Chiral Bicyclic Phosphoramidites— A New Class of Ligands for Asymmetric Catalysis

Oliver Huttenloch,[a] Jan Spieler,[b] and Herbert Waldmann*[a]

Abstract: The development of new ligands for catalytic asymmetric C–C bond formation is of great interest to organic synthesis. We describe here a new class of chiral phosphoramidites that embody one or two binaphthol units attached to an achiral azabicyclic [3.3.1] or [3.3.0] framework. These ligands were easily accessible from (*R*)-1,1′-binaphthyl-2,2′-dioxaphosphorchloridite (**4**) and the corresponding heterobicyclic core **1**, **2**, or **3**. They were employed in enantioselective Cu-catalyzed additions of different dialkylzinc reagents to cyclic and acyclic enones. The chiral ketones were obtained with an enantiomeric ratio up to 91:9. The choice of the best ligand proved to be strongly dependent on each substrate. In addition, ligand **6** was found to be the most suitable for Rh-catalyzed hydrogenations of α,β-unsaturated esters, giving rise to dimethyl 2-methylsuccinate and methyl *N*-acetylalaninate with enantiomer ratios up to 95:5.

Keywords: addition · asymmetric catalysis · heterocycles · hydrogenation · phosphoramidites

Introduction

The development of new methods for the enantioselective catalysis of widely applicable synthetic transformations like C–C bond formation and reduction reactions is at the heart of organic synthesis.[1] Of paramount importance to this field is the accessibility of efficient stereodirecting ligands that are readily available in both enantiomeric forms. Addressing this need, recently Feringa et al.[2] introduced chiral phosphoramidite ligands for the highly enantioselective copper-catalyzed conjugate addition[3] of dialkylzinc compounds to enones and α,β-unsaturated nitro compounds.[4] The combination of an axially chiral binaphthol with a bis(1-phenylethyl)amine proved to be particularly effective. A second example for the advantageous use of chiral phosphoramidites, in this case embodying a chirally modified quinoline backbone, was described by Leitner et al.[5] for the Rh-catalyzed hydrogenation of olefins such as methyl itaconate.

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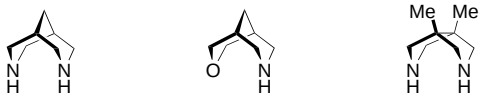
Results and Discussion

Herein we report on the development of a new class of chiral phosphoramidite ligands for asymmetric catalysis. These ligands incorporate an achiral bicyclic backbone, which determines their underlying structure, and either one or two amino groups. The heterocycle serves as basic framework to which phosphoric acid binaphthol esters are attached. The fine tuning of the heterocycle structure can serve to vary the spatial arrangement of the stereodirecting binaphthyl groups and to adapt the ligand structure to the requirements for highly enantioselective transformations of the varying substrates.

Compounds **1**–**3** were chosen as heterocyclic backbones. Bispidine **1**[6, 7] and the oxa-analogue **2**[8] were synthesized



1 **2** **3**

according to the convergent synthesis concept recently forwarded by us for the preparation of chiral amino alcohols embodying a bispidine framework.[6] Bicyclic diamine **3** was synthesized according to the literature.[9] C_2-symmetric phosphoramidites **5** and **6** were prepared with in situ generated phosphoric acid chloride **4**[2a] (Scheme 1) and isolated in pure form after chromatography on neutral alumina. Synthesis of ligand **7** required the use of isolated reagent **4**[10] at elevated

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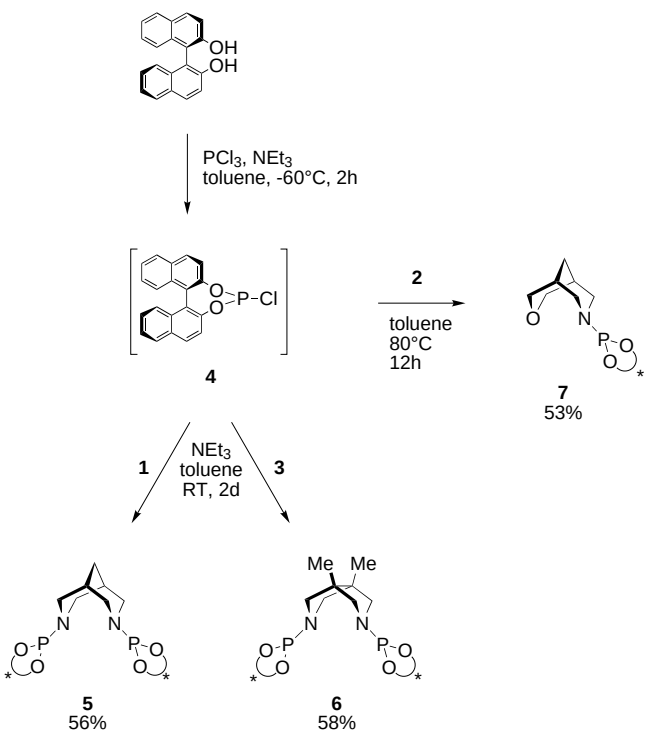


Scheme 1. Synthesis of ligands **5**–**7** with the coupling reagent **4**.

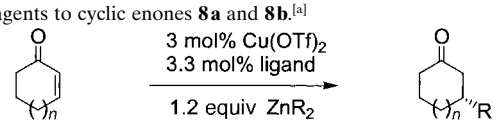
temperature and chromatography on magnesium silicate (Florisil). In line with observations of Feringa et al.,[2a,b] phosphorus(III) compounds **5**–**7** are surprisingly stable to oxygenation. However, they are acid-labile ruling out chromatographic separation on regular silica gel.

In a first set of experiments ligands **5**–**7** were used in the Cu-catalyzed conjugate addition of dimethyl- and diethylzinc to cyclohexenone (**8a**) and cycloheptenone (**8b**) (Table 1). To this end, a solution of the enone and the Cu/ligand complex was treated with a solution of the dialkylzinc reagent at $-30\,^{\circ}C$, and the enantiomer ratio of the addition product was determined by gas chromatography by employing a chiral stationary phase. The addition of dimethylzinc to cyclohexenone had to be carried out at $0\,^{\circ}C$, at $-30\,^{\circ}C$ no conversion was observed.

In the addition of diethylzinc to cyclohexenone, ligand **7** was clearly superior to C_2-symmetric bis(phosphoramidite) ligands **5** and **6** (Table 1, entries 1–3). For **5** and **6** only moderate stereoselectivity was observed, however, ligand **7** made the addition product **9a** available with an enantiomer ratio of 90:10, a result that is in the preparatively useful range. In the addition of dimethylzinc to cyclohexenone, however, C_2-symmetric ligand **5** was the best giving rise to the desired product with a selectivity of 91:9 (Table 1, entries 4 and 5). The addition of this zinc reagent to cycloheptenone in the presence of bis(phosphoramidite) **5** proceeded with very comparable results (Table 1, entry 6).

In a second series the addition of zinc reagents to an acyclic enone, namely chalcone **10** was investigated (Table 2). In the addition of diethylzinc to chalcone, bispidine-derived bis(phosphoramidite) **5** proved to be the best ligand. However, for non-C_2-symmetric ligand **7** a similar result was recorded

Table 1. Cu-catalyzed enantioselective 1,4-addition of different dialkylzinc reagents to cyclic enones **8a** and **8b**.[a]



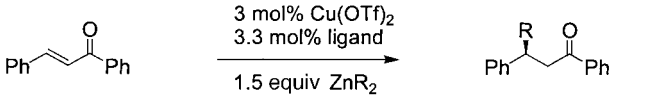
8a: $n = 1$
8b: $n = 2$

9a: $n = 1$, R = Et
9b: $n = 1$, R = Me
9c: $n = 2$, R = Me

Entry	Ligand	Substrate	R	Yield [%][b]	Enantiomer ratio[c]
1	**5**	**8a**	Et	96	78:22
2	**6**	**8a**	Et	93	73:27
3	**7**	**8a**	Et	94	90:10
4	**5**	**8a**	Me	91	91:9[d]
5[e]	**7**	**8a**	Me	67	74:26[d]
6	**5**	**8b**	Me	89	91:9

[a] All reactions were carried out in toluene/CH_2Cl_2 (6/1) at $-30\,^{\circ}C$ for 3 h in the presence of $Cu(OTf)_2$ (3 mol%) and ligand (3.3 mol%) unless otherwise indicated. Dialkylzinc solution was added within 5 min to a catalyst/substrate mixture. [b] Yield of isolated product after chromatography on silica gel. [c] Determined by gas chromatographic analysis using a capillary column (Lipodex E, Macherey&Nagel), in all cases the *R* enantiomer was formed predominantly. [d] Determined by gas chromatographic analysis using a capillary column (Lipodex E, Macherey&Nagel) using the D-(−)-2,3-butandiol acetal of **9b**. [e] Reaction temperature $0\,^{\circ}C$.

Table 2. Cu-catalyzed enantioselective 1,4-addition of different dialkylzinc reagents to chalcone **10**.[a]



10

11a : R = Et
11b : R = Bu

Entry	Ligand	R	T [°C]	Yield [%][b]	Enantiomer ratio[c]
1[d]	**5**	Et	−15	98	89:11
2[d]	**6**	Et	−15	98	79:21
3[d]	**7**	Et	−15	97	87:13
4[e]	**5**	Bu	−30	99	80:20
5[e]	**6**	Bu	−30	97	80:20
6[e]	**7**	Bu	−30	97	91:9

[a] All reactions were carried out in toluene/CH_2Cl_2 (4/1) at the indicated temperature for 3 h in the presence of $Cu(OTf)_2$ (3 mol%) and ligand (3.3 mol%). [b] Yield of isolated product after chromatography on silica gel. [c] Determined by HPLC using a Daicel Chiracel OD, in each case the *S* enantiomer of **11** was formed predominantly. [d] Diethylzinc solution was added within 5 min at $-15\,^{\circ}C$ to a catalyst/chalcone mixture. [e] Chalcone **10** was added within 1 h at the indicated reaction temperature to the catalyst/dibutylzinc solution.

(Table 2, entries 1–3). If dibutylzinc was employed, ligand **7** delivered the most advantageous results (Table 2, entries 4–6).

From the results detailed in Tables 1 and 2 a clear trend in favor of one of the three ligands cannot be delineated. Rather, it appears that the substrates and reagents need a fine tuning of ligand structure with respect to the precise structure of the bicyclic framework and the presence of one or two stereodirecting binaphthol units.

We would like to stress, however, that in the reactions with both the cyclic and the acyclic enones the zinc reagent attacks the β-carbon atom of the double bond from the *Re* face (*Re*

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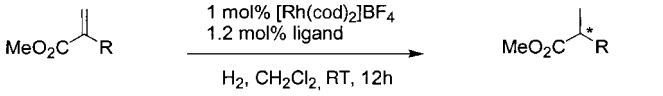
with respect to the β-carbon atom). This result differs from the observations made for the phosphoramidite ligands developed by Feringa et al.,[2e] for which a change in face-selectivity occurs. We assume that this property is imposed on our ligands by the presence of the bicyclic backbone. Evidently, the preorganization of the reactants and the ligand in the transition state is primarily determined by the steric influence of the bicyclic framework of the ligands, whereas the efficiency of the stereoselection is due to fine tuning of ligand structure. This finding indicates that our original intention (vide supra) is met by ligands **5**–**7** and clearly distinguishes this class of phosphoramidites from the ligands introduced by Feringa et al.

In order to demonstrate whether the chiral bicyclic phosphoramidites may also serve as efficient ligands in different types of reactions, the Rh-catalyzed enantioselective hydrogenation of α,β-unsaturated esters was investigated. To this end, dimethyl itaconate and methyl acetamidoacrylate were hydrogenated (Table 3). For the itaconate **12a** C_2-symmetric bicyclic ligand **6** showed the best results yielding the desired product **13a** with an enantiomer ratio of 95:5. In addition, methyl *N*-acetylalaninate (**13b**) was obtained with useful stereoselectivity. In this case the enantiomer ratio could be raised substantially by increasing the hydrogen pressure.

Table 3. Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate (**12a**) and 2-acetamido methyl acrylate (**12b**).[a]



12a: R = CH_2CO_2Me **13a:** R = CH_2CO_2Me
12b: R = NHAc **13b:** R = NHAc

Entry	Ligand	Substrate	$p(H_2)$ [bar]	Conversion [%][b]	Enantiomer ratio
1	**5**	**12a**	1.3	>99	77:23[c]
2	**6**	**12a**	1.3	>99	95:5[c]
3	**7**	**12a**	1.3	5	89:11[c]
4	**6**	**12a**	20	>99	95:5[c]
5	**6**	**12b**	1.3	98[d]	90:10
6	**6**	**12b**	20	97[d]	93:7

[a] All reactions were carried out in CH_2Cl_2 at room temperature for 12 h under the indicated pressure in the presence of $[Rh(cod)_2]BF_4$ (1 mol%) and ligand (1.2 mol%), c(substrate) = 0.05 mol L^{-1}. [b] Determined by gas chromatographic analysis. [c] Determined by gas chromatographic analysis using a capillary column (Lipodex E, Macherey&Nagel), in all cases the *R* enantiomer was formed predominantly. [d] Yield of isolated product after chromatography on silica gel.

Conclusion

We have developed a new set of chiral phosphoramidite ligands embodying one or two binaphthol units attached to an achiral azabicyclic [3.3.1] or [3.3.0] framework. These ligands were successfully employed in enantioselective Cu-catalyzed conjugate additon reactions of different dialkylzinc reagents to cyclic and acyclic enones. The *Re* face selectivity of our ligands differs from observations made by Feringa et al.[2e] Moreover the same class of ligands could be applied for the highly enantioselective Rh-catalyzed hydrogenation of α,β-unsaturated esters. The performance of each ligand is dependent on the type of substrate as well as the metal catalyst employed.

Experimental Section

General remarks: Melting points were determined in open capillaries by using a Büchi 535 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 250, AM 400, or DRX 500 spectrometer at room temperature. IR spectra were recorded on a Bruker IFS 88 spectrometer. Mass spectra, high-resolution mass spectra (HRMS), and fast-atom bombardment mass spectra (FAB) were measured on a Finnigan MAT MS70 spectrometer. Specific optical rotation values were determined with a Perkin-Elmer polarimeter 241. High-performance liquid chromatography (HPLC) was performed with a Merck Hitachi instrument equipped with a L-3000 diode array detector and for all gas chromatography a Hewlett Packard 5890 Series II gas chromatograph was used.

Materials: Solvents were dried by standard methods and used immediately or stored over molecular sieves. For hydrogenation, solvents were degassed by freezing in vacuo. For column chromatography silica gel (40–60 μm, Baker or Fluka), neutral alumina (Fluka), or Florisil (Fluka) were used. Commercial reagents were used without further purification except for PCl_3 which was distilled. (*R*)-1,1′-Binaphthyl-2,2′-diol was purchased from Merck, dibutylzinc (1.1M in heptane) and diethylzinc (1.1M in toluene) were purchased from Fluka and dimethylzinc (2M in toluene) was purchased from Aldrich. Pd/C (10%) was donated by Degussa-Hüls AG. 3,7-Diazabicyclo[3. 3.1]nonane (**1**)[6, 7], 1,5-dimethyl-3,7-diazabicyclo[3. 3.0]octane (**3**),[9] and (*R*)-1,1′-binaphthyl-2,2′-dioxaphosphorchloridite (**4**)[10] were prepared according to literature methods.

3-Benzyl-3-aza-7-oxabicyclo[3.3.1]nonane (14):[8] A solution of benzylamine (9.7 mL, 89 mmol), tetrahydropyran-4-one (**6**) (8.3 mL, 89 mmol), and acetic acid (5.1 mL, 89 mmol) in MeOH (80 mL) was added over a period of 1 h to a suspension of paraformaldehyde (5.6 g, 186 mmol), acetic acid (5.1 mL, 89 mmol) and concentrated HCl (2 mL, 25 mmol) in MeOH (80 mL) at 65 °C, and stirred for 6 h. After evaporation of the solvent, water (200 mL) was added and the pH was adjusted to 10 with 20% KOH. The aqueous phase was extracted with diethyl ether (4 × 100 mL) and the combined organic layers were dried over Na_2SO_4. Concentration in vacuo yielded a viscous yellow oil which was used without further purification in the next step. KOH (30.3 g, 0.54 mol) was added to a solution of the Mannich product and hydrazine monohydrate (21.9 mL, 0.45 mol) in diethylene glycol (300 mL). The mixture was stirred for 3 h at 140 °C. After removing the hydrazine and water by distillation at 200 °C, cooling the reaction mixture to room temperature and addition of water (300 mL), the aqueous phase was extracted with diethyl ether (4 × 100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. Distillation under reduced pressure yielded a colorless oil. Yield: 12.95 g, 59.6 mmol, 67%; b.p. 87 °C ($p = 5 \times 10^{-1}$ mbar); ^1H NMR (250 MHz, $CDCl_3$): $\delta = 7.42-7.18$ (m, 5H; arom. CH), 3.93 (d, $^2J = 10.7$ Hz, 2H; OCH_{2eq}), 3.78 (d, $^2J = 10.7$ Hz, 2H; OCH_{2ax}), 3.51 (s, 2H; CH_2Ph), 2.96 (d, $^2J = 11.8$ Hz, 2H; NCH_{2eq}), 2.24 (d, $^2J = 11.8$ Hz, 2H; NCH_{2ax}), 1.84–1.53 (m, 4H; C*H*CH_2, CH_2-bridge).

3-Aza-7-oxabicyclo[3.3.1]nonane (2): Pd/C (10%, 4 g) was added to a solution of 3-benzyl-3-aza-7-oxabicyclo[3.3.1]nonane (**14**) (12.9 g, 59.4 mmol) and acetic acid (17.4 mL, 0.3 mol) in MeOH (50 mL). The resulting suspension was stirred at room temperature overnight under an atmosphere of hydrogen. After filtration through Celite and concentration in vacuo, water (50 mL) was added. The pH of the aqueous phase was adjusted to pH 14 with 20% KOH under ice bath cooling and the aqueous phase was extracted with CH_2Cl_2 (4 × 100 mL). After drying the combined organic layers over Na_2SO_4 and evaporation of the solvent under reduced pressure the residue was purified by Kugelrohr distillation. Yield: 6.86 g, 53.9 mmol, 91%; m.p. 64 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.03-3.98$ (m, 2H; OCH_{2eq}), 3.85–3.82 (m, 2H; OCH_{2ax}), 3.18–3.13 (m, 2H; NCH_{2eq}), 3.04–2.98 (m, 2H; NCH_{2ax}), 2.76 (br s, 1H; NH), 1.97–1.88 (m, 2H; CH_2CH), 1.46–1.44 (m, 2H; CH_2-bridge); ^{13}C NMR (125.7 MHz,

$CDCl_3$): $\delta = 73.29$ (OCH_2), 51.69 (NCH_2), 32.00 (CH_2-bridge), 30.11 (CH); IR (drift): $\tilde{\nu} = 3346$ (NH), 2903, 2848 (Bohlmann-band),[11] 1559 (NH), 1456, 1415, 1326, 1264, 1198, and 1100 (OCH_2), 853 cm^{-1}; MS (70 eV); *m/z* (%): 127 (72) [M^+], 126 (13) [$M^+ - H$], 106 (11), 96 (11), 94 (11), 83 (13), 82 (26) [$M^+ - C_2H_5O$], 70 (13), 69 (11), 68 (23), 67 (23), 57 (16), 44 (100), 43 (53), 42 (29) [$C_2H_4N^+$], 39 (19); HRMS (70 eV) calcd for $C_7H_{13}NO$: 127.0997, found: 127.0973.

General procedure for the synthesis of the C_2-symmetric ligands 5 and 6: A solution of (*R*)-1,1′-binaphthyl-2,2′-diol (1.29 g, 4.5 mmol) (**4**) in hot toluene (50 mL)[2e] was added over a period of 30 min to a solution of freshly destilled PCl_3 (390 μL, 4.5 mmol) and NEt_3 (1.32 mL, 9.5 mmol) in toluene (8 mL) at $-60\,^{\circ}C$. The mixture was stirred for 2 h at $-60\,^{\circ}C$ and 15 min at room temperature. After cooling to $-40\,^{\circ}C$ a solution of the bicyclic amine (**1** or **3**) (2 mmol) and NEt_3 (0.63 mL, 4.5 mmol) in toluene (2 mL) was added. The suspension was stirred at room temperature for two days. After filtration through Celite and evaporation of the solvent under reduced pressure the residue was purified by flash chromatography on neutral alumina [2% NEt_3 in *n*-hexane/CH_2Cl_2, 2:1 (v/v)].

3,7-Bis[(*R*)-1,1′-binaphthyl-2,2′-dioxaphosphepinyl]-3,7-diazabicyclo[3.3.1]-nonane (5): Yield: 0.85 g, 1.12 mmol, 56%; m.p. 220 °C (decomp); $[\alpha]_D^{20} = -698.5$ ($c = 1$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.01$ (d, $^3J = 8.8$ Hz, 2H; arom. CH), 7.95 (d, $^3J = 8.1$ Hz, 2H; arom. CH), 7.89–7.81 (m, 4H; arom. CH), 7.78 (d, $^3J = 8.8$ Hz, 2H; arom. CH), 7.44–7.33 (m, 8H; arom. CH), 7.28–7.17 (m, 6H; arom. CH), 3.58–3.51 (m, 2H; NCH_{2eq}), 3.39 (d, $^2J = 12.9$ Hz, 2H; NCH_{2eq}), 3.15 (d, $^2J = 15.7$ Hz, 2H; NCH_{2ax}), 2.45 (d, $^2J = 12.7$ Hz, 2H; NCH_{2ax}), 1.69–1.67 (m, 2H; NCH_2CH), 1.35–1.33 (m, 2H; CH_2-bridge); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta = 150.49$, 149.92, 132.94, 132.61, 131.30, 130.73 (arom. C), 130.15, 129.97, 128.32, 128.28, 127.03, 126.90, 126.04, 125.99, 124.71, 124.46 (arom. CH), 123.19, 122.37 (arom. C), 122.17 (arom. CH), 49.54, 49.11, 46.38, 46.11 (NCH_2), 32.49 (CH_2-bridge), 27.27 (NCH_2CH); ^{31}P NMR (202.5 MHz, $CDCl_3$) $\delta = 148.06$; IR (drift): $\tilde{\nu} = 3058$, 2927, 2838 (Bohlmann band),[11] 1619, 1590, 1507, 1464, 1330, 1233 (PO), 1216 (PO), 1148, 1064, 978, 949, 824, 752, 696, 680, 617 cm^{-1}; HR-FAB (3-nitrobenzyl alcohol (3-NBA)) calcd for $C_{47}H_{37}N_2O_4P_2$: 755.2229, found: 755.2203.

1,5-Dimethyl-3,7-bis[(*R*)-1,1′-binaphthyl-2,2′-dioxaphosphepinyl]-3,7-diazabicyclo-[3.3.0]octane (6): Yield: 0.89 g, 1.16 mmol, 58%; m. p. 168 °C; $[\alpha]_D^{20} = -459.6$ ($c = 1$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.01$ (d, $^3J = 8.8$ Hz, 2H; arom. CH), 7.94 (d, $^3J = 8.1$ Hz, 2H; arom. CH), 7.82 (d, $^3J = 8.1$ Hz, 2H; arom. CH), 7.71 (d, $^3J = 8.8$ Hz, 2H; arom. CH), 7.60 (d, $^3J = 8.7$ Hz, 2H; arom. CH), 7.46 (d, $^3J = 8.5$ Hz, 2H; arom. CH), 7.44–7.40 (m, 6H; arom. CH), 7.37 (d, $^3J = 8.3$ Hz, 2H; arom. CH), 7.32–7.23 (m, 4H; arom. CH), 3.27 (dd, $^2J = 10.6$ Hz, $^4J = 2.7$ Hz, 2H; NCH_2), 3.01 (dd, $^2J = 10.6$ Hz, $^4J = 5.2$ Hz, 2H; NCH_2), 2.97 (dd, $^2J = 10.5$ Hz, $^4J = 3.1$ Hz, 2H; NCH_2), 2.69 (dd, $^2J = 10.5$ Hz, $^4J = 3.7$ Hz, 2H; NCH_2), 0.87 (s, 6H; CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 149.88$, 149.66, 132.86, 132.58, 131.37, 130.76 (arom. C), 130.29, 129.87, 128.38, 126.99, 126.92, 126.10, 126.08, 124.77, 124.54 (arom. CH), 123.93, 123.83 (arom. C), 122.12, 121.97 (arom. CH), 57.13, 57.03, 56.90, 56.76 (NCH_2), 50.46 (CCH_3), 19.07 (CH_3); ^{31}P NMR (202.5 MHz, $CDCl_3$) $\delta = 148.63$; IR (drift): $\tilde{\nu} = 3055$, 2967, 2870, 2410, 2183, 1904, 1619, 1591, 1507, 1464, 1328, 1232 (PO), 1205 (PO), 1066, 949, 824, 751, 697, 628 cm^{-1}; HR-FAB (3-NBA) calcd. for $C_{48}H_{38}N_2O_4P_2$: 769.2385, found: 769.2351.

3-[(*R*)-1,1′-Binaphthyl-2,2′-dioxaphosphepinyl]-3-aza-7-oxa-bicyclo[3.3.1]-nonane (7): A solution of (*R*)-1,1′-binaphthyl-2,2′-dioxaphosphorchloridite (**4**)[10] (0.77 g, 2.2 mmol) in toluene (2 mL) was added at room temperature to a solution of 3-aza-7-oxabicyclo[3. 3.1]nonane (**2**) (254 mg, 2 mmol) and NEt_3 (2.8 mL, 20 mmol) in toluene (2 mL). The resulting mixture was stirred at 80 °C overnight. After filtration through Celite and evaporation of the solvent under reduced pressure the residue was purified by flash chromatography on Florisil deactivated by NEt_3 [2% NEt_3 in *n*-hexane/CH_2Cl_2, 2:1 (v/v)]. Yield: 0.47 g, 1.06 mmol, 53%; m.p. 249 °C (decomp); $[\alpha]_D^{20} = -503.3$ ($c = 1$, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.96$ (d, $^3J = 8.8$ Hz, 1H; arom. CH), 7.92–7.89 (m, 3H; arom. CH), 7.58 (d, $^3J = 8.8$ Hz, 1H; arom. CH), 7.45–7.39 (m, 4H; arom. CH), 7.35 (d, $^3J = 8.5$ Hz, 1H; arom. CH), 7.30–7.22 (m, 2H; arom. CH), 3.97 (d, $^2J = 11.1$ Hz, 1H; OCH_{2eq}), 3.87 (d, $^2J = 11.1$ Hz, 1H; OCH_{2eq}), 3.75 (d, $^2J = 11.1$ Hz, 1H; OCH_{2ax}), 3.65 (d, $^2J = 11.1$ Hz, 1H; OCH_{2ax}), 3.63–3.58 (m, 1H; NCH_{2eq}), 3.41 (d, $^2J = 12.7$ Hz, 1H; NCH_{2eq}), 3.30 (d, $^2J = 13.0$ Hz, 1H; NCH_{2ax}), 2.72–2.66 (m, 1H; NCH_{2ax}), 1.87 (d, $^2J = 12.4$ Hz, 1H; CH_2-bridge), 1.76 (d, $^2J = 12.4$ Hz, 1H; CH_2-bridge), 1.64–1.61 (m, 1H; OCH_2CH), 1.38–1.35 (m, 1H; OCH_2CH); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 150.16$, 149.79, 132.80, 132.59, 131.32, 130.70 (arom. C), 130.14, 129.81, 128.32, 128.26, 126.97, 125.96, 125.93, 124.65, 124.46 (arom. CH), 123.89, 123.05 (arom. C), 122.41, 122.32 (arom. CH), 71.41, 71.05 (OCH_2), 49.55, 47.18 (NCH_2), 30.88 (CH_2-bridge), 29.20, 29.07 (OCH_2CH); ^{31}P NMR (202.5 MHz, $CDCl_3$) $\delta = 148.41$; IR (drift): $\tilde{\nu} = 3059$, 2941, 2928, 2842 (Bohlmann-band),[11] 2185, 1921, 1825, 1590, 1504, 1463, 1327, 1233 (PO), 1207 (PO), 1070, 1063, 952, 826, 791, 756 cm^{-1}; HR-FAB (3-NBA) calcd for $C_{27}H_{24}N_2O_4P_2$: 442.1572, found: 442.1588.

General procedure for the addition of dialkylzinc reagents to cyclic enones (9a, 9b, and 9c) in the presence of chiral ligands: A suspension of $Cu(OTf)_2$ (11 mg, 0.03 mmol) and the phosphoramidite (0.033 mmol) in toluene/CH_2Cl_2 = 6:1 (v/v) (3.5 mL) was stirred at room temperature for 1 h. The suspension was cooled to the indicated temperature and the substrate (1 mmol) was added. After addition of the dialkylzinc solution (1.2 mmol) the resulting mixture was stirred at that temperature for 3 h. The solution was poured onto saturated NH_4Cl and extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was carefully removed in vacuo. The residue was chromatographed on silica gel to yield the corresponding ketone. The enantiomeric ratio of **9a** and **9c** was determined by gas chromatography (capillary column: Machery&Nagel FS Lipodex E (0.25mm × 50 m)). For ketone **9b** the corresponding acetal with (D)-(−)-2,3-butanediol was used for GC analysis.

3-Ethylcyclohexanone (9a) (Table 1, entry 3): Yield: 94%; 79% *ee*, *R* enantiomer predominating; $R_f = 0.35$ [pentane/diethyl ether, 7:1 (v/v)]; $[\alpha]_D^{20} = +16.0$ ($c = 2.0$, $CHCl_3$, 79% *ee*) {ref. [12]: optical rotation positive for *R* enantiomer}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.48–2.18$ (m, 3H), 2.12–1.85 (m, 3H), 1.76–1.55 (m, 2H), 1.43–1.26 (m, 3H), 0.91 (t, $^3J = 9$ Hz, 3H; CH_3); GC (100 °C, isothermal): $t_R = 16.7$ min [*R* enantiomer], $t_R = 17.4$ min [*S* enantiomer].

3-Methylcyclohexanone (9b) (Table 1, entry 4): Yield: 91%; 81% *ee*, *R* enantiomer predominating; $R_f = 0.40$ [pentane/diethyl ether, 7:1 (v/v)]; $[\alpha]_D^{20} = +8.5$ ($c = 2.5$, $CHCl_3$, 81% *ee*) {ref. [13]: $[\alpha]_D^{28} = +11.7$ ($CHCl_3$ for *R* enantiomer)}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.42–2.17$ (m, 3H), 2.09–1.80 (m, 4H), 1.76–1.57 (m, 1H), 1.42–1.25 (m, 1H), 1.03 (t, $^3J = 7$ Hz, 3H; CH_3); GC (90 °C, isothermal, corresponding (D)-(−)-2,3-butanediol acetal): $t_R = 15.6$ min [*S* diastereomer], $t_R = 15.9$ min [*R* diastereomer].

3-Methylcycloheptanone (9c) (Table 1, entry 6): Yield: 89%; 82% *ee*, *R* enantiomer predominating; $R_f = 0.32$ [pentane/diethyl ether, 10:1 (v/v)]; $[\alpha]_D^{20} = +60.9$ ($c = 1.13$, $CHCl_3$, 82% *ee*) {ref. [14]: $[\alpha]_D^{25} = +55.2$ (MeOH for *R* enantiomer)}; ^1H NMR (250 MHz, $CDCl_3$): $\delta = 2.52–2.40$ (m, 4H), 1.96–1.82 (m, 4H), 1.70–1.57 (m, 1H), 1.49–1.22 (m, 2H), 1.00 (t, $^3J = 9$ Hz, 3H; CH_3); GC (100 °C, isothermal): $t_R = 17.4$ min [*S* enantiomer], $t_R = 18.1$ min [*R* enantiomer].

General procedure for the addition of dialkylzinc reagents to acyclic enones (11a and 11b) in the presence of chiral ligands

Method A: Addition of the zinc reagent to the catalyst/substrate mixture (Table 2, entries 1–3). A suspension of $Cu(OTf)_2$ (11 mg, 0.03 mmol) and the phosphoramidite (0.033 mmol) in toluene/CH_2Cl_2 (4:1; v/v) (4 mL) was stirred at room temperature for 1 h. The substrate (1 mmol) was added and the solution was cooled to $-15\,^{\circ}C$. After addition of the dialkylzinc solution (1.5 mmol) the resulting mixture was stirred at that temperature for 3 h. The suspension was poured onto 2 M HCl (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was chromatographed on silica gel [*n*-hexane/ethyl acetate, 30:1 (v/v)] to yield the corresponding 1,3-diphenyl ketone.

Method B: Addition of the substrate to a catalyst/dialkylzinc mixture (Table 2, entries 4–6). A suspension of $Cu(OTf)_2$ (11 mg, 0.03 mmol) and the phosphoramidite (0.033 mmol) in toluene/CH_2Cl_2 (4:1; v/v) (4 mL) was stirred at room temperature for 1 h. After cooling to $-30\,^{\circ}C$ the dialkylzinc solution (1.5 mmol) was added within 5 min. To this mixture was added over a period of 1 h a solution of the substrate (1 mmol) in toluene/CH_2Cl_2 (4:1; v/v) (1 mL). The resulting solution was stirred at that temperature for 3 h. The isolation and purification of the product was achieved following the procedure described above.

Enantiomeric ratios were determined by HPLC (column: DAICEL CHIRACEL OD, 0.2% *i*PrOH in *n*-hexane, flow rate 1.0 mL min^{-1}, UV detector (255 nm)).

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1,3-Diphenylpentan-1-one (11a) (Table 2, entry 1): Yield: 96%; 78% *ee*, *S* enantiomer predominating; $R_f = 0.24$ [*n*-hexane/ethyl acetate, 30:1 (v/v)]; $[\alpha]_D^{20} = +7.9$ ($c = 2.5$, EtOH, 78% *ee*) {ref. [15]: $[\alpha]_D^{20} = +10.5$ ($c = 2.5$, EtOH for *S* enantiomer}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.93-7.87$ (m, 2H; arom. CH), 7.55–7.50 (m, 1H; arom. CH), 7.45–7.39 (m, 2H; arom. CH), 7.31–7.15 (m, 5H; arom. CH), 3.28–3.20 (m, 3H; CH_2CO and CH-Ph), 1.83–1.54 (m, 2H; CH_2CH_3), 0.79 (t, $^3J = 7$ Hz, CH_3); HPLC: $t_R =$ 19.7 min [*S* enantiomer], $t_R = 24.2$ min [*R* enantiomer].

1,3-Diphenylheptan-1-one (11b) (Table 2, entry 6): Yield: 97%; 81% *ee*, *S* enantiomer predominating; $R_f = 0.15$ [*n*-hexane/ethyl acetate, 30:1 (v/v)]; m.p. 57 °C {ref. [16]: m.p. 58 °C}; $[\alpha]_D^{20} = +14.8$ ($c = 2.6$, CCl_4, 81% *ee*) {ref. [16]: $[\alpha]_D^{20} = -2.07$ ($c = 2.598$, CCl_4 for *R* enantiomer with 11% *ee*}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.94-7.88$ (m, 2H; arom. CH), 7.57–7.39 (m, 3H; arom. CH), 7.34–7.17 (m, 5H; arom. CH), 3.37–3.25 (m, 3H; CH, $CHCH_2CO$), 1.79–1.60 (m, 2H; $CHCH_2CH_2$), 1.35–1.08 (m, 4H; $CH_2CH_2CH_3$), 0.86 (d, $^3J = 8.6$ Hz, 3H; CH_3); HPLC: $t_R = 16.9$ min [*S* enantiomer], $t_R = 20.8$ min [*R* enantiomer].

General procedure for the rhodium-catalyzed hydrogenation of olefins: After stirring a solution of the chiral ligand (0.012 mmol) and $[Rh(cod)_2BF_4]$ (4 mg, 0.01 mmol) in degassed CH_2Cl_2 (2 mL) at room temperature for 30 min a solution of the respective substrate (1 mmol) in degassed CH_2Cl_2 (16 mL) was added. The resulting mixture was stirred at room temperature for 12 h under an atmosphere of hydrogen ($p = 1.3$ bar). In the case of high pressure hydrogenation the mixture was transferred by syringe into an autoclave previously purged with argon. The solution was stirred at room temperature for 12 h under an atmosphere of hydrogen ($p = 20$ bar). After evaporation of the solvent under reduced pressure the residue was purified by flash chromatography on silica gel. The enantiomeric ratio of **13a** was determined by gas chromatography (see above), whereas for **13b** the optical rotation value was used.

Dimethyl 2-methylsuccinate (13a) (Table 3, entry 4): Yield: 99%; 90% *ee*, *R* enantiomer predominating; $R_f = 0.26$ [*n*-hexane/ethyl acetate, 10:1 (v/v)]; $[\alpha]_D^{20} = +4.2$ ($c = 2.9$, $CHCl_3$, 52% *ee*) {ref. [17]: $[\alpha]_D^{20} = +4.8$ ($c = 2.3$, $CHCl_3$ for *R* enantiomer}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 3.69$ (s, 3H; OCH_3), 3.67 (s, 3H; OCH_3), 3.01–2.86 (m, 1H; CH), 2.75 (dd, $^2J = 16.5$ Hz, $^3J = 9.1$ Hz, 1H; CH_2), 2.41 (dd, $^2J = 16.5$ Hz, $^3J = 6.4$ Hz, 1H; CH_2), 1.21 (d, $^3J = 7.5$ Hz, 3H; $CHCH_3$); GC (85 °C, isothermal): $t_R = 22.6$ min [*S* enantiomer], $t_R = 23.5$ min [*R* enantiomer].

Methyl *N*-acetylalaninate (13b) (Table 3, entry 6): Yield: 97%; 86% *ee*, *R* enantiomer predominating; $R_f = 0.23$ [*n*-hexane/ethyl acetate, 4:1 (v/v)]; $[\alpha]_D^{20} = +7.8$ ($c = 1$, $CHCl_3$, 86% *ee*) {ref. [18]: $[\alpha]_D^{20} = -9.1$ ($c = 1$, $CHCl_3$ for *S* enantiomer}; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.08$ (br s, 1H; NH), 4.67–4.54 (m, 1H; CH), 3.76 (s, 3H; OCH_3), 2.02 (s, 3H; $C(O)CH_3$), 1.41 (d, $^3J =$ 6.4 Hz, 3H; $CHCH_3$).

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