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# Enantioselective Rh-Catalyzed Hydrogenation of *N*-Formyl Dehydroamino Esters with Monodentate Phosphoramidite Ligands

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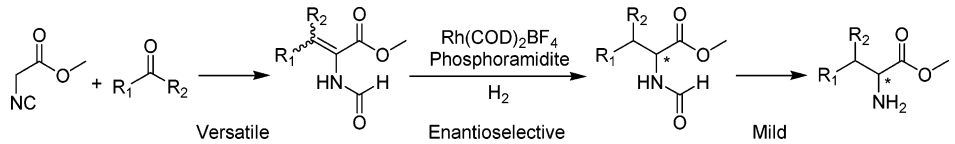


Enantioselectivities up to >99% ee were achieved in the rhodium-catalyzed asymmetric hydrogenation of *N*-formyl dehydroamino esters using monodentate phosphoramidites as chiral ligands. The substrates were synthesized by condensation of methyl isocyanoacetate with a range of aldehydes and with cyclohexanone. A highly convenient multigram scale one step synthesis of methyl 2-(formamido)acrylate was developed. This compound was used in the synthesis of methyl 2-(formamido)cinnamate via a solvent free Heck reaction. Moreover, full conversion and >99% ee were obtained in 1 h in the hydrogenation of methyl 2-(formamido)acrylate with 0.2 mol % catalyst and 2 bar hydrogen pressure. The versatility of the formyl protection was established by its removal under mild conditions.

## Introduction

Enantiopure natural and unnatural amino acids play an important role as building blocks in the preparation of many pharmaceuticals and other biologically active compounds.[1] They are also widely used in organic chemistry as chiral auxiliaries and as catalysts.[2] Unnatural amino acids in particular have received increasing attention in drug discovery and protein engineering, because of novel and interesting properties they confer to biologically relevant peptides.[3] Therefore, it is not surprising that, in industry as well as in academia, there is a great interest in the use of catalytic asymmetric approaches for the preparation of optically active amino acids and their derivatives.[4]

Among these different approaches, rhodium-catalyzed asymmetric hydrogenation is the most widely applied enantioselective chemocatalytic technology for the synthesis of amino acid derivatives.[5] The reaction is extremely clean and efficient, as only substrate, solvent, hydrogen, and a small amount of catalyst are needed. Since their introduction, an enormous number of bidentate chiral phosphorus ligands have been prepared,[6] as they were considered to be the key to high enantioselectivity. More recently,[7] a number of monodentate phosphorus based chiral ligands have been demonstrated to be equally effective or, in some cases, even superior to bidentate ligands, providing easier

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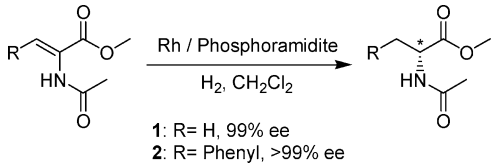


**FIGURE 1.** Asymmetric hydrogenation of α-dehydroamino esters with monodentate chiral phosphoramidite ligands.

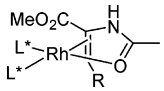

**FIGURE 2.** Coordination provided by the acyl moiety, as stereodirecting functionality.

access to new catalysts.[8] Thus, Rh-catalyzed asymmetric hydrogenation is a well-established, though still evolving,[9] technology on both laboratory and industrial scale.[10]

In our laboratories, BINOL-derived monodentate phosphoramidites have been successfully used in the Rh-catalyzed hydrogenation of a range of olefinic substrates, including the benchmark substrates methyl 2-(acetamido)acrylate (**1**) and methyl (*Z*)-2-(acetamido)cinnamate (**2**) (Figure 1).[11]

It is generally accepted that, to achieve excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of dehydroamino esters, the presence of the α-acetamido group coordinating to the rhodium is essential (Figure 2).[12]

In an early study conducted by Glaser and co-workers, the influence of the nature of the stereodirecting group has been studied in relation to the reactivity and enantioselectivity obtained. Using DIOP as a chiral bis-phosphine ligand the superiority of the acetamido substituent was clearly established in terms of both reactivity and enantioselectivity.[13] More recently, also carbamate stereodirecting groups (Boc and Z) have been shown to be effective.[14]

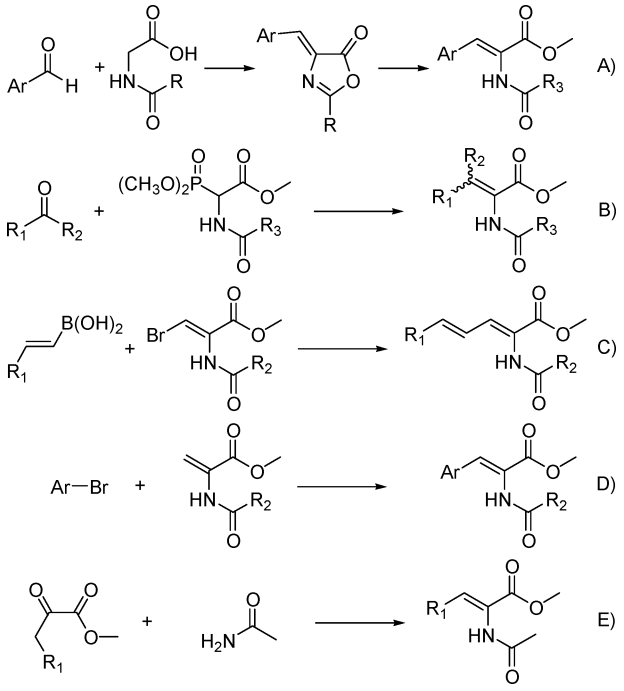


**FIGURE 3.** Synthesis of dehydroamino esters via (A) Erlenmeyer azlactone synthesis, (B) the Horner−Emmons method with Schmidt's phosphorylglycine esters, (C) Suzuki cross-coupling, (D) Heck arylation, and (E) acetamide α-ketoester condensation.

There is extensive literature on the preparation of dehydroamino acid derivatives and frequently used methods are depicted in Figure 3.[15]The Erlenmeyer synthesis via azlactone[16] (Figure 3, method A) and the condensation of aldehydes with phosphorylglycine esters (method B) are the most frequently used.[17] The main limitation of the azlactone approach lies in the harsh reaction conditions, which limits its use to aromatic aldehydes devoid of acid-sensitive groups.[18] In addition, substrates with carbamate protecting groups cannot be prepared. The use of phosphorylglycine esters is instead more versatile and the synthesis milder. This method is complementary to the Erlenmeyer synthesis as it allows access to *β*-alkyl-α-enamides. Nevertheless, although ketones also can be used, reaction times in this case are long.[19] Moreover, the preparation of the Horner−Emmons reagent requires several steps.

Both *β*-aryl- and *β*-alkenyl-substituted enamides can be conveniently obtained through Suzuki coupling (method C).[20]

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Nevertheless, also in this case the preparation of the starting methyl $\beta$-bromo(acetamido)acrylate is quite laborious and low yielding. Arylation of methyl 2-(acetamido)acrylate is achieved by using the Heck reaction (method D).[21] This method, despite its potential, is somewhat neglected, once more because of the problematic synthesis of the starting material, especially on large scale.[22] The condensation of α-ketoesters and acetamide (method E) allows, in principle, the preparation of a large variety of α-enamides. However, also in this case, its use is limited by the harsh reaction conditions and low yields.[15]

Although the acyl moiety is the most employed stereodirecting group, strongly acidic conditions are needed for its removal.[23,24] This might cause degradation of sensitive functionalities or loss of optical purity. Deprotection with basic conditions is precluded because of competing azlactone formation with subsequent racemization.[25] To overcome this problem, Burk and co-workers achieved a milder deprotection by first converting the acylamide in its Boc derivative, followed by deacetylation and Boc removal, respectively.[26] Nevertheless, this implies an extra transformation. Mild deprotection is also provided by enzymatic hydrolysis with acylases, but D-selective amino acid acylases are not commercially available.[27]

During our studies on amino acid synthesis, we realized that while the asymmetric hydrogenation step has been developed very well, both the synthesis of the substrates and the removal of the directing group on the amine after hydrogenation limit the scope and applicability of this strategy. Clearly, there is a need for (1) a more general, mild and easily applicable synthetic method for the preparation of the required dehydroamino esters, (2) a directing group that can be removed under mild conditions, and (3) a suitable protecting group that can be used directly for other transformations, such as, for example, peptide synthesis.

We propose that all these requirements can be met by using a formyl group as a stereodirecting functionality. The formyl moiety, as protective group, is considered a desirable choice due to its low cost of preparation, introduction, removal, and improved water solubility.[28] For the synthesis of the required 2-(formamido)acrylate derivatives, we adopted the Schöllkopf method involving the condensation of aldehydes and ketones with methyl isocyanoacetate.[29] The ring opening by elimination

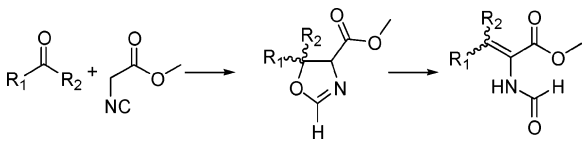

**FIGURE 4.** Synthesis of *N*-formyl protected dehydroamino esters via the Schöllkopf 2-oxazoline.

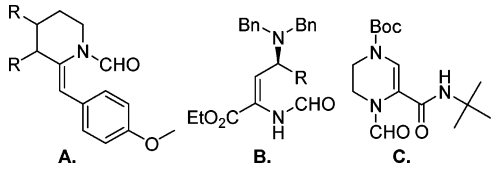

**FIGURE 5.** Use of the formyl moiety in metal-catalyzed asymmetric hydrogenation.

of the 2-oxazolines yields the desired *N*-formyl dehydroamino esters (Figure 4).

To our surprise, the formyl group as the stereodirecting group is not used in Rh-catalyzed enantioselective hydrogenation.

Cyclic *N*-formyl enamides (Figure 5A) have been hydrogenated with Ru-BINAP and Ru-BIPHEMP yielding key intermediates in the synthesis of morphine analogues, with high enantioselectivities.[30] Reetz and co-workers reported diastereoselective Rh-catalyzed asymmetric hydrogenation of enantiopure $\gamma$-amino *N*-formyl dehydroamino esters (Figure 5B) employing DIOP, DIPAMP, CHIRAPHOS, and BINAP as chiral ligands.[31] An isolated case is the Rh-catalyzed enantioselective hydrogenation of an *N*-formyl, *N*-Boc protected tetrahydropyrazine (Figure 5C).[32] However, in this case it is unclear whether the directing group was the formyl or the Boc moiety.

The main reason the formyl group is not used in asymmetric hydrogenation seems directly connected to the results obtained by Glaser and co-workers.[13] The direct comparison between the Rh-catalyzed asymmetric hydrogenation of *N*-acyl and *N*-formyl cinnamic acid methyl ester with DIOP as the chiral ligand showed a considerable decrease in enantioselectivity in the latter case (69% and 58% ee, respectively). Not surprisingly, the conclusion drawn from these studies was that an acyl group coordinates stronger to the metal center than a formyl group. In addition, from a synthetic point of view, *N*-formyl dehydroamino esters cannot be prepared by using the Erlenmeyer azlactone synthesis.[33]

In view of the fact that catalysts have evolved tremendously since the introduction of DIOP, we felt the use of formyl as a stereodirecting group should be reconsidered. Herein we report the practical preparation of *N*-formyl dehydroamino esters and their enantioselective hydrogenation, using Rh-phosphoramidites catalysts.

## Results and Discussion

**Synthesis of *N*-Formyl Dehydroamino Esters.** *N*-Formyl dehydroamino esters can be obtained by mild aldol condensation

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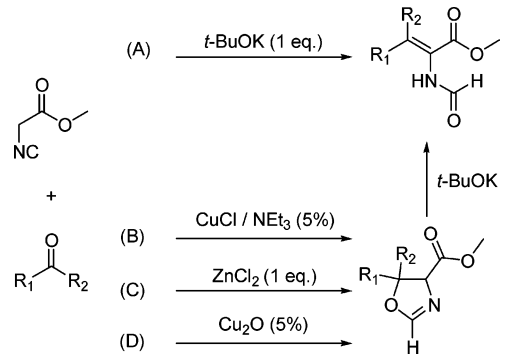
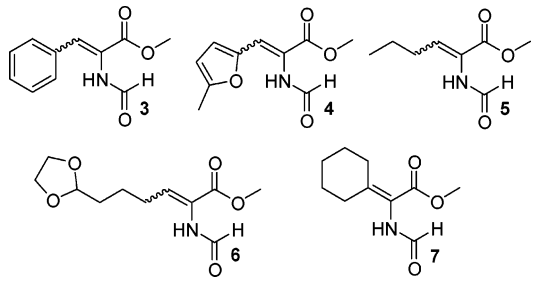
**SCHEME 1**



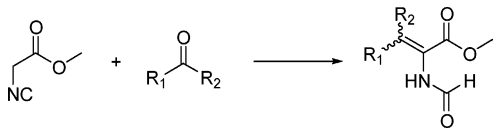

**SCHEME 2**




of methyl isocyanoacetate with a variety of alkyl, aryl, or heterocyclic aldehydes and ketones.[15a] Methyl isocyanoacetate is commercially available and can be conveniently prepared, in good yields and on a multigram scale, via *N*-formylation of glycine methyl ester followed by subsequent dehydration with $POCl_3$.[34] The dehydroamino esters can be prepared either in a single step, by performing the condensation in the presence of *t*-BuOK (Scheme 1, method A),[35] or via the isolation and subsequent ring opening of the corresponding 2-oxazolines.[36] Ito et al. introduced the use of the Lewis acids CuCl and $ZnCl_2$ for the synthesis of 2-oxazolines (methods B and C).[37] The use of $Cu_2O$ proved to be beneficial when using ketones in the condensation reaction instead of aldehydes (method D).[38] Subsequent treatment of the 2-oxazolines with *t*-BuOK leads to the dehydroamino esters.[39] It was decided to compare the various methods present in the literature for the preparation of 2-oxazolines and develop a one-pot synthesis that would avoid their isolation.

The substrates shown in Scheme 2 were prepared adopting the different methods described in Scheme 1 and the results are shown in Table 1.

**TABLE 1. Synthesis of *N*-Formyl Dehydroamino Esters with Methyl Isocyanoacetate**[a]



| entry | product | method | *Z*:*E* | yield (%) |
|---|---|---|---|---|
| 1 | **3** | D | 2.9:1 | 83 |
| 2 | **4** | A | 5.7:1 | 30 |
| 3 | **4** | B | 1.9:1 | 79 |
| 4 | **5** | A | 1.2:1 | 29 |
| 5 | **5** | B | 1.5:1 | 63 |
| 6 | **5** | D | 1.6:1 | 65 |
| 7 | **6** | B | 1.5:1 | 58 |
| 8 | **7** | C | | 35 |
| 9 | **7** | D | | 82 |

[a] Method A: (a) 1 equiv of *t*-BuOK, THF, −60 °C; (b) 1 equiv of AcOH, $CH_2Cl_2$, 0 °C. Method B: (a) CuCl/$NEt_3$ (5%), THF, rt; (b) 1 equiv of *t*-BuOK THF, 0 °C; (c) 1 equiv of AcOH, $CH_2Cl_2$, 0 °C. Method C: 1 equiv of $ZnCl_2$, THF, rt; (b) 1 equiv of *t*-BuOK THF, 0 °C; (c) 1 equiv of AcOH, $CH_2Cl_2$, 0 °C. Method D: (a) $Cu_2O$ (5%), $Et_2O$, rt; (b) 1 equiv of *t*-BuOK THF, 0 °C; (c) 1 equiv of AcOH, $CH_2Cl_2$, 0 °C.

Method A proved to be less efficient (Table 1, entries 2 and 4) as the products **4** and **5** were obtained in 30% and 29% yield, respectively, from complex crude mixtures. On the other hand, the same products could be obtained in good yields by using the stepwise approach of method B (entries 3 and 5). The reactions were run overnight at room temperature in the presence of a catalytic amount of CuCl and $NEt_3$ (5%). In most cases, $^1$H NMR of the crude mixtures showed complete conversion to the 2-oxazoline intermediate.[40] In all cases with Cu(I) or Zn(II) the 2-oxazolines were converted in situ to the desired *N*-formyl protected dehydroamino esters by adding *t*-BuOK in THF to the reaction mixture, followed by acetic acid in $CH_2Cl_2$. The use of Cu(I) also allowed a satisfactory synthesis of the more delicate substrate **6** (entry 7).[41] Aldol condensation with methyl isocyanoacetate using ketones as electrophiles has not been frequently described in the literature. Ito reported the use of $ZnCl_2$ in combination with 2-cyclohexenone yielding the corresponding 2-oxazoline in 29% yield.[37] Applying the same methodology, dehydroamino ester **7** was obtained in 35% yield (entry 8).[42] However, a very good 82% yield was obtained with use of catalytic $Cu_2O$ (entry 9).[43] The same procedure was adopted by using benzaldehyde for the synthesis of **3**, which was obtained in 83% yield (entry 1).[44] Furthermore, $Cu_2O$ was also used for the preparation of **5** and the result was similar to that obtained when using CuCl (entry 6). As a general

(33) When *N*-formyl glycine was used in the Erlenmeyer azlactone synthesis with benzaldehyde, the corresponding methyl-substituted azlactone was isolated in 70% yield, due to the in situ acylation−deformylation of the substrate.

(34) A slight modification of a literature procedure was used: Park, W. K. C.; Auer, M.; Jaksche, H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 10150.

(35) See for example: (a) Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 687. For the use of NaH, see: (b) Numani, K.-I.; Hiramatsu, K.; Hayashi, K.; Matsumoto, K. *Tetrahedron* **1988**, *44*, 5467.

(36) For a review, see: Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339.

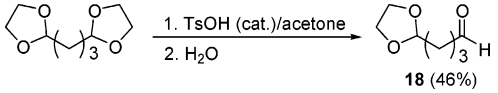
(37) Ito, Y.; Matsuura, T.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5781.

(38) (a) Saegusa, T.; Ito, Y.; Kinoshita, H.; Tomita, S. *J. Org. Chem.* **1971**, *36*, 3316. (b) Soloshonok, V. A.; Hayashi, T.; Ishikawa, K.; Nagashima, N. *Tetrahedron Lett.* **1994**, *35*, 1055. (c) Arnone, A.; Gestmann, D.; Meille, S. V.; Resnati, G.; Sidoti, G. *Chem. Commun.* **1996**, *22*, 2569.

(39) For an example with NaCN in the condensation step, see: Hoppe, I.; Schöllkopf, U. *Synthesis* (*Stuttg.*) **1982**, *2*, 129.

(40) The coordination of methyl isocyanoacetate with transition metals such as Cu or Zn increases the acidity of the α-protons.

(41) The aldehyde 5-(1,3-dioxolan-2-yl)-1-pentanal, used as starting material for the synthesis of substrate **6**, was obtained by monodeprotection of the corresponding bis-1,3-dioxolane, following a modified literature procedure: Takacs, J. M.; Myoung, Y.-C.; Anderson, L. G. *J. Org. Chem.* **1994**, *59*, 6928.



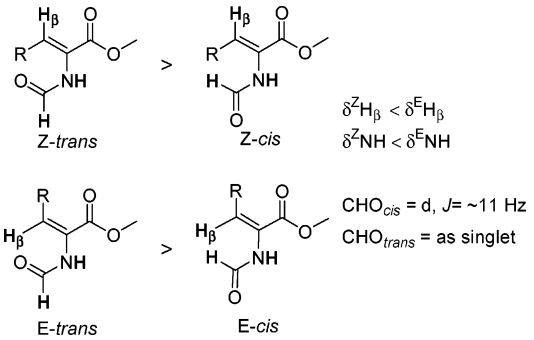

**18** (46%)

(42) The same compound was obtained in 59% yield, using NaH: Yim, N. C. F.; Bryan, H.; Huffman, W. F.; Moore, M. L. *J. Org. Chem.* **1988**, *53*, 4605.

(43) Adapted synthesis from a literature procedure (ref 38c) with the $Cu_2O$ content reduced to 5%.

(44) This substrate could also be prepared by using NaH (ref 35b) or $ZnCl_2$ (ref 37).

**SCHEME 3. *Z* and *E* Isomers and Trans and cis Rotamers Observed for *N*-Formyl Dehydroamino Methyl Esters[45]**



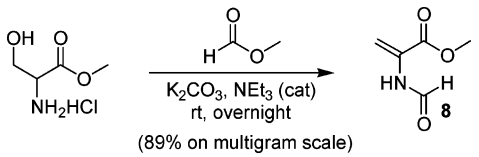

conclusion, the most versatile procedures involve the use of catalytic Cu(I), with the subsequent in situ ring opening of the 2-oxazolines formed to yield the desired *N*-formyl dehydroamino esters.

In all cases a mixture of *Z* and *E* isomers was obtained (entries 1−7). The isomers were separated by flash chromatography, as we were interested in the influence of the double bond configuration on the activity and enantioselectivity in the Rh-catalyzed hydrogenation. In addition, every isomer consisted of a mixture of trans and cis rotamers corresponding to slow isomerization of the formamide bond (Scheme 3).

Identification of the different isomers and rotamers was achieved by $^1$H NMR based on previous studies.[46] To identify the *Z* and *E* isomers, the position of the vinylic $H_\beta$ and of the proton on the nitrogen is very diagnostic. In the case of the *Z* isomer both signals appear at higher field compared to the corresponding *E* isomer (Scheme 3). In both *Z* and *E* isomers, the proton on the formyl group appears as a singlet for the trans rotamer and as a doublet for the cis rotamer. Not only the position of the formyl and the amido protons differs between trans and cis rotamers, but also the $H_\beta$ vinylic proton. This facilitates further identification of the *Z* and *E* isomers, as the trans and cis $H_\beta$ vinylic protons of the *E* isomer appear at clearly different chemical shifts. For both *Z* and *E* isomers the trans rotamer is generally present in major amount. The ratio decreases with the increasing bulkiness of the $\beta$-substituent.[47]

As a second versatile method for the preparation of *N*-formyl dehydroamino esters, the Heck reaction between aryl halides and methyl 2-(formamido)acrylate (**8**) was explored. This approach is analogous to the one reported, among others, by RajanBabu and co-workers for the *N*-acyl substrate (Figure 3, method D).[48] This methodology gives access in two steps to numerous substrates for asymmetric hydrogenation. Thus, methyl 2-(formamido)acrylate would appear as extremely valuable starting material, providing the possibility of establishing a cheap, practical and efficient preparation.[49] The approach adopted is shown in Scheme 4.

**SCHEME 4. Synthesis of Methyl 2-(Formamido)acrylate (8)**

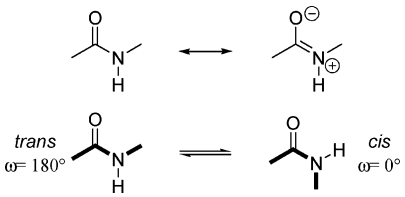



Product **8** is obtained by formylation and dehydration of inexpensive and readily available racemic serine methyl ester hydrochloric salt, in one step on a multigram scale with methyl formate as solvent. The use of $K_2CO_3$ turned out to be essential as the salts formed are not soluble in the reaction mixture and, next to driving the reaction to completion, could be easily removed by filtration.[50] Quick flash chromatography of the crude mixture, after removal of volatiles, afforded **8** in one step and high yield (Scheme 4), making this a highly competitive alternative to the existing synthesis of the *N*-acyl equivalent.[49] Having achieved an efficient protocol for the preparation of **8**, methyl (*Z*)-2-(formamido)cinnamate (**3**) was prepared by reacting **8** under Heck reaction conditions (Table 2).

Initially, the conditions used by RajanBabu et al. with methyl 2-(acetamido)acrylate were applied (11.5% palladium acetate).[51] Product **3** was obtained in higher yield with use of phenyl iodide (Table 2, entry 2) than when the less reactive phenyl bromide was used (entry 1). Upon lowering the amount of palladium acetate to 5% and 2%, the yields slightly increased when phenyl iodide was used (entries 4 and 6 vs entry 2). Good regioselectivities were obtained, with the *Z* isomer being the major product in all cases.

**Asymmetric Hydrogenation of *N*-Formyl Dehydroamino Esters.** The substrates prepared (Scheme 2) were used in the

(45) Sewald, N.; Jakubke, H.-D. *Peptides*: *Chemistry and Biology*; Wiley-VCH: Weinheim, Germany, 2002; Chapter 2.1. The definition of trans and cis conformers adopts the definition of the conformation of the amide bond in the peptide backbone:




(46) (a) Glaser, R.; Geresh, S.; Schöllkopf, U.; Meyer, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, *1*, 1746. (b) Mazurkiewicz, R.; Kuźnik, A.; Grymel, M.; Kuźnik, N. *Magn. Reson. Chem.* **2005**, *43*, 36.

(47) The difference in chemical shift between the signals of trans and cis rotamers allowed via variable-temperature $^1$H NMR the determination, for methyl 2-(formamido)cinnamate, of a coalescence temperature of $T_c$ = 45 °C. From this value, the free energy of activation, which corresponds to the rotational barrier, was calculated to be $\Delta G^{\#}$ = 63.3 kJ/mol. Once the rotational barrier was known, a frequency of rotation at room temperature of 50 $s^{-1}$ (180 000 $h^{-1}$) was calculated, using the Eyring equation. Due to this fast rotation, no influence was expected on the hydrogenation reactions outcome. (a) Hesse, M.; Meier, H.; Zeeh, B. *Spectroscopic Methods in Organic Synthesis*; Thieme: New York, 1997; p 95. (b) Oki, M. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1983; Vol. 14, Chapter 1.

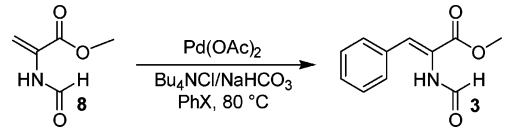
(48) For examples of Heck reactions employed in the synthesis of 2-(acetamido)cinnamic methyl ester derivatives, see: (a) Reference 21. (b) Harrington, P. H.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. (c) Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584. (d) Gallou-Dagommer, I.; Gastaud, P.; RajanBabu, T. V. *Org. Lett.* **2001**, *3*, 2053. (e) Willans, C. E.; Mulders, J. M. C. A.; de Vries, J. G.; de Vries, A. H. M. *J. Organomet. Chem.* **2003**, *687*, 494.

(49) For a multigram scale synthesis of methyl 2-(acetamido)acrylate, see: (a) Nugent, W. A.; Feaster, J. E. *Synth. Commun.* **1998**, *28*, 1617. (b) Nugent, W. A. U. S. Patent 5,559,268, 1996. This protocol provides a 1:1 mixture of mono- and diacetylated product. In a later report (ref 48d) the same protocol was applied and methyl 2-(acetamido)acrylate was isolated in 38% yield.

(50) The use of a catalytic amount of $NEt_3$ (100 $\mu$L on a 10 g scale), in addition to $K_2CO_3$, ensured enough base in solution to keep the reaction going. When only $NEt_3$ was used, the reaction was much slower and eventually stopped. The use of $Cs_2CO_3$, under the same reaction conditions, resulted in a slightly faster reaction, but the product was obtained in lower yield as a polymerization process started to take place. The product **8** was obtained in 92% isolated yield starting from 1 g of racemic serine hydrochloric acid methyl ester and in 89% starting from 10 g.

(51) According to literature procedure (ref 48d), see the Supporting Information.

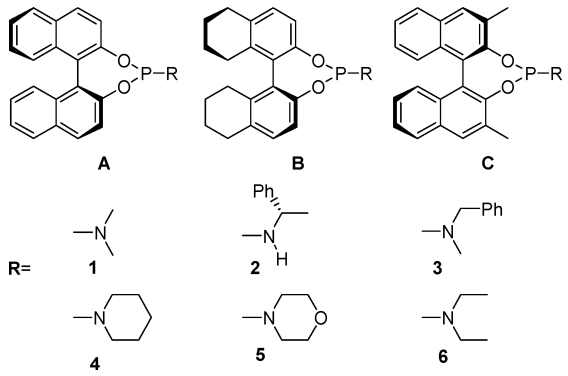
**TABLE 2. Reaction of Methyl 2-(Formamido)acrylate under Heck Reaction Conditions**




| entry | Pd (%)[a] | PhX | *Z*:*E*[b] | yield[c] (%) |
|---|---|---|---|---|
| 1 | 11.5 | PhBr | 28:1 | 59 |
| 2 | 11.5 | PhI | 12:1 | 68 |
| 3 | 5.0 | PhBr | 12:1 | 64 |
| 4 | 5.0 | PhI | 11:1 | 73 |
| 5 | 2.0 | PhBr | 13:1 | 45 |
| 6 | 2.0 | PhI | 13:1 | 73 |

[a] Reactions performed in a sealed tube at 80 °C for 22 h. [b] *Z*:*E* ratio determined by $^1$H NMR. [c] Isolated yields, not optimized.

**SCHEME 5. Phosphoramidites Used in This Study**

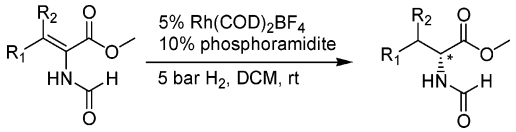



asymmetric Rh-catalyzed hydrogenation reaction employing chiral phosphoramidites as ligands (Scheme 5).

For screening purposes, a catalyst loading of 5% was employed. Dichloromethane was used as solvent, as it previously has proven to be the solvent of choice.[11b] PipPhos (**A4**) was selected as it showed superior performance in terms of reactivity and enantioselectivity with many other substrates.[11e,g] Both *Z* and *E* isomers of substrates **3**−**6** were hydrogenated. All reactions went to full conversion and the results are listed in Table 3.

We were pleased to see that both *N*-formyl phenylalanine methyl ester (**9**) and *N*-formyl alanine methyl ester (**14**) were obtained with excellent enantioselectivity (>99% ee). This proved our hypothesis that the formyl group is comparable to the acyl group in directing the enantioselectivity, at least for this catalyst.[52] A high 94% ee (Table 3, entry 3) was obtained for heterocyclic substrate **4** (*Z*). When **A1** (MonoPhos) and **A5** were used, the same product **10** was obtained in only 75% and 88% ee, respectively (entries 4 and 5).[53] A class of substrates that has not been used before in Rh-catalyzed hydrogenation using monodentate ligands are *β*-alkyl substituted dehydroamino

**TABLE 3. Asymmetric Hydrogenation of *N*-Formyl Dehydroamino Methyl Esters[a]**




| entry | substrate | product | ligand | ee (%)[b,c] |
|---|---|---|---|---|
| 1 | **3** (*Z*) | **9** | **A4** | **99** (*R*) |
| 2 | **3** (*E*) | **9** | **A4** | 46 (*R*) |
| 3 | **4** (*Z*) | **10** | **A4** | **94** (*R*) |
| 4 | **4** (*Z*) | **10** | **A1** | 75 (*R*) |
| 5 | **4** (*Z*) | **10** | **A5** | 88 (*R*) |
| 6 | **4** (*E*) | **10** | **A4** | 64 (*R*) |
| 7 | **5** (*Z*) | **11** | **A4** | >**99** (*R*) |
| 8 | **5** (*Z*) | **11** | **A1** | 98 (*R*) |
| 9 | **5** (*E*) | **11** | **A4** | 96 (*R*) |
| 10 | **6** (*Z*) | **12** | **A4** | >**99** (*R*) |
| 11 | **6** (*E*) | **12** | **A4** | 97 (*R*) |
| 12 | **7** | **13** | **A4** | 61 (*R*) |
| 13 | **8** | **14** | **A4** | >**99** (*R*) |
| 14 | **8** | **14** | **A1** | 97 (*R*) |

[a] Reactions performed in 4 mL of solvent with 0.2 mmol of substrate for 16 h. Conversions determined by $^1$H NMR and GC. [b] ee values determined by chiral GC. [c] In all cases, the (*S*)-enantiomer of the ligand was used.

esters.[54] Excellent results (>99% ee in both cases) were obtained for substrates **5** (*Z*) and **6** (*Z*) with use of **A4** (entries 7 and 10).[55]

In contrast to the high enantioselectivity achieved with the *Z* isomers, with use of bidentate phosphine ligands the hydrogenation of the *E* isomers usually proceeds at much lower rates and gives poor enantioselectivities.[56,57] The results of the hydrogenation of the *E* isomer of substrates **3** and **4** seem to confirm this trend also for monodentate phosphoramidites (entries 2 and 6). Products **9** and **10** were obtained with enantioselectivities of 46% and 64%, respectively, without a change in the configuration. Remarkably, the hydrogenation of the *E* isomer of substrates **5** and **6** proceeded with much higher enantioselectivities (96% and 97% ee, entries 9 and 11).[58] These results are particularly important as alkyl dehydroamino acid derivatives are difficult to prepare in geometrically pure form. The excellent results obtained for product **12** are very interesting as this compound bears an additional functionality, which could be used for further transformations.[59]

Due to the excellent results obtained with substrates **3**−**6** and **8**, it was decided to test the activity of the system by lowering the catalyst loading with **A4** as ligand (Table 4).

(52) On methyl 2-(acetamido)acrylate, Rh-**A4** gave 99% ee and Rh-**A1** gave 97% ee. On 2-(acetamido)cinnamic methyl ester Rh-**A4** gave 99% ee (ref 11e).

(53) A similar substrate, (*Z*)-2-acetamido-3-(2-furfuryl)acrylic acid methyl ester, has been used previously; see: (a) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570. (b) Li, X.; Lou, R.; Yeung, C.-H.; Chan, A. S. C.; Wong, W. K. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2077. (c) Zhang, F.-Y.; Kwok, W. H.; Chan, A. S. C. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2337. (d) Guo, R.; Li, X.; Wu, J.; Kwok, W. H.; Chen, J.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 6803. (e) Lin, C. W.; Lin, C.-C.; Lam, L. F.-L.; Au-Yeung, T. T.-L.; Chan, A. S. C. *Tetrahedron Lett.* **2004**, *45*, 7379.

(54) For the only exception, see: Fu, Y.; Xie, J.-H.; Hu, A.-G.; Zhou, H.; Wang, L.-X.; Zhou, Q.-L. *Chem. Commun.* **2002**, 480.

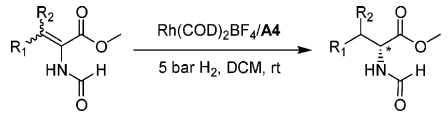
(55) The same selectivity was obtained by using DuPHOS on the *N*-acyl derivative of **5**: (a) Reference 14b. For more recent examples of asymmetric hydrogenation of the *N*-acyl lower homologue of **5** (with enantioselectivities between 91% and 96%) see: (b) Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168. (c) Kuwano, R.; Sawamura, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2571. (d) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534.

(56) For some studies see: (a) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946. (b) Scott, J. W.; Kieth, D. D.; Nix, G., Jr.; Parrish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, D., Jr.; Yang, R. *J. Org. Chem.* **1981**, *46*, 5086. In this study the *N*-acyl derivative of **5** was also considered, the *Z* isomer gave 96% ee and the *E* isomer 95% ee, using DIPAMP.

(57) With Rh-Binap, hydrogenation of the *Z* and *E* isomeric substrates generates even products with opposite configurations: Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

(58) Very high enantioselectivities have been reported also by using Rh-DuPHOS on alkyl-substituted enamides: ref 14a.

**TABLE 4. Asymmetric Hydrogenation of *N*-Formyl Dehydroamino Methyl Esters: Optimization of the Catalyst Loading**[a]



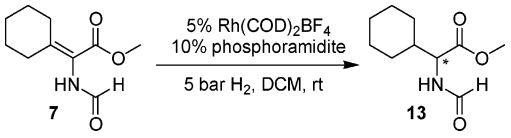

| entry | substrate | catalyst (mol %) | conv (%) | ee (%)[b,c] |
|---|---|---|---|---|
| 1 | **3** (*Z*) | 1 | 100 | 98 (*R*) |
| 2 | **4** (*Z*) | 2 | >99 | 93 (*R*) |
| 3 | **5** (*Z*) | 1 | 100 | >99 (*R*) |
| 4 | **5** (*E*) | 2 | 100 | 93 (*R*) |
| 5 | **5** (*E*) | 1 | 65 | 90 (*R*) |
| 6 | **6** (*Z*) | 1 | 100 | >99 (*R*) |
| 7 | **6** (*E*) | 2 | 100 | 96 (*R*) |
| 8 | **8** | 1 | 100 | >99 (*R*) |

[a] Reactions performed in 4 mL of solvent with 0.2 mmol of substrate for 16 h. Conversions determined by $^1$H NMR and GC. [b] ee values determined by chiral GC. [c] In all cases, the (*S*)-enantiomer of the ligand was used.

The catalyst loading could be lowered to 1 mol % for most *Z* isomers and 2-(formamido)acrylic acid methyl ester (Table 4, entries 1, 3, 6, and 8) without compromising reactivity and enantioselectivity. Under these conditions, the hydrogenations of 2-(formamido)acrylic acid methyl ester (**8**) and of the corresponding alkyl-substituted derivatives **5** (*Z*) and **6** (*Z*) were finished within 15 min, according to the hydrogen uptake.[60] Moreover, upon reducing the catalyst loading to 0.2 mol % and the hydrogen pressure to 2 bar in the hydrogenation of **8**, full conversion and >99% ee were still obtained in less than 1 h. On the other hand, for substrates **5** (*E*) and **6** (*E*) the catalyst loading could be lowered to 2 mol % maintaining good enantioselectivities (entries 4 and 8). When **5** (*E*) was hydrogenated with 1 mol % of catalyst a decrease in enantioselectivity was observed together with an incomplete conversion (entry 4 vs 5). This means that the use of 2 mol % of catalyst allows the hydrogenation of mixtures of *Z* and *E* isomers of alkyl-substituted dehydroamino esters affording full conversion and excellent ee values.[61] According to Scott et al., the superior results obtained with the *E* isomers of alkyl substrates compared to the *E* isomers of aryl substrates suggest less interference in the coordination to the metal center.[56b] Moreover, no influence of the presence of trans and cis rotamers of the formamido group was noticed.

The hydrogenation of methyl 2-(formamido)-3,3-cyclohexylidene acetate (**7**) turned out to be more challenging. With use of PipPhos (**A4**) as ligand, the reaction went to completion but afforded **13** with only 61% ee (Table 3, entry 12). $\beta,\beta$-Disubstituted α-dehydroamino acid derivatives are known to be problematic substrates.[10b] The first example of selective hydrogenation of the *N*-acyl equivalent of **7** was reported by Burk et al., using DuPHOS and BPE-type ligands. Enantioselectivities of 96% and 99%, respectively, were obtained.[62a] The sole report of a monodentate ligand describes the use of a chiral secondary phosphine oxide (85% ee).[62g] Due to the moderate enantioselectivity obtained it was decided to test a few more phosphoramidite ligands maintaining the same conditions. The results are listed in Table 5.

**TABLE 5. Asymmetric Hydrogenation of Methyl 2-(Formamido)-3,3-cyclohexylidene Acetate (7)**[a]




| entry | ligand | conv (%) | ee (%)[b,c] |
|---|---|---|---|
| 1 | **A4** | 100 | 61 (*R*) |
| 2 | **A1** | 93 | 25 (*R*) |
| 3 | **A5** | 54 | 42 (*R*) |
| 4 | **B4** | 100 | 41 (*R*) |
| 5 | **C4** | 35 | 62[d] (*S*) |

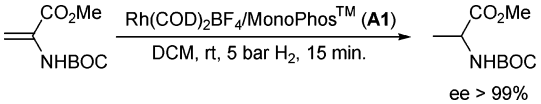
[a] Reactions performed in 4 mL of solvent with 0.2 mmol of substrate for 16 h. Conversions determined by $^1$H NMR and GC. [b] ee values determined by chiral GC. [c] Unless otherwise stated, the (*S*)-enantiomer of the ligand was used. [d] In this case, the (*R*)-enantiomer of the ligand was used.

It turned out that PipPhos (**A4**) was the best ligand in terms of both reactivity and enantioselectivity (Table 5, entry 1) among the ligands tested. Full conversion was achieved also by using **B4** but with considerable loss in enantioselectivity (entry 4). Comparable enantioselectivity (62% ee) was obtained with **C4**, but the ligand was clearly too bulky as only 35% conversion was reached (entry 5).

To improve the results obtained in the hydrogenation of **7**, combinations of ligands were applied.[63] The potential of forming new highly selective chiral catalysts by mixing chiral monodentate ligands with other chiral,[64] achiral,[65a,11f] or fluxionally chiral[65b,c] monodentate ligands has been recently described by the groups of Reetz and Piarulli/Gennari as well as by our group.[66] The method has been applied not only in Rh-catalyzed hydrogenation and hydroformylation reactions,[64−65,11f] but also in Rh-catalyzed boronic acid addition.[67]

(59) For an example of further transformation of a homologous compound into a tetrahydropyridine derivative, see: (a) Botman, P. N. M.; Dommerholt, F. J.; de Gelder, R.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2004**, *6*, 4941. (b) Wijdeven, M. A.; Botman, P. N. M.; Wijtmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2005**, *7*, 4005.

(60) An identical result was obtained for the Boc protected version of this substrate, using MonoPhos (**A1**) under the same conditions (DSM private communication).




(61) *E* isomers of substrates **3** and **4** have not been tested at lower catalyst loading, due to the lower enantioselectivities previously obtained (see Table 3).

(62) (a) Burk, M. J.; Gross, M. F.; Martinez, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 9375. For other examples, see: (b) Reference 55b. (c) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988. (d) Gridnev, I. D.; Yamanoi, Y.; Higashi, N.; Tsuruta, H.; Yasutake, M.; Imamoto, T. *Adv. Synth. Catal.* **2001**, *343*, 118. (e) Ohashi, A.; Imamoto, T. *Tetrahedron Lett.* **2001**, *42*, 1099. (f) Reference 55d. (g) Jiang, X.-B.; van den Berg, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2223.

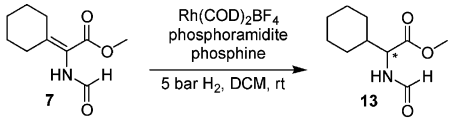
(63) For an early example of the influence of added phosphines in 1,4-addition reactions, see: Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649.

(64) (a) Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 790. (b) Peña, D.; Minnaard, A. J.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Org. Biomol. Chem.* **2003**, *1*, 1087. (c) Reetz, M. T.; Mehler, G.; Meiswinkel, A. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2165.

(65) For combinations of chiral and achiral ligands, see: (a) Reetz, M. T.; Mehler, G. *Tetrahedron Lett.* **2003**, *44*, 4593. For combinations of chiral and fluxionally chiral ligands see: (b) Monti, C.; Gennari, C.; Piarulli, U. *Tetrahedron Lett.* **2004**, *45*, 6859. (c) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959. For combinations of different achiral ligands applied in hydroformylation, see: (d) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2962.

(66) Hartwig, J. *Nature* **2005**, *437*, 487.

**TABLE 6. Asymmetric Hydrogenation of Methyl 2-(Formamido)-3,3-cyclohexylidene Acetate (7) with Heterocombinations of Ligands**[a]




| entry | ligand | phosphine | conv. (%) | ee (%)[b] |
|---|---|---|---|---|
| 1 | **A4** (*S*) | - | 100 | 61 (*R*) |
| 2 | **A4** (*S*) |  | 95 | 70 (*R*) |
| 3 | **C4** (*R*) | - | 35 | 62 (*S*) |
| 4 | **C4** (*R*) |  | **100** | **85 (*S*)** |
| 5 | **A1** (*S*) | - | 93 | 25 (*R*) |
| 6 | **A1** (*S*) |  | 40 | 48 (*R*) |
| 7 | **C1** (*S*) | - | 97 | 78 (*R*) |
| 8 | **C1** (*S*) |  | **98** | **82 (*R*)** |
| 9 | **C6** (*R*) | - | 76 | 74 (*S*) |
| 10 | **C6** (*R*) |  | 87 | 74 (*S*) |

[a] Reactions performed in 4 mL of solvent with 0.2 mmol of substrate, 0.01 mmol of $Rh(COD)_2BF_4$, 0.02 mmol of chiral phosphoramidite, and 0.01 mmol of achiral phosphine (if present). Reactions were run for 16 h. [b] ee values were determined by chiral GC.

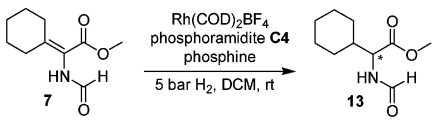
Due to the recent successful application in our laboratories of this concept in the hydrogenation of cinnamic acids,[11f] it was decided to employ a combination of chiral phosphoramidites and achiral phosphines (with a ratio of 2:1). The phosphoramidites used were also tested without addition of phosphine. The results are shown in Tables 6 and 7.

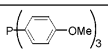
First, PipPhos (**A4**) was tried in combination with tri-*o*-tolylphosphine (Table 6, entry 2). Pleasingly, an increase in enantioselectivity was observed compared to the homocombination (entry 1), although the reaction was slightly slower. The same increase in enantioselectivity but decrease in activity was observed for MonoPhos (**A1**) (entries 5 and 6). On the contrary, when the 3,3′-dimethyl-BINOL version of PipPhos (**C4**) was used, an increase in terms of both reactivity and enantioselectivity was observed (entries 3 vs 4). A very exciting result was that the heterocombination of **C4** and tri-*o*-tolylphosphine provided full conversion to the product and a remarkable 85% ee, as the best result so far. The influence of the phosphine was less dramatic in the case of the 3,3′-dimethyl-BINOL version of MonoPhos (**C1**) (entries 7 vs 8), where only a slight increase in enantioselectivity was achieved. When another 3,3′-dimethyl-substituted phosphoramidite ligand was used (**C6**), a somewhat higher conversion to the product was observed for the heterocombination, but with the same degree of enantioselectivity (entries 9 and 10). It should be noted that the homocombinations of **C1** and **C6** showed better enantioselectivity than PipPhos (**A4**) although the catalyst is slower (entries 7 and 9 vs 1). In view of the good results obtained with **C4** and tri-*o*-tolylphosphine as ligands, it was decided to test additional achiral phosphines. The outcome of this investigation is shown in Table 7.

Complete conversion was achieved in almost all cases. Interestingly, with tricyclohexylphosphine the opposite configuration of the product was obtained. The influence of the presence and position of the methyl group on the enantioselec-

(67) (a) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L *Org. Lett.* **2003**, *5*, 3111. (b) Duursma, A.; Boiteau, J. G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045. (c) Duursma, A.; Peña, D.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron*: *Asymmetry* **2005**, *16*, 1901.

**TABLE 7. Asymmetric Hydrogenation of Methyl 2-(Formamido)-3,3-cyclohexylidene Acetate (7) with Heterocombination of Ligand C4 and Different Phosphines**[a]

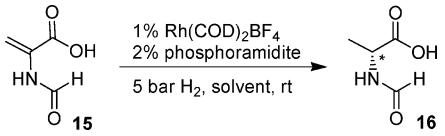



| entry | ligand | phosphine | conv. (%) | ee (%)[b] |
|---|---|---|---|---|
| 1 | **C4** (*R*) | - | 35 | 62 (*S*) |
| 2 | **C4** (*R*) |  | 100 | 69 (*S*) |
| **3** | **C4** (*R*) |  | **100** | **85 (*S*)** |
| 4 | **C4** (*R*) |  | 100 | 72 (*S*) |
| 5 | **C4** (*R*) |  | 100 | 59 (*S*) |
| 6 | **C4** (*R*) |  | 100 | 68 (*S*) |
| 7 | **C4** (*R*) |  | 93 | 36 (*R*) |
| 8 | **C4** (*R*) |  | 100 | 71 (*S*) |
| 9 | **C4** (*R*) |  | 100 | 62 (*S*) |
| 10 | **C4** (*R*) |  | 100 | 72 (*S*) |
| 11 | **C4** (*R*) |  | 100 | 65 (*S*) |
| 12 | **C4** (*R*) |  | 57 | 73 (*S*) |

[a] Reactions performed in 4 mL of solvent with 0.2 mmol of substrate, 0.01 mmol of $Rh(COD)_2BF_4$, 0.02 mmol of chiral phosphoramidite, and 0.01 mmol of achiral phosphine. Reactions were run for 16 h. [b] ee values were determined by chiral GC.

tivity was tested by comparing triphenylphosphine, tri-*o*-, tri-*m*-, tri-*p*-tolylphosphine, and tri-3,5-dimethylphenylphosphine (entries 2−6). The enantioselectivity obtained with tri-*o*-tolylphosphine remained the highest. Poorer and comparable results were achieved with or without methyl substituent in the other positions. Only by using tri-*p*-tolylphosphine was a consistent decrease in ee observed. Moreover, the hydrogen uptake showed an opposite trend between reactivity and enantioselectivity, with the catalyst based on tri-*o*-tolylphosphine being the slowest (85% ee, 16 h) and the use of tri-*p*-tolylphosphine as ligand provided the fastest reaction (59% ee, approximately 4 h). Electron-donating or -withdrawing substituents seemed to have little influence (entries 9−11) on the enantioselectivity, compared to triphenylphosphine. In all three cases the reaction rate appeared to be comparable to the one observed with tri-*p*-tolylphosphine, with the *p*-methoxy-substituted triphenylphosphine slightly faster than *p*-fluoro and *p*-chloro, respectively. In conclusion, the results suggest that the steric effect of the phosphine substituents plays a larger role than their electronic properties.

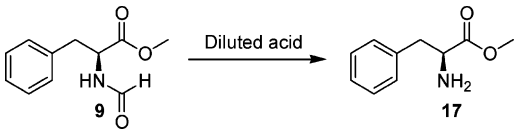
**TABLE 8. Asymmetric Hydrogenation of 2-(Formamido)acrylic Acid**[a]




| entry | solvent | ligand | conv (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | DCM | (*S*)-**A1** | 100 | 92 (*R*) |
| 2 | EtOAc | (*S*)-**A1** | 70 | 89 (*R*) |
| 3 | *i*-PrOH | (*S*)-**A1** | 85 | 53 (*R*) |
| 4 | DCM | (*S,R*)-**A2** | 21 | 54 (*R*) |
| 5 | DCM | (*S*)-**A3** | 96 | 86 (*R*) |

[a] Reactions performed in 4 mL of solvent with 0.2 mmol of substrate overnight. [b] Conversions determined by $^1$H NMR and GC. [c] ee values were determined by chiral GC after conversion to methyl ester.

**TABLE 9. Removal of *N*-Formyl Protection**




| entry | conditions | yield (%) | ee (%)[a] |
|---|---|---|---|
| 1 | HCl (1 equiv), MeOH reflux, 1 h | >99 | >99 |
| 2 | HCl (1 equiv), MeOH rt, 8 h | >99 | >99 |
| 3 | $H_3PO_4$ (1.5 equiv), THF, reflux, 9 h | 89 | >99 |

[a] ee values were determined by chiral GC after *N*-formyl protection of the product.

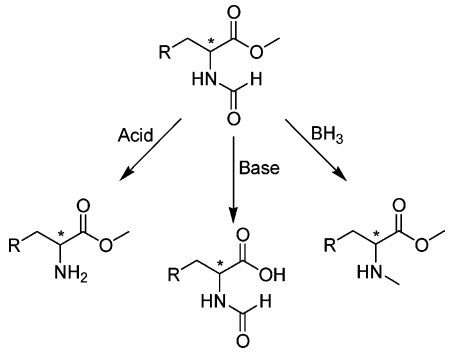
Thus, by using a combination of a chiral phosphoramidite and an achiral phosphine, full conversion and high enantioselectivities are obtained in the hydrogenation of $\beta,\beta$-dialkyl dehydroamino ester **7**. Moreover, this investigation showed that heterocombinations of ligands lead to better results.

To show that not only esters but also *N*-formyl dehydroamino acids can be successfully hydrogenated, hydrogenation of 2-(formamido)acrylic acid (**15**)[68] was studied with MonoPhos (**A1**)[69] as the chiral ligand. Dichloromethane turned out to be the best solvent and an enantioselectivity of 92% was obtained. In the same solvent the corresponding methyl ester **8** was hydrogenated providing 97% ee (Table 3, entry 15). Lower conversion and enantioselectivity were obtained in EtOAc (Table 8, entry 2), which, however, was the best solvent with 2-(acetamido)acrylic acid (99% ee).[7d]

To establish the utility of the formyl moiety as a protecting group, it is necessary to prove its superiority compared to the acyl functionality during the deprotection step. As the final part of our investigation, the removal of the formyl group was studied. *N*-formyl phenylalanine methyl ester[70] was converted into the corresponding amino ester under mild acidic conditions.

Interestingly, the formyl group is removed at room temperature in the presence of 1 equiv of hydrochloric acid (Table 9, entry 2).[71] These conditions are even milder than those previously reported by Sheehan and Yang.[28a] Alternatively, the formyl group was removed with use of recently reported conditions for Boc deprotection, with the weaker acid $H_3PO_4$ (entry 3).[72] In all cases no racemization was observed.[73] Moreover, the formyl group is remarkably resistant toward basic hydrolysis and azlactone formation. The orthogonal removal of formyl and ester groups makes a stepwise approach toward the synthesis of peptides possible.[28a] Another interesting feature connected with the use of *N*-formyl protection is their convenient transformation, in one step via borane reduction, into *N*-methylamino acid derivatives.[74] The properties exhibited by various natural products, in which *N*-methylamino acids are present, make them of great interest from a medicinal and synthetic point of view.[75]

**SCHEME 6. Transformations of *N*-Formylamino Esters**




## Conclusions

We have demonstrated that *N*-formyl-protected dehydroamino esters are excellent substrates for Rh-catalyzed asymmetric hydrogenation in combination with monodentate phosphoramidites as ligands. Excellent enantioselectivities (up to >99% ee) were obtained for the *Z* isomers. An important finding is that very high enantioselectivities can also be achieved (up to 97% ee) for the *E* isomers of substrates with alkyl substituents (**5**, **6**). Good results were obtained for a $\beta,\beta$-disubstituted substrate (**7**, up to 85% ee) by using combinations of phosphoramidites and achiral phosphines. Moreover, the use of *N*-formyl protection allows an efficient one-pot synthesis of a large variety of substrates, in terms of both possible functionalities tolerated and ease of preparation. An inexpensive, efficient, and multigram scale protocol for the synthesis of methyl 2-(formamido)acrylate (**8**) was developed. This makes the Heck reaction even more interesting as methodology for the preparation of aromatic dehydroamino esters. Finally, the protecting group can be easily removed under very mild reaction conditions.

(68) Prepared with pyruvic acid and formamide in 16% yield according to a literature procedure: Frankel, M.; Reichmann, M. E. *J. Chem. Soc.* **1952**, *105*, 289.

(69) This allowed comparison with results previously obtained for 2-acetamidoacrylic acid (ref 11b).

(70) Prepared from commercially available (*L*)-phenylalanine methyl ester hydrochloric salt (ref 28a).

(71) No reaction was observed applying the same conditions to the *N*-acyl protected amino ester.

(72) For the use of $H_3PO_4$ in the removal of *tert*-butoxycarbonyl groups, see: (a) Li, B.; Bemish, R.; Buzon, R. A.; Chiu, C. K.-F.; Colgan, S. T.; Kissel, W.; Le, T.; Leeman, K. R.; Newell, L.; Roth, J. *Tetrahedron Lett.* **2003**, *44*, 8113. For the use of $H_3PO_4$ in the removal of *N*-sulfinylimidazolidines, see: (b) Viso, A.; de la Predilla, R. F.; López-Rodríguez, M.; Gracía, A.; Flores, A.; Alonso, M. *J. Org. Chem.* **2004**, *69*, 1542.

(73) Examples of racemization occurring during deprotection in acidic conditions of *N*-benzoyl functionalized products have been reported: (a) Krause, H.-W.; Kreuzfeld, H. J.; Döbler, C.; Taudien, S. *Tetrahedron*: *Asymmetry* **1992**, *3*, 555. (b) Taudien, S.; Schinkowski, K.; Krause, H.-W. *Tetrahedron*: *Asymmetry* **1993**, *4*, 73.

(74) (a) Krishnamurthy, S. *Tetrahedron Lett.* **1982**, *23*, 3315. (b) Konopelski, J. P.; Chu, K. S.; Negrete, G. R. *J. Org. Chem.* **1991**, *56*, 1355. (c) Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698.

(75) For a review, see: Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B. *Chem. Rev.* **2004**, *104*, 5823.

On the basis of our results, it is evident that the *N*-formyl protection is a very versatile, useful, and underestimated synthetic tool and provides a link between preparation and asymmetric hydrogenation of optically active amino acids.

## Experimental Section

**General Method D (Scheme 1): Synthesis of 2-(Formamido)-hex-2-enoic Acid Methyl Ester (5).** To a solution containing methyl isocyanoacetate (1.0 mL, 11.0 mmol) and butyraldehyde (1.2 mL, 13.2 mmol, 1.2 equiv) in dry ether (10 mL) was added $Cu_2O$ (79 mg, 0.55 mmol, 5 mol %) in one portion causing an exothermic reaction. The mixture was stirred for 3 h at room temperature, until TLC (heptanes−ethyl acetate 1:1) showed complete conversion of the starting material. At that point the temperature was lowered to 0 °C and a solution of potassium *tert*-butoxide (1.28 g, 11.0 mmol) in THF (10 mL) was added. After the solution was stirred for 30 min, acetic acid (0.65 mL, 11.0 mmol) in $CH_2Cl_2$ (27 mL) was added, and the reaction mixture was allowed to reach room temperature and extracted with water. The organic layer was dried over $Na_2SO_4$ and the solvent removed under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (heptanes−ethyl acetate 2:1) affording the desired compounds **5** (*Z*/*E* 1.6:1, 1.22 g, 65%). ***E* isomer**: colorless oil, $R_f$ 0.22 (heptanes−ethyl acetate 2:1), trans:cis = 80:20. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.31 (s, 1H, trans), 8.24 (d, $J$ = 11.1 Hz, 1H, cis), 7.52 (br s, 1H), 7.29 (t, $J$ = 7.5 Hz, 1H, trans), 6.04 (t, $J$ = 7.5 Hz, 1H, cis), 3.85 (s, 3H, trans), 3.83 (s, 3H, cis), 2.63−2.50 (m, 2H), 1.58−1.40 (m, 2H), 0.95 (dt, $J$ = 7.2, 2.4 Hz, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 164.6 (s, trans), 163.8 (s, cis), 162.3 (d, cis), 159.2 (d, trans), 134.5 (d, trans), 134.1 (d, cis), 124.8 (s, cis), 123.9 (s, trans), 52.4 (q, trans), 52.3 (q, cis), 30.4 (t, trans), 30.0 (t, cis), 22.7 (t, trans), 22.6 (t, cis), 13.8 (q, trans), 13.7 (q, cis). MS, *m*/*z* (%) 171 ($M^+$, 41.9%); HRMS ($EI^+$) for $C_8H_{13}NO_3$, calcd 171.0895, found 171.0908. ***Z* isomer**: colorless oil, $R_f$ 0.19 (heptanes−ethyl acetate 2:1), trans:cis = 58:42. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.24 (s, 1H, trans), 8.17 (d, $J$ = 11.1 Hz, 1H, cis), 7.20−7.00 (br, 1H), 6.75 (m, 1H, trans), 6.64 (m, 1H, cis), 3.80 (s, trans), 3.78 (s, cis), 2.32−2.08 (m, 2H), 1.60−142 (m, 2H), 1.04−0.88 (m, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 164.8 (s, trans), 164.4 (s, cis), 163.9 (d, cis), 158.9 (d, trans), 139.6 (d, trans), 135.2 (d, cis), 125.4 (s, cis), 123.2 (s, trans), 52.6 (q, cis), 52.5 (q, trans), 31.2 (t, trans), 29.9 (t, cis), 22.1 (t, cis), 21.4 (t, trans), 13.9 (q, trans), 13.7 (q, cis). MS, *m*/*z* (%) 171 ($M^+$, 26.9%); HRMS ($EI^+$) for $C_8H_{13}NO_3$, calcd 171.0895, found 171.0904.

**Synthesis of 2-(Formamido)cinnamic Acid Methyl Ester (3) under Heck Reaction Conditions.**[76] A mixture of iodobenzene (365 mg, 1.79 mmol), 2-(formamido)acrylic acid methyl ester **8** (305 mg, 2.13 mmol, 1.2 equiv), $Pd(OAc)_2$ (8.0 mg, 0.036 mmol, 2%), tetra-*n*-butylammonium chloride (599 mg, 2.16 mmol, 1.2 equiv), and $NaHCO_3$ (407 mg, 4.84 mmol, 2.7 equiv) was flushed with nitrogen and heated in a sealed tube at 80 °C for 22 h. Subsequently, the reaction mixture was cooled to room temperature and a mixture of $CH_2Cl_2$/$H_2O$ (1:1, 100 mL) was added. The organic layer was washed with $H_2O$ (25 mL) and the combined aqueous layers were extracted with $CH_2Cl_2$ (25 mL). The combined organic layers were washed with brine and dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (heptanes−ethyl acetate 2:1) afforded the desired product **3** (*Z*/*E* 13:1, 268 mg, 73%). ***E* isomer**: colorless oil, $R_f$ 0.50 (heptanes−ethyl acetate 1:1), trans:cis = 75:25. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.45 (d, $J$ = 14.4 Hz, 1H, cis), 8.41 (s, 1H, trans), 8.23 (s, 1H, trans), 7.61 (br, 1H, trans), 7.52 (br, 1H, cis), 7.42−7.22 (m, 5H), 6.92 (s, 1H, cis), 3.70 (s, 3H, cis), 3.65 (s, 3H, trans). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 164.7 (s), 159.2 (d), 135.1 (s), 129.3 (d), 128.7 (s), 128.8 (d, 2C), 128.1 (d), 127.8 (d, 2C), 52.4 (q). MS, *m*/*z* (%) 205 ($M^+$, 28.6%); HRMS ($EI^+$) for $C_{11}H_{11}NO_3$, calcd 205.0739, found 205.0734. ***Z* isomer**: white solid, $R_f$ 0.46 (heptanes−ethyl acetate 1:1), trans:cis = 47:53. Mp 92.4−93.0 °C (lit.[28a] mp 88−89 °C). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.10 (s, 1H, trans), 8.06 (d, $J$ = 11.2 Hz, 1H, cis), 7.92 (br, 1H, trans), 7.58 (d, $J$ = 8.0 Hz, 1H, cis), 7.50−7.18 (m, 6H), 3.77 (s, 3H, cis), 3.71 (s, 3H, trans). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.3 (s, trans), 164.9 (s, cis), 163.8 (d, cis), 159.3 (d, trans), 133.4 (s, trans), 132.9 (d, trans), 132.6 (s, cis), 129.8 (d, cis), 129.6 (d), 129.5 (d), 129.1 (d), 129.0 (d, trans), 128.5 (d, cis), 123.9 (s, cis), 122.3 (s, trans), 52.9 (q, cis), 52.7 (q, trans). MS, *m*/*z* (%) 205 ($M^+$, 31.0%); HRMS ($EI^+$) for $C_{11}H_{11}NO_3$, calcd 205.0739, found 205.0735.

**Synthesis of 2-(Formamido)acrylic Acid Methyl Ester (8).**[77] A mixture of serine methyl ester hydrochloric salt (1 g, 6.4 mmol), $K_2CO_3$ (3.5 g, 4 equiv), and a catalytic amount of $NEt_3$ (10 $\mu$L) in methyl formate (20 mL) was stirred overnight at room temperature. The salts were filtered and the solvent removed under reduced pressure. Quick purification by column chromatography (heptanes−ethyl acetate 1:1) afforded the desired product (0.76 g, 92%). White solid, $R_f$ 0.56 (heptanes−ethyl acetate 1:1), trans:cis 88:12. Mp 56.9−57.2 °C (lit. mp 53−56 °C). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.56 (d, $J$ = 11.4 Hz, 1H, cis), 8.41 (s, 1H, trans), 7.87 (br, 1H, trans), 7.60 (br, 1H, cis), 6.63 (s, 1H, trans), 5.95 (s, 1H, trans), 5.69 (s, 1H, cis), 5.44 (s, 1H, cis), 3.85 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 164.1 (s), 160.9 (d, cis), 159.4 (d, trans), 130.1 (s), 110.37 (t, trans), 104.5 (t, cis), 53.1 (q). MS, *m*/*z* (%) 129 ($M^+$, 100%); HRMS ($EI^+$) for $C_5H_7NO_3$, calcd 129.0426, found 129.0434. Elemental Anal.: calcd C 46.51, H 5.46, N 10.85; found C 46.60, H 5.51, N 10.77.

**Hydrogenation General Procedure.** Hydrogenations were performed in an Endeavor, an autoclave with eight reactors equipped with glass reaction vessels. In a typical run each glass liner was charged open to air with $Rh(COD)_2BF_4$ (2 $\mu$mol), monodentate phosphoramidite (4 $\mu$mol), and substrate (0.2 mmol). Solvent was added (4 mL), the glass liners were placed in the reactors, and the system was closed. After repetitive purging with $N_2$ (3 × 2.5 bar) the system was pressurized with hydrogen and the reactions were stirred at room temperature with 750 rpm. The conversion of the reactions was monitored by following $H_2$ consumption. The reactions were stopped via release of $H_2$ pressure. The resulting mixture was filtered over a short silica column and subjected to conversion ($^1$H NMR and GC) and enantiomeric excess determination (capillary chiral GC).

***N*-Formyl Deprotection of 2-(Formamido)-3-phenylpropionic Acid Methyl Ester (9) with Hydrochloric Acid.**[78] Hydrochloric acid (10 mmol) in methanol (6 mL) was added to a solution of *N*-formyl-(L)-phenylalanine methyl ester (2.0 g, 10 mmol) in methanol (4 mL). The reaction mixture was stirred at reflux for 1 h or at room temperature for 8 h. The reaction mixture was concentrated under reduced pressure. (L)-Phenylalanine methyl ester hydrochloric salt was isolated after recrystallization from methanol (99%).

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**Supporting Information Available:** Experimental procedures, spectral data for substrates and products, and methods for enantiomeric excess determination. This material is available free of charge via the Internet at http://pubs.acs.org.

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