Chiral Phosphites and Phosphoramidites Based on the Tropane Skeleton and Their Application in Catalysis

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A class of novel BINOL-containing tropanes was accessible by treating enantiopure (6*S*)-configured tropinone acetals **5a** and **8** with chlorophosphites **7**. When applied to Cu-catalyzed 1,4-additions of dialkylzinc to cyclic and acyclic enones **14** and **16**, the bidentate phosphoramidite (*S*,*S*)-**9a** bearing two (*S*)-binaphthol units worked selectively in most cases (up to 90% ee). (*S*,*S*)-**9a** was also superior to the other ligands in Rh-mediated hydrogenations of dimethyl itaconate **18** and methyl acetamidocinnamate **20** (85% ee and 95% ee). In both reactions, a matched/mismatched case was observed for (*S*,*S*)-**9a** and its congener (*R*,*R*)-**9a**.

Introduction

The Cu-catalyzed enantioselective conjugate addition of organozinc and organomagnesium reagents to α,β-unsaturated carbonyl compounds has been intensively investigated over the last couple of years.[1] Particularly phosphites,[2] aryldiphosphites,[3] phosphoramidites,[4] and *P*,*N*-ligands[5] have been successfully employed for this purpose. Unfortunately, the ligands developed so far are not universially suitable for all kinds of cyclic and acyclic enones with regard to yield and enantioselectivity. Thus, there is still a demand for new classes of ligands that might meet these requirements. Upon searching for suitable ligand scaffolds, we turned our attention to the tropane alkaloids.[6] In contrast to 2-azabicyclo[2.2.1]heptanes[7] and 2-azabicyclo[3.3.0]-octanes,[8] the corresponding tropanes, i.e., 8-azabicyclo[3.2.1]-octanes, have rarely been used as ligands for asymmetric catalysis. Armstrong reported the enantioselective epoxidation of alkenes catalyzed by 2-fluoro-*N*-carbethoxytropinones.[9] This lack of examples is surprising because tropane chemistry is well established.[10]

Recently, we have published the synthesis of tropinone derivatives such as **5a** via [4+3] cycloaddition of *N*-protected pyrrol **1** with tetrabromoacetone **2** followed by acetalization and enantioselective hydroboration[11] or alternatively starting from 2,5-dihydro-2,5-dimethoxyfurane **4** via a lipase-catalyzed resolution as the key step (Scheme 1).[12] As illustrated, the resulting tropinones **5a**,**b** provide at least three different positions for further manipulation toward a mono-, bi-, or tridentate phosphorus ligand, and the rigidity of the tropane scaffold is assumed to enhance the selectivity. Thus, tropinone derivatives seem to be promising candidates for ligand synthesis. Our attempts were further motivated by recent reports on phosphoramidites derived from bispidine, which gave good enantioselectivities in conjugate additions.[13] In the present paper we report the synthesis of chiral mono- and bidentate tropane ligands bearing phosphorus at the 6-hydroxy group and/or the *N*-bridge and their applications in conjugate additions and hydrogenations.

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(1) (a) Alexakis, A. *Methodologies in Asymmetric Catalysis*; ACS Symposium Series 880; American Chemical Society: Washington, DC, 2004; pp 43−59. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (c) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 224−258. Reviews: (d) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196. (e) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (f) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415.

(2) (a) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J.-M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011−4027. (b) Pamies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2007−2014. (c) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, *38*, 7745−7748. (d) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869−7872. (e) Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3193−3196. (f) Morimoto, T.; Mochizuki, N.; Suzuki, M. *Tetrahedron Lett.* **2004**, *45*, 5717−5722, and references therein.

(3) (a) Liang, L.; Au−Yeung, T. T.-L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799−3801. (b) Yan, M.; Zhou, Z.-Y.; Chan, A. S. C. *Chem. Commun.* **2000**, 115−116. (c) Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645−6648. (d) Yan, M.; Yang, L.-W.; Wong, K.-Y.; Chan, A. S. C. *Chem. Commun.* **1999**, 11−12.

(4) (a) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865−2878. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (d) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104−1105. (e) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem.* **1997**, *109*, 2733−2736; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620−2623.

(5) (a) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−781. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345. (c) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879−2888. (d) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem.* **1999**, *111*, 3720−3723; *Angew. Chem., Int. Ed.* **1999**, *38*, 3518−3521. (e) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429−1431.

(6) (a) Singh, S. *Chem. Rev.* **2000**, *100*, 925−1024. (b) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (c) Hemscheidt, T. *Top. Curr. Chem.* **2000**, *209*, 175−206. (d) Newman, A. H.; Agoston, G. E. *Curr. Med. Chem.* **1998**, *5*, 305−319. (e) Fodor, G. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Saimburg, M., Ed.; Elsevier: Amsterdam, 1997; pp 4251−4276. (f) Lounasmaa, M.; Tamminen, T. *Alkaloids* **1993**, *44*, 1−114.

(7) (a) Dubrovina, N. V.; Tararov, V. I.; Kodyrova, Z.; Monsees, A.; Börner, A. *Synthesis* **2004**, 2047−2051. (b) Trifonova, A.; Källström, K. E.; Andersson, P. G. *Tetrahedron* **2004**, *60*, 3393−3403. (c) Bertilsson, S. K.; Andersson, P. G. *J. Organomet. Chem.* **2000**, *603*, 13−17. (d) Södergren, M. J.; Bertilsson, S. K.; Andersson P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610−6618. (e) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760−10761. (f) Zhang, X. (The Penn State Research Foundation) WO 98-US146 19980113; *Chem. Abstr.* **1998**, *129*, 149093.

(8) (a) Aurich, H. G.; Soeberdt, M. *Tetrahedron Lett.* **1998**, *39*, 2553−2554. (b) Tomio, K.; Kawabatu, T.; Nagato, M. (Daisow Co., Ltd., Japan) JP 96-233965, 1996; *Chem. Abstr.* **1998**, *128*, 270540. (c) Wilken, J.; Martens, J. *Liebigs Ann./Recl.* **1997**, 563−571. (d) Stingh, K.; Martens, J. *Liebigs Ann. Chem.* **1994**, 485−490. (e) Martens, J.; Luebben, S. *Arch. Pharm. (Weinheim, Ger.)* **1991**, *324*, 59−60. (f) Martens, J.; Lübben, S.; Bhushan, R. *Tetrahedron Lett.* **1989**, *30*, 7181−7182. (g) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547−5550.

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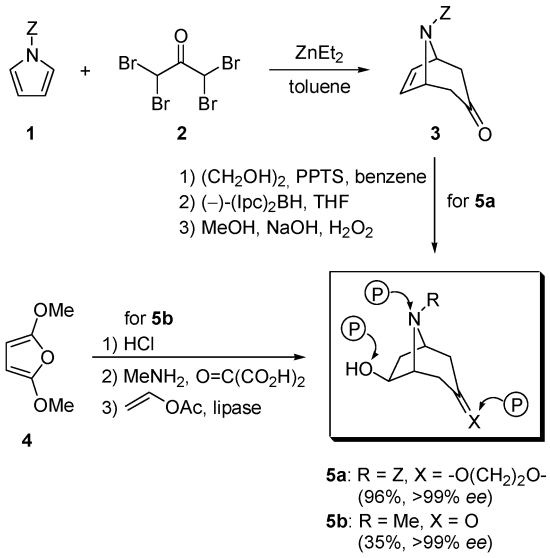
Scheme 1

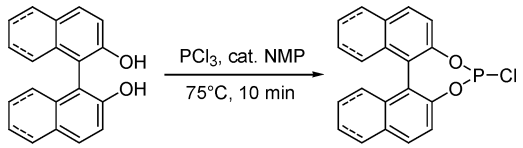


Results and Discussion

Synthesis of Tropinone-Based Ligands. First, the chlorophosphites **7a**−**d** were prepared by treating BINOL and 8*H*-BINOL, respectively, with an excess of PCl_3 as reagent and solvent in the presence of *N*-methylpyrrolidinone (NMP) as catalyst (Scheme 2).[14] After azeotropic removal of excess PCl_3 with toluene, derivatives **7** were isolated almost quantitatively. The configuration of the BINOL moiety in compounds **7** is given in Scheme 2.

Due to its easy accessibility, the enantiopure *Z*-protected tropinone acetal **5a**[11] was used as ligand backbone. The absolute configuration was elucidated by NMR analysis using a modified Mosher method[15] as illustrated in Figure 1 for MTPA-ester **5c**. By H,H COSY measurements proton signals were assigned with

Scheme 2



6, 7	a	b	c	d
	(*S*)	(*R*)	8*H*-(*S*)	8*H*-(*R*)

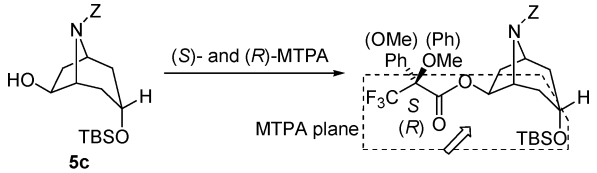
respect to each of the (*R*)- and (*S*)-MTPA esters and the $\Delta\delta(\delta_S - \delta_R)$ values were obtained. Applying Kakisawa's rules[15b] the configuration was assigned to be *S*.

Acetal **5a** was submitted to catalytic hydrogenation in ethyl acetate, yielding enantiomerically pure amino alcohol **8** as starting material for the ligand synthesis in 93% (Scheme 3).[16] Compound **8** was treated with the (*S*)- and (*R*)-BINOL-derived chlorophosphite (*S*)-**7a** and (*R*)-**7b** in the presence of NEt_3 and catalytic amounts of DMAP in toluene at room temperature to afford the bidentate (*S*,*S*)-configured phosphoramidite (*S*,*S*)-**9a** in 74% yield and the corresponding counterpart (*R*,*R*)-**9a** in 64% yield.

A different method was employed for the 8*H*-(*S*)- and 8*H*-(*R*)-BINOL-derived chlorophosphites 8*H*-(*S*)-**7c** and 8*H*-(*R*)-**7d**. Amino alcohol **8** was deprotonated with *n*-BuLi in the presence of catalytic amounts of TBAI in a mixture of NMP and THF followed by treatment with **7c** or **7d** (3 equiv) at 40 °C to give the desired phosphoramidites 8*H*-(*S*,*S*)-**9b** and 8*H*-(*R*,*R*)-**9b** albeit with low yields of 18% and 13%, respectively. The yields could not be improved even by prolonged reaction times. The given configuration of ligands **9** is referred to the BINOL units.

The monodentate ligands were prepared as outlined in Scheme 4. The phosphites (*S*)-**11a**,**b**, with a thioether moiety, are accessible starting from amino alcohol **8** by treatment with methylthioethyl chloride to give the 2-hydroxytropinone derivative **10** in 62% yield. The latter was further converted with (*S*)-**7a** and 8*H*-(*S*)-**7c** to afford the phosphite derivatives (*S*)-**11a** and 8*H*-(*S*)-**11b** bearing the (*S*)-BINOL and 8*H*-(*S*)-BINOL moiety, respectively. Finally, the Z-protected tropinone acetal **5a** was treated with MOMCl[17] and subsequently the protective group was removed by hydrogenolysis to yield the amine **12** in 80% over two steps. Conversion to the MOM-protected phosphoramidite (*S*)-**13** was achieved in 79% yield under the above-mentioned conditions (Scheme 4). The configuration given for ligands **11** and **13** is referred to the BINOL moiety.

Conjugate 1,4-Additions. Having this set of phosphorus ligands in hand, we investigated the asymmetric catalytic conjugate additions. First, cyclic enones **14a**−**d** were reacted



Δδ values (10^{-3} ppm)			
6-H	–4	5-H	+68
7-H	–67	4-H	+23
7-H'	–120	4-H'	+9
1-H	–16	3-H	+3
2-H	–8		

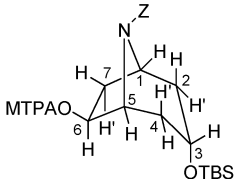


Figure 1. Assignment of the absolute configuration according to Kakisawa.[15b]

(9) Armstrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B. R.; Wailes, J. S. *J. Org. Chem.* **2002**, *67*, 8610−8617.

(10) (a) Aggarwal, V. K.; Astle, C. J.; Rogers-Evans, M. *Org. Lett.* **2004**, *6*, 1469−1471. (b) Albrecht, U.; Armbrust, H.; Langer, P. *Synlett* **2004**, 143−145. (c) Petrović, G. B.; Saičić, R. N.; Čeković, Z. M. *Helv. Chim. Acta* **2003**, *86*, 3179−3186. (d) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867−8878. (e) Aggarwal, V. K.; Grainger, R. S.; Newton, G. K.; Spargo, P. L.; Hobson, A. D.; Adams, H. *Org. Biomol. Chem.* **2003**, *1*, 1884−1893. (f) Mikami, K.; Ohmura, H. *Chem. Commun.* **2002**, 2626−2627. (g) Airaksinen, A. J.; Lipsonen, J.; Ahlgren, M.; Vainiotalo, P.; Bergström, K. A.; Laatikainen, R.; Vepsäläinen, J. *Tetrahedron* **2003**, *59*, 377−383. (h) Lazny, R.; Nodzewska, A. *Tetrahedron Lett.* **2003**, *44*, 2441−2444. (i) Airaksinen, A. J.; Ahlgren, M.; Vepsäläinen, J. *J. Org. Chem.* **2002**, *67*, 5019−5021. (j) Cheng, J.; Moore, Z.; Stevens, E. D.; Trudell, M. L. *J. Org. Chem.* **2002**, *67*, 5433−5436. (k) Zhao, L.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J.; Kozikowski, A. P. *J. Med. Chem.* **2000**, *43*, 3283−3294. (l) Petrović, G.; Saičić, R. N.; Čeković, Z. *Synlett* **1999**, 635−637. (m) Bremner, J. B.; Smith, R. J.; Tarrant, G. J. *Tetrahedron Lett.* **1996**, *37*, 97−100. (n) Justice, D. E.; Malpass, J. R. *Tetrahedron Lett.* **1995**, *36*, 4689−4692. (o) Katoh, T.; Kakiya, K.; Nakai, T.; Nakamura, S.; Nishide, K.; Node, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2351−2358. (p) Lee, J. C.; Lee, K.; Cha, J. K. *J. Org. Chem.* **2000**, *65*, 4773−4775. (q) Giblin, G. M. P.; Jones, C. D.; Simpkins, N. S. *Perkin Trans. 1* **1998**, 3689−3697.

(11) Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Synlett* **2003**, 2175−2177.

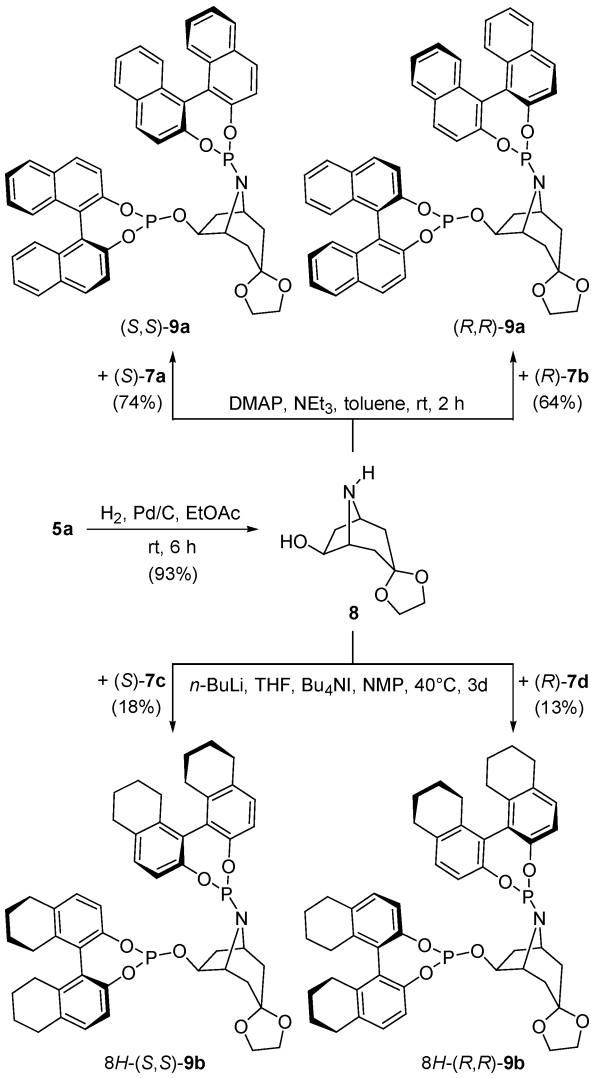
(12) Cramer, N.; Laschat, S.; Baro, A. *Synlett* **2003**, 2178−2181.

(13) (a) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Commun.* **2002**, 673−675. (b) Huttenloch, O.; Laxman, E.; Waldmann, H. *Chem. Eur. J.* **2002**, *8*, 4767−4780. (c) Huttenloch, O.; Spieler, J.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 671−675.

(14) Gergely, I.; Hegedüs, C.; Gulyás, H.; Szöllösy, A.; Monsees, A.; Riermeier, T.; Bakos, J. *Tetrahedron: Asymmetry* **2003**, *14*, 1087−1090.

(15) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

Scheme 3

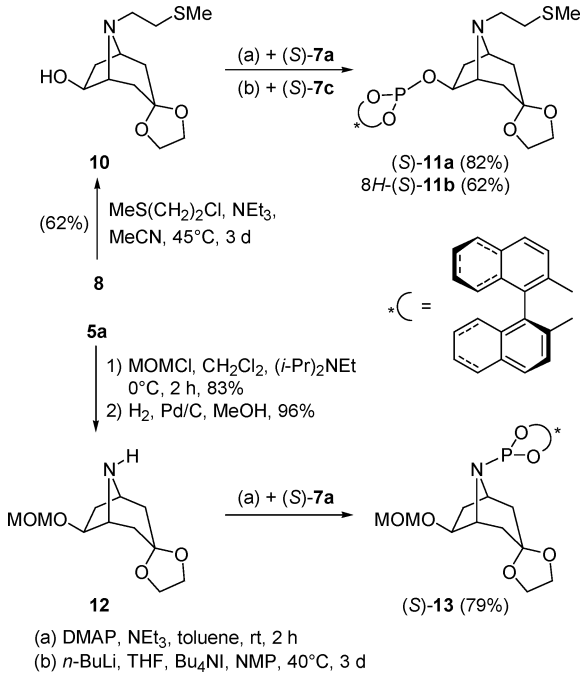


with Et_2Zn in toluene at −20 °C in the presence of $Cu(OAc)_2 \cdot H_2O$ and phosphoramidite ligands **9**, **11**, and **13** (**A**, Scheme 5). The resulting β-ethyl ketones **15a**−**d** were analyzed by GC or HPLC using chiral stationary phases. Cyclohexenone (**14b**) was also treated with Me_2Zn at 0 °C under the same reaction conditions (**B**, Scheme 5). The results are summarized in Table 1. A first glance indicated that each ligand behaved differently for the various enones **14**. For cyclopentenone **14a** moderate to good yields were obtained with the four bidentate ligands **9a**,**b** (entries 1−4). In contrast, the monodentate ligands (*S*)-**11a**, 8*H*-(*S*)-**11b**, and (*S*)-**13** turned out to be less efficient (entries 5−7). A very pronounced matched/mismatched selectivity was observed. Whereas (*S*)-BINOL-derived phosphoramidite (*S*,*S*)-**9a** gave 87% ee, the congener (*R*,*R*)-**9a** resulted in a significant decrease of the selectivity to 5% ee. A similar phenomenon was observed for the 8*H*-BINOL-derived ligands 8*H*-(*S*,*S*)-**9b** and 8*H*-(*R*,*R*)-**9b** (entries 3, 4).

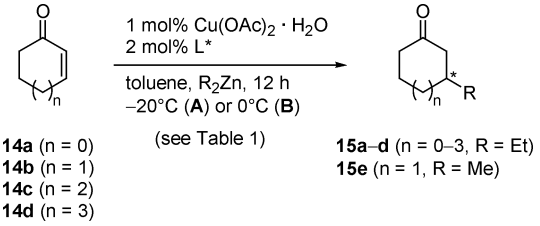
In the case of cyclohexenone (**14b**) the bidentate ligands (*S*,*S*)-**9a** and (*R*,*R*)-**9a** gave 90% ee and 69% ee, respectively, with excellent yields (entries 8, 9). Again the (*S*,*S*)-diastereomer turned out to be the matched ligand. Whereas also high enantioselectivity of 91% ee could be achieved with ligand 8*H*-(*S*,*S*)-**9b** (entry 10), all other ligands resulted in much lower

(16) Cramer, N. Diplomarbeit, Universität Stuttgart, 2003.
(17) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275−1276.

Scheme 4



Scheme 5



selectivities (entries 11−14). As expected, lowering the ligand/Cu ratio to 1:1 for the bidentate ligand (*S*,*S*)-**9a** resulted in only a slight drop of the enantioselectivity from 90% to 86% ee, indicating that both P-sites bind to the metal. On the other hand, upon increasing the ligand/Cu ratio to 4:1 for the monodentate ligand (*S*)-**13**, no improvement of the enantioselectivity was detected (entries 8, 15).

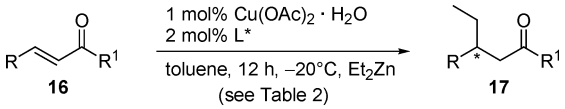
Both $Cu(OTf)_2$ and $Cu(OAc)_2 \cdot H_2O$ have been used as Cu source in the reactions of cycloheptenone (**14c**) and cyclooctenone (**14d**). With all ligands in the presence of $Cu(OTf)_2$ **14c** was converted to **15c** in good yields, but only moderate enantioselectivities (up to 41% ee with ligand (*S*)-**13**). However, the replacement of $Cu(OTf)_2$ with $Cu(OAc)_2 \cdot H_2O$ significantly improved the selectivities for **14c**, as revealed in Table 1. Particularly for the bidentate phosphoramidites (*S*,*S*)-**9a** and (*R*,*R*)-**9a** the enantioselectivities increased up to 81% (entries 15, 16) as compared to 16% ee with $Cu(OTf)_2$. The strong dependency of the selectivity on the copper precursor agrees well with results by Alexakis.[4a] In the 1,4-additions of cyclooctenone (**14d**) again increased enantioselectivites were realized with $Cu(OAc)_2 \cdot H_2O$ as compared to $Cu(OTf)_2$ with the exception of the MOM-protected phosphoramidite (*S*)-**13**, which seemed to be unaffected by the Cu precursor (83% ee versus 89% ee). As can be seen from Table 1, the bidentate ligand 8*H*-(*R*,*R*)-**9b** gave a selectivity of 88% ee (entry 25), being exceeded only by the monodentate phosphoramidite (*S*)-**13** with 89% ee at 88% yield (entry 28). Obviously due to the more flexible eight-membered ring, the difference of matched/mismatched ligands disappeared, resulting in comparable selectivities except ligand (*S*)-**11a** (entry 26). Finally, dimethylzinc

Table 1. Cu-Catalyzed Conjugate 1,4-Addition of Dialkylzinc to Cyclic Enones 14

entry	substrate	ligand L*	product	yield (%)[a]	ee (%)[b]	config[c]
1	**14a**	(*S*,*S*)-**9a**	**15a**	46	87	*S*
2		(*R*,*R*)-**9a**		81	5	*R*
3		8*H*-(*S*,*S*)-**9b**		55	81	*S*
4		8*H*-(*R*,*R*)-**9b**		70	1	n.d.
5		(*S*)-**11a**		10	3	n.d.
6		8*H*-(*S*)-**11b**		22	25	*R*
7		(*S*)-**13**		37	15	*S*
8	**14b**	(*S*,*S*)-**9a**	**15b**	99 (99)[d]	90 (86)[d]	*S*
9		(*R*,*R*)-**9a**		96	69	*R*
10		8*H*-(*S*,*S*)-**9c**		98	91	*S*
11		8*H*-(*R*,*R*)-**9d**		89	47	*R*
12		(*S*)-**11a**		50	17	*S*
13		8*H*-(*S*)-**11b**		91	20	*S*
14		(*S*)-**13**		95 (97)[e]	30 (30)[e]	*S*
15	**14c**	(*S*,*S*)-**9a**	**15c**	70	81	*S*
16		(*R*,*R*)-**9a**		76	75	*R*
17		8*H*-(*S*,*S*)-**9b**		79	73	*S*
18		8*H*-(*R*,*R*)-**9b**		78	56	*R*
19		(*S*)-**11a**		28	3	n.d.
20		8*H*-(*S*)-**11b**		14	4	n.d.
21		(*S*)-**13**		83	43	*S*
22	**14d**	(*S*,*S*)-**9a**	**15d**	89	79	*S*
23		(*R*,*R*)-**9a**		85	86	*R*
24		8*H*-(*S*,*S*)-**9b**		83	83	*S*
25		8*H*-(*R*,*R*)-**9b**		82	88	*R*
26		(*S*)-**11a**		28	3	n.d.
27		8*H*-(*S*)-**11b**		58	86	*S*
28		(*S*)-**13**		88	89	*S*
29	**14b**	(*S*,*S*)-**9a**	**15e**[f]	11	77	*S*
30		(*R*,*R*)-**9a**		76	55	*R*
31		(*S*)-**13**		76	3	n.d.

[a] Determined by GC with dodecane as internal standard. [b] Determined by GC on a chiral phase. [c] Comparison of optical rotation values with literature values.[18] [d] With 1% ligand. [e] With 4% ligand. [f] According to **B** at 0 °C (Scheme 5). n.d. = not determined.

Scheme 6



16, 17	R	R[1]	16, 17	R	R[1]
a	*n*-Bu	Me	**e**	2-furyl	Me
b	Ph	Me	**f**	4-MeOC$_6$H$_4$	Me
c	Ph	Ph	**g**	4-ClC$_6$H$_4$	Me
d	2-thienyl	Me			

was added to cyclohexenone (**14b**) to give addition product **15e**. Surprisingly, Me_2Zn was found to be less reactive than Et_2Zn, making a temperature increase from −20 °C to 0 °C necessary. However, even at this temperature the conversion was incomplete. The obtained selectivities clearly depend on the ligands (entries 29−31). Bidentate ligand (*S*,*S*)-**9a** gave 77% ee, albeit with only 11% yield.

After (*S*)-BINOL-derived bidentate phosphoramidite (*S*,*S*)-**9a** was identified as the most promising ligand for cyclic enones, we were suspicious about its behavior in 1,4-additions of Et_2Zn to acyclic enones **16** (Scheme 6, Table 2).

To our surprise a different behavior of the ligands was observed. In the reactions of 3-octen-2-one (**16a**) monodentate thioether-containing phosphites (*S*)-**11a** and 8*H*-(*S*)-**11b** produced the best selectivities of 62% ee and 50% ee, respectively (entries 5, 6) as compared to bidentate phosphoramidites (*S*,*S*)- and (*R*,*R*)-**9a** and the MOM-protected phosphite (*S*)-**13** (entries 1−4, 7). The results reversed when the *n*-butyl group was substituted by phenyl as in enone **16b**, and the bidentate ligands (*S*,*S*)- and (*R*,*R*)-**9a** proved to be most suitable (entries 8, 9).

Table 2. Cu-Catalyzed Conjugate 1,4-Addition of Diethylzinc to Acyclic Enones 16

entry	substrate	ligand	product	yield (%)[a]	ee (%)[b]	config[c]
1	**16a**	(*S*,*S*)-**9a**	**17a**	96	18	*R*
2		(*R*,*R*)-**9a**		94	9	*S*
3		8*H*-(*S*,*S*)-**9b**		9	0	
4		8*H*-(*R*,*R*)-**9b**		67	17	*R*
5		(*S*)-**11a**		88	62	*S*
6		8*H*-(*S*)-**11b**		74	50	*S*
7		(*S*)-**13**		100	10	*S*
8	**16b**	(*S*,*S*)-**9a**	**17b**	46	36[d]	*R*
9		(*R*,*R*)-**9a**		87	48[d]	*S*
10		(*S*)-**11a**		21	24[d]	*R*
11		8*H*-(*S*)-**11b**		41	22[d]	*R*
12		(*S*)-**13**		53	21[d]	*R*
13	**16c**	(*S*,*S*)-**9a**	**17c**	61	1[d]	n.d.
14		(*R*,*R*)-**9a**		99	8[d]	n.d.
15		(*S*)-**11a**		90	11[d]	n.d.
16		8*H*-(*S*)-**11b**		97	1[d]	n.d.
17		(*S*)-**13**		45	4[d]	n.d.
18	**16d**	(*S*,*S*)-**9a**	**17d**	42	51	(−)
19		(*R*,*R*)-**9a**		98	56	(+)
20		8*H*-(*S*,*S*)-**9b**		98	42	(−)
21		8*H*-(*R*,*R*)-**9b**		96	67	(+)
22	**16e**	(*S*,*S*)-**9a**	**17e**	32	56	(−)
23		(*R*,*R*)-**9a**		83	56	(+)
24		8*H*-(*S*,*S*)-**9b**		97	24	(−)
25		8*H*-(*R*,*R*)-**9b**		70	15	(+)
26		(*S*)-**13**		80	27	(−)
27	**16f**	(*S*,*S*)-**9a**	**17f**	54	59	(−)
28		(*R*,*R*)-**9a**		94	57	(+)
29		8*H*-(*S*,*S*)-**9b**		84	39	(−)
30		8*H*-(*R*,*R*)-**9b**		92	19	(+)
31		(*S*)-**11a**		18	22	(−)
32		8*H*-(*S*)-**11b**		26	n.d.	n.d.
33	**16g**	(*S*,*S*)-**9a**	**17g**	57	0[d]	n.d.
34		(*R*,*R*)-**9a**		59	53[d]	(+)
35		8*H*-(*S*,*S*)-**9b**		56	0[d]	n.d.
36		8*H*-(*R*,*R*)-**9b**		47	0[d]	n.d.
37		(*S*)-**11a**		33	n.d.	n.d.
38		8*H*-(*S*)-**11b**		45	n.d.	n.d.
39		(*S*)-**13**		80	2[d]	(+)

[a] Determined by GC with dodecane as internal standard. [b] Determined by GC on a chiral phase. [c] Comparison of optical rotation values with literature values.[18] [d] Determined by HPLC on a chiral phase. n.d. = not determined.

Almost no selectivity was found for chalcone **16c** independently of the ligands (entries 13−17). Next the electronic properties of 4-aryl-3-buten-2-ones **16d**−**g** were modified by 2-thienyl, 2-furyl, 4-anisylphenyl, and 4-chlorophenyl groups. Electron-rich aryl groups at the enone seem to improve the performance particularly of bidentate (*S*,*S*)-**9a**, resulting in ee's up to 59% (entries 18, 22, 27), while monodentate (*S*)-**11a** and 8*H*-(*S*)-**11b** were less enantioselective (entries 31, 32). No clear-cut matched/mismatched cases were observed, although the (*R*,*R*)-diastereomer **9a** gave slightly better results than (*S*,*S*)-**9a**. A binary matched/mismatched case was found for 4-chlorophenyl-substituted enone **16g**. The addition of Et_2Zn to **16g** provided ketone **17g** in 59% yield with 53% ee in the presence of (*R*,*R*)-**9a**, whereas the corresponding congener (*S*,*S*)-**9a** yielded the racemic product **17g** in 57% (entries 33, 34).

Catalytic Hydrogenations. The utility of the novel tropinone-based ligands in catalytic hydrogenations[19] of

(18) (a) Shi, M.; Wang, C.-J.; Zhang, W. *Chem. Eur. J.* **2004**, *10*, 5507−5516. (b) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756. (c) Hu, X. Q.; Chen, H. L.; Zhang, X. M. *Acta Chim. Sin.* **2000**, *58*, 1163−1167. (d) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2004**, *126*, 12784−12785. (e) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4148−4149. (f) Wan, H.; Hu, Y.; Liang, Y.; Gao, S.; Wang, J.; Zheng, Z.; Hu, X. *J. Org. Chem.* **2003**, *68*, 8277−8280.

Scheme 7

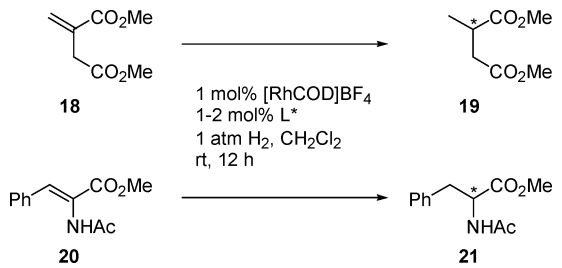


Table 3. Catalytic Hydrogenation of Dimethyl Itaconate (18) and Methyl Acetamidocinnamate (20)

entry	enoate	ligand	product	conv (%)[a]	ee (%)[b]	config[c]
1	**18**	(*S*,*S*)-**9a**	**19**	100	85	*S*
2		(*R*,*R*)-**9a**		100	62	*R*
3		8*H*-(*S*,*S*)-**9b**		100	80	*S*
4		8*H*-(*R*,*R*)-**9b**		100	17	*R*
5		(*S*)-**11a**		0		
6		(*S*)-**13**		43	71	*S*
7	**20**	(*S*,*S*)-**9a**	**21**	100	95	*R*
8		(*R*,*R*)-**9a**		100	85	*S*
9		8*H*-(*S*,*S*)-**9b**		100	88	*R*
10		8*H*-(*R*,*R*)-**9b**		100	84	*S*
11		(*S*)-**11a**		0		
12		(*S*)-**13**		63	55	*R*

[a] Determined by GC. [b] Determined by GC on a chiral phase. [c] Comparison of optical rotation values with literature data.[20]

dimethyl itaconate **18** and methyl acetamidocinnamate **20** was investigated in order to explore their scope and limitations (Scheme 7, Table 3).

As shown in Table 3, rhodium/bidentate phosphoramidite (*S*,*S*)-**9a** represented an effective system, which resulted in the formation of dimethyl 2-methylsuccinate **19** with 85% ee and methyl *N*-acetylphenylalaninate **21** with 95% ee (entries 1, 7). Again a matched/mismatched case was seen for both (*S*,*S*)-**9a** and its counterpart (*R*,*R*)-**9a** in the hydrogenation of itaconate **18** (85% ee versus 62% ee) and acetamidocinnamate **20** (95% ee versus 85% ee) (entries 1, 2, 8, 9). In contrast, both ligands (*S*,*S*)-**9b** and (*R*,*R*)-**9b** derived from 8*H*-BINOL displayed different results for **18** and **20**. Whereas itaconate **18** produced a pronounced matched/mismatched case (80% ee versus 17% ee) (entries 3, 4), similar selectivities are achieved in the hydrogenation of cinnamate **20** (88% ee versus 84% ee) (entries 9, 10). The configuration of the products **19** and **21** was clearly dominated by the BINOL moieties.

Conclusion

Several novel mono- and bidentate ligands with BINOL and 8*H*-BINOL moieties using an enantiomerically pure tropane scaffold have been prepared and investigated in Cu-mediated 1,4-additions to cyclic and acyclic enones **14** and **16** as well as in Rh-catalyzed hydrogenations of itaconate **18** and acetamidocinnamate **20**. Whereas the monodentate ligands **11** and **13** gave poor results with regard to yields and selectivities in most cases, the bidentate phosphoramidites **9** yielded promising selectivities. In both asymmetric 1,4-additions and hydrogenations the (*S*)-BINOL-containing phosphoramidite (*S*,*S*)-**9a** was superior to all other ligands. Although this ligand cannot be considered as a "one size fits all" ligand, it is certainly worthy of further exploration due to the convenient modification of the tropinone ligand, which allows for optimization of the ligand preferably tethered to a solid-phase resin, as was successfully demonstrated by Waldmann and co-workers for bispidines.[13]

Experimental Section

4-Chlorodinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepines 7.[14] A solution of (*S*)-, (*R*)-BINOL **6a**,**b** (2.86 g, 10.0 mmol) or 8*H*-(*S*)-, 8*H*-(*R*)-BINOL **6c**,**d** (2.94 g, 10.0 mmol), azeotropically dried with absolute toluene, freshly distilled PCl_3 (10 mL), and 3 drops of NMP was heated at reflux for 10 min. The reaction mixture was concentrated in vacuo and the residue distilled twice azeotropically with absolute toluene to give products **7** quantitatively. For further use, a 1 M solution of the respective **7** in toluene was prepared.

Spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolan]-6-ol (8). A solution of **5a** (26 mg, 0.081 mmol) in EtOAc (5 mL) and catalytic amounts of Pd/C was stirred under 1 atm of H_2 for 6 h. The catalyst was filtered off through a short pad of Celite and washed with MeOH. The combined filtrates were concentrated. The residue crystallized to give **8** (14 mg, 93%) as a colorless solid. Mp: 124 °C. $[\alpha]_D^{20} = -7.8$ (*c* 0.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (ddddd, $J = 13.4$ Hz, $J = 7.5$ Hz, $J = 2.3$ Hz, $J = 1.2$ Hz, $J = 1.1$ Hz, 1H, 7-H), 1.73 (ddd, $J = 13.5$ Hz, $J = 2.1$ Hz, $J = 2.1$ Hz, 1H, 4-H), 1.82−1.91 (m, 3H, 2-H, 4-H), 2.02 (br, 2H, OH, NH), 2.63 (dd, $J = 13.4$ Hz, $J = 6.7$ Hz, 1H, 7-H), 3.32 (dd, $J = 3.5$ Hz, $J = 3.5$ Hz, 1H, 5-H), 3.67 (ddd, $J = 7.5$ Hz, $J = 3.6$ Hz, $J = 3.6$ Hz, 1H, 1-H), 3.77−3.83 (m, 2H, OCH_2), 3.90−3.94 (m, 2H, OCH_2), 4.53 ppm (dd, $J = 6.7$ Hz, $J = 2.1$ Hz, 1H, 6-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 40.3 (C-2), 41.2 (C-7), 42.0 (C-4), 54.5 (C-1), 63.28 (C-5), 63.33 (OCH_2), 75.2 (C-6), 106.9 ppm (C-3). MS (EI): *m*/*z* (%) 185 (20) [M^+], 141 (100) [$M^+ - C_2H_4O$], 113 (85), 99 (15), 87 (87), 69 (25). HRMS (EI): calcd for $C_9H_{15}NO_3$ 185.1052, found 185.1052 [M^+].

(6*S*)-8-[*N*-(Methylthio)ethyl]spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolan]-6-ol (10). Methylthioethyl chloride (109 μL, 1.10 mmol) was added to a mixture of **8** (185 mg, 1.00 mmol) and NEt_3 (200 μL, 1.42 mmol) in absolute MeCN (6 mL), and the reaction mixture stirred at 45 °C for 3 days. The reaction mixture was concentrated in vacuo and the residue chromatographed on basic Al_2O_3 (EtOAc/MeOH, 4:1, $R_f = 0.5$). Yield of the light yellow oil, which slowly solidified to a colorless solid: 161 mg (62%, >95% NMR purity). Mp: 60−61 °C. $[\alpha]_D^{20} = +14.1$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (dt, $J = 14.0$ Hz, $J = 2.2$ Hz, 1H, 2-H), 1.61 (dt, $J = 14.3$ Hz, $J = 1.9$ Hz, 1H, 4-H), 1.71 (dd, $J = 14.0$ Hz, $J = 7.5$ Hz, 1H, 2-H), 1.97 (dd, $J = 14.3$ Hz, $J = 4.1$ Hz, 1H, 4-H), 1.98 (dd, $J = 13.5$ Hz, $J = 3.1$ Hz, 1H, 7-H), 2.13 (s, 3H, *Me*S), 2.57 (dd, $J = 13.5$ Hz, $J = 7.1$ Hz, 1H, 7-H), 2.64 (t, $J = 7.4$ Hz, 2H, 9-H), 2.93 (t, $J = 7.4$ Hz, 2H, 8-H), 3.17 (br, 1H, 1-H), 3.40−3.45 (m, 1H, 5-H), 3.77−3.85 (m, 2H, OCH_2CH_2O), 3.90−3.95 (m, 2H, OCH_2CH_2O), 4.37 ppm (d, $J = 6.9$ Hz, 1H, 6-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.8 (*Me*S), 33.1 (C-9), 33.4 (C-7), 34.7 (C-2), 40.2 (C-4), 46.6 (C-8), 56.5 (C-1), 63.0 (OCH_2CH_2O), 64.2 (OCH_2CH_2O), 65.0 (C-5), 74.6 (C-6), 106.5 ppm (C-3). MS (EI): *m*/*z* (%) 259 (3) [M^+], 198 (100), 168 (5), 140 (8), 100 (8), 75 (15). HRMS (EI): calcd for $C_{12}H_{21}NO_3S$ 259.1242, found 259.1242 [M^+]. FT-IR (ATR): $\tilde{\nu}$ 3245 (m), 3087 (s), 2948 (s), 2879 (s), 1425 (m), 1338 (s), 1141 (s), 1118 (s), 1081 (vs), 1033 cm^{-1} (vs).

(6*S*)-(Methoxymethoxy)spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] (12). (a) MOMCl (323 μL, 4.26 mmol) was added to a solution of **5a** (340 mg, 1.07 mmol) and ethyldiisopropylamine

(19) Reviews: (a) Rossen, K. *Angew. Chem.* **2001**, *113*, 4747−4749; *Angew. Chem., Int. Ed.* **2001**, *40*, 4611−4613. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 1, pp 1−62.

(20) (a) Sato, T.; Otera, J. *J. Org. Chem.* **1995**, *60*, 2627−2629. (b) Huang, H. T.; Niemann, C. *J. Am. Chem. Soc.* **1952**, *74*, 101−105.

(0.93 mL, 5.30 mmol) in absolute CH_2Cl_2 (5 mL) at 0 °C. After being warmed to room temperature within 2 h, the reaction mixture was poured into H_2O. The organic layer was separated, washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 [hexanes (PE)/EtOAc, 2:1, $R_f = 0.27$). Yield of the colorless oil benzyl (6*S*)-(methoxymethoxy)-8*H*-spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane]-8-carboxylate: 320 mg (83%, >95% NMR purity). $[\alpha]_D^{20} = +6.8$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66−1.72 (m, 1H, 2-H), 1.80−1.96 (m, 3H, 2-H, 4-H, 7-H), 2.00−2.07 (m, 1H, 4-H), 2.52−2.57 (m, 1H, 7-H), 2.28 (s, 3H, *Me*O), 3.35 (s, 3H, *Me*O*), 3.75−3.82 (m, 2H, OCH_2CH_2O), 3.87−3.94 (m, 2H, OCH$_2$CH_2O), 4.29 (br, 1H, 1-H), 4.34 (br, 1H, 1-H*), 4.38−4.50 (m, 2H, 5-H, 6-H), 4.57 (d, $J = 7.0$ Hz, 1H, MeOCH*H*O), 4.59 (d, $J = 7.0$ Hz, 1H, MeOC*H*HO), 4.61 (s, 2H, MeOCH_2O*), 5.13 (s, 2H, CH_2Ar), 7.24−7.36 ppm (m, 5H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.7 (C-7), 37.4* (C-7), 38.2 (C-2), 39.1* (C-2), 39.5 (C-4), 40.3* (C-4), 52.6 (MeO), 55.0 (C-1), 55.1* (C-1), 59.1 (C-5), 59.2* (C-5), 63.1 (O*C*H$_2$*C*H$_2$O), 64.2 (O*C*H$_2$*C*H$_2$O), 66.4 (*C*H$_2$Ar), 66.5* (*C*H$_2$Ar), 78.4 (C-6), 79.5* (C-6), 95.2 (MeO*C*H$_2$O), 95.3* (MeO*C*H$_2$O), 106.5 (C-3), 127.4 (Ar), 127.5* (Ar), 127.6 (Ar), 127.7* (Ar), 128.1 (Ar), 128.2* (Ar), 136.4 (Ar), 136.4* (Ar), 153.4 (*C*O), 153.6* ppm (*C*O) [*signals of the second rotamer (54:46)].

(b) A suspension of the protected intermediate (305 mg, 0.84 mmol) and 10% Pd/C (10 mg) in MeOH (5 mL) was stirred for 2 h under 1 atm of H_2. The catalyst was filtered off through a short pad of Celite, and the filtrate was concentrated in vacuo. Yield of the colorless viscous oil **12**: 185 mg (96%, >95% NMR purity). $[\alpha]_D^{20} = -4.4$ (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57−1.62 (m, 2H, 7-H, 2-H), 1.65 (dt, $J = 13.8$ Hz, $J = 2.4$ Hz, 1H, 4-H), 1.91 (dd, $J = 13.8$ Hz, $J = 3.9$ Hz, 2H, 2-H, 4-H), 2.51 (dd, $J = 13.5$ Hz, $J = 6.9$ Hz, 1H, 7-H), 3.29 (s, 3H, *Me*O), 3.40−3.46 (m, 1H, 5-H), 3.64−3.70 (m, 1H, 1-H), 3.70−3.86 (m, 4H, OCH_2CH_2O), 3.92 (br, 1H, N*H*), 4.38 (dd, $J = 6.8$ Hz, $J = 2.2$ Hz, 1H, 6-H), 4.52 ppm (d, $J = 1.2$ Hz, 2H, MeOCH_2O). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.1 (C-7), 39.7 (C-2), 41.1 (C-4), 54.3 (C-1), 55.2 (MeO), 60.6 (C-5), 63.2 (O*C*H$_2$*C*H$_2$O), 64.1 (O*C*H$_2$*C*H$_2$O), 79.9 (C-6), 95.1 (MeO*C*H$_2$O), 106.5 ppm (C-3). MS (EI): *m*/*z* (%) 229 (5) [M$^+$], 198 (10), 184 (45), 141 (100), 98 (60), 87 (70), 82 (20), 80 (18), 70 (20), 69 (45), 68 (30). HRMS (EI): calcd for $C_{11}H_{19}NO_4$ 229.1314, found 229.1301 [M$^+$]. FT-IR (ATR): $\tilde{\nu}$ 3291 (w), 2943 (s), 2883 (s), 2822 (m), 1472 (m), 1439 (m), 1405 (m), 1337 (m), 1216 (s), 1144 (vs), 1096 (vs), 1033 (vs), 916 (vs), 851 cm^{-1} (vs).

General Procedure for the Synthesis of Ligands 9a, 11a, and 13 (Method a). A 1 M solution of the appropriate chlorophosphite **7a**,**b** (2 mL) was added to a solution of **8**, **10**, or **12** (1 equiv), NEt_3 (5 equiv), and DMAP (0.15 equiv) in absolute toluene (5 mL), and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then concentrated and the residue chromatographed on SiO_2 with PE/EtOAc to give product **9a**, **11a**, or **13**.

(*S*,*S*,6*S*)-8-Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yl-6-(dinaphtho[1,2-*f*:1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)spiro-[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] [(*S*,*S*)-9a]. Yield: 74% (>95% ^{31}P NMR purity). $R_f = 0.3$ (PE/EtOAc, 6:1). $[\alpha]_D^{20} = +722$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.32 (br d, $J = 13.6$ Hz, 1H, 2-H), 1.46 (br d, $J = 13.5$ Hz, 1H, 4-H), 1.65−1.85 (m, 3H, 2-H, 4-H, 7-H), 2.23 (dd, $J = 13.1$ Hz, $J = 6.9$ Hz, 1H, 7-H), 2.72−2.82 (m, 1H, OC*H*HCH$_2$O), 3.20−3.27 (m, 1H, OCH*H*CH$_2$O), 3.39−3.55 (m, 2H, OCH$_2$CH_2O), 3.65−3.72 (m, 1H, 1-H), 3.80−3.87 (m, 1H, 5-H), 4.70−4.80 (m, 1H, 6-H), 7.20−7.55 (m, 16H, Ar), 7.82−8.05 ppm (m, 8H, Ar). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 39.6, 39.7, 39.9, 41.7 (C-2, C-4, C-7), 53.25 53.26, 53.58, 53.62 (C-1), 62.7 (O*C*H$_2$*C*H$_2$O), 62.81, 62.83, 63.0 (O*C*H$_2$*C*H$_2$O), 63.2, 63.4 (C-5), 78.6 (C-6), 106.0 (C-3), 121.42, 121.44, 121.6, 121.9, 121.9, 122.18, 122.20, 123.31, 122.33, 123.4, 123.5, 123.6, 124.2, 124.3, 124.5, 124.6, 125.57, 125.64, 125.8, 125.9, 126.29, 126.35, 126.40, 126.44, 127.9, 128.02, 128.04, 129.3, 129.8, 129.9, 130.0, 130.5, 130.8, 130.9, 131.2, 132.12, 132.14, 132.25, 132.27, 132.39, 132.41, 147.4, 147.5, 148.51, 148.54, 148.59, 148.61, 149.15, 149.18 ppm. (Due to interference and P−C-coupling, signals are given as they appear in the spectrum.) ^{31}P NMR (121.5 MHz, CD_2Cl_2): δ 136.9, 143.5 ppm. MS (EI): *m*/*z* (%) 813 (35) [M$^+$], 768 (10), 673 (10), 646 (15), 600 (10), 498 (10), 482 (40), 455 (10), 346 (20), 332 (55), 315 (80), 268 (100), 239 (40), 226 (10), 119 (10). HRMS (EI): calcd for $C_{49}H_{37}NO_7P_2$ 813.2045, found 813.2056 [M$^+$]. FT-IR (ATR): $\tilde{\nu}$ 2947 (m), 1732 (s), 1588 (s), 1505 (s), 1461 (s), 1430 (s), 1353 (m), 1324 (s), 1228 (vs), 1200 (vs), 1065 (vs), 980 (s), 940 (vs), 819 (vs), 746 cm^{-1} (vs).

(*R*,*R*,6*S*)-8-Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yl-6-(dinaphtho[1,2-*f*:1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)spiro-[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] [(*R*,*R*)-9a]. Yield: 64% (>95% ^{31}P NMR purity). $R_f = 0.3$ (PE/EtOAc, 6:1). $[\alpha]_D^{20} = -479$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_2Cl_2): δ 1.40−1.80 (m, 5H, 2-H, 4-H, 7-H), 2.31 (dd, $J = 13.6$ Hz, $J = 6.9$ Hz, 1H, 7-H), 2.82−2.90 (m, 1H, OC*H*HCH$_2$O), 3.27−3.35 (m, 1H, OC*H*HCH$_2$O), 3.40−3.47 (m, 1H, 1-H), 3.52 (t, $J = 6.3$ Hz, 2H, OCH_2CH$_2$O), 3.90−3.97 (m, 1H, 5-H), 4.81 (ddt, $J = 10.9$ Hz, $J = 6.8$ Hz, $J = 2.1$ Hz, 1H, 6-H), 7.20−7.60 (m, 16H, Ar), 7.82−8.07 ppm (m, 8H, Ar). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 40.6, 40.8, 41.6 (C-2, C-4, C-7), 52.6, 53.25, 53.27, 53.7 (C-1), 60.88, 60.91, 61.27, 61.31 (C-5), 62.8 (O*C*H$_2$*C*H$_2$O), 63.2 (O*C*H$_2$*C*H$_2$O), 78.0 (C-6), 106.1 (C-3), 121.3, 121.4, 121.5, 122.0, 122.2, 122.47, 122.51, 123.35, 123.41, 123.5, 123.7, 124.2, 124.4, 124.7, 125.6, 125.7, 125.9, 126.0, 126.2, 126.3, 126.5, 127.8, 127.9, 127.99, 128.03, 129.1, 129.75, 129.82, 130.1, 130.5, 130.6, 130.9, 131.0, 131.2, 132.1, 132.3, 132.4, 147.55, 147.59, 148.1, 148.2, 148.6, 148.7, 149.4 ppm. (Due to interference and P−C-coupling, signals are given as they appear in the spectrum.) ^{31}P NMR (121.5 MHz, CD_2Cl_2): δ 134.2, 137.0 ppm. MS (EI): *m*/*z* (%) 813 (20) [M$^+$], 768 (5), 674 (5), 646 (5), 600 (10), 499 (10), 482 (20), 332 (90), 286 (100), 268 (85), 239 (45), 226 (15), 141 (20). HRMS (EI): calcd for $C_{11}H_{21}N_4O_5$ 813.2045, found 813.2071 [M$^+$]. FT-IR (ATR): $\tilde{\nu}$ 3052 (m), 2970 (m), 2950 (s), 2877 (m), 1735 (vs), 1618 (m), 1588 (s), 1505 (s), 1462 (s), 1430 (m), 1368 (s), 1325 (s), 1228 (vs), 1202 (vs), 1085 (s), 1067 (vs), 978 (vs), 940 (vs), 819 (vs), 746 cm^{-1} (vs).

(*S*,6*S*)-6-(Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)-8-[(2-methylthio)ethyl]spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] [(*S*)-11a]. Yield: 82% (>95% ^{31}P NMR purity). $R_f = 0.3$ (EtOAc). $[\alpha]_D^{20} = +471$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ 1.25−1.35 (m, 2H, 2-H, 4-H), 1.72 (dd, $J = 13.7$ Hz, $J = 4.1$ Hz, 1H, 4-H), 1.84 (s, 3H, *Me*S), 1.97 (dd, $J = 13.1$ Hz, $J = 3.3$ Hz, 1H, 2-H), 2.06−2.16 (m, 1H, 7H), 2.35 (dd, $J = 13.4$ Hz, $J = 7.4$ Hz, 1H, 7-H), 2.42−2.56 (m, 3H, OC*H*HC*H*$_2$O, 9-H), 2.70−2.80 (m, 1H, 8-H), 2.86−2.96 (m, 2H, OC*H*HCH$_2$O, 8-H), 3.05−3.10 (m, 2H, 1-H, OC*H*HCH$_2$O), 3.12−3.21 (m, 1H, OC*H*HCH$_2$O), 3.37−3.41 (br, 1H, 5-H), 6.87−6.95 (m, 2H, Ar), 7.07−7.17 (m, 2H, Ar), 7.40−7.74 ppm (m, 8H, Ar). ^{13}C NMR (75 MHz, C_6D_6): δ 15.8 (*Me*S), 34.2 (C-9), 37.4 (C-4), 38.0 (C-7), 39.7 (C-2), 51.8 (C-8), 59.2 (C-1), 62.9 (O*C*H$_2$*C*H$_2$O), 63.4 (O*C*H$_2$*C*H$_2$O), 67.18, 67.23 (C-5), 80.4 (C-6), 106.8 (C-3), 122.3, 122.6, 123.0, 124.1, 124.6, 124.7, 124.9, 125.2, 125.7, 126.4, 126.7, 127.4, 127.7, 128.4, 128.5, 128.6, 128.8, 129.3, 130.4, 130.9, 131.5, 132.0, 133.3, 133.5, 148.6, 149.8 ppm. (Due to interference and P−C-coupling, signals are given as they appear in the spectrum.) ^{31}P NMR (121.5 MHz, CD_2Cl_2): δ 149.8 ppm. MS (EI): *m*/*z* (%) 573 (8) [M$^+$], 572 (10) [M − H$^+$], 558 (60), 512 (100), 413 (5), 286 (35), 268 (10), 239 (10), 180 (20). HRMS (EI): calcd for $C_{32}H_{32}NO_5PS$ 573.1739, found 573.1736 [M$^+$]. FT-IR (ATR): $\tilde{\nu}$ 3054 (w), 2946 (s), 2879 (m), 1734 (m), 1589 (s), 1506 (s), 1462

(s), 1430 (m), 1326 (s), 1229 (vs), 1200 (vs), 1093 (vs), 981 (s), 940 (vs), 820 (vs), 804 (vs), 748 cm^{-1} (vs).

(*S*,6*S*)-8-Dinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yl-6-(methoxymethoxy)spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] [(*S*)-13]. Yield: 79% (>95% ^{31}P NMR purity). $R_f = 0.2$ (PE/EtOAc, 6:1). $[\alpha]_D^{20} = +430$ (*c* 1.00, CH_2Cl_2). ^1H NMR (300 MHz, CD_2Cl_2): δ 1.45 (dt, $J = 13.6$ Hz, $J = 2.1$ Hz, 1H, 2-H), 1.55−1.65 (m, 1H, 7-H), 1.75 (ddd, $J = 13.6$ Hz, $J = 3.6$ Hz, $J = 1.0$ Hz, 1H, 2-H), 1.85−2.02 (m, 2H, 4-H), 2.30 (dd, $J = 12.9$ Hz, $J = 6.9$ Hz, 1H, 7-H), 3.39 (s, 3H, *Me*O), 3.62−3.70 (m, 1H, 1-H), 3.75−3.97 (m, 5H, 5-H, OCH_2CH_2O), 4.42 (dt, $J = 6.8$ Hz, $J = 2.3$ Hz, 1H, 6-H), 4.61 (d, $J = 6.8$ Hz, 1H, CH*H*OMe), 4.66 (d, $J = 6.8$ Hz, 1H, C*H*HOMe), 7.10−7.52 (m, 8H, Ar), 7.90−8.05 ppm (m, 4H, Ar). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 38.5 (C-7), 40.95, 41.04 (C-2), 41.6 (C-4), 53.1, 53.2 (C-1), 54.88, 54.90 (*Me*O), 61.1, 61.5 (C-5), 63.0 (OCH_2CH_2O), 63.9 (OCH_2CH_2O), 79.6 (C-6), 95.0 (MeOCH_2O), 106.7 (C-3), 121.55, 121.57, 122.2, 122.25, 122.29, 123.4, 123.46, 123.52, 123.7, 124.2, 124.3, 125.5, 125.7, 126.3, 126.4, 127.91, 127.94, 129.1, 129.8, 130.5, 130.86, 130.93, 132.08, 132.11, 132.32, 132.34, 148.6, 148.7, 149.2, 149.3 ppm. (Due to interference and P−C-coupling, signals are given as they appear in the spectrum.) ^{31}P NMR (121.5 MHz, CD_2Cl_2): δ 144.5 ppm. MS (DCI, CH_4): *m*/*z* (%) 543 (100) [M^+], 512 (15), 483 (15), 346 (10), 315 (30), 286 (20), 268 (25), 239 (10), 141 (20). HRMS (DEI): calcd for $C_{31}H_{30}NO_6P$ 543.1811, found 543.1813 [M^+]. FT-IR (ATR): $\tilde{\nu}$ 3314 (w), 3054 (m), 2946 (s), 2880 (s), 1733 (m), 1618 (m), 1588 (m), 1504 (m), 1462 (s), 1326 (s), 1229 (vs), 1203 (vs), 1144 (s), 1081 (vs), 1064 (vs), 1037 (vs), 944 (vs), 820 cm^{-1} (vs).

General Procedure for the Synthesis of Ligands 9b and 11b (Method b). Butyllithium (4 mL, 1.6 M in hexane) was added to a solution of **8** or **10** (2.0 mmol) in absolute THF (3 mL) at 0 °C and the reaction mixture stirred for 30 min. Then a 1 M solution of the respective **7** (6 mL), absolute NMP (4.4 mL), and tetrabutylammonium iodide (36 mg, 0.10 mmol) was added. The reaction mixture was heated at 40 °C for 3 days and concentrated and the residue chromatographed on SiO_2 with PE/EtOAc to give product **9b** or **11b**.

(*S*,*S*,6*S*)-8-(8,9,10,11,12,13,14,15-Octahydrodinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yl)-6-(8,9,10,11,12,13,14,15-octahydrodinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] [8*H*-(*S*,*S*)-9b]. Yield: 18% (>95% ^{31}P NMR purity). $R_f = 0.3$ (PE/EtOAc, 6:1). $[\alpha]_D^{20} = +290$ (*c* 1.00, CH_2Cl_2). ^1H NMR (500 MHz, CD_2Cl_2): δ 1.38 (br d, $J = 13.6$ Hz, 1H, 2-H), 1.50−1.84 (m, 20H, 2′-H, 3′-H, 2-H, 4-H, 7-H), 2.16−2.31 (m, 5H, 1′-H, 7-H), 2.60−2.90 (m, 12H, 1′-H, 4′-H), 3.47−3.52 (m, 1H, 1-H), 3.67−3.80 (m, 4H, OCH_2CH_2O), 3.81−3.85 (m, 1H, 5-H), 4.79 (ddt, $J = 11.0$ Hz, $J = 6.7$ Hz, $J = 2.0$ Hz, 1H, 6-H), 6.81−7.12 ppm (m, 8H, Ar). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.3, 22.4, 22.47, 22.52, 22.54, 22.6 (C-2′, C-3′), 27.4, 27.5, 27.6, 27.7 (C-4′), 28.9, 29.0 (C-1′), 40.1, 40.2, 40.38, 40.43, 41.6 (C-2, C-4, C-7), 52.8, 52.9, 53.08, 53.11 (C-1), 63.1 (OCH_2CH_2O), 63.16, 63.19, 63.41, 63.43 (C-5), 64.0 (OCH_2CH_2O), 78.5, 78.6 (C-6), 106.7 (C-3), 118.49, 118.51, 118.58, 118.61, 118.71, 118.74, 127.36, 127.38, 127.75, 127.77, 128.6, 129.0, 129.06, 129.09, 129.13, 129.2, 133.1, 133.4, 133.9, 134.6, 137.2, 137.3, 137.8, 138.2, 146.5, 146.58, 146.61, 146.96, 147.01, 148.50, 148.53 ppm. (Due to interference and P−C-coupling, signals are given as they appear in the spectrum.) ^{31}P NMR (202.5 MHz, CD_2Cl_2): δ 133.9, 138.1 ppm. MS (EI): *m*/*z* (%) 829 (10) [M^+], 616 (5), 507 (10), 490 (10), 462 (5), 367 (10), 340 (100), 324 (20), 294 (20), 276 (10), 141 (20). HRMS (EI): Calcd for $C_{49}H_{53}NO_7P_2$ 829.3297, found 829.3283 [M^+]. FT-IR (ATR): $\tilde{\nu}$ 2926 (s), 2857 (s), 1737 (vs), 1583 (s), 1465 (s), 1436 (m), 1370 (m), 1351 (m), 1228 (vs), 1216 (vs), 1068 (s), 1047 (s), 933 (vs), 782 cm^{-1} (vs).

(*R*,*R*,6*S*)-8-(8,9,10,11,12,13,14,15-Octahydrodinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yl)-6-(8,9,10,11,12,13,14,15-octahydrodinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)spiro[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] [8*H*-(*R*,*R*)-9b]. Yield: 13% (>95% ^{31}P NMR purity). $R_f = 0.3$ (PE/EtOAc, 6:1). $[\alpha]_D^{20} = -194$ (*c* 1.00, CH_2Cl_2). ^1H NMR (500 MHz, CD_2Cl_2): δ 1.40 (br d, $J = 13.5$ Hz, 1H, 2-H), 1.50−1.84 (m, 20H, 2′-H, 3′-H, 2-H, 4-H, 7-H), 2.16−2.32 (m, 4H, 4′-H), 2.36 (dd, $J = 13.0$ Hz, $J = 7.1$ Hz, 1H, 7-H), 2.60−2.90 (m, 12H, 1′-H, 4′-H), 3.31−3.35 (m, 1H, 1-H), 3.63−3.80 (m, 5H, 5-H, OCH_2CH_2O), 4.77 (ddt, $J = 10.7$ Hz, $J = 6.7$ Hz, $J = 1.9$ Hz, 1H, 6-H), 6.68−7.12 ppm (m, 8H, Ar). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 22.1, 22.16, 22.24, 22.29, 22.32, 22.5 (C-2′, C-3′), 27.2, 27.3, 27.36, 27.43 (C-4′), 28.66, 28.73 (C-1′), 40.5, 40.8, 41.6 (C-2, C-4, C-7), 53.0, 53.2 (C-1), 61.0, 61.3 (C-5), 62.9 (OCH_2CH_2O), 63.8 (OCH_2CH_2O), 77.7 (C-6), 106.5 (C-3), 118.05, 118.10, 118.4, 118.5, 127.5, 127.6, 128.3, 128.8, 128.9, 129.0, 132.9, 133.3, 133.8, 134.5, 136.9, 137.6, 137.7, 138.0, 146.27, 146.34, 146.77, 146.81, 147.9, 148.4, 148.8 ppm. (Due to interference and P−C-coupling, signals are given as they appear in the spectrum.) ^{31}P NMR (202.5 MHz, CD_2Cl_2): δ 132.8, 133.9 ppm. MS (DCI, CH_4): *m*/*z* (%) 929 (2) [M^+], 681 (3), 507 (2), 490 (2), 389 (18), 343 (100), 341 (100), 294 (20), 276 (10). HRMS (EI): calcd for $C_{11}H_{21}N_4O_5$ 829.3297, found 829.3288 [M^+]. FT-IR (ATR): $\tilde{\nu}$ 2926 (vs), 2857 (s), 1737 (vs), 1583 (m), 1465 (s), 1436 (s), 1351 (m), 1216 (vs), 1164 (m), 1081 (s), 1051 (s), 978 (s), 933 (vs), 781 cm^{-1} (vs).

(*S*,6*S*)-8-[2-(Methylthio)ethyl]-6-(8,9,10,11,12,13,14,15-octahydrodinaphtho[1,2-*f*:2′,1′-*d*][1,3,2]dioxaphosphepin-4-yloxy)spiro-[8-azabicyclo[3.2.1]octane-3,2′-[1,3]dioxolane] [8*H*-(*S*)-11b]. Yield: 62% (>95% ^{31}P NMR purity). $R_f = 0.3$ (EtOAc). $[\alpha]_D^{20} = +200$ (*c* 1.00, CH_2Cl_2). ^1H NMR (500 MHz, CD_2Cl_2): δ 1.48 (dt, $J = 13.8$ Hz, $J = 2.3$ Hz, 1H, 2-H), 1.51−1.60 (m, 3H, 4-H, 2′-H, 3′-H), 1.73−1.82 (m, 6H, 2′-H, 3′-H), 1.85 (dd, $J = 13.8$ Hz, $J = 4.1$ Hz, 1H, 2-H), 1.92 (dd, $J = 14.1$ Hz, $J = 2.8$ Hz, 1H, 4-H), 1.96 (dd, $J = 13.5$ Hz, $J = 7.3$ Hz, 1H, 7-H), 2.10 (s, 3H, *Me*S), 2.19−2.28 (m, 2H, 1′-H), 2.43 (dd, $J = 13.5$ Hz, $J = 7.4$ Hz, 1H, 7-H), 2.57 (t, $J = 7.6$ Hz, 2H, 9-H), 2.61−2.70 (m, 2H, 1′-H), 2.75−2.90 (m, 6H, 8-H, 4′-H), 3.30−3.33 (br, 1H, 5-H), 3.39−3.43 (m, 1H, 1-H), 3.72−3.86 (m, 4H, OCH_2CH_2O), 4.90 (ddd, $J = 10.3$ Hz, $J = 7.4$ Hz, $J = 2.6$ Hz, 1H, 6-H), 6.86 (d, $J = 8.1$ Hz, 1H, Ar), 6.97 (d, $J = 8.1$ Hz, 1H, Ar), 7.08 ppm (t, $J = 8.1$ Hz, 2H, Ar). ^{13}C NMR (125 MHz, CD_2Cl_2): δ 15.3 (*Me*S), 22.1, 22.2, 22.29, 22.32 (C-2′, C-3′), 27.3, 27.4 (C-4′), 28.7 (C-1′), 33.1 (C-9), 35.6 (C-2), 37.1 (C-4), 37.67, 37.70 (C-7), 49.4 (C-8), 57.6 (C-1), 62.8 (OCH_2CH_2O), 63.8 (OCH_2CH_2O), 65.25, 65.28 (C-5), 78.6, 78.7 (C-6), 106.2 (C-3), 118.26, 118.31, 118.4, 127.26, 127.31, 128.8, 128.86, 128.89, 133.3, 134.4, 137.2, 138.0, 146.1, 146.16, 146.19 ppm. (Due to interference and P−C-coupling, signals are given as they appear in the spectrum.) ^{31}P NMR (202.5 MHz, CD_2Cl_2): δ 137.2 ppm. MS (EI): *m*/*z* (%) 581 (8) [M^+], 580 (8) [$M - H^+$], 566 (60), 520 (100), 340 (15), 180 (25), 136 (10). HRMS (EI): calcd for $C_{32}H_{40}NO_5PS$ 581.2365, found 531.2371 [M^+]. FT-IR (ATR): $\tilde{\nu}$ 2970 (m), 2927 (m), 1738 (vs), 1588 (m), 1506 (m), 1463 (s), 1432 (m), 1365 (s), 1229 (vs), 1220 (vs), 1091 (s), 1068 (s), 938 (vs), 819 (s), 799 cm^{-1} (s).

General Procedure for the Synthesis of Racemic 1,4-Addition Products 15 and 17.[2c] Triethyl phosphite (10 μL, 59 μmol) and $Cu(OTf)_2$ (10 mg, 27 μmol) in absolute toluene (5 mL) were ultrasonificated at room temperature and cooled to −20 °C, and a 1 M solution of diethylzinc in hexane (1.5 mL) was added. After stirring for 5 min, a solution of the respective enone (1.00 mmol) in toluene (250 μL) was added and the reaction mixture stirred at −20 °C (aliphatic enones) or 0 °C to room temperature (aromatic enones) (tlc control). The reaction was quenched with saturated NH_4Cl and EDTA solution, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. In the case of lower

homologues, toluene was removed by chromatography with pentane. The residue was chromatographed on SiO_2 with pentane/Et_2O to give the products which were used as reference compounds for ee determination.

General Procedure for Asymmetric 1,4-Additions. The respective ligand (2 mol %) and $Cu(OAc)_2 \cdot H_2O$ (1.0 mg, 1 mol %) in absolute toluene (0.7 mL) were ultrasonificated. After addition of a 1 M solution of Et_2Zn in toluene (0.75 mL), the reaction mixture was ultrasonificated until a clear solution was obtained. Then it was cooled to −20 °C (method A) or 0 °C (method B), the respective substrate **14** or **16** (0.50 mmol) was added, and the reaction mixture was stirred for 12 h. The reaction was quenched with a saturated NH_4Cl and EDTA solution, and the reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine and dried ($MgSO_4$), and then a defined amount of internal standard dodecane was added to the product **15** or **17**. After dilution, the mixture was directly analyzed by GC or HPLC.

3-Ethylcyclopentanone (15a).[18] **Method A.** The spectroscopic data are in accordance with the literature. GC: Bondex un α (20 m × 0.25 mm, 0.4 bar H_2), 40 °C isotherm (3 min), then gradient 1 °C min^{-1}. t_{R1} = 31.25 min, t_{R2} = 31.72 min.

3-Ethylcyclohexanone (15b).[18] **Method A.** The spectroscopic data are in accordance with the literature. GC: GTA (Astec) [30 m × 0.25 mm, H_2 (flow 15 mL min^{-1})], 40 °C isotherm (1 min), then gradient 1 °C min^{-1}. t_{R1} = 15.40 min, t_{R2} = 15.82 min.

3-Ethylcycloheptanone (15c).[18] **Method A.** The spectroscopic data are in accordance with the literature. GC: Bondex un β (20 m × 0.25 mm, 0.4 bar H_2), 60 °C isotherm (2 min), then gradient 2 °C min^{-1}. t_{R1} = 19.03 min, t_{R2} = 19.56 min.

3-Ethylcyclooctanone [15d].[18] **Method A.** The spectroscopic data are in accordance with the literature. GC: Bondex un α (20 m × 0.25 mm, 0.4 bar H_2), 40 °C isotherm (1 min), then gradient 2.5 °C min^{-1}. t_{R1} = 28.95 min, t_{R2} = 29.21 min.

3-Methylcyclohexanone [15e].[18] **Method B.** The spectroscopic data are in accordance with the literature. GC: ATA (Astec) [30 m × 0.25 mm, H_2 (flow 6 mL min^{-1})], 40 °C isotherm (1 min), then gradient 1 °C min^{-1}. t_{R1} = 15.48 min, t_{R2} = 16.56 min.

3-Ethyloctanone [17a].[18] **Method A.** The spectroscopic data are in accordance with the literature. GC: Amidex P22.10 (20 m × 0.25 mm, 0.4 bar H_2), 40 °C isotherm (1 min), then gradient 2 °C min^{-1}. t_{R1} = 17.18 min, t_{R2} = 17.51 min.

4-Phenylhexan-2-one (17b).[18] **Method B.** The spectroscopic data are in accordance with the literature. HPLC: Chiralcel ODH (250 mm × 4.6 mm), hexane/*i*-PrOH, 98:2, flow 1 mL min^{-1}. t_{R1} = 10.02 min, t_{R2} = 11.39 min.

1,3-Diphenylpentanone (17c).[2a] **Method B.** The spectroscopic data are in accordance with the literature. HPLC: Chiralcel ODH (250 mm × 4.6 mm), hexane/*i*-PrOH, 99:1, flow 1.5 mL min^{-1}. t_{R1} = 17.63 min, t_{R2} = 21.81 min.

4-(2-Thienyl)hexan-2-one (17d). Method B. R_f = 0.35 (PE/EtOAc, 3:1). ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.3 Hz, 3H, 6-H), 1.52−1.76 (m, 2H, 5-H), 2.07 (s, 3H, 1-H), 2.73 (dd, *J* = 16.4 Hz, *J* = 6.7 Hz, 1H, 3-H), 2.78 (dd, *J* = 16.4 Hz, *J* = 7.4 Hz, 1H, 3-H), 3.36−3.42 (m, 1H, 4-H), 6.80 (d, *J* = 3.4 Hz, 1H, Ar), 6.90 (dd, *J* = 5.1 Hz, *J* = 3.4 Hz, 1H, Ar), 7.13 ppm (d, *J* = 5.1 Hz, 1H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7 (C-6), 30.3 (C-5), 30.6 (C-1), 38.1 (C-4), 51.1 (C-3), 122.9 (Ar), 123.9 (Ar), 126.4 (Ar), 148.2 (Ar), 207.3 ppm (C-2). MS (EI): *m*/*z* (%) 182 (100) [M^+], 153 (70), 139 (70), 125 (95), 124 (40), 111 (20), 97 (95). HRMS (EI): calcd for $C_{10}H_{14}OS$ 182.0765, found 182.0765 [M^+]. FT-IR (ATR): $\tilde{\nu}$ 2962 (m), 2928 (m), 2874 (m), 1713 (vs), 1458 (m), 1408 (m), 1356 (s), 1160 (s), 825 (m), 691 cm^{-1} (vs). GC: GTA [30 m × 0.25 mm, H_2 (flow 15 mL min^{-1})], 60 °C isotherm (1 min), then gradient 2.5 °C min^{-1}. t_{R1} = 20.13 min, t_{R2} = 20.43 min.

4-(2-Furyl)hexan-2-one (17e).[18] **Method A.** The spectroscopic data are in accordance with the literature. GC: Amidex P22.10 (20 m × 0.25 mm, 0.4 bar H_2), 40 °C isotherm (1 min), then gradient 2.5 °C min^{-1}. t_{R1} = 19.49 min, t_{R2} = 19.83 min.

4-(*p*-Methoxyphenyl)hexan-2-one (17f).[18] **Method B.** The spectroscopic data are in accordance with the literature. HPLC: Chiralcel ODH (250 mm × 4.6 mm), hexane/*i*-PrOH, 98:2, flow 1 mL min^{-1}. t_{R1} = 14.23 min, t_{R2} = 16.87 min.

4-(*p*-Chlorophenyl)hexan-2-one (17g).[18] **Method A.** The spectroscopic data are in accordance with the literature. HPLC: Chiralcel OJH (250 mm × 4.6 mm), hexane/*i*-PrOH, 98:2, flow 1 mL min^{-1}. t_{R1} = 7.84 min, t_{R2} = 8.83 min.

General Procedure for the Synthesis of Racemic Hydrogenation Products 19 and 21. A suspension of **18** or **20** (0.50 mmol) and 10% Pd/C (15 mg) in MeOH (5 mL) was vigorously stirred for 1 h under H_2 atmosphere. The catalyst was filtered off through a short pad of Celite, and the filtrate was concentrated in vacuo. The product **19** or **21** was obtained quantitatively and used as reference for enantioselectivity determination.

Asymmetric Hydrogenation. The respective **18** or **20** (0.50 mmol) was added to a solution of the appropriate ligand (5.00 μmol, 1 mol %) and [RhCOD]BF_4 (2.0 mg, 5 μmol, 1 mol %) in absolute CH_2Cl_2 (4 mL) under 1 atm of H_2, and the reaction mixture was stirred for 14 h. Then it was diluted and directly used for determination of conversion and selectivity by GC.

Dimethyl 2-Methylsuccinate (20).[20] The spectroscopic data are in accordance with the literature. GC: GTA [30 m × 0.25 mm, H_2 (flow 8 mL min^{-1})], 40 °C isotherm (1 min), then gradient 1 °C min^{-1}. t_{R1} = 38.96 min, t_{R2} = 40.24 min.

Methyl *N*-Acetylphenylalaninate (21).[20] The spectroscopic data are in accordance with the literature. GC: Bondex un β (20 m × 0.25 mm, 0.4 bar H_2), 100 °C isotherm (3 min), then gradient 1.5 °C min^{-1}. t_{R1} = 33.40 min, t_{R2} = 33.93 min.

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