisphosphetanes.[14] However, this approach is limited to those primary diphosphines as nucleophilic reagents, which are easily accessible. Obviously, due to the limited selection of available diphosphines, the variation of the bridge connecting both phospholane units, being decisive for the proper adjustment of the bite angle of the ligand, was strongly restricted up to now. Moreover, electrophiles bearing other reactive functional groups such as carbonyl groups cannot be employed because of the strong nucleophilicity of primary phosphides serving as reagents.

Highly promising for the synthesis of bisphospholanes seems to be the use of a reactive monophospholane reagent like **5**, which could be coupled to a large variety of dielectrophiles. A first attempt to establish such a modular approach was reported by Burk et al.[12] They tried to generate lithium phosphide **5** by reductive cleavage of the P−Ph bond in **4b** with lithium. However, this reaction was accompanied by the formation of P−P coupling products[12a] and by epimerization at C2 and C5, especially when larger alkyl substituents were linked to these positions.[12c,15] Moreover, when **5** was reacted with propylene dichloride, only a poor yield of the desired bisphospholane was achieved.[16] As an alternative, secondary phospholane **4a** was employed for the generation

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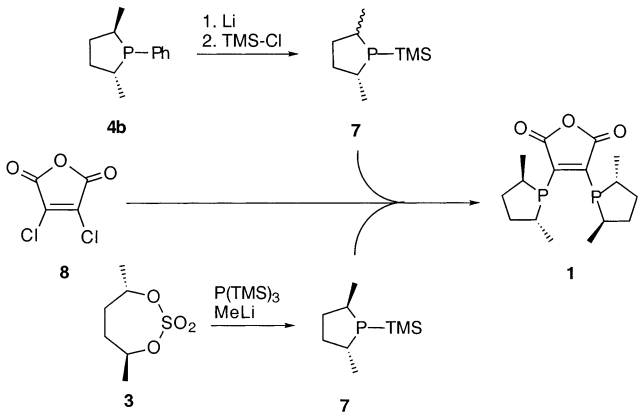
SCHEME 2



of **5**.[15] However, the former was revealed to be quite volatile and difficult to isolate in good yield and pure form.

More advantageous was the use of borane adducts of **4a** and **4b** reported by Burk[15] and Achiwa,[17] respectively. Unfortunately, this method is limited to the preparation of ligands with remote phospholane groups. Up to now, the placement of two vicinal phosphine-borane groups at a double bond could not be achieved, probably due to steric reasons.[18] In addition, the borane protection−deprotection procedure prolongs the synthetic pathway by two steps and decreases the overall yield.

Another study of Burk and co-worker was focused on the use of *P*-trimethylsilyl phospholane **7**, which was prepared from cyclic sulfate **3** by reaction with $(TMS)_2PLi$ to give **6** and subsequent ring closure with MeLi.[15] However, all trials to use this uncharacterized compound as a source of phosphide anion **5** failed. The P-TMS bond proved to be resistant to nucleophilic cleavage. This failure is surprising, because the reaction of simple TMS-diaryl- and -dialkylphosphines with chlorides was described years ago by Fenske and Tillack.[19]

To determine if the low reactivity of TMS-phospholane **7** reported is associated with its unique ring structure, we investigated its formation and reaction in more detail (Scheme 2).

In a first trial, we generated **7** by treatment of **4b** with lithium and subsequent addition of TMS−Cl. Surprisingly, the ^{31}P NMR spectrum of **7** gave not a single resonance as expected. Two signals at δ −53.0 and −54.5 in a ratio of 1:4 were found. This observation gave the first hint related to an earlier report of Burk et al.[12c] that even with 2,5-dimethyl-substituted phospholane **4b** under the conditions of the P−Ph cleavage reaction, epimerization at the chiral centers may occur, which leads in our case finally to a mixture of a chiral and a *meso*-TMS-phospholane **7**. The degree of epimerization, also well-known for 2,5-diphenylphospholane oxide derivatives under basic conditions,[20] varied from run to run. To rule out that diastereomeric impurities in the commercial starting diol are responsible for the formation of diastereomeric TMS-phospholanes, we used a mixture consisting of racemic and *meso*-diol for the synthesis of **7**. Under these conditions, significant deviations of the diastereoselectivity of the TMS-phospholane from the diastereomeric purity of diol **2**, its sulfate **3**, and *P*-phenyl phospholane **4b** were noted. This gave clear evidence that the epimerization takes place in the P−Ph cleavage step and showed that phosphine **4b** is not a suitable precursor for optically pure TMS-phospholane **7**. However, we were pleased to see that the latter reacted cleanly with 2,3-dichloromaleic anhydride **8** representing an activated electrophile to give bisphospholane **1**. Unexpectedly, the reaction of a mixture of chiral and *meso*-phospholane **7** with dichloromaleic anhydride gave in all trials diastereomerically pure **1**. The ^{31}P NMR spectrum of the bisphosphine was characterized by a single resonance at δ −2.2. Obviously the formation of bisphospholane **1** proceeds in a highly diastereoselective manner, avoiding the formation of diastereomers with mixed configurations.[21]

In the next run, we prepared TMS-phospholane **7** by reaction of sulfate **3** with $P(SiMe_3)_3$ in the presence of methyllithium. The ^{31}P NMR spectrum of compound **7** obtained in 70% yield showed only traces of the *meso*-isomer (<2%), which can be traced back to a small diastereomeric impurity of starting diol **2**. TMS-Phospholane **7** proved to be a remarkable stable reagent. It could be distilled at 93 °C/20 mbar and stored under argon without any tendency of epimerization. When this building block was reacted with 2,3-dichloromaleic anhydride **8** in ethereal solution at 0 °C in the absence of any base, a smooth and clean coupling reaction took place. The optically pure ligand **1** could be precipated in 53% yield as dark-red crystals from the reaction solution. Reaction of **1** with $[Rh(COD)_2]BF_4$ at −20 °C, being necessary in order to rule out the formation of the bis-ligand complex, afforded a precatalyst of the type [Rh(COD)(**1**)]BF_4, which was characterized in the ^{31}P NMR spectrum by a doublet at δ 63.8 with a Rh−P coupling constant of 151 Hz.

To compare the bite angle change from Me−DuPHOS to **1**, the structures of $[Rh(COD)(Me-DuPHOS)]^+$ and $[Rh(COD)(\mathbf{1})]^+$ complexes and the free ligands were optimized at the B3LYP level of density functional theory with the LANL2DZ basis set as implemented in the Gaussian 98 program (Figure 1).[22] As expected, the PRhP bite angle of the complex based on **1** (86.1°) is larger than that of the Me−DuPHOS complex (83.6°).[23] Compared

(16) Low yields might be due to the reaction of the very reactive Li-phosphide **5** with THF used as a solvent and its propensity to engage in electron-transfer processes (ref 12).

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(21) When such a ligand **1** derived from the reaction of a mixture consisting of an excess of (*R*,*R*)-**7** and some *meso*-**7** with 2,3-dichloromaleic anhydride was used in a [Rh(COD)(**1**)]BF_4 precatalyst for the enantioselective hydrogenation of methyl (*Z*)-*N*-acetamido cinnamate in MeOH, 94.0% ee was achieved.

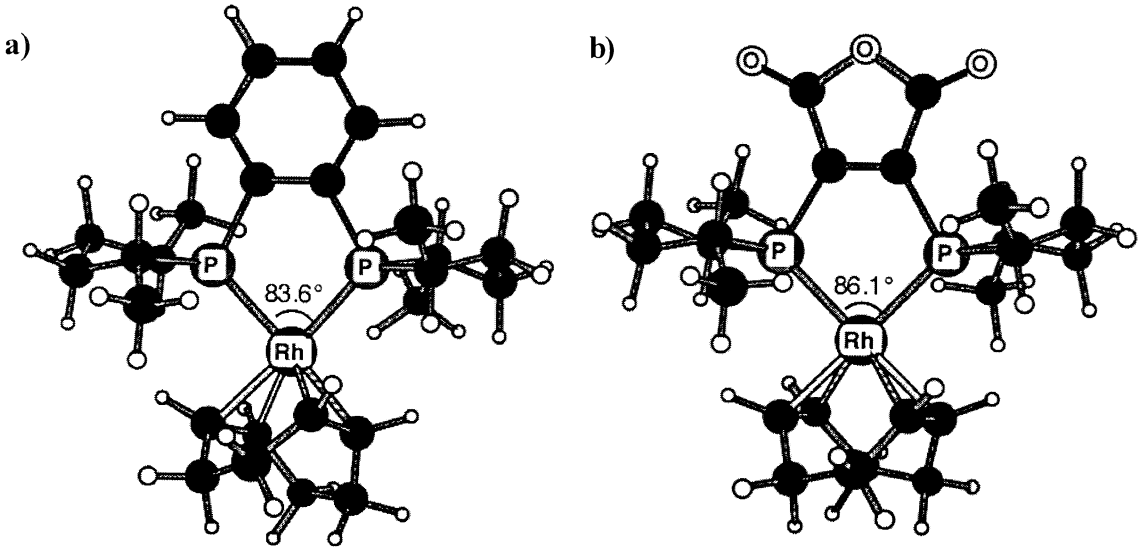


FIGURE 1. Comparison of bite angles of [Rh(COD)(Me−DuPHOS)]$^+$ (a) and [Rh(COD)(**1**)]$^+$ (b).

to the benzene backbone in Me−DuPHOS, the five-membered maleic anhydride backbone has a larger *exo* PC═C angle (125.2° vs 118.8°). This in turn widens the bite angle in [Rh(COD)(**1**)]$^+$.[24]

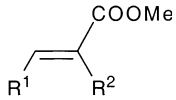
First, the new precatalyst was tested in the hydrogenation of standard substrates such as methyl (*Z*)-*N*-acetamido cinnamate (**9**) and dimethyl itaconate (**10**) in order to assess its catalytic performance. Relevant results are listed in Table 1. For comparison, some results obtained with the closely related Me−DuPHOS precatalyst are detailed.

As can be clearly seen, the catalyst derived from ligand **1** induces good or excellent enantioselectivities. However, the ees achieved with the DuPHOS catalyst are mostly higher, in particular when polar solvents have been used.

However, it is interesting to note that in several cases a reversal of this order was found in the hydrogenation of *β*-acylamido acrylates (Table 2).

In particular for the hydrogenation of the important (*Z*)-configured substrates bearing bulkier substituents in the 3-position (Et, *i*-Pr, Ph), the new catalyst gave significantly higher enantioselectivities. Differences of up to 75% ee were found (compare, e.g., substrate (*Z*)-**17**), whereas in the hydrogenation of relevant (*E*)-substrates only marginal differences in the ee were noted for both catalysts. In general, with increasing size of the substituent in the 3-position of (*Z*)-substrates, a decrease in the enantioselectivity was observed, independent of the catalyst and the solvent used. The nature of the acyl groups (Ac, Bz) as well as electronic alterations in the benzyl ester group did not significantly change the enantioselectivity.

TABLE 1. Enantioselective Hydrogenation of Standard Substrates with [Rh(COD)(ligand)]BF_4[a]



substrate				ligand	
compd	R^1	R^2	solvent	(*R*,*R*)-**1** % ee	(*R*,*R*)-Me−DuPHOS % ee
9	Ph	NHAc	MeOH	94.4 (*R*)	97.6 (*R*)
			THF	98.6 (*R*)	97.4 (*R*)
			CH_2Cl_2	97.9 (*R*)	98.0 (*R*)
			toluol	98.4 (*R*)	96.3 (*R*)
10	H	CH_2COOMe	MeOH	60.2 (*S*)	95.3 (*S*)
			THF	86.0 (*S*)	97.0 (*S*)

[a] Conditions: 0.01 mmol of precatalyst and 1.0 mmol of prochiral olefin in 15.0 mL of solvent at 25.0 °C, 1.0 atm overall pressure over the solution, 1 h.

Conclusion

In summary, the highly stereoselective synthesis of a chiral silyl-substituted monophospholane has been described, which can be advantageously used as an optically pure building block under base-free conditions for the construction of new bisphospholane ligands. The applicability of TMS-phospholane **7**, which is available in both enantiomeric forms, has been exemplarily proven in the synthesis of a bisphospholane bearing a maleic anhydride backbone. The new ligand **1** (MalPHOS) and Rh(I) form a complex with a larger bite angle than a related Me−DuPHOS complex. Both have been tested in the asymmetric hydrogenation of unsaturated standard substrates as a benchmark test and *β*-amino acid precur-

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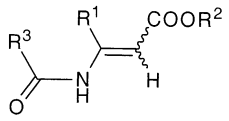
(23) The bite angle of a [Rh(COD)(Me−DuPHOS)]SbF_6 complex in the crystal was found to be 84.7° (ref 11b). The difference from the calculated value could be due to the effect of the counteranion SbF_6.

(24) When the structures of the [Rh(COD)(Me−DuPHOS)]$^+$ and [Rh(COD)(**1**)]$^+$ complexes and the free ligands were free optimized by using the PM3 semiempirical method as implemented in the Spartan program (Spartan 2002; Wavefunction, Inc.: Irvine, CA, 2002), similar angles were obtained: [Rh(COD)(**1**)]$^+$, 85.8°; [Rh(COD)(Me−DuPHOS)]$^+$, 82.8°. Exo PC═C angles: **1**, 124.5°; Me−DuPHOS, 120.3°.

TABLE 2. Enantioselective Hydrogenation of *β*-Acylamido Acrylates with [Rh(COD)(ligand)]BF_4[a]



substrate						ligand	
compd	R^1	R^2	R^3	configuration	solvent	(*R*,*R*)-**1** % ee	(*R*,*R*)-Me−DuPHOS % ee
11	Me	Me	Me	*Z*	MeOH	83.0 (*R*)	87.8 (*R*)[b]
					THF	83.5 (*R*)	83.0 (*R*)
				E	MeOH	97.9 (*R*)	98.2 (*R*)[b]
					THF	97.8 (*R*)	98.8 (*R*)
12	Me	Me	Ph	*Z*	MeOH	83.9 (*R*)	83.5 (*R*)
					THF	79.1 (*R*)	67.1 (*R*)
				E	MeOH	98.1 (*R*)	96.6 (*R*)
					THF	98.0 (*R*)	98.3 (*R*)
13	Me	Bn	Me	*Z*	MeOH	89.9 (*R*)	84.3 (*R*)
					THF	85.2 (*R*)	81.6 (*R*)
				E	MeOH	>99.5 (*R*)	>99.5 (*R*)
					THF	96.8 (*R*)	>99.5 (*R*)
14	Me	4-F-Bn	Me	*Z*	MeOH	88.1 (*R*)	85.6 (*R*)
					THF	87.5 (*R*)	82.7 (*R*)
				E	MeOH	95.1 (*R*)	>99.5 (*R*)
					THF	94.9 (*R*)	>99.5 (*R*)
15	Me	4-Me-Bn	Me	*Z*	MeOH	88.9 (*R*)	84.2 (*R*)
					THF	85.0 (*R*)	82.2 (*R*)
				E	MeOH	97.8 (*R*)	98.7 (*R*)
					THF	97.2 (*R*)	97.3 (*R*)
16	Et	Me	Me	*Z*	MeOH	81.2 (*R*)	68.4 (*R*)
					THF	73.8 (*R*)	58.1 (*R*)
				E	MeOH	98.0 (*R*)	99.4 (*R*)
					THF	96.9 (*R*)	99.6 (*R*)
17	*i*-Pr	Me	Me	*Z*	MeOH	80.4 (*S*)	3.7 (*S*)
					THF	57.8 (*S*)	22.5 (*S*)
				E	MeOH	98.2 (*S*)	98.7 (*S*)
					THF	98.3 (*S*)	98.4 (*S*)
18	*i*-Pr	Et	Me	*Z*	MeOH	69.4 (*S*)	3.6 (*S*)
					THF	63.0 (*S*)	35.9 (*S*)
				E	MeOH	97.3 (*S*)	98.6 (*S*)
					THF	99.1 (*S*)	98.4 (*S*)
19	Ph	Me	Me	*Z*	MeOH	85.5 (*S*)	81.4 (*S*)
					THF	78.3 (*S*)	86.0 (*S*)
				E	MeOH	84.8 (*S*)	97.2 (*S*)
					THF	83.0 (*S*)[c]	97.2 (*S*)[c]
20	Ph	Et	Me	*Z*	MeOH	84.8 (*S*)	78.0 (*S*)
					THF	81.6 (*S*)	73.0 (*S*)
				E	MeOH	83.3 (*S*)[c]	98.3 (*S*)[c]
					THF	81.0 (*S*)[c]	97.6 (*S*)[c]
21	Ph	4-Me-Bn	Me	*Z*	MeOH	81.7 (*S*)	75.9 (*S*)
					THF	83.0 (*S*)	74.8 (*S*)
				E	MeOH	84.2 (*S*)[c]	96.9 (*S*)[c]
					THF	79.4 (*S*)[c]	91.8 (*S*)[c]

[a] Conditions: see Table 1; time for hydrogenation < 3 h. [b] From ref 7. [c] No complete conversion after 3 h.

sors. In particular, in the hydrogenation of pharmaceutically important (*Z*)-configured *β*-dehydroamino acid derivatives, the new catalyst was mostly superior in comparison to the Me−DuPHOS complex. Our results clearly demonstrate that for each substrate, an individual catalyst has to be identified in order to induce the maximum enantioselectivity. Therefore, the search for synthetic routes that allow the facile modular construction of ligands represents a great challenge in future asymmetric catalysis. Work is in progress to show the versatility of TMS-phospholanes also for the synthesis of other ligands.

Experimental Section

General. Solvents were dried and freshly distilled under argon before use. The syntheses of *β*-acylamido acrylates **11**, **16**, **18,** and **19** used as substrates were carried out following known protocols.[4b,c] All reactions were performed under an argon atmosphere by using standard Schlenk techniques. Thin-layer chromatography was performed on precoated TLC plates (silica gel). Flash chromatography was carried out with silica gel 60 (particle size 0.040−0.063 mm). Melting points are corrected. NMR spectra were recorded at the following frequencies: 400.13 MHz (^{1}H), 100.63 MHz (^{13}C), 161.98 MHz (^{31}P). Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in parts per million downfield from TMS as an internal standard. Chemical shifts of ^{31}P NMR spectra are referred to H_3PO_4 as an external standard. Signals are quoted as s (singlet), d (doublet), br (broad), and m (multiplet).

Hydrogenation experiments have been carried out under normal pressure and isobaric conditions with an automatically registering gas measuring device (1.0 atm overall pressure over the solution). The experiments were performed with 0.01 mmol of precatalyst and 1.0 mmol of prochiral olefin in 15.0 mL of

solvent at 25.0 °C. The conversion of the prochiral α- and β-dehydroamino acids and the reduction of dimethyl itaconate and their % ees were determined by GC or HPLC. Methyl (*Z*)-acetamido cinnamate (**9**): 25 m Lipodex E, 145 °C. Dimethyl itaconate (**10**): 25 m Lipodex E, 80 °C. Methyl 3-acetamido butenoate (**11**): 50 m Chiraldex β-PH, 130 °C. Methyl 3-benzamido butenoate (**12**): Chiralcel OB, 90:10 hexane/EtOH. Benzyl 3-acetamido butenoate (**13**): CHIRALCEL OD-H, 95:5 hexane/EtOH. 4-Fluoro-benzyl 3-acetamido butenoate (**14**): CHIRALCEL OJ, 95:5 hexane/EtOH. 4-Methyl-benzyl 3-acetamido butenoate (**15**): CHIRALCEL OJ, 90:10 hexane/EtOH. Methyl 3-acetamido pentenoate (**16**): 25 m, Lipodex E, 130 °C. Methyl 4-methyl-3-acetamido-2-pentenoate (**17**): 25 m, Lipodex E, 130 °C. Ethyl 4-methyl-3-acetamido-2-pentenoate (**18**): 25 m, Lipodex E, 130 °C. Methyl 3-phenyl-3-acetamido propenoate (**19**): CHIRALCEL OD-H, 96:4 hexane/EtOH. Ethyl 3-phenyl-3-acetamido propenoate (**20**): CHIRALCEL OD-H, 95:5 hexane/EtOH. 4-Methyl-benzyl 3-phenyl-3-acetamido propenoate (**21**): CHIRALPAK AD, 95:5 hexane/EtOH.

(*R,R*)-2,5-Dimethyl-1-trimethylsilyl-phospholane (7). To a solution of tris(trimethylsilyl)phosphine[25] (9.5 g, 37.9 mmol) in THF (300 mL) was slowly added a 1.4 M solution of methyllithium (1.05 equiv, 28.4 mL) in ether. After the mixture was stirred overnight, the solvent was evaporated under reduced pressure and the residue dissolved in ether (300 mL). Cyclic sulfate **3** (6.83 g, 37.9 mmol) dissolved in ether (100 mL) was added dropwise to the lithium-salt solution, and after 3 h a second equivalent of methyllithium solution (28.4 mL) was added slowly via a syringe. For completion of the reaction, the solution was stirred overnight and then the ether removed by evaporation. The residue was carefully distilled in vacuo to give the desired TMS-phospholane in a yield of 70% (5.0 g). The compound starts burning immediately in air and should be therefore handled carefully under argon: bp = 93 °C/20 mbar; $[\alpha]^{23}_D = +132°$ (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.20 (9H, d, $^3J_{H,P} = 4.2$ Hz), 1.25−1.15 (6H, m), 2.54−1.20 (6H, m); ^{13}C NMR ($CDCl_3$) δ −0.2 (d, $^2J_{C,P} = 11.4$ Hz), 18.0 (d, $^2J_{C,P} = 1.9$ Hz), 22.8 (d, $^2J_{C,P} = 30.5$ Hz), 31.3 (d, $^1J_{C,P} = 7.6$ Hz), 33.6 (d, $^1J_{C,P} = 11.4$ Hz), 38.9 (s), 40.1 (d, $^1J_{C,P} = 4.8$ Hz); ^{31}P NMR ($CDCl_3$) δ −54.5; $C_9H_{21}PSi$ (188.32). Due to the high flamability, elemental analysis could not be performed.

2,3-Bis[(*R,R*)-2,5-dimethyl-phospholanyl]maleic Anhydride (1). TMS-Phospholane **7** (0.55 g, 2.91 mmol) dissolved in ether (1.5 mL) was added by a cannula dropwise over a period of 15 min to a solution of 0.5 equiv of 2,3-dichloromaleic anhydride (0.24 g, 1.45 mmol) in ether (2 mL) at 0 °C. The suspension was stored at −78 °C for 3 days, and the precipitated dark-red crystals were filtered off and dried. The yield of compound **1** was 0.25 g (53%): ^{1}H NMR ($CDCl_3$) δ 1.06 (6H, dd, $^3J_{H,P} = 10.5$ Hz, $^3J_{H,H} = 7.1$ Hz), 1.22 (6H, dd, $^3J_{H,P} = 20.4$ Hz, $^3J_{H,H} = 7.2$ Hz), 2.49−1.25 (12H, m), 3.32 (2H, m); ^{13}C NMR ($CDCl_3$) δ 16.8 (s), 20.5 (m), 31.5 (s), 36.6 (m), 36.9 (s), 37.6 (s), 158.9 (m), 163.6 (s); ^{31}P NMR ($CDCl_3$) δ −2.2; $C_{16}H_{24}O_3P_2$ (326.31).

[Rh(COD)(1)]BF$_4$. Bisphospholane **1** (0.19 g, 0.58 mmol) was dissolved in THF (2 mL) and slowly added to a suspension of $[Rh(COD)_2]BF_4$ (0.24 g, 0.58 mmol) in THF (2 mL) at −20 °C. The mixture was allowed to warm at ambient temperature. During this time, a brown solid precipitated, which was filtered off. After the solid was washed with ether (2 × 5 mL) and dried under reduced pressure, 0.22 g (62%) of the precatalyst were obtained. If necessary, product could be purified by recrystallization from CH_2Cl_2/ether: ^{1}H NMR (acetone-d_6) δ 1.23 (6H, dd, $^3J_{H,P} = 16.0$ Hz, $^3J_{H,H} = 7.1$ Hz), 1.57 (6H, dd, $^3J_{H,P} = 19.5$ Hz, $^3J_{H,H} = 7.0$ Hz), 2.67−1.50 (18 H, m), 3.07 (2H, m), 5.15 (2H, s(br)), 5.85 (2H, s(br)); ^{13}C NMR (acetone-d_6) δ 14.1 (s), 17.6 (m), 29.0 (s), 32.8 (s), 36.4 (s), 37.7 (s), 38.0 (m), 40.8 (m), 94.9 (m), 108.5 (m), 160.1 (m) and 165.1 (m); ^{31}P NMR δ 63.8 (d, $^1J_{P,Rh} = 151$ Hz); $C_{24}H_{36}O_3P_2RhBF_4$ (624.20).

Methyl 3-Benzamido-2-butenoate (12). To a solution of methyl 3-aminocrotonate (2.0 g, 17.4 mmol) and pyridine (2.1 g, 26.1 mmol) in ether (30 mL) was slowly added 1 equiv of benzoyl chloride (2.45 g). The mixture was stored overnight in a refrigerator. Workup was carried out by dillution with ether (20 mL) and washing of the organic phase with water (10 mL), 1 N HCl (10 mL), and brine (10 mL). After drying and evaporation of the solvent, the raw product was purified by column chromatography with a gradient of *n*-hexane/ethyl acetate (from 9:1 to 4:1). The yields were 1.0 g of the (*Z*)-isomer (26%) and 1.2 g of the (*E*)-isomer (32%).

(*Z*)-Isomer: mp = 55−57 °C; ^{1}H NMR (acetone-d_6) δ 2.50 (3H), 3.72 (3H, s), 5.10 (1H, s), 7.55−7.67 (3H, m), 7.98 (2H, m), 12.14 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 21.9, 51.5, 97.2, 128.3, 129.8, 133.3, 135.0, 156.5, 165.3, 170.6. Anal. Calcd for $C_{12}H_{13}O_3N$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 66.06; H, 6.17; N, 5.83.

(*E*)-Isomer: mp = 109−113 °C; ^{1}H NMR (acetone-d_6) δ 2.50 (3H, s), 3.64 (3H, s), 7.03 (1H, s), 7.46−7.60 (3H, m), 7.89 (2H, m), 9.03 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 18.1, 50.8, 102.4, 128.4, 129.3, 132.7, 135.6, 151.6, 167.3, 169.0. Anal. Calcd for $C_{12}H_{13}O_3N$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.88; H, 6.10; N, 6.29.

Benzyl 3-Acetamido-2-butenoate (13). According to the protocol of Zhang et al.,[4c] benzyl acetylacetate (2.31 g, 12 mmol) was dissolved in methanol (20 mL). The solution was stirred over a period of 3 days with NH_4OAc (4.6 g, 60 mmol). The workup was performed as described. The product was treated with pyridine (2 mL) and acetic anhydride (6 mL) in THF (15 mL). The product thus obtained was treated with a 1:1 mixture of *n*-hexane/ether to give the (*E*)-isomer as a white product (0.95 g, 34%). The filtrate was concentrated, and after column chromatography with a gradient of *n*-hexane/ethyl acetate (from 4:1 to 1:1), the (*Z*)-isomer of **13** (1.20 g, 43%) and additional (*E*)-isomer (0.15 g, 5%) could be isolated.

***(Z)*-Isomer:** mp = 50−53 °C; ^{1}H NMR (acetone-d_6) δ 2.11 (3H, s), 2.34 (3H, s), 4.99 (1H, s), 5.17 (2H, s), 7.29−7.40 (5H, m), 11.03 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 21.1, 25.1, 65.9, 95.9, 128.8, 128.9, 129.3, 137.5, 156.6, 169.4, 169.1. Anal. Calcd for $C_{13}H_{15}O_3N$ (233.27): C, 66.94; H, 6.48; N, 6.00. Found: C, 66.69; H, 6.23; N, 5.83.

(*E*)-Isomer: mp = 104−106 °C; ^{1}H NMR (acetone-d_6) δ 2.02 (3H, s), 2.30 (3H, s), 5.09 (2H, s), 6.92 (1H, s), 7.27−7.39 (5H, m), 8.76 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 18.1, 24.6, 65.4, 100.9, 128.5, 128.7, 129.2, 138.2, 151.7, 168.5, 170.1. Anal. Calcd for $C_{13}H_{15}O_3N$ (233.27): C, 66.94; H, 6.48; N, 6.00. Found: C, 66.77; H, 6.25; N, 5.89.

4-Fluoro-benzyl 3-Acetamido-2-butenoate (14). A solution of ethyl acetoacetate (13.0 g, 0.1 mol) and 4-fluoro benzyl alcohol (12.6 g, 0.1 mol) in toluene (200 mL) was heated under reflux over a period of 16 h. During this time, a mixture of toluene/ethanol was distilled slowly. Finally, the solvent was removed and the residue was distilled to give 4-fluoro-benzyl acetoacetate ($Kp_{0.3}$ = 110−115 °C).

Related to the procedure of Zhang et al.,[4c] 4-fluoro-benzyl acetoacetate was transformed into (*E*)-/(*Z*)-isomers of 4-fluoro-benzyl 3-acetamido-butenoate (**14**) as described above for compound **13**. The separation of isomers was carried out by column chromatography with a gradient of *n*-hexane/ethyl acetate (from 4:1 to 1:1). The yield of the (*Z*)-isomer was 1.35 g (45%), and that of the (*E*)-isomer was 1.0 g (33%).

(*Z*)-Isomer: mp = 88−92 °C; ^{1}H NMR (acetone-d_6) δ 2.11 (3H, s), 2.33 (3H, s), 4.97 (1H, s), 5.15 (2H, s), 7.13 (2H, m), 7.45 (2H, m), 11.00 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 21.9, 25.1, 65.2, 95.9, 116.0 (d, J = 21 Hz), 131.2 (d, J = 9 Hz), 133.6 (d, J = 4 Hz), 156.7, 163.3 (d, J = 244 Hz), 169.1, 169.3. Anal. Calcd for $C_{13}H_{14}O_3FN$ (251.26): C, 62.14; H, 5.62; N, 5.57. Found: C, 62.28; H, 5.34; N, 5.38.

(*E*)-Isomer: mp = 130−133 °C; ^{1}H NMR (acetone-d_6) δ 2.04 (3H, s), 2.30 (3H, s), 5.09 (2H, s), 6.93 (1H, s), 7.13 (2H, m),

(25) Popova, E. V.; Patsanovskii, I. I.; Livantsov, M. V.; Ishmaeva, E. A. *Russ. J. Gen. Chem.* **1996**, *66*, 1369; *Zh. Obshch. Khim.* **1996**, *66*, 1369.

7.45 (2H, m), 8.79 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 18.1, 24.6, 64.7, 100.8, 115.8 (d, J = 21 Hz), 131.0 (d, J = 8 Hz), 134.3 (d, J = 3 Hz), 151.8, 163.2 (d, J = 244 Hz), 168.5, 170.1. Anal. Calcd for $C_{13}H_{14}O_3FN$ (251.26): C, 62.14; H, 5.62; N, 5.57. Found: C, 62.23; H, 5.75; N, 5.47.

4-Methyl-benzyl 3-Acetamido-2-butenoate (15). According to the synthesis of **14**, ethyl acetoacetate (13.0 g, 0.1 M) and 4-methylbenzyl alcohol (12.2 g, 0.1 M) in toluene (200 mL) were heated. After removal of the solvent, the residue was distilled to give 4-methyl-benzyl acetoacetate ($Kp_{0.3}$ = 110−112 °C). Related to the procedure of Zhang et al.,[4c] 4-methylbenzyl acetoacetate was transformed into the (*E*)-/(*Z*)-isomers of 4-methyl-benzyl 3-acetamido-butenoate (**15**) as described above for compound **13**. The separation of the isomers was carried out by column chromatography with a gradient of *n*-hexane/ethyl acetate (from 2:1 to 1:1). The yield of the (*Z*)-isomer was 1.05 g (35%), and that of the (*E*)-isomer was 1.2 g (39%).

(*Z*)-Isomer: mp = 49−53 °C; ^{1}H NMR (acetone-d_6) δ 2.10 (3H, s), 2.32 (3H, s), 2.33 (3H, s), 4.96 (1H, s), 5.11 (2H, s), 7.18 (2H, m), 7.27 (2H, m), 11.04 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 21.1, 21.9, 25.1, 65.9, 96.0, 129.0, 129.9, 134.4, 138.5, 156.4, 169.1, 169.4. Anal. Calcd for $C_{14}H_{17}O_3N$ (247.30): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.20; H, 6.76; N, 5.46.

(*E*)-Isomer: mp = 78−80 °C; ^{1}H NMR (acetone-d_6) δ 2.03 (3H, s), 2.31 (3H, s), 2.32 (3H, s), 5.06 (2H, s), 6.92 (1H, s), 7.16 (2H, m), 7.28 (2H, m), 8.77 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 18.1, 21.1, 24.6, 65.3, 101.1, 128.9, 129.7, 135.1, 138.1, 151.5, 168.5, 170.1. Anal. Calcd for $C_{14}H_{17}O_3N$ (247.30): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.12; H, 6.75; N, 5.67.

Methyl 4-Methyl-3-acetamido-2-pentenoate (17). According to the protocol of Zhang et al.,[4c] methyl 4-methyl-3-oxo-pentanoate (1.73 g, 12 mmol) was dissolved in methanol (20 mL) and stirred over a period of 3 days with NH_4OAc (4.60 g, 60 mmol). After workup as described, the residue was treated with pyridine (2 mL) and acetic anhydride (6 mL) in THF (15 mL). The raw product obtained was purified by column chromatography with a gradient of *n*-hexane/ethyl acetate (from 4:1 to 1:1) to give the (*Z*)-isomer (0.85 g, 38%) and the (*E*)-isomer (0.68 g, 31%).

(*Z*)-Isomer: liquid, ^{1}H NMR (acetone-d_6) δ 1.10 (6H, d), 2.11 (3H, s), 3.68 (3H, s), 5.04 (1H, s), 11.10 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 21.5, 25.4, 29.9, 51.3, 92.3, 166.3, 169.6, 170.5. Anal. Calcd for $C_9H_{15}O_3N$ (185.23): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.27; H, 7.88; N, 7.42.

(*E*)-Isomer: mp = 62−65 °C; ^{1}H NMR (acetone-d_6) δ 1.13 (6H, d), 2.09 (3H, s), 3.59 (3H, s), 4.34 (1H, q), 6.98 (1H, s), 8.15 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 19.7, 24.7, 27.9, 50.7, 100.5, 159.0, 168.8, 170.8. Anal. Calcd for $C_9H_{15}O_3N$ (185.23): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.48; H, 7.77; N, 7.33.

Ethyl 3-Acetamido-3-phenyl-2-propenoate (20). Ethyl benzoyl acetate (2.31 g, 12 mmol) was transformed in a two-step procedure into ethyl 3-acetamido-3-phenyl-butenoate. The raw product was purified by column chromatography with a gradient of *n*-hexane/ethyl acetate (from 4:1 to 1:1). Besides the unchanged intermediate, ethyl 3-amino-3-phenyl-propenoate, the desired (*Z*)-**20** (1.26 g, 45%) was obtained. The (*E*)-isomer could only be isolated in a low yield (0.15 g, 5%).

The yield of the (*E*)-isomer could be improved by application of another acetylation procedure described for the synthesis of methyl 3-acetamido-butenoate (**11**).[26] Thus, to a solution of ethyl-3-amino-phenylpropenoate (1.91 g, 10 mmol) and pyridine (1.78 g, 20 mmol) in ether (20 mL) was added dropwise at 0 °C a solution of acetyl chloride (1.56 g, 20 mmol) in ether (10 mL). The mixture was warmed to ambient temperature, and stirring was continued for 48 h. For the workup, the mixture was diluted with ether (25 mL) and poored in ice−water (20 mL). The ether phase was washed with 1 N HCl (15 mL), saturated $NaHCO_3$ (15 mL), and brine (15 mL). After drying (Na_2SO_4) and evaporation of the solvent, the raw product was purified as described above. The yields were 0.75 g of the (*Z*)-isomer (32%) and 0.48 g of the (*E*)-isomer (21%).

(*Z*)-Isomer: mp = 42−45 °C; ^{1}H NMR (acetone-d_6) δ 1.28 (3H, t ^3J = 7.1 Hz), 2.12 (3H, s), 4.20 (2H, q, ^3J = 7.1 Hz), 5.28 (1H, s), 7.33−7.44 (5H, m), 10.46 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 14.5, 24.5, 60.7, 101.6, 128.0, 128.7, 130.1, 137.3, 155.2, 168.5, 168.7. Anal. Calcd for $C_{13}H_{15}O_3N$ (233.27): C, 66.94; H, 6.48; N, 6.00. Found: C, 66.89; H, 6.24; N, 5.94.

(*E*)-Isomer: mp = 106−109 °C; ^{1}H NMR (acetone-d_6) δ 1.04 (3H, t ^3J = 7.1 Hz), 2.11 (3H, s), 3.89 (2H, q, ^3J = 7.1 Hz), 7.11 (1H, s), 7.29−7.46 (5H, m), 8.68 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 14.4, 24.6, 59.5, 103.4, 128.6, 129.4, 129.5, 137.5, 150.9, 167.3, 170.4. Anal. Calcd for $C_{13}H_{15}O_3N$ (233.27): C, 66.94; H, 6.48; N, 6.00. Found: C, 66.72; H, 6.32; N, 5.88.

4-Methyl-benzyl 3-Acetamido-3-phenyl-2-propenoate (21). A solution of ethyl benzoyl acetate (19.2 g, 0.1 mol) and 4-methylbenzyl alcohol (12.2 g, 0.1 mol) in toluene (200 mL) was heated under reflux over a period of 16 h. During this time, a mixture of toluene/ethanol was distilled slowly. Finally, the solvent was removed and the residue was distilled to give 4-methyl-benzyl benzoyl acetate ($Kp_{0.3}$ = 178−185 °C). The β-ketoester (3.2 g, 12 mmol) was transformed into 4-methyl-benzyl 3-amino-3-phenyl-2-propenoate by stirring with NH_4-OAc (4.6 g, 60 mmol) in methanol (40 mL) over a period of 3 days at ambient temperature. After workup as described,[4c] the raw product was dissolved in a mixture of ether (30 mL) and pyridine (1.90 g, 24 mmol) at 0 °C. A solution of 2 equiv of acetyl chloride (1.88 g) in ether (10 mL) was added slowly via a syringe over a period of 30 min. During this time, a white solid precipitated (pyridinium chloride). The mixture was stirred at room temperature for 3 days. Then, the mixture was diluted with additional ether (50 mL) and poored in ice−water (30 mL). After phase separation, the ethereal solution was washed with 1 N HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (25 mL). After drying with Na_2SO_4 and evaporation of the solvent, the raw product was purified by chromatography with a gradient of *n*-hexane/ethyl acetate (from 4:1 to 1:1) and yielded the (*Z*)-isomer (0.95 g, 26%) and the (*E*)-isomer (0.73 g, 20%).

(*Z*)-Isomer: mp = 74−77 °C; ^{1}H NMR (acetone-d_6) δ 2.12 (3H, s), 2.33 (3H, s), 5.19 (2H, s), 5.33 (1H, s), 7.20−7.45 (9H, m), 10.42 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 21.1, 24.5, 66.3, 101.5, 128.0, 128.7, 129.2, 129.9, 130.2, 134.3, 137.3, 138.6, 155.6, 168.5, 168.5; Anal. Calcd for $C_{19}H_{19}O_3N$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.57; H, 5.88; N, 5.52.

(*E*)-Isomer: mp = 128−132 °C; ^{1}H NMR (acetone-d_6) δ 2.11 (3H, s), 2.30 (3H, s), 4.90 (2H, s), 7.17 (1H, s), 7.13−7.39 (9H, m), 8.69 (1H, s(br)); ^{13}C NMR (acetone-d_6) δ 21.1, 24.6, 65.5, 103.0, 128.7, 128.8, 129.5, 129.6, 129.7, 134.8, 137.4, 138.0, 151.4, 167.3, 170.4. Anal. Calcd for $C_{19}H_{19}O_3N$ (309.37): C, 73.77; H, 6.19; N, 4.53. Found: C, 73.74; H, 5.99; N, 4.49.

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