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PipPhos and MorfPhos: Privileged Monodentate Phosphoramidite Ligands for Rhodium-Catalyzed Asymmetric Hydrogenation

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A library of 20 monodentate phosphoramidite ligands has been prepared and applied in rhodium-catalyzed asymmetric hydrogenation. This resulted in the identification of two ligands, PipPhos and MorfPhos, that afford excellent and in several cases unprecedented enantioselectivities in the hydrogenation of N-acyldehydroamino acid esters, dimethyl itaconate, acyclic N-acylenamides, and cyclic N-acylenamides. In addition, a method for the parallel enantioselectivity determination of eight acylated amines is presented.

Introduction

The rhodium-catalyzed homogeneous enantioselective hydrogenation of prochiral olefins has proven to be one of the most powerful tools in asymmetric catalysis.1,2 This clean, efficient, and atom-economical reaction has a broad scope and is one of the best studied transition-metal-catalyzed reactions. Although chiral monophosphines including CAMP (Figure 1) were the first ligands successfully applied in the pioneering studies on enantioselective hydrogenation,3 this area has been dominated by chiral bidentate ligands for more than three decades.4 As a common view, bidentate ligands were considered as a conditio sine qua non to achieve high stereoselection in catalytic asymmetric hydrogenation reactions. An enormous number of chiral bidentate ligands has been developed for enantioselective hydrogenation, but only a limited number including DIOP, DuPhos and its analogues, the Josiphos family, and BINAP (Figure 1) are commercially available, and even fewer are used in industrial processes.6 One of the major drawbacks of bidentate phosphorus ligands, especially phosphines, is their often cumbersome synthesis. This, in turn, makes them relatively expensive. In addition, it is very difficult to establish a library of bidentate ligands for fine-tuning to a specific target molecule. These reasons led us to focus instead on the development of monodentate ligands for asymmetric catalysis.

Recent breakthroughs have shown that the use of a bidentate ligand is not essential to obtain good stereodiscrimination. Chiral monodentate phosphorus ligands have proven to be able to induce excellent enantioselectivity in rhodium-catalyzed asymmetric hydrogenation reactions, comparable to or even better than those reached by bidentate ligands.7 Thus, monodentate phosphines,8 phosphonites,9 phosphites,10 and phosphoramid-
Monodentate phosphonites, phosphites, and phosphoramidites have the advantage of being readily accessible, highly diverse in structure, and extraordinarily inexpensive compared to various bidentate ligands. MonoPhos (1A), one of the simplest members of the monodentate phosphoramidite ligand family based on a BINOL backbone and first synthesized 10 years ago, has proven to be an excellent ligand in the asymmetric rhodium-catalyzed hydrogenation of dehydroamino acids and esters, aromatic enamides, and itaconic acid derivatives showing enantioselectivities comparable to the most successful bidentate ligands. After its disclosure, closely related ligands were reported which with some substrates surpass 1A in enantioselectivity. To be synthetically versatile, however, ee’s of 99% or higher are required, especially when the products are oils and recrystallization to raise the ee is prohibited. In addition, several more challenging substrates require further improvement of the MonoPhos ligand structure. Ideally, for a chiral catalyst tool kit the ligands should be readily available, yet highly diverse, allowing the production of a true ligand library.

Herein, we report the synthesis of a focused library of monodentate phosphoramidites and their application in the rhodium-catalyzed asymmetric hydrogenation of N-acyldehydroamino esters, itaconic acid derivatives, and N-acyl enamides. Two new privileged ligands, PipPhos...
5A and MorfPhos 7A, are disclosed which induce enantioselectivities of 99% or higher in the hydrogenation of most of the substrates.

Results and Discussion

The modular structure of phosphoramidites in general allows in principle the preparation of a ligand library with enormous diversity (Scheme 1). However, in view of our successful results with MonoPhos we focused on the use of BINOL and H8-BINOL as the diol backbone. Moreover, our initial studies indicated the use of a sterically demanding amine part should be avoided since bulky amines only showed low reaction rates and poor enantioselectivities in hydrogenation reactions. To keep the preparation of the ligands simple we restricted ourselves to the use of achiral or cheap chiral amines. Based on a simplified procedure for the preparation of BINOL-derived monodentate phosphoramidites, which allows in principle the preparation of a ligand library (Scheme 1), we then designed a focused library of 20 ligands (Scheme 1).

Refluxing BINOL in neat PCl5,25 evaporation of excess reagent, and azeotropic distillation of the residue with toluene yield the intermediate chlorophosphite in quantitative yield. This intermediate is stable and can be kept as a 1 M stock solution for months, setting the stage for a facile parallel synthesis of phosphoramidite ligands. Simple treatment of the chlorophosphite with an equimolar sbase gives rise to the phosphoramidites in good to high yields.26 MonoPhos (1A) and its H8-analogue 1B were prepared as described previously from the corresponding diol and HMPT.12a,21

For a first screening we turned our attention to the hydrogenation of α-dehydroamino acid esters with a focus on the two benchmark substrates methyl 2-acetamidoacrylic acid and methyl 2-acetamidocinnamic acid.

<table>
<thead>
<tr>
<th>entry</th>
<th>R ligand</th>
<th>% ee</th>
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<th>% ee</th>
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<td>40</td>
<td>phenyl 13A</td>
<td>68</td>
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</table>

For reaction conditions, see the Supporting Information. Reactions were run for 4 h and went to completion. Use of (S)-ligand results in (R)-product. a 94% conversion.

*Table 1*. Asymmetric Hydrogenation of α-Dehydroamino Esters


(27) Reaction performed at 0 °C.

(28) See the Supporting Information.

(29) In contrast, most of the H8-BINOL-derived ligands are foams and have a tendency to hold on to solvent molecules.
Variation of the amine moiety in the ligand had a dramatic influence on the level of enantioselection. Chan et al. found a significant increase in ee when changing from MonoPhos to the corresponding diethylamine-derived phosphoramidite 2A.12b In our hands, ligand 2A induced a lower enantioselectivity in the hydrogenation of methyl 2-acetamidoacrylic acid (Table 1, entry 3) but a slightly higher enantioselectivity in the reduction of methyl 2-acetamidoacrylic acid (Table 1, entry 23) compared with MonoPhos when these hydrogenations were performed in the same solvent.10a Whereas changing from diethyl- to di-n-propylamine in phosphoramidite 3A only led to a small decrease in ee (Table 1, entries 5 and 25), the use of the pyrrolidine-derived ligand 4A led to a clear drop in selectivity for both substrates (Table 1, entries 6 and 26).

Remarkably, however, when piperidine was introduced as the amine moiety a dramatic improvement in enantioselectivity was observed. Hydrogenation of both substrates with Rh/PipPhos 5A gave the desired α-amino acid esters with >99% ee (Table 1, entries 7 and 27). Comparing the hydrogenation of methyl 2-acetamidoacrylic acid, and methyl 2-acetamidoacrylic acid on a 1 mmol scale clearly showed that the rates of hydrogenation using the piperidyl ligand 5A are similar to the rates obtained with MonoPhos (1A).

Use of the corresponding H8-BINOL-derived ligand 5B produced the alanine derivative in a slightly lower ee (Table 1, entry 8) whereas the phenylalanine derivative was obtained with near-perfect enantioselectivity (Table 1, entry 28). Further increasing the ring size of the amine led to a minor decrease in ee (ligand 6A, Table 1, entries 9 and 29) while concomitant change to the H8-BINOL backbone (ligand 6B) resulted in a lower ee in the hydrogenation of methyl 2-acetamidoacrylic acid (Table 1, entry 10). Not surprisingly, the use of ligands 7A (MorfPhos) and 7B, derived from morpholine and thus also incorporating a six-membered heterocyclic moiety, resulted in a comparable high level of enantiodiscrimination as ligand 5A and 5B. Changing morpholine to thiomorpholine, as in ligand 8A, resulted not only in a drastic drop in enantioselectivity but also led to incomplete reaction in the hydrogenation of methyl 2-acetamidoacrylic acid. This is possibly due to inhibition of the catalyst by sulfur–rhodium interactions. On the other hand, the corresponding N-phenylpiperazinederived ligands 9A and 9B (Table 1, entries 14, 15 and 34, 35) again compare favorably not only to ligand 8A but also to MonoPhos (1A) in the hydrogenation of methyl 2-acetamidoacrylic acid. An additional phenyl moiety on the heterocyclic secondary amine has only little influence on the outcome of the hydrogenation. Thus, ligand 10A derived from indoline31 resulted in lower enantioselectivity comparable to pyrrolidine ligand 4A, whereas ee’s induced by ligand 11A and 11B derived from tetrahydroisouquinoline are almost as high as those found for piperidine ligand 5A and 5B. The proline derived ligands 12 and 13 induce only moderate enantioselectivity which can be ascribed to the increased steric bulk of the amine moiety.

The hydrogenation of dimethyl itaconate has been extensively studied including the use of monodentate ligands. In our first studies, the use of MonoPhos led to an ee of 87% at 25 °C and 94% at 0 °C for this substrate.32,33 Reetz and co-workers reported enantioselectivities of 90% for the hydrogenation of dimethyl itaconate with BINOL-derived monophosphonites9b and ee’s >99% for monophosphite ligands.10 Zhou’s SIPHOS ligand resulted in an ee of 94.7%, but 5 mol % of catalyst was required to reach full conversion.12 The groups of Chen,13a Ojima,13b Rampf,13c and Xia13d recently reported ee’s ranging from 75% to >99% applying monophosphite ligands based on biphenol backbones. Monophosphite ligands based on other backbones13d,e and monophosphines13e–f have also been reported to induce moderate to good enantioselectivities.

The hydrogenation of dimethyl itaconate with 2 mol % of Rh-precursor and 4 mol % of MonoPhos (1A) as ligand under a hydrogen pressure of 5 bar at rt in dichloromethane using the Endeavor autoclave gave rise to the saturated diester with an ee of only 92% (Table 2). For this substrate the same trends in enantioselectivity were observed as for the α-dehydroamino esters. In this case, ligands with (S)-configuration gave rise to the corresponding (S)-configured product.28c With the exception of ligands 9A and 9B (Table 2, entries 14 and 15) alteration of the diol backbone from BINOL to H8-BINOL is accompanied by a more or less distinct decrease in ee (Table 2, entries 1/2, 3/4, 9/10, 11/12, and 16/17). Also, the effect of the variation of the amine moiety on the enantioselectivity follows a similar trend as observed in the α-dehydroyamo ester hydrogenation. Whereas a slight increase in steric bulk changing from dimethylamine in MonoPhos (1A) to diethylamine in ligand 2A positively influences the enantioselectivity (Table 2, entries 1/3), a further increase as in the di-n-propyl derived ligand 3A results in a dramatic drop in ee. Comparably low enantioselectivities are observed for the pyrrolidine derived ligand 4A (Table 2, entry 6).

![Image](327x684 to 548x728)

**Table 2. Hydrogenation of Dimethyl Itaconate**

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand % ee</th>
<th>entry</th>
<th>ligand % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1A 92</td>
<td>11</td>
<td>7A 98</td>
</tr>
<tr>
<td>2</td>
<td>1B 90</td>
<td>12</td>
<td>7B 98</td>
</tr>
<tr>
<td>3</td>
<td>2A 94</td>
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<td>8A 40</td>
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</tr>
<tr>
<td>5</td>
<td>3A 79</td>
<td>15</td>
<td>9B &gt;99</td>
</tr>
<tr>
<td>6</td>
<td>4A 83</td>
<td>16</td>
<td>11A 97</td>
</tr>
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<td>5A &gt;99</td>
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<tr>
<td>10</td>
<td>6B 90</td>
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</tr>
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</table>

* For reaction conditions see the Supporting Information. Reactions were run for 4 h and went to completion. Use of (S)-ligand results in (S)-product.5 5% conversion.

(31) An X-ray structure of 10A has been obtained; see the Supporting Information. Data have been deposited at the CCDC (no. 246960).
(32) At 1 bar of Hz with 5 mol % of catalyst in a Schlenk tube.
(33) Whereas for itaconic acid, MonoPhos induced ee’s up to 97%; see ref 12a.
Most rewarding, when changing the amine moiety to piperidine as in ligand 5A and 5B (Table 2, entries 7 and 8) the same excellent enantioselectivities are observed as for the reduction of α-dehydroamino esters. Notably, when a preformed complex of [Rh(COD/5A)BF₄ at a H₂-pressure of 10 bar was applied in dichloromethane, the amount of catalyst could be lowered to 0.1 mol % and the hydrogenation still proceeded smoothly with a turnover frequency of 1333 h⁻¹ without any loss in selectivity. Similar high ee’s are induced by ligands 7A and 7B derived from morpholine (Table 2, entries 11 and 12). On the other hand, increased steric bulk as in ligand 6A and 6B (Table 2, entries 9/10) led to diminished selectivity whereas incorporation of a thiomorpholine moiety as in 8A not only leads to poor ee, but again prevents complete conversion (Table 2, entry 13). Whereas the piperazinederived ligand 9A induces only moderate ee (Table 2, entry 14), the H₈-BINOL analogue 9B surprisingly leads to near complete enantioselectivity (Table 2, entry 15). The tetrahydroisoquinoline-derived ligands 11A and 11B give reasonable ee’s with both the BINOL (Table 2, entry 16) and the H₈-BINOL (Table 2, entry 17) backbone. The sterically more demanding proline-derived ligands 12A and 13A only show low (Table 2, entry 18) or moderate (Table 2, entry 19) selectivity for the hydrogenation of dimethyl itaconate. A solvent screening with ligand 5A disclosed a strong dependency of the ee as already found for MonoPhos and also observed by Ozima in the context of his phosphonite ligands. The enantioselectivity obtained in the hydrogenation of methyl 2-acetamidoacrylic acid, methyl 2-acetamidocinnamic acid, and methyl itaconate only gives good ee’s when performed in dichloromethane and 2-propanol. In contrast, the hydrogenation of diacetals only show low (Table 2, entry 18) or moderate ee’s (vide infra) is not sensitive to solvent effects employing solvents such as CH₂Cl₂, EtOAc, THF, and 2-propanol. In contrast, the hydrogenation of dimethyl itaconate only gives good ee’s when performed in dichloromethane and ee values dropped to 20–62% in other solvents.

Chiral a-aryllalkylamines play an important role as building blocks for pharmaceutical compounds and are extensively used in organic synthesis and catalysis. Much attention has been drawn to the development of practical asymmetric routes to these valuable compounds. One approach, the catalytic asymmetric hydrogenation of enamides initially reported by Kagan, makes chiral amine derivatives readily accessible. However, many of the privileged bidentate ligands, e.g., DIOP and BINAP (Figure 1), used so far induce low stereoselectivity in the Rh-catalyzed asymmetric hydrogenation of enamides. Meanwhile, excellent results have been obtained with Burk’s BPE and DuPhos ligands, and subsequently other phosphorus based bidentate ligands have been reported to be useful in the selective hydrogenation of enamides. Only recently, we and others reported the first successful application of monodentate phosphoramidite ligands for this transformation.

For the screening of our ligands, a small library of divers enamides was synthesized (Scheme 2). To demonstrate the broadened scope of the new phosphoramidite ligands we not only focused on standard substrates such as 14a but also investigated the influence of substituents with different electronic properties (14b,c), the effect of increased substitution (15a,b,16), and aliphatic enamide 17. More demanding cyclic enamides 18–20 were also prepared. All enamides, except for substrate 20, were prepared according to a procedure developed by Barton and Zard. This method involves transformation of a ketone into the corresponding oxime followed by subsequent reduction with iron metal in the presence of acetic anhydride.

For a first screening of the ligand library we turned our attention to the hydrogenation of acyclic enamides 14–17 (Table 3). In our initial studies, hydrogenation of the standard enamide substrate 14a with MonoPhos at

\[ 14a: X = H \]
\[ 15a: Z = E \]
\[ 16 \]
\[ 17 \]

\[ 18 \]
\[ 19a: X = CH₂ \]
\[ 20: o = O \]

**Scheme 2.** Synthesis of Enamide Substrates

---

34) The application of PipPhos and MorfPhos in the hydrogenation of substituted itaconates is currently under investigation in our laboratory and will be reported in due course.


43) For subsequent reports using monodentate phosphorus ligands, see ref 13a-c.


45) Recently, a different approach was described: Wallace, D. J.; Klauber, D. J.; Chen, C.-Y.; Volante, R. P. Org. Lett. 2005, 7, 4749.

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rt gave rise to the corresponding acylated amine with an ee of only 86% while lowering the temperature to −5 °C increased the ee to 90%. Chan reported improved ee's (up to 99% at 5 °C) using ligand 2A.\textsuperscript{12b} Applying phosphites, Reetz observed ee's up to 95.3%,\textsuperscript{13j} whereas the use of SIPHOS resulted in the corresponding amine with an ee of 98.7%.\textsuperscript{13j} These results with monodentate ligands are already quite remarkable, since most of the privileged bidentate ligands such as BICP\textsuperscript{38a} (86.3%), PennPhos\textsuperscript{38c} (75%), DIOP\textsuperscript{38d} (68%), and BIPHEP\textsuperscript{38f} (70%) are not suitable for the hydrogenation of enamides such as 14a. DuPhos\textsuperscript{37a} BPE\textsuperscript{37a} (95.2%), and TangPhos\textsuperscript{38e} (>99%) show high to excellent enantioselectivity in the hydrogenation of this substrate.

Enamides are less reactive substrates than α-dehydroamino esters or itaconates. Therefore, the Endeavor autoclave was pressurized to 25 bar of hydrogen and the reactions were performed at rt with the catalyst being formed in situ from 2 mol % Rh precursor and 4 mol % ligand. For rapid screening of new ligands using a variety of enamide substrates, we developed an easy one-pot multisubstrate procedure to test the level of asymmetric induction in a parallel manner.\textsuperscript{46} As shown in Figure 2, the enantiomeric composition of a mixture of up to eight different racemic N-acylamines could be determined in a single chiral GC run. As a control experiment, the hydrogenation of a mixture of five different enamides with a chiral catalyst complex formed from ligand 5A gave the corresponding chiral amines with the same ee.

enantioselectivities as obtained in the separate asymmetric hydrogenation of the single enamides. This excludes any induction by either starting materials or products.

Under these conditions, MonoPhos (1A) led to a reproducible ee of 85%, with no improvement being achieved by changing to the $H_2$-BINOL analogue 1B. Varying the amine moiety to diethylamine in 2A indeed led to an increased ee of 94% (Table 3, entry 3), whereas the pyrrolidine-derived ligand 4A induced only a moderate ee.

Again, the most dramatic improvement was observed when changing to ligands incorporating a six-membered cyclic secondary amine as a common structural motive. Thus, in the case of ligands 5A, 7A, and 9A, enamide 14a was hydrogenated with almost complete enantioselectivity even at rt (Table 3, entries 5, 8, and 11). Moreover, when applying the preformed complex [Rh(COD)5A][BF4] under the same conditions as mentioned above, the hydrogenation still proceeded smoothly with a TOF of 250 h$^{-1}$ and an ee of 98.4% even when the amount of catalyst was reduced to 0.1 mol %.

Substituting the aryl moiety of enamide 14a with an electron- withdrawing group as in 14b or with an electron-donating substituent as in 14c had a significant influence on the catalysts based on 1A, 1B, and 2A. Thus, using MonoPhos (1A) as ligand the introduction of a chloro substituent as in 14b increased the enantioselectivity to 88% (Table 3, entry 13), whereas the methoxy substituted enamide 14c was hydrogenated with a lower ee of 81% (Table 3, entry 25). Remarkably, substitution of the arene moiety did not influence the enantioselectivity when the very successful piperidyl- and morpholine-derived ligands 5A and 7A were used. Thus 14a, 14b, and 14c could all be hydrogenated in 99% ee (Table 3, entries 5, 8, 17, 20, 29, and 32).

Additional substitution at the olefinic moiety as in 15a and 15b had a large influence on the enantioselectivity of the hydrogenation. Although Monophos (1A) in the hydrogenation of the trisubstituted enamide 15a with a Z configuration gave rise to the corresponding amine with an ee of 80%, again excellent ee’s up to 97% were obtained with the piperidyl- and morpholine-derived ligands 5A and 7A (Table 3, entries 41 and 44). For this particular substrate the enantioselectivity could be increased to 99% (Table 3, entry 45) applying $H_2$-BINOL analogue 7B.

The situation is completely different in case of enamide 15b with an E configuration. Although complete conversion was achieved with almost all ligands, the enantioselectivity for the hydrogenation of 15b was disappointingly low. A selectivity of at best 26% ee was obtained with ligand 7B. The same tendency with respect to the geometry of the substrate has been observed with monodentate phosphites. Reetz observed full conversion and an ee of 97.0% for a trisubstituted enamide with Z configuration whereas hydrogenation of the corresponding E-enamide proceeded with only 69% conversion yielding the amine with an ee of 76.2%. However, excellent enantioselectivities were reported for the hydrogenation of E/Z-mixtures of trisubstituted enamides using carbohydrate derived monophosphites. In addition, we recently discovered a simple catechol-based phosphoramidite ligand which enables the hydrogenation of E/Z-mixtures of trisubstituted enamides with excellent enantioselectivity.

Thus far, no good enantioselectivities have been reported for the Rh-catalyzed asymmetric hydrogenation of tetrasubstituted enamides such as 16 using monodentate ligands. Even with diphosphorus ligands, the number of successful reports has been limited to Imamoto’s Rh-BisP. Thus, it was not too surprising that using our monodentate phosphoramidite ligands the enantioselectivities were only 27% at best (Table 3, entry 63).

Another interesting enamide is tert-butyl-substituted enamide 17. For this particular substrate excellent enantioselectivities have been obtained using DuPhos. In that case, the sense of enantiodiscrimination using 17 is opposite to that observed for $\alpha$-aryl enamides. The same reversal of enantiodiscrimination for aryl and tert-butyl enamides was found using phosphoramidite ligands. Using (S)-MonoPhos (1A) as ligand, 17 was...
and PennPhos (98% ee) at rt, and an ee of 96% was
found when this substrate was hydrogenated with
Rh-PennPhos has been reported to induce high selec-
tivity (98% ee) at rt whereas BIPHEP leads to the same
selectivity at 20 °C. BPE induces 69% ee at rt and
20 °C. BPE induces 69% ee at rt and
20 °C was reached, showing that the
37). When the reaction was performed at 0 °C the ee could
be increased to 71% (Table 3, entry 72) while cooling to
−20 °C further improved the ee to 82% with only little
decrease in conversion (Table 3, entry 73). Disappoint-
ionally, the morpholine derived ligand 7A only resulted in
an ee of 27% in the hydrogenation product of 17.

Next, we turned our attention to the hydrogenation of
the more challenging cyclic enamides (Table 4). Although
the metal-catalyzed asymmetric hydrogenation of cyclic enamides provides access to bioactive chiral aminotetra-
lines and aminoindanes only few successful catalysts,
all based on bidentate phosphines, for this transformation
can be found in the literature. Thus, enamide 18 derived
from α-indanone could be hydrogenated with high enan-
tioselectivity using Duphos (98% ee), BPE (99% ee) and
and PennPhos (98% ee) at rt, and an ee of 96% was
found when this substrate was hydrogenated with
BIPHEP at −20 °C. Notably, with monodentate ligands
only Zheng13X has reported high enantioselectivities (96% ee)
in the hydrogenation of 18 to the best of our
knowledge. Using the same conditions as for the hydro-
genation of acyclic enamides the catalyst formed from
[Rh(COD)]2BF4 and (S)-MonoPhos (1A) gave the corre-
sponding aminotetraline with a moderate ee of 44%. How-
ever, we were delighted to see that the scope of the
piperidyl ligand 5A is not limited to acyclic enamides.
Even at rt it was possible to hydrogenate substrate 18
using Rh/5A with high enantioselectivity (89%) (Table 4,
entry 5). Lowering the temperature did improve the
selectivity in this case as well leading to 94% ee at 0 °C
(entry 6) and an excellent ee of 98% at −20 °C (Table 4,
entry 7) while full conversion was maintained in both
cases. Although similar selectivities were obtained with
the morpholine derived ligand 7A a slight decrease in
rate results in a conversion of 89% at −20 °C.

For the α-tetralone-derived enamide 19a only
Rh-PennPhos has been reported to induce high selec-
tivity (98% ee) at rt whereas BIPHEP leads to the same
selectivity at −20 °C. BPE induces 69% ee at rt and
92% ee at −20 °C, respectively, while Duphos induces
no enantioselectivity at all in the hydrogenation of 19a.
Again, we were pleased to see that modifying MonoPhos
by simply altering the amino moiety from dimethylamine
to piperidine as in ligand 5A significantly increased
the stereoselectivity. Performing the hydrogenation at 0 °C
gave the desired acylated aminotetraline with 95% ee and
an ee of 98% at −20 °C was reached, showing that the

### TABLE 4. Hydrogenation of Cyclic Enamides

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*For reaction conditions see the Supporting Information. Reactions were run for 8 h. b Reaction performed at 0 °C under a pressure of 55 bar of H2. c Reaction performed at −20 °C under a pressure of 55 bar of H2.

monodentate phosphoramidite 5A induces the same enantioselectivity as the most successful bidentate ligands. The corresponding morpholine derived ligand 7A again exhibited a very similar behavior in terms of enantioselectivity (Table 4, entries 26–28).

For the hydrogenation of the chromanone derived enamide 19b only two catalysts have been reported in the literature. While PennPhos induces a high ee of 90% at rt,38c BIPHEP only leads to moderate enantioselectivity (66% ee) even at −20 °C.38f Thus, it was surprising that in our hands, with one exception, all ligands resulted in ees of 94% or higher. Again, the piperidyl- and morpholine-derived phosphoramidites PipPhos 5A and MorfPhos 7A distinguished themselves from the other ligands since the corresponding 4-aminochromane was obtained with near perfect (>99%) enantioselectivity (Table 4, entries 37 and 40).

The hydrogenation of the β-tetralone derived enamides is best accomplished using Ru-based catalyst systems. Bruneau reported excellent enantioselectivities in the hydrogenation of trisubstituted enamides derived from various 2-tetralones and 3-chromanones using chiral Ru-BINAP complexes.36 Rh-catalyzed hydrogenation of β-tetralone derived enamides such as 20 has only been reported with limited success. While PennPhos38c leads to an ee of 71% at rt for the hydrogenation of 20, the use of BIPHEP38f provided a moderate ee of 45% in the corresponding acylated amine. Disappointingly, the monodentate phosphoramidites reported here gave unsatisfactory results in the hydrogenation of 20 as well. However, it was unforeseen that the thiomorpholine-derived ligand 8A which did not show any spectacular results in the hydrogenation of the previously investigated enamides displayed the best selectivity in the hydrogenation of 20.

Conclusion

In conclusion, we have synthesized and explored a library of new monodentate phosphoramidites. Simply by changing the dimethylamino group of Monophos (1A) into a piperidyl or morpholine moiety, the selectivity for the hydrogenation of a broad range of substrates could be dramatically increased. In particular, the ligands 5A (PipPhos) and 7A (MorfPhos) (Figure 3) are broadly applicable and show extremely high selectivity in the catalytic hydrogenation of a number of structurally highly divers substrates (Table 5). As PipPhos 5A and MorfPhos 7A can easily be obtained via a two-step synthesis starting from extraordinarily cheap starting materials, they can be considered as the most versatile monodentate ligands for asymmetric hydrogenation at this time. Further applications of these ligands are in progress.

Acknowledgment. We thank T. D. Tiemersma-Wegman and E. P. Schudde for technical support, A. Meetsma for X-ray crystallography, and A. Kiewiet for mass spectrometry. Financial support from the NWO/CW is gratefully acknowledged.

Supporting Information Available: Experimental details, spectral data, 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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