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Asymmetric Hydrogenation Using Rhodium Complexes Generated from Mixtures of Monodentate Neutral and Anionic Phosphorus Ligands

Dominik J. Frank,[a, b] Axel Franzke,[a, c] and Andreas Pfaltz*[a]

Abstract: A series of monodentate neutral and anionic phosphorus ligands was synthesized and evaluated in the asymmetric rhodium-catalyzed hydrogenation of functionalized olefins by using either catalysts containing identical ligands or catalysts generated from mixtures of two different ligands. We expected that the combination of an anionic ligand with a neutral ligand would favor the formation of hetero over homo bis-ligand complexes due to charge repulsion. NMR spectroscopic studies confirmed that charge effects can indeed shift the equilibrium toward the hetero bis-ligand complexes. In several cases, the combination of a neutral phosphane with an anionic phosphane, one chiral and the other achiral, furnished significantly higher enantioselectivities than analogous mixtures of two neutral ligands. The best results were obtained with a mixture of an anionic phosphoramidite and a neutral phosphoric acid diester. It is supposed that in this case a hydrogen bond between the two ligands additionally stabilizes the hetero ligand combination.

Keywords: asymmetric catalysis · hydrogenation · phosphanes · phosphoramidites · phosphoric acid diesters

Introduction

Since Dang and Kagan introduced the chiral diphosphane 1,4-bis(diphenylphosphino)butane (DIOP) in 1971,[1] bidentate ligands have been playing a dominant role in asymmetric catalysis.[2] The success of bidentate ligands in a wide range of enantioselective metal-catalyzed reactions led to the generally accepted view that chiral chelate complexes based on bidentate ligands are inherently superior catalysts relative to complexes based on monodentate ligands. Although many examples of successful applications of monodentate ligands have been reported over the years, in asymmetric hydrogenation chelate-forming bidentate ligands indeed seemed to be essential for high enantioselectivity. This long-standing dogma was refuted in 2000 by the research groups of Feringa and co-workers,[3] Pringle and co-workers,[4] and Reetz and Mehler,[5] who discovered that monodentate phosphoramidites, phosphonites, and phosphites derived from 1,1′-bi-2-naphthol (BINOL) can induce high enantioselectivities in Rh-catalyzed asymmetric hydrogenation reactions. Because ligands of this type are readily synthesized from inexpensive precursors, they soon found many applications in asymmetric hydrogenation, including reactions on an industrial scale.[3b]

Moreover, the work on chiral monodentate phosphorus ligands has led to a new approach to combinatorial-catalyst development. By using mixtures of two different monodentate ligands, Rh catalysts were generated in situ, which in many reactions gave higher enantioselectivities than the corresponding homo-ligand complexes.[3b,6,7] Even mixtures of a chiral and an achiral ligand proved effective. It may have come as a surprise that this approach was successful, taking into account that mixtures of homo- and hetero-ligand complexes are likely to be present in the reaction solution. Although excellent enantioselectivities were achieved in certain cases, the outcome of combinatorial experiments of this kind is unpredictable and, in general, a large number of ligands has to be tested.

A more selective formation of a specific hetero-ligand combination can be achieved by means of selective binding units that promote the self-assembly of two ligands, thus resulting in a supramolecular analogue of a bidentate ligand. Successful examples of this strategy are the hydrogen-bridged bis(monophosphane) complexes developed by Breit and Seiche[8] or the supramolecular metal-bridged systems devised by the groups of Takacs et al.[9] and Reek, van Leeuwen, and co-workers.[10] These strategies led to more defined catalysts than a combinatorial approach based on ligand mixtures. However, the incorporation of selective recognition units makes the synthesis of such supramolecular ligand systems more elaborate and costly.

[a] Dr. D. J. Frank, Dr. A. Franzke, Prof. Dr. A. Pfaltz
Department of Chemistry
University of Basel
St. Johanns-Ring 19, 4056 Basel (Switzerland)
Fax: (+41) 61-267-1103
E-mail: andreas.pfaltz@unibas.ch

[b] Dr. D. J. Frank
Current Address: School of Chemistry
Joseph Black Building, West Mains Road
Edinburgh, EH93JJ (UK)

[c] Dr. A. Franzke
Current address: Home Care and Formulation Technologies Europe
BASF SE, 67056 Ludwigshafen (Germany)

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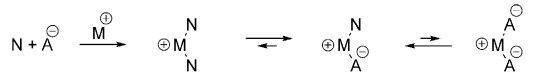
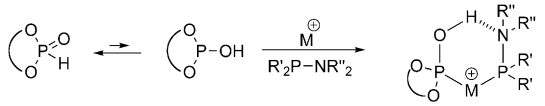
An alternative way to favor the formation of hetero- over homo-ligand combinations would be to incorporate an anionic group in one of the ligands. In the case of a cationic metal ion such as Rh^+, charge repulsion should shift the equilibrium toward the neutral hetero-ligand complex (Scheme 1). Alternatively, the combination of a phosphoramidite, which possesses a basic nitrogen atom, and a potential hydrogen-bond donor, such as a phosphoric acid diester, should also favor the hetero-ligand complex by hydrogen-bond formation (Scheme 2). This approach seems attractive because complementary ligands of this type are readily available from simple precursors. Herein, we report the synthesis of a series of anionic phosphite and phosphoramidite ligands and phosphoric acid diesters, the results of complexation studies, and Rh-catalyzed hydrogenation reactions that use mixtures of these ligands.



Scheme 1. Formation of bis-ligand metal complexes from a mixture of a neutral (**N**) and an anionic (**A**) ligand.



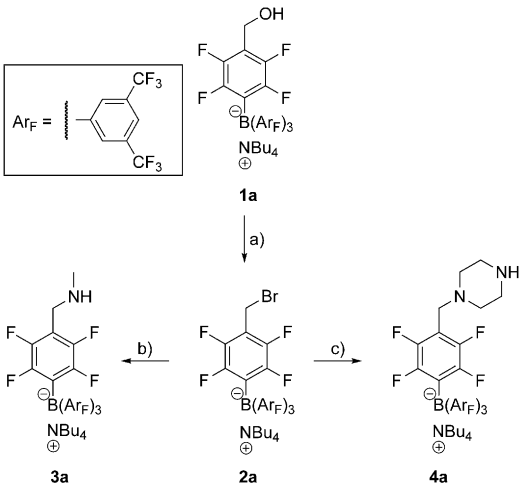
Scheme 2. Formation of a mixed phosphoramidite/phosphoric acid diester metal complex.

Results and Discussion

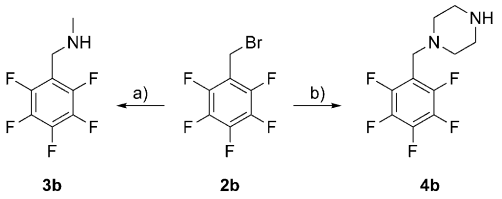
Synthesis of monodentate phosphite and phosphoramidite ligands: In connection with our work on zwitterionic iridium complexes with anionic N,P ligands,[11] we developed fluorinated tetraarylborate **1a**,[12] which we thought would be a suitable building block for the synthesis of phosphites and phosphoramidites bearing a non-coordinating anionic unit. Two secondary amines **3a** and **4a** were prepared from **1a** through bromide **2a** (Scheme 3). We also prepared analogous neutral amines **3b** and **4b** by starting from the fluorinated benzyl bromide **2b** (Scheme 4).[13]

Following reported procedures[14] a small library of three pairs of anionic chiral ligands **A1**–**A3** and their neutral analogues **N1**–**N3** was prepared by reaction of (*R*)-BINOL with PCl_3 and subsequent nucleophilic substitution with the corresponding alcohol or secondary amine (Scheme 5). In addition, achiral phosphites **N4**, **N5**, and **A6** and the anionic phosphinite **A7** were prepared in a similar way by starting from biphenol or diphenylphosphanyl chloride (Scheme 6).

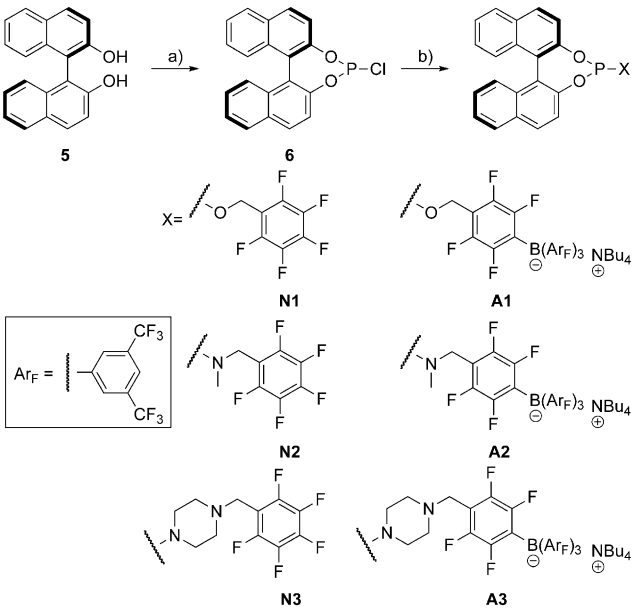
Hydrogenation studies: These new chiral and achiral ligands were subsequently evaluated in the Rh-catalyzed hydrogenation of selected functionalized olefins. The pairs of struc-



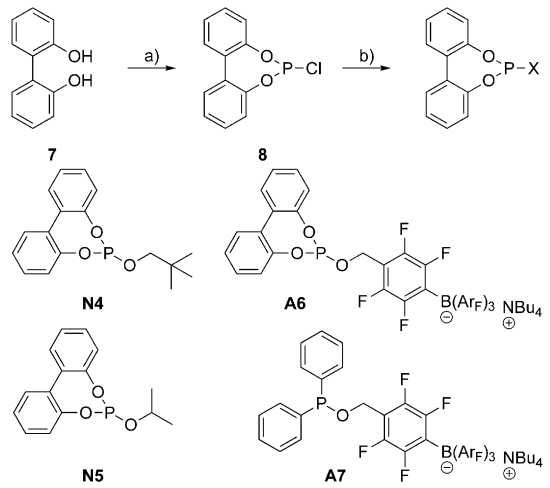
Scheme 3. Synthesis of anionic secondary amines **3a** and **4a** for the preparation of monodentate phosphane ligands. Reagents and conditions: a) PBr_3, NBu_4Br, CH_2Cl_2, 0 °C, 3 h, then 0 °C→rt, 17 h (97%); b) CH_3NH_2, THF, 0 °C, then 0 °C→rt, 3 h (73%); c) piperazine, THF, rt, 16 h (95%).



Scheme 4. Synthesis of neutral secondary amines **3b** and **4b** for the preparation of monodentate phosphane ligands. Reagents and conditions: a) CH_3NH_2, THF, 0 °C, then 0 °C→rt, 4 h (95%); b) piperazine, toluene, 85 °C, 2 h (74%).



Scheme 5. Preparation of BINOL ligands **N1**–**N3** and **A1**–**A3**. Reagents and conditions: a) PCl_3, NEt_3, THF, 0 °C, 80 min, then rt, 75 min (79%); b) amine or alcohol, Et_2O, toluene or THF, NEt_3, 0 °C→rt, 19 h (66–96%).



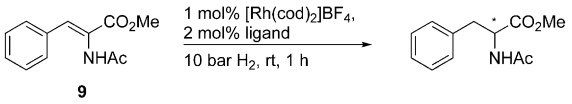
Scheme 6. Preparation of biphenol ligands **N4**, **N5**, and **A6** and diphenylphosphinite **A7**. Reagents and conditions: a) PCl_3, NEt_3, THF, 0 °C, 80 min, then rt, 75 min (50%); b) alcohol, THF, NEt_3, 0 °C→rt, 19 h (46–91%).

turally analogous neutral and anionic ligands were included in this study to evaluate the influence of the anionic group. First, we studied the performance of the individual neutral and anionic chiral ligands in the hydrogenation of (*Z*)-methyl 2-acetamido-3-phenylacrylate (**9**) and dimethyl itaconate (**10**) (Tables 1 and 2). The precatalysts were prepared in situ from $[Rh(cod)_2]BF_4$ and two equivalents of the ligand. The reactions were carried out under standard conditions at 10 bar hydrogen for 1 hour in *i*PrOH, EtOAc, CH_2Cl_2, or toluene. The highest reactivities and enantioselectivities were observed in CH_2Cl_2. The neutral and anionic phosphoramidites **N3** and **A3** derived from piperazine proved to be the overall most efficient ligands, thereby giving up to 99% *ee* in the hydrogenation of **9** (Table 1, entries 15 and 18) and 98 and 96% *ee* in the hydrogenation of dimethyl itaconate (Table 2, entries 15 and 18, respectively).

Clear differences in enantioselectivity and conversion values were found between anionic ligands and their neutral counterparts. However, no uniform trends were observed. Depending on the structure of the fluorinated *P*-aryl group and the solvent, either the anionic or neutral ligand performed better.

Next, binary mixtures comprising one of the less successful chiral BINOL ligands (**N1**, **N2**, **A1**, or **A2**) in combination with the achiral ligands PPh_3, $P(o\text{-Tol})_3$, $P(OPh)_3$, **N4**, **N5**, **A6**, or **A7** were evaluated. In the hydrogenation of **9**, the chiral phosphites **A1** and **N1** were tested that had furnished only moderate enantioselectivities in the screening of individual ligands. Most combinations of the anionic phosphite **A1** with neutral achiral phosphites led to improved selectivities. The most significant improvement was obtained with the mixture of **A1** and **N4** in EtOAc with 70% *ee* instead of 52% *ee* (Table 3, entry 12). On the other hand, the combination of the chiral phosphoramidite **A2** with **N4** did not improve the already quite high enantioselectivities further (Table 3, entries 6, 10, and 14). Significantly lower

Table 1. Hydrogenation of (*Z*)-methyl 2-acetamido-3-phenylacrylate (**9**) with catalysts derived from the individual ligands.



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Entry	L^1	Solvent	Conv. [%][a]	*ee* [%][b]
1	**N1**	toluene	80	80 (*S*)
2	**N2**	toluene	98	97 (*S*)
3	**N3**	toluene	29	89 (*S*)
4	**A1**	toluene	>99	84 (*S*)
5	**A2**	toluene	61	53 (*S*)
6	**A3**	toluene	81	93 (*S*)
7	**N1**	*i*PrOH	5	44 (*S*)
8	**N2**	*i*PrOH	17	94 (*S*)
9	**N3**	*i*PrOH	24	97 (*S*)
10	**A1**	*i*PrOH	>99	52 (*S*)
11	**A2**	*i*PrOH	78	88 (*S*)
12	**A3**	*i*PrOH	81	98 (*S*)
13	**N1**	CH_2Cl_2	>99	76 (*S*)
14	**N2**	CH_2Cl_2	>99	96 (*S*)
15	**N3**	CH_2Cl_2	>99	99 (*S*)
16	**A1**	CH_2Cl_2	>99	54 (*S*)
17	**A2**	CH_2Cl_2	>99	82 (*S*)
18	**A3**	CH_2Cl_2	>99	99 (*S*)
19	**N1**	EtOAc	>99	84 (*S*)
20	**N2**	EtOAc	>99	97 (*S*)
21	**N3**	EtOAc	74	91 (*S*)
22	**A1**	EtOAc	>99	52 (*S*)
23	**A2**	EtOAc	2	90 (*S*)
24	**A3**	EtOAc	>99	95 (*S*)

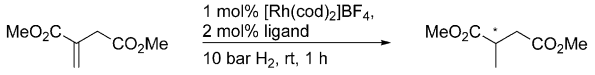
[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by HPLC on a chiral stationary phase. cod = 1,5-cyclooctadiene.

values were measured for all the binary mixtures of two neutral ligands (Table 3, entries 1, 3, 5, 7, 9, 11, 13, and 15).

In the hydrogenation of **10**, the application of binary ligand mixtures again improved the enantioselectivities in many cases. Because the phosphoramidites showed lower selectivities as individual ligands relative to the corresponding phosphites, combinations of **N2** and **A2** with achiral ligands were first investigated. Subsequently, the most promising achiral derivatives were also tested in mixtures with the more efficient chiral phosphites **N1** and **A1**. Ligand $P(o\text{Tol})_3$ in combination with the anionic phosphite **A1** in ethyl acetate gave the most spectacular improvement, with a selectivity of 87% *ee* instead of only 6% *ee* induced by **A1** alone or 18% *ee* for the corresponding mixture of $P(o\text{Tol})_3$ with **N1** (Table 4, entries 13 and 14). In addition, a large increase in reactivity was observed as the conversion was raised from 2 to 93%. The mixtures of anionic **A2** with $P(OPh)_3$, **N4**, or **N5** showed the best performance in the rather nonpolar solvent toluene with improved enantioselectivities of 82, 81, and 72% *ee*, respectively, relative to 56% *ee* for **A2** as an individual ligand (Table 4, entries 2, 6, and 8).

In general, mixtures of neutral and anionic ligands furnished better results in the hydrogenation of **9** and **10** than combinations of two neutral or anionic ligands.

Table 2. Hydrogenation of **10** with catalysts derived from individual ligands.



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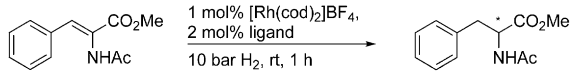
Entry	L^1	Solvent	Conv. [%][a]	*ee* [%][b]
1	**N1**	toluene	33	2 (*R*)
2	**N2**	toluene	12	19 (*R*)
3	**N3**	toluene	>99	racemic
4	**A1**	toluene	78	97 (*R*)
5	**A2**	toluene	37	56 (*R*)
6	**A3**	toluene	54	87 (*R*)
7	**N1**	*i*PrOH	3	10 (*R*)
8	**N2**	*i*PrOH	17	81 (*R*)
9	**N3**	*i*PrOH	20	88 (*R*)
10	**A1**	*i*PrOH	39	53 (*R*)
11	**A2**	*i*PrOH	75	84 (*R*)
12	**A3**	*i*PrOH	49	96 (*R*)
13	**N1**	CH_2Cl_2	>99	93 (*R*)
14	**N2**	CH_2Cl_2	>99	86 (*R*)
15	**N3**	CH_2Cl_2	>99	98 (*R*)
16	**A1**	CH_2Cl_2	>99	94 (*R*)
17	**A2**	CH_2Cl_2	>99	91 (*R*)
18	**A3**	CH_2Cl_2	>99	96 (*R*)
19	**N1**	EtOAc	>99	4 (*S*)
20	**N2**	EtOAc	>99	72 (*R*)
21	**N3**	EtOAc	>99	17 (*R*)
22	**A1**	EtOAc	2	6 (*R*)
23	**A2**	EtOAc	>99	73 (*R*)
24	**A3**	EtOAc	>99	53 (*R*)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by GC analysis on a chiral stationary phase.

Table 3. Hydrogenation of substrate **9** by using binary mixtures of ligands.



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Entry	L^1	L^2	Solvent	L^1+L^2 Conv. [%][a]	L^1+L^2 *ee* [%][b]	L^1+L^1 Conv. [%][a]	L^1+L^1 *ee* [%][b]
1	**N1**	$P(OPh)_3$	CH_2Cl_2	>99	49 (*S*)	>99	76 (*S*)
2	**A1**	$P(OPh)_3$	CH_2Cl_2	>99	58 (*S*)	>99	54 (*S*)
3	**N1**	**N4**	CH_2Cl_2	>99	35 (*S*)	>99	76 (*S*)
4	**A1**	**N4**	CH_2Cl_2	>99	61 (*S*)	>99	54 (*S*)
5	**N2**	**N4**	CH_2Cl_2	>99	72 (*S*)	>99	96 (*S*)
6	**A2**	**N4**	CH_2Cl_2	>99	62 (*S*)	>99	82 (*S*)
7	**N1**	**N4**	*i*PrOH	>99	17 (*S*)	5	44 (*S*)
8	**A1**	**N4**	*i*PrOH	>99	60 (*S*)	>99	52 (*S*)
9	**N2**	**N4**	*i*PrOH	38	17 (*S*)	2	94 (*S*)
10	**A2**	**N4**	*i*PrOH	1	60 (*S*)	2	88 (*S*)
11	**N1**	**N4**	EtOAc	>99	30 (*S*)	>99	84 (*S*)
12	**A1**	**N4**	EtOAc	>99	70 (*S*)	>99	52 (*S*)
13	**N2**	**N4**	EtOAc	>99	66 (*S*)	>99	97 (*S*)
14	**A2**	**N4**	EtOAc	93	59 (*S*)	2	90 (*S*)
15	**N1**	**N5**	EtOAc	>99	26 (*S*)	>99	84 (*S*)
16	**A1**	**N5**	EtOAc	>99	56 (*S*)	>99	52 (*S*)

[a] Conversions determined by GC. [b] Enantioselectivities determined by HPLC on a chiral stationary phase.

We next studied the hydrogenation of simple enamides.[15,16] The reactions were carried out at 20 bar hydrogen pressure with a reaction time of 4 h in CH_2Cl_2 or EtOAc, the conditions under which the best results had been achieved so far. In the hydrogenation of *N*-(1-phenylvinyl)acetamide (**11**), which serves as a benchmark for this class of olefin, excellent enantioselectivities of up to >99% *ee* were obtained in CH_2Cl_2 by using the anionic phosphoramidite **A3** as a ligand (Table 5, entry 6).

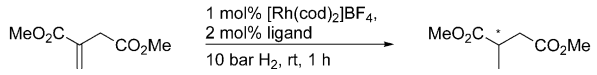
In view of the almost perfect enantioselectivites obtained for this substrate, the enamide derived from pinacolone (**12**) was chosen as a more challenging substrate. The best result was obtained with the anionic phosphite ligand **A1**, which furnished 81% *ee* in CH_2Cl_2 (Table 6, entry 4). However, the enantioselectivities dramatically decreased in EtOAc as the solvent. Interestingly, phosphite ligands **A1** and **N1** gave the (−)-enantiomer, whereas phosporamidites **N2**, **N3**, **A2**, and **A3** induced the opposite configuration.

No heterocombination of chiral and achiral ligands was found that improved the enantioselectivity of 81% *ee* obtained with **A1** alone in CH_2Cl_2. However, a beneficial effect of achiral ligands was observed for the less efficient chiral derivatives **N2** and **A3** in CH_2Cl_2 and for several combinations in EtOAc as the solvent (Table 7). In the former case, enhanced enantioselectivities were found for mixtures with achiral phosphites $P(OPh)_3$, **N4**, or **A6**, and the strongest increase in selectivity was measured by using a combination of neutral and anionic phosphites **N2** and **A6** (Table 7, entry 4). The best result in EtOAc was obtained for the combination of **A1** and $P(OPh)_3$ with an increase in enantioselectivity from 36 to 65% (Table 7, entry 11). However, at the same time, the conversion dropped from 89 to 38%. Significant increases in enantioselectivity were also found for combinations of the chiral neutral ligands **N1** and **N2** with achiral anionic phosphites **A6** and **A7** (Table 7, entries 4, 5, and 12). Interestingly, the achiral ligand **A7** inverted the sense of chiral induction observed with **N2** alone (Table 7, entry 5). Binary mixtures of two anionic ligands showed no improvement in enantioselectivity (see the Supporting Information).

The hydrogenation of *N*-(3,4-dihydronaphthalen-1-yl)acetamide (**13**) derived from α-tetralone generally proceeded with higher enantioselectivities than the hydrogenation of the sterically hindered enamide **12**. The best results were obtained with **A1**, with 96 and 97% *ee* in CH_2Cl_2 and EtOAc, respectively. However, the conversion reactions were still incomplete after 4 h (Table 8, entries 4 and 10). Interestingly, the + enantiomer was formed when the anionic phosphoramidite **A2** was used (Table 8, entries 5 and 11), whereas all the other ligands gave the − enantiomer.

As observed for enamide **12**, the application of ligand mixtures did not furnish higher enantioselectivities for the optimal ligand **A1**, but again the selectivities obtained for the less efficient phosphor-

Table 4. Hydrogenation of alkene **10** using binary mixtures of ligands.



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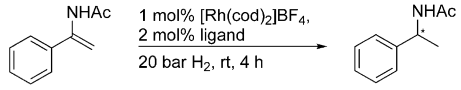
Entry	L^1	L^2	Solvent	L^1+L^2 Conv. [%][a]	L^1+L^2 *ee* [%][b]	L^1+L^1 Conv. [%][a]	L^1+L^1 *ee* [%][b]
1	**N2**	$P(OPh)_3$	toluene	7	33 (*R*)	12	19 (*R*)
2	**A2**	$P(OPh)_3$	toluene	70	82 (*R*)	37	56 (*R*)
3	**N1**	**N4**	toluene	24	56 (*R*)	33	2 (*R*)
4	**A1**	**N4**	toluene	38	63 (*R*)	78	97 (*R*)
5	**N2**	**N4**	toluene	18	12 (*R*)	12	19 (*R*)
6	**A2**	**N4**	toluene	45	81 (*R*)	37	56 (*R*)
7	**N2**	**N5**	toluene	29	13 (*R*)	12	19 (*R*)
8	**A2**	**N5**	toluene	37	72 (*R*)	37	56 (*R*)
9	**N2**	**N4**	CH_2Cl_2	>99	86 (*R*)	>99	86 (*R*)
10	**A2**	**N4**	CH_2Cl_2	>99	92 (*R*)	>99	91 (*R*)
11	**N1**	**A6**	CH_2Cl_2	>99	48 (*R*)	>99	93 (*R*)
12	**N2**	**A6**	CH_2Cl_2	>99	87 (*R*)	>99	86 (*R*)
13	**N1**	P(*o*Tol)$_3$	EtOAc	>99	18 (*R*)	>99	4 (*R*)
14	**A1**	P(*o*Tol)$_3$	EtOAc	93	87 (*R*)	2	6 (*R*)
15	**N2**	P(*o*Tol)$_3$	EtOAc	>99	80 (*R*)	>99	72 (*R*)
16	**A2**	P(*o*Tol)$_3$	EtOAc	>99	64 (*R*)	>99	73 (*R*)
17	**N1**	$P(OPh)_3$	EtOAc	>99	10 (*R*)	>99	4 (*R*)
18	**A1**	$P(OPh)_3$	EtOAc	>99	39 (*R*)	2	6 (*R*)
19	**N2**	$P(OPh)_3$	EtOAc	>99	65 (*R*)	>99	72 (*R*)
20	**A2**	$P(OPh)_3$	EtOAc	>99	78 (*R*)	>99	73 (*R*)
21	**N2**	**N4**	EtOAc	>99	76 (*R*)	>99	72 (*R*)
22	**A2**	**N4**	EtOAc	>99	48 (*R*)	>99	73 (*R*)
23	**N1**	**A7**	EtOAc	>99	47 (*R*)	>99	4 (*R*)
24	**A1**	**A7**	EtOAc	>99	26 (*R*)	2	6 (*R*)
25	**N2**	**A7**	EtOAc	>99	87 (*R*)	>99	72 (*R*)
26	**A2**	**A7**	EtOAc	>99	79 (*R*)	>99	73 (*R*)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by GC analysis on a chiral stationary phase.

Table 5. Reduction of *N*-(1-phenylvinyl)acetamide (**11**).



11

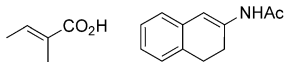
Entry	L^1	Solvent	Conv. [%][a]	*ee* [%][b]
1	**N1**	CH_2Cl_2	>99	95 (−)
2	**N2**	CH_2Cl_2	>99	91 (−)
3	**N3**	CH_2Cl_2	>99	99 (−)
4	**A1**	CH_2Cl_2	>99	89 (−)
5	**A2**	CH_2Cl_2	>99	49 (−)
6	**A3**	CH_2Cl_2	>99	>99 (−)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by GC analysis on a chiral stationary phase.

amidites **N2**, **N3**, and **A2** were improved by the addition of an achiral phosphite ligand. The most significant increases in enantiomeric excess in CH_2Cl_2 were measured for the mixture of neutral ligands **N3** and $P(OPh)_3$ (from 47 to 75% *ee*; Table 9, entry 1) and the combination of the anionic and neutral ligands **A2** and **N4** (from +24 to −68% *ee*; Table 9, entry 5). In the latter example, the achiral ligand **N4** caused a reversal of enantioselectivity, as had already been observed for other achiral ligands. The mixture of the anionic phosphoramidite **A3** and $P(OPh)_3$ in EtOAc resulted in the highest increase in selectivity from 20 to 52% *ee* for **A3** alone and the mixture, respectively (Table 9, entry 12).

Taken together, in contrast to substrates **9** and **10**, no general beneficial effect of the anionic ligands in binary mixtures with neutral ligands was observed for enamides **12** and **13**. However, the anionic phosphite **A1** applied as an individual ligand gave the best result in the hydrogenation of these substrates.

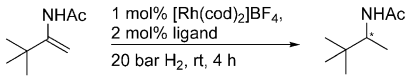
Finally, we also investigated compounds **14** and **15** as substrates (Figure 1). Only very low enantioselectivities of 18% *ee* at best were obtained when individual ligands were used. Improved enantioselectivities were observed in several cases for binary mixtures of chiral BINOL derivatives with achiral ligands. The neutral phosphoramidite **N2** and PPh_3 represented the best heterocombination in the asymmetric hydrogenation of **14**, thus yielding 62% *ee* instead of 10% *ee* with **N2** alone. In the hydrogenation of enamide **15**, derived from β-tetralone, the anionic phosphoramidite **A2** performed best in combination with PPh_3, thus furnishing 36% *ee* relative to 11% *ee* with **A2** alone (see the Supporting Information).



14 **15**

Figure 1. Tiglic acid (**14**) and *N*-(3,4-dihydronaphthalen-2-yl)-acetamide (**15**) as substrates for the asymmetric hydrogenation reaction.

Table 6. Hydrogenation of *N*-(3,3-dimethylbut-1-en-2-yl)acetamide (**12**) with catalysts derived from individual ligands.

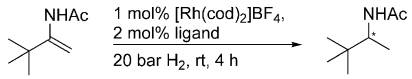


12

Entry	L^1	Solvent	Conv. [%][a]	*ee* [%][b]
1	**N1**	CH_2Cl_2	99	46 (+)
2	**N2**	CH_2Cl_2	80	29 (−)
3	**N3**	CH_2Cl_2	78	69 (−)
4	**A1**	CH_2Cl_2	97	81 (+)
5	**A2**	CH_2Cl_2	93	71 (−)
6	**A3**	CH_2Cl_2	84	27 (−)
7	**N1**	EtOAc	>99	4 (+)
8	**N2**	EtOAc	>99	8 (−)
9	**N3**	EtOAc	>99	racemic
10	**A1**	EtOAc	89	36 (+)
11	**A2**	EtOAc	<1	50 (−)
12	**A3**	EtOAc	41	15 (−)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by GC analysis on a chiral stationary phase.

Table 7. Hydrogenation of **12** by using binary mixtures of ligands.

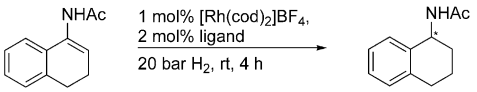


12

Entry	L^1	L^2	Solvent	L^1+L^2 Conv. [%][a]	L^1+L^2 *ee* [%][b]	L^1+L^1 Conv. [%][a]	L^1+L^1 *ee* [%][b]
1	**N2**	$P(OPh)_3$	CH_2Cl_2	35	50 (−)	80	29 (−)
2	**N2**	**N4**	CH_2Cl_2	99	48 (−)	80	29 (−)
3	**A3**	**N4**	CH_2Cl_2	>99	42 (−)	84	27 (−)
4	**N2**	**A6**	CH_2Cl_2	98	58 (−)	80	29 (−)
5	**N2**	**A7**	CH_2Cl_2	>99	46 (+)	80	29 (−)
6	**N2**	PPh_3	EtOAc	99	20 (−)	>99	8 (−)
7	**A3**	PPh_3	EtOAc	87	19 (−)	41	15 (−)
8	**N1**	$P(o\text{Tol})_3$	EtOAc	32	26 (−)	>99	4 (+)
9	**N2**	$P(o\text{Tol})_3$	EtOAc	29	31 (−)	>99	8 (−)
10	**N2**	$P(OPh)_3$	EtOAc	5	45 (−)	>99	8 (−)
11	**A1**	$P(OPh)_3$	EtOAc	38	65 (+)	89	36 (+)
12	**N1**	**A6**	EtOAc	72	33 (+)	>99	4 (+)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by GC analysis on a chiral stationary phase.

Table 8. Hydrogenation results for **13** with catalysts derived from individual ligands.



13

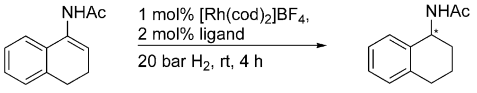
Entry	L^1	Solvent	Conv. [%][a]	*ee* [%][b]
1	**N1**	CH_2Cl_2	68	68 (−)
2	**N2**	CH_2Cl_2	19	27 (−)
3	**N3**	CH_2Cl_2	80	47 (−)
4	**A1**	CH_2Cl_2	88	96 (−)
5	**A2**	CH_2Cl_2	45	24 (+)
6	**A3**	CH_2Cl_2	>99	76 (−)
7	**N1**	EtOAc	19	43 (−)
8	**N2**	EtOAc	43	9 (−)
9	**N3**	EtOAc	29	34 (−)
10	**A1**	EtOAc	63	97 (−)
11	**A2**	EtOAc	15	45 (+)
12	**A3**	EtOAc	>99	20 (−)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by HPLC on a chiral stationary phase.

^{31}P NMR spectroscopic studies of rhodium(I) complexes formed from binary ligand mixtures: As a working hypothesis, we assumed that the equilibrium between the hetero-ligand metal complex and the corresponding homo-ligand complexes would be shifted toward the hetero-ligand complex by introducing a negative charge on one of the ligands. In the case of rhodium(I) complexes, the formation of a neutral zwitterionic hetero-ligand complex should be favored due to charge repulsion between the anionic ligands and an attractive interaction between the rhodium cation and the anionic ligand. This effect should be especially pronounced in apolar media. We carried out ^{31}P NMR spectroscopic studies to examine whether the combination of an anionic and a neutral ligand indeed leads to a higher proportion of the hetero-ligand complex than the mixture of structurally analogous neutral ligands.

$P(OPh)_3$ (**N8**) was chosen as an exemplary achiral partner ligand **L** in these investigations. The phosphites **N1** and **A1** and the phosphoramidites **N3** and **A3** were used as chiral counterparts **L***. A clear trend was observed when the chiral neutral ligands on the one hand or the corresponding anionic derivatives on the other hand were combined with $P(OPh)_3$. All the spectra obtained from [Rh(cod)$_2$]BF_4 and 1:1 mixtures of chiral BINOL-derived ligands with $P(OPh)_3$ showed the expected signals for the two homo-ligand complexes [Rh(cod)**L**$_2$] and [Rh(cod)(**L***)$_2$] and the mixed species ([Rh(cod)**LL***]). The homo combinations showed two doublets with large Rh–P couplings of about $J=250$ Hz. The hetero complex gave rise to two doublets of doublets with an additional smaller P–P coupling close to $J=50$ Hz. The effect of the negative charge on ligands **A1** and **A3** was reflected by the ratios of the three species [Rh(cod)**L**$_2$], [Rh(cod)**LL***], and [Rh(cod)(**L***)$_2$], which differed from the ratios obtained for the analogous mixtures of the corresponding two neutral ligands. The combination of the neutral ligands **N1** and **N3** with $P(OPh)_3$ resulted in proportions of the hetero complex of 60 and 56%, respectively, which is close to the statistical ratio of 1:2:1. In contrast, the corresponding mixtures of $P(OPh)_3$ with the anionic counterparts **A1** and **A3** showed increased amounts of the hetero complexes [Rh(cod)**LL***] close to 75%, thus corresponding to a ratio of 1:6:1. The ^{31}P NMR spectrum obtained for the binary mixture of $P(OPh)_3$ (**N8**) and the anionic phosphite **A1** is shown in Figure 2.

Table 9. Hydrogenation of **13** with binary mixtures of ligands.



13

Entry	L^1	L^2	Solvent	L^1+L^2 Conv. [%][a]	L^1+L^2 *ee* [%][b]	L^1+L^1 Conv. [%][a]	L^1+L^1 *ee* [%][b]
1	**N3**	$P(OPh)_3$	CH_2Cl_2	33	75 (−)	80	47 (−)
2	**A2**	$P(OPh)_3$	CH_2Cl_2	26	29 (+)	45	24 (+)
3	**N2**	**N4**	CH_2Cl_2	83	52 (−)	19	27 (−)
4	**N3**	**N4**	CH_2Cl_2	96	53 (−)	80	47 (−)
5	**A2**	**N4**	CH_2Cl_2	88	68 (−)	45	24 (+)
6	**N2**	**A6**	CH_2Cl_2	95	40 (−)	19	27 (−)
7	**N3**	**A6**	CH_2Cl_2	88	66 (−)	80	47 (−)
8	**A2**	**A6**	CH_2Cl_2	60	42 (−)	45	24 (+)
9	**N2**	**A6**	EtOAc	24	41 (−)	43	9 (−)
10	**A3**	**A6**	EtOAc	24	25 (−)	>99	20 (−)
11	**N2**	PPh_3	EtOAc	98	18 (+)	43	9 (−)
12	**A3**	$P(OPh)_3$	EtOAc	30	52 (−)	>99	20 (−)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by HPLC on a chiral stationary phase.

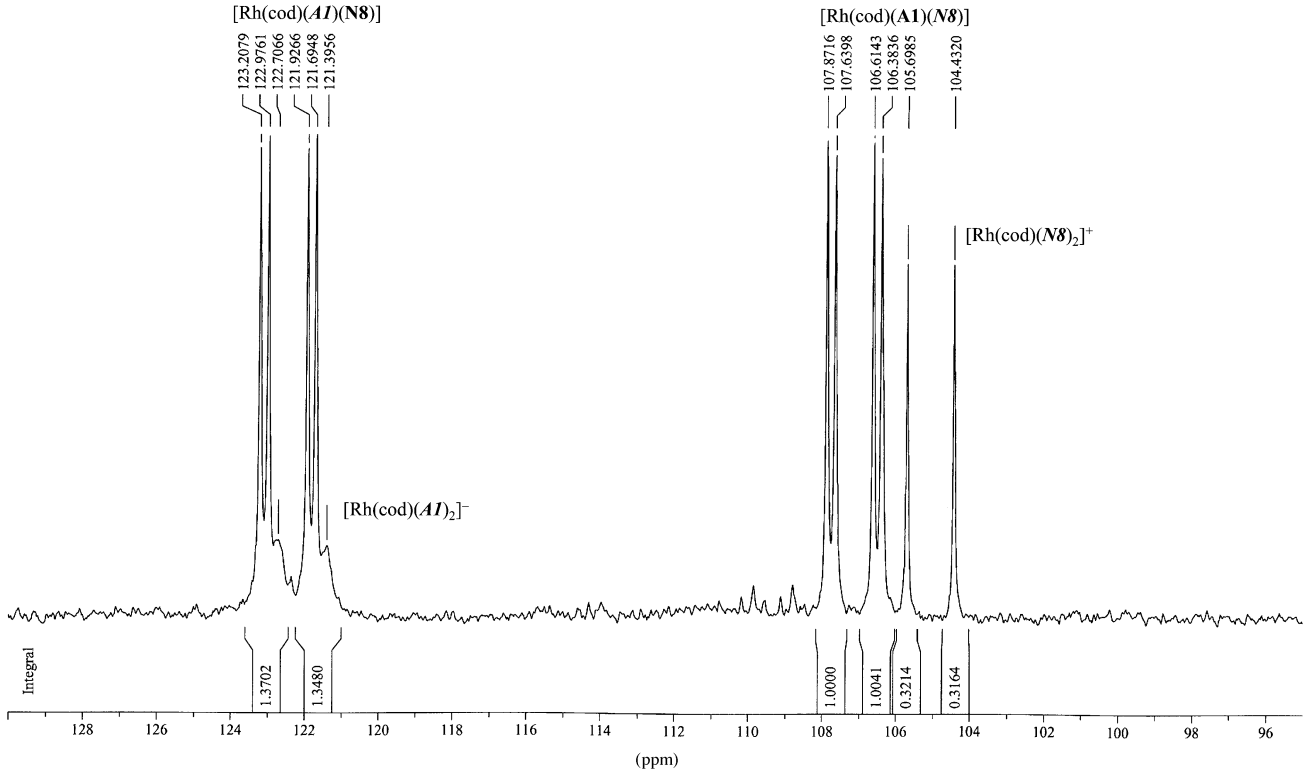
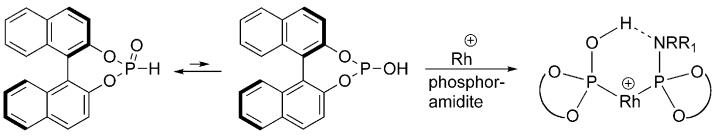


Figure 2. $^{31}P\{^1H\}$ NMR spectrum obtained after mixing $[Rh(cod)_2]BF_4$ (6 μmol), $P(OPh)_3$ (**N8**; 6 μmol) and **A1** (6 μmol) in CD_2Cl_2 at 295 K: $\delta = 122.5$ (dd, $^1J_{PRh} = 259$, $^2J_{PP} = 47$ Hz; $Rh(P^{A1})(P^{N8})$), 122.1 (d, $^1J_{PRh} = 265$ Hz; $Rh(P^{A1})_2$), 107.1 (dd, $^1J_{PRh} = 254$, $^2J_{PP} = 47$ Hz; $Rh(P^{A1})(P^{N8})$), 105.1 ppm (d, $^1J_{PRh} = 257$ Hz; $Rh(P^{N8})_2$).

These results confirm our expectation that the use of an anionic ligand in combination with a neutral ligand favors the formation of the mixed bis-ligand complex over the corresponding homo-ligand complexes. However, a word of caution should be added: Because the catalytic activities of the homo- and hetero-ligand complexes can differ quite substantially, a higher proportion of the hetero-ligand complex does not necessarily mean that the reaction is predominantly catalyzed by this species.

Binary mixtures of phosphorous acid diesters and phosphoramidites: Phosphoric acid diesters exist in two tautomeric forms in solution, that is, a P^V oxoform, which according to IUPAC recommendations is called a phosphonic acid diester, and a P^{III} hydroxy species. The trivalent hydroxy tautomer usually binds to transition metals through the phosphorus atom, thus forming a complex with the structural subunit $(ArO)_2P(OH)$. The hydroxy function can form a hydrogen bond within the metal complex that comprises a properly chosen second ligand with a hydrogen-acceptor group, such as, for example, a phosphoramidite moiety. Therefore, the combination of a phosphoric acid diester with a phosphoramidite species is expected to preferentially form the corresponding mixed-ligand complex (Scheme 7).

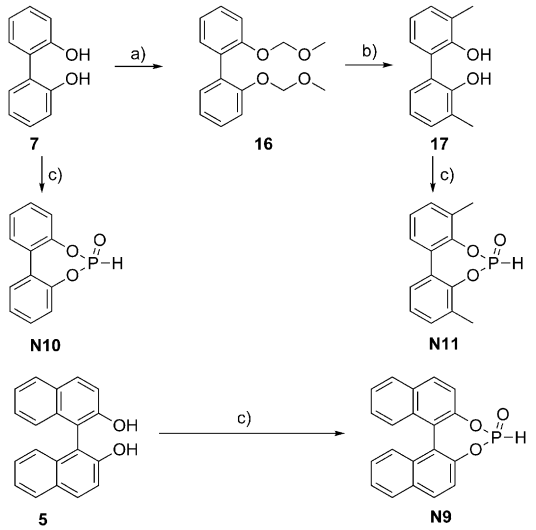
To explore binary ligand mixtures of this type, a set of four phosphonic acid diesters was prepared, namely, both enantiomers of BINOL-P(O)H (**N9**)[17] and two achiral biphenol-based ligands **N10**[14b] and **N11**. These compounds



Scheme 7. Formation of rhodium complexes from binary mixtures of phosphoric acid diesters and phosphoramidites.

were readily synthesized as shown in Scheme 8. Protection of biphenol (**7**) as the corresponding MOM ether **16**, subsequent introduction of the methyl substituents, and deprotection provided the sterically more demanding derivative **17**.[18] Finally, the diols were transformed into the corresponding chlorophosphanes and converted into the phosphoric acid diesters **N9**–**N11** by the addition of *t*BuOH.[17]

With these ligands in hand, the rhodium complexes obtained from mixtures of phosphoric acid diesters **N9**–**N11** with BINOL-based ligands **N1**–**N3** and **A1**–**A3** were investigated by ^{31}P NMR spectroscopy to determine the ratios between the homo- and hetero-ligand complexes. By using (*R*)-**N9** as a potential hydrogen-donor ligand, only the combination with **A3** led to a moderate increase in the proportion of the hetero complex (68%). In contrast, the combination of the *R*-configured piperazine-derived phosphoramidites **N3** and **A3** with (*S*)-**N9** resulted in the exclusive formation of the corresponding hetero complexes (Figure 3). For other combinations of (*S*)-**N9** with phosphites **N1** or **A1** or phosphoramidites **N2** or **A2**, the preference for the



Scheme 8. Preparation of phosphoric acid diesters **N9**–**N11**. Reagents and conditions: a) NaH; THF, 0 °C→rt, 75 min, then MOMCl, 0 °C→rt, 16 h (60 %); b) *n*BuLi, THF, rt, 1 h, then MeI, rt, 1 h, then Amberlyst 15, THF/MeOH (1:1), Δ, 17 h (54 %); c) PCl_3, NEt_3, toluene/THF (10:1), 0 °C→rt, 1 h, then *t*BuOH, toluene, 0 °C→rt, 2 h (41–53 %). MOMCl = methoxymethyl chloride.

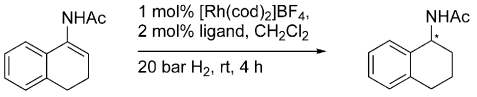
hetero complex was less pronounced. Apparently, the mixture of (*R*)-**N9** and phosphoramidite **A3** seems to represent the mismatched combination with respect to thermodynamic stability, whereas the mixture of (*S*)-**N9** and **A3** corresponds to the matched case.

The achiral phosphoric acid diesters **N10** and **N11** also formed the corresponding hetero complexes quantitatively in combination with the neutral and anionic piperazine-derived phosphoramidites **N3** and **A3**. This outcome is illustrated by the ^{31}P NMR spectrum of the rhodium complex obtained from **A3** and **N11** (Figure 4).

The binary mixtures that had led to the quantitative formation of the hetero complexes were then applied to the hydrogenation of the demanding enamide substrates **12** and **13**. In the hydrogenation of substrate **12**, only the combination of ligand **A3** with (*S*)-**N9** led to a slight improvement of selectivity from 27 to 39 % *ee*, whereas all the other combinations gave lower or similar values relative to **N3** or **A3** alone (see the Supporting Information).

Much better results were obtained in the hydrogenation of the dihydronaphthalene derivative **13**. A significant increase in enantioselectivity to 91–97 % *ee* was achieved by using hetero complexes generated from the anionic ligand **A3** in combination with the neutral phosphoric acid diesters (*S*)-**N9**, **N10**, and **N11** relative to 76 % *ee* for the homoligand complex (Table 10, entries 5–7). The corresponding neutral ligand **N3** once again gave inferior results. Only the

Table 10. Application of binary mixtures of phosphoramidites **N3** and **A3** and phosphoric acid diesters **N9**–**N11** in the hydrogenation of **13** in CH_2Cl_2.



13

Entry	L^1	L^2	L^1+L^2 Conv. [%][a]	L^1+L^2 *ee* [%][b]	L^1+L^1 Conv. [%][a]	L^1+L^1 *ee* [%][b]
1	**N3**	(*S*)-**N9**	90	76 (−)	80	47 (−)
2	**N3**	**N10**	74	37 (−)	80	47 (−)
3	**N3**	**N11**	94	50 (−)	80	47 (−)
4	**A3**	(*R*)-**N9**	89	20 (−)	>99	76 (−)
5	**A3**	(*S*)-**N9**	>99	97 (−)	>99	76 (−)
6	**A3**	**N10**	>99	91 (−)	>99	76 (−)
7	**A3**	**N11**	>99	97 (−)	>99	76 (−)

[a] Conversions determined by GC analysis. [b] Enantioselectivities determined by HPLC on a chiral stationary phase.

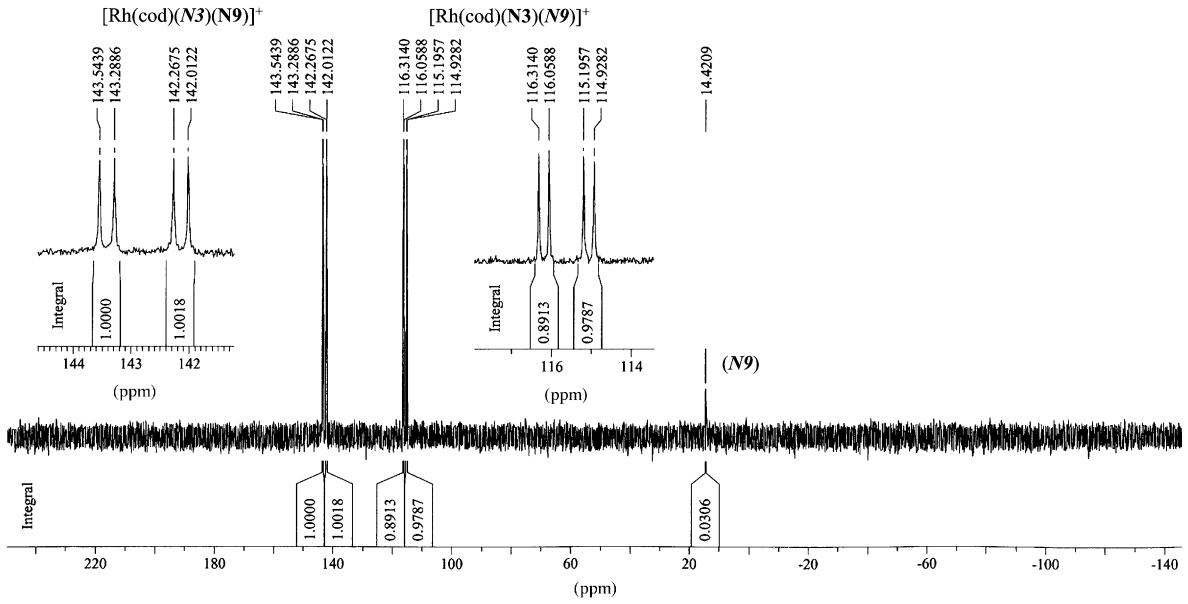


Figure 3. $^{31}P\{^1H\}$ NMR spectrum of the binary mixture of $[Rh(cod)_2]BF_4$ (6 μmol), (*S*)-**N9** (6 μmol), and **N3** (6 μmol) in CD_2Cl_2 at 295 K: $\delta = 142.8$ (dd, $^1J_{PRh} = 259$, $^2J_{PP} = 52$ Hz; Rh(P^{N3})(P^{N9})), 115.7 (dd, $^1J_{PRh} = 228$, $^2J_{PP} = 53$ Hz; Rh(P^{N3})(P^{N9})), 14.4 ppm (s; **N9**).

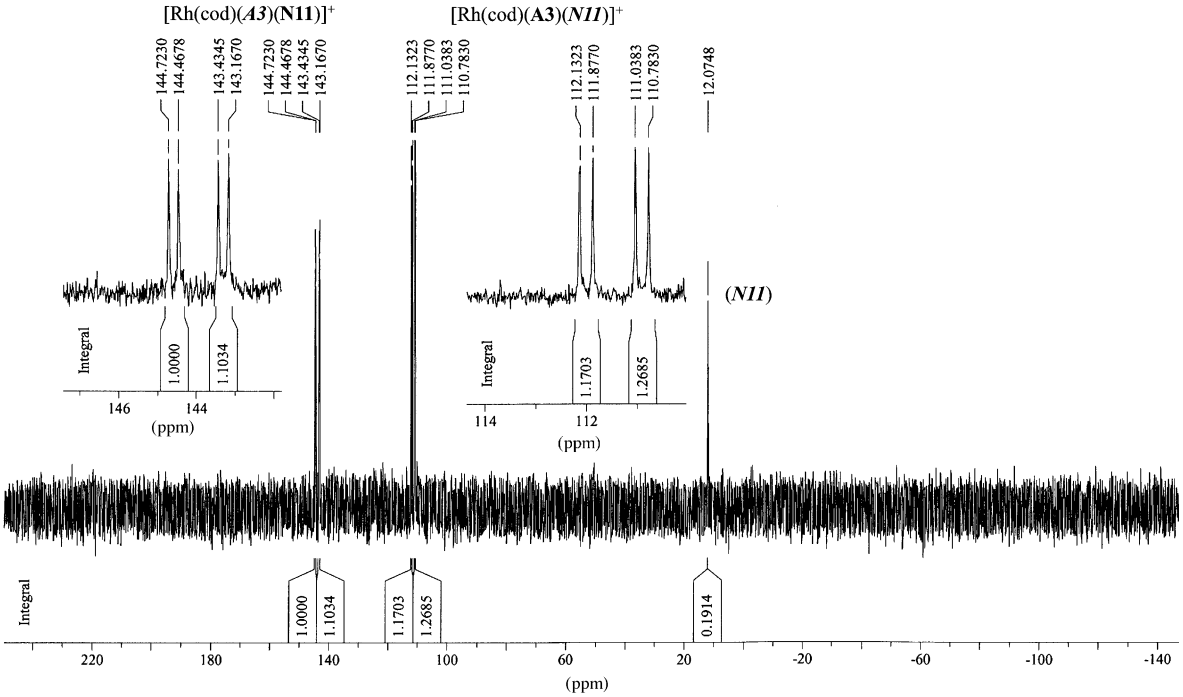


Figure 4. $^{31}P\{^1H\}$ NMR spectrum of the binary mixture of $[Rh(cod)_2]BF_4$ (6 μmol), **N11** (6 μmol), and **A3** (6 μmol) in CD_2Cl_2 at 295 K: $\delta = 143.9$ (dd, $^1J_{PRh} = 262$, $^2J_{PP} = 53$ Hz; $Rh(P^{A3})(P^{N11})$), 111.5 (dd, $^1J_{PRh} = 222$, $^2J_{PP} = 52$ Hz; $Rh(P^{A3})(P^{N11})$), 12.1 ppm (s; **N11**).

combination with (*S*)-**N9** led to a notable improvement from 47 to 76% *ee* in this case (Table 10, entry 1). Consistent with the results from the NMR spectroscopic studies, pronounced matched and mismatched effects were observed with (*R*)- and (*S*)-**N9**. In the case of ligand **A3**, the selectivity dropped from 97 to 20% *ee*, when (*R*)-**N9** was used instead of the *S* enantiomer (Table 10, entries 4 and 5).

The results obtained for combinations of phosphoric acid diesters with phosphoramidites are very promising. The strong preference for the formation of hetero- rather than homo-ligand complexes and the high enantioselectivities in the hydrogenation of enamide **13** indicate that mixtures of potential hydrogen-donor and -acceptor ligands of this type offer new possibilities for combinatorial-catalyst development.

Conclusion

With the incorporation of an anionic group in chiral monodentate phosphite and phosphoramidite ligands, we have added an additional structural feature that can have a distinct effect on the catalytic activity and enantioselectivity of a metal complex. When these ligands were tested in rhodium-catalyzed hydrogenation reactions, pronounced differences in enantiomeric excess and conversion were observed between anionic ligands and their neutral counterparts. Depending on the substrate, the ligand structure, and the solvent, the charge effects were either positive or negative, so no uniform trends could be discerned from the results. However, the high enantioselectivities induced by anionic ligands in some cases, indicate that the introduction of a negative charge may result in a useful diversification of monophosphane libraries.

Moreover, anionic ligands such as **A1**–**A3** offer new possibilities for catalyst preparation from binary mixtures of monodentate phosphanes. As we have shown in NMR studies, the combination of an anionic ligand with a neutral ligand can shift the equilibrium from the statistical distribution of complexes toward the hetero bis-ligand complex. This behavior may have a beneficial effect on the enantioselectivity, especially when a mixture of an achiral and a chiral ligand is used. Indeed, in the hydrogenation of substrates **9** and **10**, the combination of a neutral with an anionic phosphorus donor, one chiral and the other achiral, often furnished significantly better enantioselectivities than mixtures of two structurally analogous neutral ligands.

The formation of hetero bis-ligand complexes can be further promoted by a hydrogen bond between the two ligands. On the basis of this concept, we explored combinations of phosphoric acid diesters as hydrogen donors with phosphoramidites as hydrogen acceptors. Some of these ligand mixtures formed the hetero bis-ligand complex exclusively, as evidenced by NMR analysis, and also induced very high enantioselectivities in rhodium-catalyzed hydrogenation reactions that clearly exceeded the enantioselectivities of the corresponding homo bis-ligand complexes. By far the best results were obtained with the anionic phosphoramidite **A3** in combination with neutral phosphoric acid diesters (*S*)-**N9** or **N11**. Evidently, the combination of negatively charged and neutral monophosphanes with complimentary hydrogen-donor and -acceptor properties seems to be a strategy

with considerable potential for combinatorial-catalyst development.

Experimental Section

All the reactions were performed in flame-dried glassware under argon by using Schlenk techniques. The solvents, PCl_3, and NEt_3 were dried by using standard procedures in a nitrogen or argon atmosphere or by passage over a column of activated alumina under nitrogen (PureSolv, Innovative Technology Inc).[19,20] All the other commercial reagents were used as received. Deuterated solvents for NMR analysis were degassed by mean of three freeze/pump/thaw cycles, dried over 4 Å molecular sieves, and stored in argon. The solvents for the workup and the chromatographic purification of air-sensitive compounds were purged with a stream of argon for at least 15 min prior to use. Chromatographic separations were performed on silica gel 60 (Merck, Darmstadt; 40–63 nm). Precoated Macherey–Nagel Polygram SIL G/UV_{254} plates were used for TLC analysis, and the compounds were visualized with UV light.

NMR spectroscopic experiments were performed on Bruker Avance 400 or 500 spectrometers. The ^1H and ^{13}C spectra were referenced relative to $SiMe_4$ by using the solvent signals as internal standards.[21,22] The ^{31}P, ^{19}F, and ^{11}B spectra were calibrated with H_3PO_4 (85 wt%), $CFCl_3$, and $BF_3{\cdot}OEt_2$ as external standards. The term dm_c refers to a doublet of centered multiplets. Mass spectra were measured on VG70–250, Finnigan MAT 95Q (EI), Finnigan MAT 312, Finnigan MAR 8400 (FAB), or Finnigan MAT LCQ (ESI) spectrometers. Elemental analyses were performed by the Micro-Analysis Laboratory at the University of Basel. IR spectra were measured on a Perkin–Elmer 1600 FTIR spectrometer. Specific rotations were measured on a Perkin–Elmer 314 polarimeter. HPLC analyses were performed on a Shimadzu system and GC measurements on Carlo Erba Instruments. The abbreviation Ar_F refers to the 3,5-bis(trifluoromethyl)phenyl substituent.

Preparation of anionic secondary amine 4a: Piperazine (304 mg, 3.53 mmol, 4.00 equiv) was added to a solution of anionic benzyl bromide **2a** (1.00 g, 880 μmol, 1.00 equiv) in THF (5 mL). After stirring the mixture overnight (19 h) at room temperature, a solution of 1 M NaOH (20 mL) was added to the resulting colorless suspension, and the reaction mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with water (2×20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and evaporated. The product was obtained as a colorless solid, which was used without further purification (954 mg, 95%). ^1H NMR (400.1 MHz, $CDCl_3$, 300 K): $\delta=7.78$ (s, 6H; Ar_F-*o*-*H*), 7.48 (s, 3H; Ar_F-*p*-*H*), 3.65 (s, 2H; $ArCH_2$), 2.91 (m_c, 8H; $NCH_2CH_2CH_2CH_3$), 2.87 (d, $J=4.8$ Hz, 2H; $HN(CHH)_2$), 2.49 (s, 4H; $CH_2N(CH_2)_2$), 1.54 (s, 2H; $HN(CHH)_2$), 1.47 (m_c, 8H; $NCH_2CH_2CH_2CH_3$), 1.25 (sext, $J=7.4$ Hz, 8H; $NCH_2CH_2CH_2CH_3$), 0.89 ppm (t, $J=7.2$ Hz, 12H; $NCH_2CH_2CH_2CH_3$); $^{11}B\{^1H\}$ NMR (160.2 MHz, $CDCl_3$, 295 K): $\delta=-7.5$ ppm; $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 300 K): $\delta=134.1$ (Ar_F-*o*-*C*H), 128.8 (q, $J=31$ Hz; Ar_F-*m*-*C*), 124.7 (q, $J=273$ Hz; *C*F_3), 117.3 (m_c; Ar_F-*p*-CH), 111.2 (Ar-*p*-*C*), 58.9 ($NCH_2CH_2CH_2CH_3$), 53.7 ($CH_2N(CH_2)_2$), 49.9 (CH_2Ar), 46.2 ($HN(CH_2)_2$), 23.7 ($NCH_2CH_2CH_2CH_3$), 19.6 ($NCH_2CH_2CH_2CH_3$), 13.3 ppm ($NCH_2CH_2CH_2CH_3$); despite prolonged data acquisition, the signals for Ar-*i*-*C*, Ar-*o*-*C*, Ar-*m*-*C*, and Ar_F-*i*-*C* were not detected; $^{19}F\{^1H\}$ NMR (376.5 MHz, $CDCl_3$, 300 K): $\delta=-63.3$ (s, 18F; *C*F_3), −128.0 (dd, $J=25$, 14 Hz, 2F; Ar-*o*-*F*), −146.1 ppm (dd, $J=25$, 14 Hz, 2F; Ar-*m*-*F*); IR (KBr): $\tilde{\nu}=2973$, 2885, 1616, 1443, 1360, 1280, 1125, 1012, 887, 837, 713, 680 cm^{-1}; MS (ESI, CH_2Cl_2, 323 K): *m/z* (%): 897 (100) $[M-NBu_4]^-$; elemental analysis calcd (%) for $C_{51}H_{56}BF_{22}N_3$ (1139.79): C 53.74, H 4.95, N 3.69; found: C 53.98, H 4.90, N 3.63.

General procedure for the synthesis of monodentate phosphite and phosphoramidite ligands:[14] Triethylamine (2.20 equiv) and the amine or alcohol (1.10 equiv) were subsequently added to a solution of the respective phosphorochloridite (1.00 equiv) in THF (10 mL mmol^{-1}), toluene (40 mL mmol^{-1}), or Et_2O (10 mL mmol^{-1}) at 0 °C. The resulting colorless suspension was stirred at room temperature overnight. After filtration and washing of the remaining solid with THF, toluene, or Et_2O (10 mL), the filtrate was concentrated under reduced pressure and the product was purified by column chromatography.

The preparation of phosphoramidite A3: Compound **A3** was prepared according to the general procedure from phosphorochloridite **7** (328 mg, 925 μmol, 1.05 equiv), amine **4a** (954 mg, 836 μmol, 1.00 equiv), and NEt_3 (369 μL, 268 mg, 2.65 mmol, 3.00 equiv) in THF (15 mL). After purification by column chromatography (SiO_2, 3×11 cm, CH_2Cl_2/MeOH 25:1) **A3** was obtained as a colorless solid (1.08 g, 89%). $R_f=0.83$–0.44 (SiO_2, CH_2Cl_2/MeOH=25:1); $[\alpha]_D^{20}=-128.5$ ($c=0.930$, $CHCl_3$); ^1H NMR (400.1 MHz, CD_2Cl_2, 300 K): $\delta=8.00$ (d, $J=8.8$ Hz, 1H; Naph-*H*), 7.96–7.91 (m, 3H; Naph-*H*), 7.88 (s, 6H; Ar_F-*o*-*H*), 7.57 (s, 3H; Ar_F-*p*-*H*), 7.54 (d, $J=8.8$ Hz, 1H; Naph-*H*), 7.45–7.41 (m, 2H; Naph-*H*), 7.37 (d, $J=8.9$ Hz, 2H; Naph-*H*), 7.33 (d, $J=8.3$ Hz, 1H; Naph-*H*), 7.30–7.24 (m, 2H; Naph-*H*), 3.62 (s, 2H; $ArCH_2N$), 3.12–3.06 (m, 2H; $PN(CHH)_2$), 3.01 (br s, 2H; $PN(CHH)_2$), 2.90 (m_c, 8H; $NCH_2CH_2CH_2CH_3$), 2.38 (br s, 4H; $CH_2N(CH_2)_2$), 1.47 (m_c, 8H; $NCH_2CH_2CH_2CH_3$), 1.27 (sext, $J=7.4$ Hz, 8H; $NCH_2CH_2CH_2CH_3$), 0.91 ppm (t, $J=7.3$ Hz, 12H; $NCH_2CH_2CH_2CH_3$); $^{11}B\{^1H\}$ NMR (128.4 MHz, CD_2Cl_2, 295 K): $\delta=-8.1$ ppm; $^{13}C\{^1H\}$ NMR (100.6 MHz, CD_2Cl_2, 300 K): $\delta=161.1$ (dm_c, $J=60$ Hz; Ar_F-*i*-*C*), 149.7 (d, $J=4$ Hz; Naph-*C*), 149.6 (Naph-*C*), 148.2 (dm_c, $J=241$ Hz; Ar-*m*-*C*), 145.5 (dm_c, $J=244$ Hz; Ar-*o*-*C*), 134.1 (Ar_F-*o*-*C*H), 132.8 (Naph-*C*), 132.6 (Naph-*C*), 131.5 (Naph-*C*), 131.1 (Naph-*C*), 130.4 (Naph-*C*H), 130.3 (Naph-*C*H), 128.8 (q, $J=31$ Hz; Ar_F-*m*-*C*), 128.6 (Naph-*C*H), 128.6 (Naph-*C*H), 126.8 (Naph-*C*H), 126.7 (Naph-*C*H), 126.3 (Naph-*C*H), 126.3 (Naph-*C*H), 125.0 (Naph-*C*H), 124.8 (q, $J=272$ Hz; *C*F_3), 124.8 (Naph-*C*H), 124.1 (d, $J=5$ Hz; Naph-*C*), 122.7 (d, $J=2$ Hz; Naph-*C*), 122.2 (Naph-*C*H), 122.1 (Naph-*C*H), 117.4 (m_c; Ar_F-*p*-*C*H), 111.6 (t, $J=18$ Hz; Ar-*p*-*C*), 58.9 (t, $J=3$ Hz; $NCH_2CH_2CH_2CH_3$), 49.5 ($CH_2N(CH_2)_2$), 44.4 ($ArCH_2$), 44.3 ($PN(CH_2)_2$), 23.7 ($NCH_2CH_2CH_2CH_3$), 19.6 (t, $J=1$ Hz; $NCH_2CH_2CH_2CH_3$), 13.2 ppm ($NCH_2CH_2CH_2CH_3$); despite prolonged data acquisition time, the signal for Ar-*i*-*C* was not detected; $^{19}F\{^1H\}$ NMR (376.5 MHz, CD_2Cl_2, 300 K): $\delta=-63.7$ (s, 18F; *C*F_3), −128.6 (dd, $J=25$, 14 Hz, 2F; Ar-*o*-*F*), −146.8 ppm (dd, $J=24$, 14 Hz, 2F; Ar-*m*-*F*); $^{31}P\{^1H\}$ NMR (202.5 MHz, CD_2Cl_2, 295 K): $\delta=142.2$ ppm; IR (KBr): $\tilde{\nu}=3063$, 2971, 2882, 1615, 1441, 1359, 1279, 1126, 943, 680 cm^{-1}; MS (ESI, CH_2Cl_2, 323 K): *m/z* (%): 1211 (100) $[M-NBu_4]^-$; elemental analysis calcd (%) for $C_{71}H_{67}BF_{22}N_3O_2P$ (1454.06): C 58.65, H 4.64, N 2.89; found: C 58.77, H 4.59, N 2.92.

General procedure for the synthesis of phosphoric acid diesters:[17] A solution of the diol (1.00 equiv) in absolute toluene (3 mL mmol^{-1}) and a small amount of THF (<0.1 mL mmol^{-1}) to ensure solubilization was added dropwise to an ice-cooled solution of PCl_3 (2.00 equiv) and NEt_3 (3.00 equiv) in toluene (1.5 mL mmol^{-1}) over 30 min. The resulting yellow mixture was stirred for 1 h at room temperature and filtered through $MgSO_4$, and the filtrate was concentrated in high vacuum. The remaining colorless foam was redissolved in CH_2Cl_2 (2×5 mL), and the solvent was removed by evaporation twice. *t*BuOH (1.00 equiv) was added to the resulting phosphorochloridite dissolved in toluene (1 mL mmol^{-1}) at 0 °C, and the reaction mixture stirred for 2 h at room temperature. The precipitated product was collected by filtration and washed with pentane. The filtrate was concentrated, the crude product redissolved in toluene, and the ligand precipitated by addition of a triple volume of pentane. The product was obtained as a colorless solid after filtration.

Preparation of phosphoric acid diester (*S*)-N9: According to the general procedure, the PCl species was formed from PCl_3 (506 μL, 796 mg, 5.80 mmol, 2.00 equiv), NEt_3 (1.21 mL, 880 mg, 8.70 mmol, 3.00 equiv), and (*S*)-BINOL (830 mg, 2.90 mmol, 1.00 equiv) in toluene (5 mL) and THF (1.5 mL), filtered over $MgSO_4$, and transformed into the phosphonate by reaction with *t*BuOH (272 μL, 2.90 mmol, 1.00 equiv) in toluene (5 mL). Compound (*S*)-**N9** precipitated as a colorless solid from the reaction mixture and was washed with pentane after filtration (10 mL) to yield the product (510 mg, 53%). $[\alpha]_D^{20}=+673$ ($c=0.740$, $CHCl_3$); ^1H NMR (400.1 MHz, $CDCl_3$, 300 K): $\delta=8.07$ (d, $J=8.8$ Hz, 1H; Naph-*H*), 8.06 (d, $J=8.8$ Hz, 1H; Naph-*H*), 7.98 (d, $J=8.3$ Hz, 2H; Naph-*H*), 7.58 (d, $J=8.8$ Hz, 1H; Naph-*H*), 7.55–7.48 (m, 3H; Naph-*H*), 7.37–7.28

(m, 4H; Naph-*H*), 7.30 ppm (d, $J=734$ Hz, 1H; P(O)*H*); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$, 300 K): $\delta=145.8$ (d, $J=10$ Hz; Naph-*C*), 147.0 (d, $J=11$ Hz; Naph-*C*), 132.5 (Naph-*C*), 132.3 (Naph-*C*), 132.0 (d, $J=2$ Hz; Naph-*C*), 132.0 (d, $J=1$ Hz; Naph-*C*), 131.4 (Naph-*C*H), 131.4 (Naph-*C*H), 128.6 (Naph-*C*H), 128.6 (Naph-*C*H), 127.1 (Naph-*C*H), 127.1 (Naph-*C*H), 127.0 (Naph-*C*H), 126.9 (Naph-*C*H), 126.1 (Naph-*C*H), 126.0 (Naph-*C*H), 122.1 (d, $J=2$ Hz; Naph-*C*), 121.7 (d, $J=3$ Hz; Naph-*C*), 120.8 (d, $J=2$ Hz; Naph-*C*H), 120.2 ppm (d, $J=3$ Hz; Naph-*C*H); ^{31}P NMR (162.0 MHz, $CDCl_3$, 300 K): $\delta=14.4$ ppm (d, $J=733$ Hz); IR (KBr): $\tilde{\nu}=3509$, 3433, 3055, 1671, 1595, 1507, 1469, 1383, 1221, 1183, 1148, 1021, 815, 749 cm^{-1}; MS (EI, 70 eV): *m/z* (%): 332 (100) [M^+], 286 (10), 268 (78), 239 (53), 119 (12); elemental analysis calcd (%) for $C_{20}H_{13}O_3P$ (332.29): C 72.29, H 3.94; found: C 72.22, H 4.17.

General procedure for Rh-catalyzed hydrogenation reactions: The substrate (0.33 M, usually 200 μmol, 1.00 equiv), $[Rh(cod)_2]BF_4$ (0.010 equiv), and the monodentate ligand(s) (0.020 equiv in total) were dissolved in the desired solvent (usually 600 μL) in a 2 mL screw-cap vial equipped with a magnetic stirrer bar. Alternatively, stock solutions of $[Rh(cod)_2]BF_4$ and the olefin were sometimes used. Reactions in CH_2Cl_2, EtOAc, and toluene were set up in a glove box in a nitrogen atmosphere. Hydrogenation reactions in *i*PrOH were quickly set up in air. Four vials were transferred into a 50 mL autoclave, which was pressurized with hydrogen (usually 10–20 bar). The reaction was started by switching on the stirrer (700 min^{-1}). After the desired time, hydrogen was released and hexanes or pentanes (1 mL) added. The resulting mixture was filtered through a pad of silica gel, which was washed with hexanes/EtOAc or pentanes/EtOAc (1:1). The filtrate was concentrated under reduced pressure and the residue redissolved in Et_2O, pentane, or EtOH (3 mL). The conversion and enantioselectivity were directly determined by GC or HPLC analysis (see the Supporting Information).

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