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

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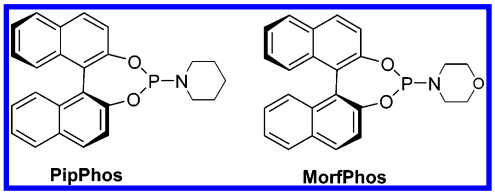

A library of 20 monodentate phosphoramidite ligands has been prepared and applied in rhodium-catalyzed asymmetric hydrogenation. This resulted in the identification of two ligands, PipPhos and MorfPhos, that afford excellent and in several cases unprecedented enantioselectivities in the hydrogenation 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[3] 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,[4] this area has been dominated by chiral bidentate ligands for more than three decades.[5] 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-

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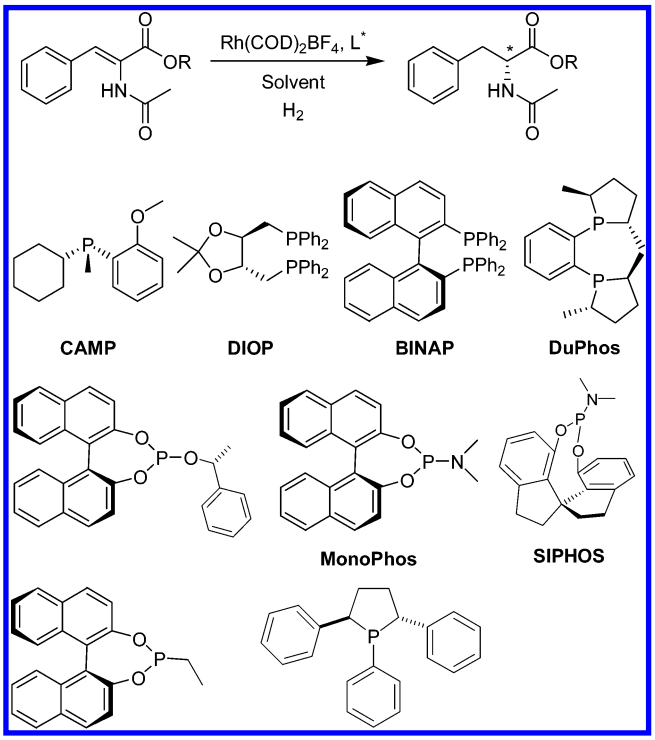

FIGURE 1. Examples of effective ligands in asymmetric hydrogenation of 2-acetamidocinnamic acid or its ester.

ites[11] have been successfully applied in the enantioselective rhodium-catalyzed hydrogenation of *N*-acyl-α-dehydroamino acids and esters, itaconic acid derivatives,[12,13] *N*-acylenamides,[7,13] and recently *N*-acyl-*β*-dehydroamino esters[14] and vinylcarboxylates.[15] Furthermore, other monodentate phosphorus ligands such as aminophosphinites,[16] diazaphospholidines,[17] secondary phosphine oxides[18] and polymer-supported, heterogenized, or dendritic phosphoramidites[19] have been developed and successfully applied in asymmetric hydrogenations. A recent study showed that a number of monodentate ligands not only show comparable or higher enantioselectivities than state-of-the-art bidentate ligands but also can compete in terms of reaction rates.[20]

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,[21] 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.[11]

After its disclosure, closely related ligands were reported which with some substrates surpass **1A** in enantioselectivity.[22] 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.[23,24]

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

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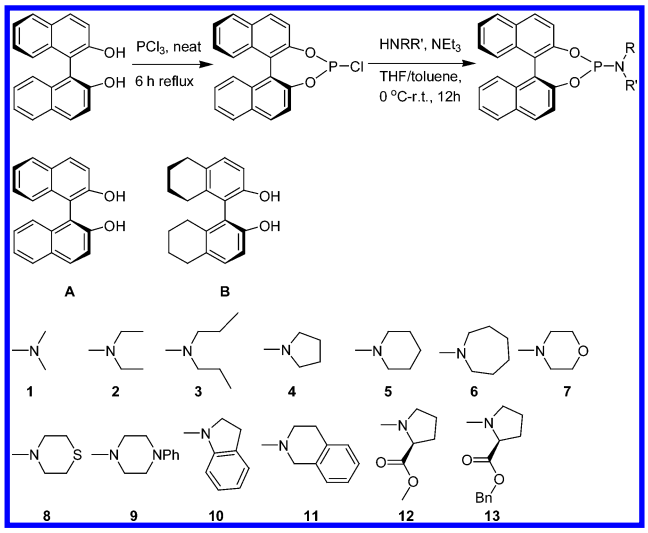
SCHEME 1. Synthesis of a Phosphoramidite Ligand Library



5A and MorfPhos **7A**, are disclosed which induce enantioselectivities of 99% or higher in the hydrogenation of most of the substrates.

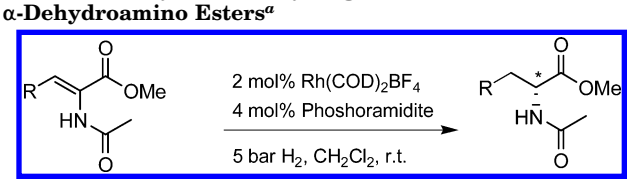
Results and Discussion

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 H_8-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 for a parallel synthesis, we then designed a focused library of 20 ligands (Scheme 1).

Refluxing BINOL in neat PCl_3,[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 amount of secondary amine in the presence of triethylamine gives rise to the phosphoramidites in good to high yields.[26] MonoPhos (**1A**) and its H_8-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 1). These substrates have been successfully hydrogenated with a number of monodentate ligand based catalysts, and ee's of 99% have occasionally been reached.[8−13] After our initial studies using MonoPhos,[11] Zhou et al. introduced the spirobiindanediol-derived analogue SIPHOS and observed ee's up to 97.1% for methyl 2-acetamidoacrylic acid and 97.8%[27] for methyl 2-acetamidocinnamic acid.[12g] Chan and co-workers reported slightly improved enantioselectivity in hydrogenations of α-dehydroamino esters and enamides by exchanging BINOL for H_8-BINOL.[12e,f]

TABLE 1. Asymmetric Hydrogenation of α-Dehydroamino Esters[a]



entry	R	ligand	% ee	entry	R	ligand	% ee
1	H	**1A**	97	21	phenyl	**1A**	95
2	H	**1B**	94	22	phenyl	**1B**	95
3	H	**2A**	94	23	phenyl	**2A**	97
4	H	**2B**	84	24	phenyl	**2B**	91
5	H	**3A**	90	25	phenyl	**3A**	93
6	H	**4A**	85	26	phenyl	**4A**	76
7	**H**	**5A**	**99**	**27**	**phenyl**	**5A**	**99**
8	H	**5B**	97	**28**	**phenyl**	**5B**	**>99**
9	H	**6A**	97	29	phenyl	**6A**	97
10	H	**6B**	87	30	phenyl	**6B**	96
11	**H**	**7A**	**99**	**31**	**phenyl**	**7A**	**98**
12	H	**7B**	95	**32**	**phenyl**	**7B**	**99**
13	H	**8A**	86	33	phenyl	**8A**	47[b]
14	H	**9A**	96	34	phenyl	**9A**	97
15	H	**9B**	96	**35**	**phenyl**	**9B**	**99**
16	H	**10A**	85	36	phenyl	**10A**	90
17	**H**	**11A**	**99**	**37**	**phenyl**	**11A**	**99**
18	H	**11B**	96	38	phenyl	**11B**	98
19	H	**12A**	88	39	phenyl	**12A**	52
20	H	**13A**	84	40	phenyl	**13A**	68

[a] 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. [b] 94% conversion.

To compare the performance of the ligands shown in Scheme 1, all hydrogenations were performed under a hydrogen pressure of 5 bar at room temperature in dichloromethane as solvent. An Endeavor multireactor autoclave was used that contains eight parallel reactors.[28] The actual catalyst was prepared in situ from 2 mol % of the precursor $[Rh(COD)_2]BF_4$ and 4 mol % of ligand. In all cases, ligands with (*S*)-configuration gave rise to the corresponding (*R*) amino acid esters.[28] In our hands, and deviating from Chan's results,[12e] the enantioselectivity induced by H_8-BINOL-derived ligands was found to be of the same level or lower than that reached by ligands consisting of a BINOL backbone (compare entries 1/2, 3/4, 7/8, 9/10, 11/12, 14/15, and 17/18 of Table 1 for methyl acetamidoacrylic acid as the substrate and 21/22, 23/24, 27/28, 29/30, 31/32, 34/35, and 37/38 for methyl acetamidocinnamic acid). An advantage of ligands with a BINOL backbone is their often increased tendency to crystallize which facilitates their isolation.[29]

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(27) Reaction performed at 0 °C.

(28) See the Supporting Information.

(29) In contrast, most of the H_8-BINOL-derived ligands are foams and have a tendency to hold on to solvent molecules.

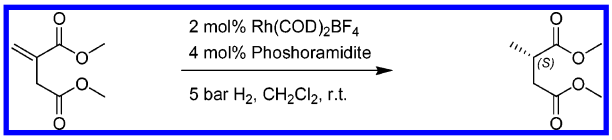
Variation of the amine moiety in the ligand had a dramatic influence on the level of enantioselection. Chan et al. found a significant increase in ee when changing from MonoPhos to the corresponding diethylamine-derived phosphoramidite **2A**.[12b] In our hands ligand **2A** induced a lower enantioselectivity in the hydrogenation of methyl 2-acetamidoacrylic acid (Table 1, entry 3) but a slightly higher enantioselectivity in the reduction of methyl 2-acetamidocinnamic acid (Table 1, entry 23) compared with MonoPhos when these hydrogenations were performed in the same solvent.[30] 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-acetamidocinnamic 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 H_8-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 H_8-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-acetamidocinnamic acid. This is possibly due to inhibition of the catalyst by sulfur−rhodium interactions. On the other hand, the corresponding *N*-phenylpiperazine-derived 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-acetamidocinnamic 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 indoline[31] resulted in lower enantioselectivity comparable to pyrrolidine ligand **4A**, whereas ee's induced by ligand **11A** and **11B** derived from tetrahydroisoquinoline 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.

(30) In ref 12b, an ee of 98% for the hydrogenation of methyl 2-acetamidoacrylic acid with ligand **2A** in THF is compared with an ee of 93% for ligand **1A** in ethyl acetate.

TABLE 2. Hydrogenation of Dimethyl Itaconate[a]



entry	ligand	% ee	entry	ligand	% ee
1	**1A**	92	**11**	**7A**	**98**
2	**1B**	90	**12**	**7B**	**98**
3	**2A**	94	13	**8A**	40[b]
4	**2B**	81	14	**9A**	91
5	**3A**	79	**15**	**9B**	>**99**
6	**4A**	83	16	**11A**	97
7	**5A**	>**99**	17	**11B**	95
8	**5B**	**99**	18	**12A**	15
9	**6A**	93	19	**13A**	68
10	**6B**	90			

[a] 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. [b] 50% conversion.

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 monophosphonites[9b] 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.[12j] The groups of Chen,[13a] Ojima,[13b] Rampf,[13c] and Xiao[13h] recently reported ee's ranging from 75% to >99% applying monophosphite ligands based on biphenol backbones. Monophosphite ligands based on other backbones[13d,14] and monophosphines[13e−g] have also been reported to induce moderate to good enantioselectivities.

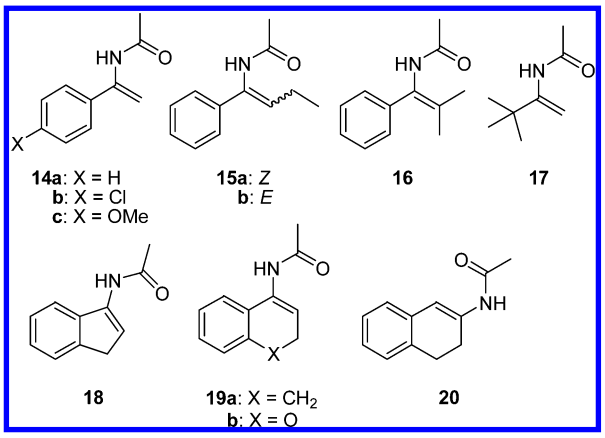
The hydrogenation of dimethyl itaconate with 2 mol % of Rh-precursor and 4 mol % of MonoPhos (**1A**) as ligand with a hydrogen pressure of 5 bar at rt in dichloromethane using the Endeavor autoclave gave rise to the saturated diester with an ee of only 92% (Table 2). For this substrate the same trends 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.[28] With the exception of ligands **9A** and **9B** (Table 2, entries 14 and 15) alteration of the diol backbone from BINOL to H_8-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-dehydroamino 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).

(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 H_2, 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**$_2$]BF_4 at a H_2-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 piperazine-derived ligand **9A** induces only moderate ee (Table 2, entry 14), the H_8-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 H_8-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[12a] and also observed by Ojima in the context of his phosphonite ligands.[13b] The enantioselectivity obtained in the hydrogenation of methyl 2-acetamidoacrylic acid, methyl 2-acetamidocinnamic acid, and the enamide **14** (vide infra) is not sensitive to solvent effects employing solvents such as CH_2Cl_2, 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.[34]

Chiral α-arylalkylamines 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,[35] 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.[36] Meanwhile, excellent results have been achieved with Burk's BPE and DuPhos ligands,[37] and subsequently other phosphorus based bidentate ligands have been reported to be useful in the selective hydrogenation of

SCHEME 2. Synthesis of Enamide Substrates



enamides.[38−42] Only recently, we[12a,d] and others[12b,h,i,j] reported the first successful application of monodentate phosphoramidite ligands for this transformation.[43]

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**,[35] were prepared according to a procedure developed by Barton and Zard.[44] This method involves transformation of a ketone into the corresponding oxime followed by subsequent reduction with iron metal in the presence of acetic anhydride.[45]

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

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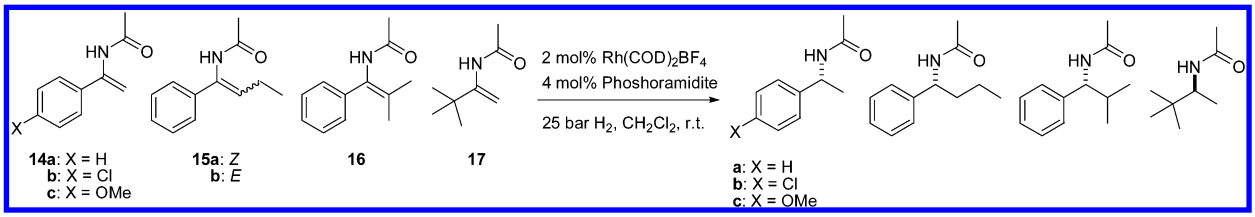
TABLE 3. Hydrogenation of Acyclic Enamides[a]



entry	substrate	ligand	% ee	conv (%)	config	entry	substrate	ligand	% ee	conv (%)	config
1	**14a**	**1A**	85	100	*R*	41	**15a**	**5A**	96	100	*R*
2	**14a**	**1B**	84	100	*R*	42	**15a**	**5B**	97	100	*R*
3	**14a**	**2A**	94	100	*R*	43	**15a**	**6A**	88	100	*R*
4	**14a**	**4A**	82	100	*R*	**44**	**15a**	**7A**	**98**	**100**	***R***
5	**14a**	**5A**	**99**	**100**	***R***	**45**	**15a**	**7B**	**99**	**100**	***R***
6	**14a**	**5B**	98	100	*R*	46	**15a**	**8A**	62	100	*R*
7	**14a**	**6A**	94	100	*R*	**47**	**15a**	**9A**	**98**	**100**	***R***
8	**14a**	**7A**	>**99**	**100**	*R*	48	**15a**	**11A**	89	71	*R*
9	**14a**	**7B**	97	100	*R*	49	**15b**	**1A**	6	100	*R*
10	**14a**	**8A**	97	100	*R*	50	**15b**	**1B**	5	100	*R*
11	**14a**	**9A**	**99**	**100**	*R*	51	**15b**	**2A**	1	100	
12	**14a**	**11A**	94	100	*R*	52	**15b**	**4A**	0	100	*R*
13	**14b**	**1A**	88	100	*R*	53	**15b**	**5A**	3	100	*R*
14	**14b**	**1B**	86	100	*R*	54	**15b**	**5B**	5	100	*R*
15	**14b**	**2A**	90	100	*R*	55	**15b**	**6A**	1	100	*R*
16	**14b**	**4A**	83	100	*R*	56	**15b**	**7A**	23	100	*R*
17	**14b**	**5A**	**99**	**100**	*R*	57	**15b**	**7B**	26	100	*R*
18	**14b**	**5B**	98	100	*R*	58	**15b**	**9A**	17	100	*R*
19	**14b**	**6A**	94	100	*R*	59	**15b**	**11A**	12	76	*R*
20	**14b**	**7A**	**99**	**100**	*R*	60	**16**	**1A**	5 (97)	97	
21	**14b**	**7B**	97	100	*R*	61	**16**	**5A**	−17	100	
22	**14b**	**8A**	85	100	*R*	62	**16**	**5B**	−1	100	
23	**14b**	**9A**	**99**	**100**	*R*	63	**16**	**6A**	−27	100	
24	**14b**	**11A**	93	100	*R*	64	**16**	**7A**	−5 (70)	70	
25	**14c**	**1A**	81	100	*R*	65	**16**	**7B**	−5 (84)	84	
26	**14c**	**1B**	75	100	*R*	66	**16**	**9A**	−4 (39)	39	
27	**14c**	**2A**	87	100	*R*	67	**17**	**1A**	49	100	*S*
28	**14c**	**4A**	76	100	*R*	68	**17**	**1B**	29	100	*S*
29	**14c**	**5A**	**99**	**100**	*R*	69	**17**	**2A**	42	100	*S*
30	**14c**	**5B**	**99**	**100**	*R*	70	**17**	**4A**	50	100	*S*
31	**14c**	**6A**	92	100	*R*	**71**	**17**	**5A**	**59**	**100**	***S***
32	**14c**	**7A**	**99**	**100**	*R*	72	**17**	**5A**	71[b]	100	*S*
33	**14c**	**7B**	98	100	*R*	**73**	**17**	**5A**	**82c**	**97**	***S***
34	**14c**	**8A**	90	100	*R*	74	**17**	**5B**	44	100	*S*
35	**14c**	**9A**	98	100	*R*	75	**17**	**6A**	38	100	*S*
36	**14c**	**11A**	94	100	*R*	76	**17**	**7A**	27	100	*S*
37	**15a**	**1A**	80	100	*R*	77	**17**	**7B**	13	100	*S*
38	**15a**	**1B**	83	100	*R*	78	**17**	**8A**	10	100	*S*
39	**15a**	**2A**	85	100	*R*	79	**17**	**9A**	21	100	*S*
40	**15a**	**4A**	77	100	*R*						

[a] For reaction conditions, see the Supporting Information. Reactions were run for 8 h. [b] The reaction was performed at 0 °C at a pressure of 55 bar of H_2. [c] The reaction was performed at −20 °C at a pressure of 55 bar of H_2.

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**.[12b] Applying phosphites, Reetz observed ee's up to 95.3%,[13j] whereas the use of SIPHOS resulted in the corresponding amine with an ee of 98.7%.[12j] These results with monodentate ligands are already quite remarkable, since most of the privileged bidentate ligands such as BICP[38a] (86.3%), PennPhos[38c] (75%), DIOP[38d] (68%), and BIPHEP[38f] (70%) are not suitable for the hydrogenation of enamides such as **14a**. DuPhos,[37a] BPE[37a] (95.2%), and TangPhos[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.[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

(46) A similar procedure has been applied in other asymmetric catalytic reactions: (a) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773. (b) Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120. (c) Brouwer, A. J.; Van der Linden, H. J.; Liskamp, R. M. B. *J. Org. Chem*. **2000**, *65*, 1750.

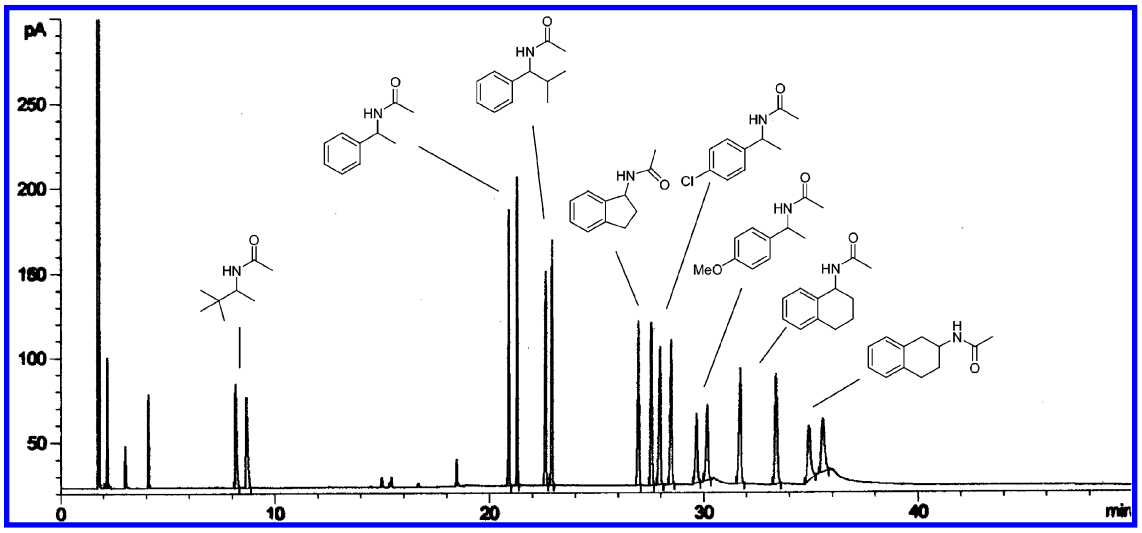


FIGURE 2. Chiral GC separation of the racemates of eight different acylated amines derived via hydrogenation of a mixture of corresponding enamide.

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_8-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**$_2$]BF_4 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_8-BINOL analogue **7B**.

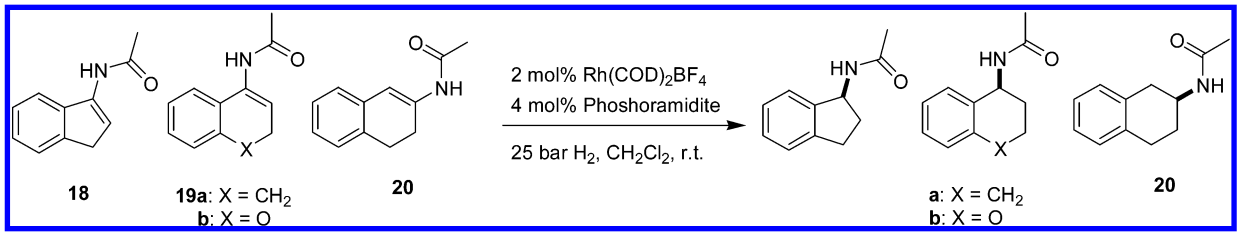
The situation is completely different in case of enamide **15b** with an *E* configuration. Although complete conversion was achieved with almost all ligands, the enantioselectivity for the hydrogenation of **15b** was disappointingly low. A selectivity of at best 26% ee was obtained with ligand **7B**. 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%.[13j] However, excellent enantioselectivities were reported for the hydrogenation of *E*/*Z*-mixtures of trisubstituted enamides using carbohydrate derived monophosphites.[13a] 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.[47]

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*.[39b] 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 α-aryl enamides.[37b,c,39a,b] The same reversal of enantiodiscrimination for aryl and *tert*-butyl enamides was found using phosphoramidite ligands. Using (*S*)-MonoPhos (**1A**) as ligand, **17** was

(47) Hoen, R.; Van den Berg, M.; Bernsmann, H.; Minnaard, A. J.; De Vries, J. G.; Feringa, B. L. *Org. Lett.* **2004**, *6*, 1433.

TABLE 4. Hydrogenation of Cyclic Enamides



entry	substrate	ligand	% ee	conv (%)	config	entry	substrate	ligand	% ee	conv (%)	config
1	**18**	**1A**	44	100	*R*	**29**	**19a**	**7B**	**88**	100	*R*
2	**18**	**1B**	29	100	*R*	30	**19a**	**8A**	11	94	*R*
3	**18**	**2A**	58	100	*R*	31	**19a**	**9A**	82	95	*R*
4	**18**	**4A**	63	100	*R*	32	**19a**	**11A**	53	94	*R*
5	**18**	**5A**	**89**	**100**	*R*	33	**19b**	**1A**	97	100	
6	**18**	**5A**	94[b]	100	*R*	34	**19b**	**1B**	94	100	
7	**18**	**5A**	**98**[c]	**100**	*R*	35	**19b**	**2A**	94	100	
8	**18**	**5B**	82	100	*R*	36	**19b**	**4A**	97	100	
9	**18**	**6A**	37	100	*R*	**37**	**19b**	**5A**	>**99**	100	
10	**18**	**7A**	**90**	**100**	*R*	**38**	**19b**	**5B**	**99**	100	
11	**18**	**7A**	95[b]	100	*R*	39	**19b**	**6A**	94	100	
12	**18**	**7A**	**97**[c]	**89**	*R*	**40**	**19b**	**7A**	>**99**	**100**	
13	**18**	**7B**	**89**	**100**	*R*	**41**	**19b**	**7B**	>**99**	**100**	
14	**18**	**8A**	25	75	*R*	42	**19b**	**8A**	40	100	
15	**18**	**9A**	87	100	*R*	43	**19b**	**9A**	>99	100	
16	**18**	**11A**	51	100	*R*	44	**19b**	**11A**	98	100	
17	**19a**	**1A**	52	100	*R*	45	**20**	**1A**	6	81	
18	**19a**	**1B**	46	100	*R*	46	**20**	**1B**	3	100	
19	**19a**	**2A**	31	100	*R*	47	**20**	**2A**	18	100	
20	**19a**	**4A**	56	100	*R*	48	**20**	**4A**	−11	100	
21	**19a**	**5A**	**84**	**100**	*R*	49	**20**	**5A**	21	100	
22	**19a**	**5A**	95[b]	100	*R*	50	**20**	**5B**	28	100	
23	**19a**	**5A**	**98**[c]	**94**	*R*	51	**20**	**6A**	20	100	
24	**19a**	**5B**	76	100	*R*	52	**20**	**7A**	13	100	
25	**19a**	**6A**	4	95	*R*	53	**20**	**7B**	15	94	
26	**19a**	**7A**	**87**	**100**	*R*	**54**	**20**	**8A**	**34**	**94**	
27	**19a**	**7A**	94[b]	100	*R*	55	**20**	**9A**	8	65	
28	**19a**	**7A**	**97**[c]	**94**	*R*						

[a] 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 H_2. [c] Reaction performed at −20 °C under a pressure of 55 bar of H_2.

hydrogenated to give the S enantiomer of the desired amine with an ee of 49%. Using ligand **5A**, enamide **17** could be hydrogenated with an ee of 59% (Table 3, entry 71). 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). Disappointingly, 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 aminotetralines and aminoindanes[48] 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 enantioselectivity using Duphos[37b] (98% ee), BPE[37b] (>99% ee) and PennPhos[38c] (98% ee) at rt, and an ee of 96% was found when this substrate was hydrogenated with BIPHEP[38f] at −20 °C. Notably, with monodentate ligands only Zheng[13k] has reported high enantioselectivities (96% ee) in the hydrogenation of **18** to the best of our knowledge. Using the same conditions as for the hydrogenation of acyclic enamides the catalyst formed from $[Rh(COD)_2]BF_4$ and (*S*)-MonoPhos (**1A**) gave the corresponding aminoindane with a moderate ee of 44%. However, 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[38c] has been reported to induce high selectivity (98% ee) at rt whereas BIPHEP[38f] leads to the same selectivity at −20 °C. BPE[37b] induces 69% ee at rt and 92% ee at −20 °C, respectively, while DuPhos[37b] 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

(48) Iida, T.; Mase, T. *Curr. Opp. Drug Discuss. Dev*. **2002**, *5*, 834.

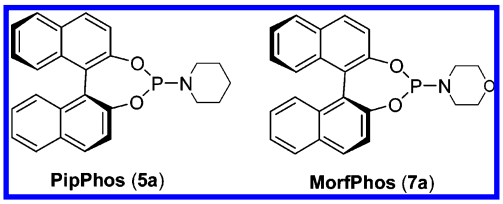


FIGURE 3.

TABLE 5. Selected Hydrogenation Results with PipPhos and MorfPhos[a]

entry	substrate	PipPhos (**5a**) (% ee)	MorfPhos (**7a**) (% ee)
1	methylacetamidoacrylic acid	99	99
2	methylacetamidocinnamic acid	99	98
3	dimethyl itaconate	>99	98
4	**14a**	99	>99
5	**14b**	99	99
6	**14c**	99	99
7	**15a**	96	98
8	**18**	98	97
9	**19a**	98	97
10	**19b**	>99	>99

[a] For reaction conditions see Tables 1−4 and the Supporting Information.

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 ee's 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 PennPhos[38c] leads to an ee of 71% at rt for the hydrogenation of **20**, the use of BIPHEP[38f] 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.

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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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