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Rh-Catalyzed Asymmetric Hydroformylation of Heterocyclic Olefins Using Chiral Diphosphite Ligands. Scope and Limitations

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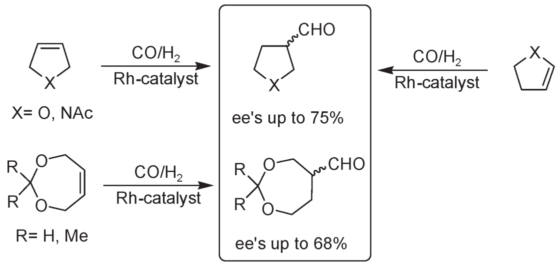

We used a series of diphosphite ligands to study the effect of the ligand backbone, the length of the bridge, and the substituents of the biphenyl moieties and determine the scope of this type of ligand in the Rh-catalyzed asymmetric hydroformylation of several hetereocylic olefins. By carefully selecting the ligand components, we achieved high chemo-, regio-, and enantioselectivities in different substrate types. Unprecedentedly high enantioselectivities for five-membered heterocyclic olefins were therefore obtained. Note that both enantiomers of the hydroformylation products can be synthesized using the same ligand by a simple substrate change. For the seven-membered heterocyclic dioxepines, our results are among the best obtained. Also, both enantiomers of the hydroformylation products can be obtained by using pseudoenantiomer ligands or by carefully tuning the ligand parameters.

1. Introduction

Asymmetric hydroformylation has attracted much attention as a potential tool for preparing enantiomerically pure aldehydes.[1] Despite its importance, asymmetric hydroformylation is underdeveloped compared to other processes such as hydrogenation. Traditionally, vinylarenes have been the most studied substrates. Although Rh−diphosphites and Rh−Binaphos-type phosphine−phosphites have proved to be the most efficient catalytic systems,[2] recently diphospholane,[3] bis(diazaphospholodine),[4] and phosphine−phosphoroamidite[5] have emerged as suitable alternatives. The use of these latter ligands has allowed the successful Rh-catalyzed hydroformylation of other type of substrates, like allyl cyanide, vinyl acetate, and some byciclic olefins.[3−5] However, more research is still needed to expand the range of substrates to be studied. In this respect, few studies have been made on the asymmetric hydroformylation of heterocyclic

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(1) See, for example: (a) Claver, C.; Diéguez, M.; Pàmies, O.; Castillón, S. In *Topics in Organometallic Chemistry*; Beller, M., Ed.; Springer: Berlin, 2006; Chapter 2, p 35. (b) Claver, C.; Godard, C., Ruiz, A.; Pàmies, O.; Diéguez, M. In *Modern Carbonylation Methods*; Kollár, L., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 3. (c) Nozaki, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Chapter 11, p 382.

(2) See, for example: (a) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. (b) Breit, B. *Top. Curr. Chem.* **2007**, *279*, 139. (c) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251. (d) *Rhodium Catalysed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Press: Dordrecht, 2000. (e) Claver, C.; Pàmies, O.; Diéguez, M. In *Phosphorous Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 3, Vol. 2.

(3) See, for example: (a) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5834. (b) Huang, J.; Bunel, E.; Allgeier, A.; Tedrow, J.; Storz, T.; Preston, J.; Correll, T.; Manley, D.; Soukup, T.; Jensen, R.; Syed, R.; Moniz, G.; Larsen, R.; Martinelli, M.; Reider, P. J. *Tetrahedon Lett.* **2005**, *46*, 7831.

(4) See, for instance: (a) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040. (b) Thomas, P. J.; Axtell, A. T.; Klosin, J.; Peng, W.; Rand, C. L.; Clark, T. P.; Landis, C. R.; Abboud, K. A. *Org. Lett.* **2007**, *9*, 2665. (c) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4106. (d) Peng, X.; Wang, Z.; Xia, C.; Ding, K. *Tetrahedron Lett.* **2008**, *49*, 4862.

(5) Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198.

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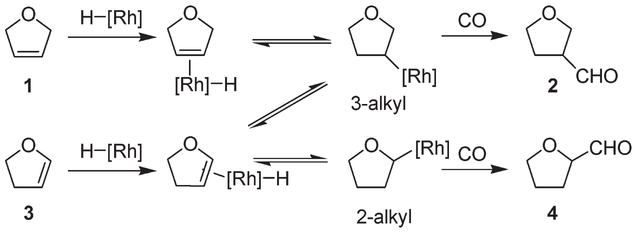
olefins, which provide access to important building blocks for synthesizing natural products and pharmaceuticals.[6] This is mainly because, for this kind of substrate, as well as having to control the enantioselectivity of the process, chemo- and regioselectivity are often a problem.[6,7] For example, in the hydroformylation of 2,5-dihydrofuran **1** the expected product is tetrahydrofuran-3-carbaldehyde **2** (Scheme 1). However, considerable amounts of 2,3-dihydrofuran **3** and tetrahydrofuran-2-carbaldehyde **4** can also be formed due to an isomerization process that takes place simultaneously with the hydroformylation reaction. When the 2,5-dihydrofuran **1** reacts with the rhodium hydride complex, the 3-alkyl intermediate is formed. This can evolve to 2,3-dihydrofuran **3** via the β-hydride elimination reaction. Similarly, this new substrate can evolve to produce the 2-alkyl and 3-alkyl intermediates. Although the formation of the 3-alkyl intermediate is thermodynamically favored, the acylation occurs faster in the 2-alkyl intermediate.[6b] Regioselectivity is therefore dominated by the rate at which the acyl complex is formed.

For a considerable time, only the phosphine−phosphite binaphos ligand provided good regio- and enantiocontrol in the Rh-catalyzed asymmetric hydroformylation of heterocyclic compounds.[8] Several diphosphines,[6c] including some diphospholanes and the bis-(diazaphospholodine) ESPHOS ligand,[9] have been applied but with little success (ee's up to 32%). When diphosphites were used as ligands for the Rh-catalyzed hydroformylation of vinylarenes, activities and enantioselectivities were comparable to the best in the literature, obtained using the binaphos ligand.[2] However, they have been used very little in the hydroformylation of heterocyclic substrates. This is mainly because extensive isomerization had been observed when phosphite ligands are used.[7]

In 2005, we reported the first successful application of a diphosphite ligand in the Rh-catalyzed asymmetric hydroformylation of 2,5- and 2,3-dihydrofurans.[10] Despite this success, other diphosphite ligands have not yet been reported, and the possibilities offered by diphosphites as new ligands for this process still need to be studied. To fully investigate these possibilities, in this paper we extend our previous study (2005) to other diphosphite ligands (Figure 1) and other types of heterocyclic olefins.

To do so, we have synthesized and screened a library of 64 potential diphosphite ligands.[11] The ligands we have chosen are representative of the most successfully applied families of diphosphite ligands in hydroformylation (chiraphite **L3**, sugar derivatives **L4** and **L7**, and kelliphite **L17**). We have also evaluated systematic modifications of several ligand parameters in these prominent ligands, which are known to have an important effect on catalytic performance. Therefore, with this library, we have investigated how the ligand backbone, the length of the bridge, and the substituents of the biphenyl moieties affected activities and selectivities (chemo-, regio-, and enantioselectivity). By carefully selecting these elements, we have achieved high regio- and enantioselectivities and activities in different substrates.

SCHEME 1. Proposed Mechanism for the Isomerization Process



2. Results and Discussion

2.1. Asymmetric Hydroformylation of Five-Membered Heterocyclic Olefins. Diphosphite ligands **L1**−**L17a**−**e** were first used in the Rh-catalyzed asymmetric hydroformylation of 2,5-dihydrofuran **1**. The catalysts were prepared in situ by adding the corresponding diphosphite ligand to [Rh(acac)-$(CO)_2$] as a catalyst precursor.

Initially, we determined the optimal reaction conditions by conducting a series of experiments with ligand **L10c** in which the ligand-to-rhodium ratio, CO/H_2 pressure ratio, temperature, reaction time, and substrate-to-rhodium ratio were varied (Table 1).

Varying the ligand-to-rhodium ratio showed that the combination of chemo-, regio-, and enantioselectivities was best when 2 equiv of ligand was used (Table 1, entries 1−3). A lower ligand-to-rhodium ratio decreased the regio- and enantioselectivities in aldehyde **2** (Table 1, entry 1), while a higher ligand-to-rhodium ratio negatively affected chemoselectivity and increased the formation of isomerized product **3** (Table 1, entry 3).

It is generally accepted that isomerization occurs as a result of competition between the β-hydride elimination process and CO insertion (Scheme 1). Since a high CO pressure is needed to suppress isomerization, we conducted experiments with increased CO partial pressure. This did not affect the rate of hydroformylation vs isomerization (Table 1, entries 2 vs 5), though decreasing the CO/H_2 pressure ratio negatively affected chemoselectivity, which increased the formation of isomerized product **3** (Table 1, entries 2 vs 6).

A prolonged reaction time increased conversion into aldehydes (Table 1, entry 4) but decreased regio- and enantioselectivity in the desired product **2** (Table 1, entry 2 vs 4). To study whether the hydroformylation of the formed isomer 2,3-dihydrofuran **3** accounts for this lost of selectivity, we performed the hydroformylation of **3** under the same reaction conditions. After 48 h, the hydroformylation of **3** afforded a 78:22 mixture of (*R*)-**2** (48% ee) and **4** in 88% conversion (Table 3, entry 11). By comparing these results, we concluded that the loss of regioselectivity with the

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[6] (a) Vietti, D. E. U.S. Patent 4376208, 1983.(b) Hoiuchi, T.; Ota, T.; Shirakawa, E.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1997**, *62*, 4285. (c) del Rio, I.; van Leeuwen, P. W. N. M.; Claver, C. *Can. J. Chem.* **2001**, *79*, 560.

[7] (a) Polo, A.; Real, J.; Claver, C.; Castillón and, S.; Bayón, J. C. *J. Chem. Soc., Chem. Commun.* **1990**, 600. (b) Polo, A.; Claver, C.; Castillón, S.; Ruiz, A.; Bayón, J. C.; Real, J.; Mealli and, C.; Masi, D. *Organometallics* **1992**, *11*, 3525.

[8] Several modifications of the Binaphos-type ligand have been studied. See ref 6b.

[9] Unpublished results. For instance: (*R,R*)-Ph-BPE (22% ee), (*R,R*)-^{i}Pr-BPE (18% ee), and ESPHOS (32% ee).

[10] Diéguez, M.; Pàmies, O.; Claver, C. *Chem. Commun.* **2005**, 1221.

[11] These ligands have the advantages of phosphite ligands: they are obtainable at a low price from readily available alcohols, are highly resistant to oxidation, and have facile modular constructions. See, for instance: (a) Reference 2e. (b) Diéguez, M.; Pàmies, O.; Ruiz, A.; Claver, C. In *Methodologies in Asymmetric Catalysis*; American Chemical Society: Washington, DC, 2004; Chapter 11.

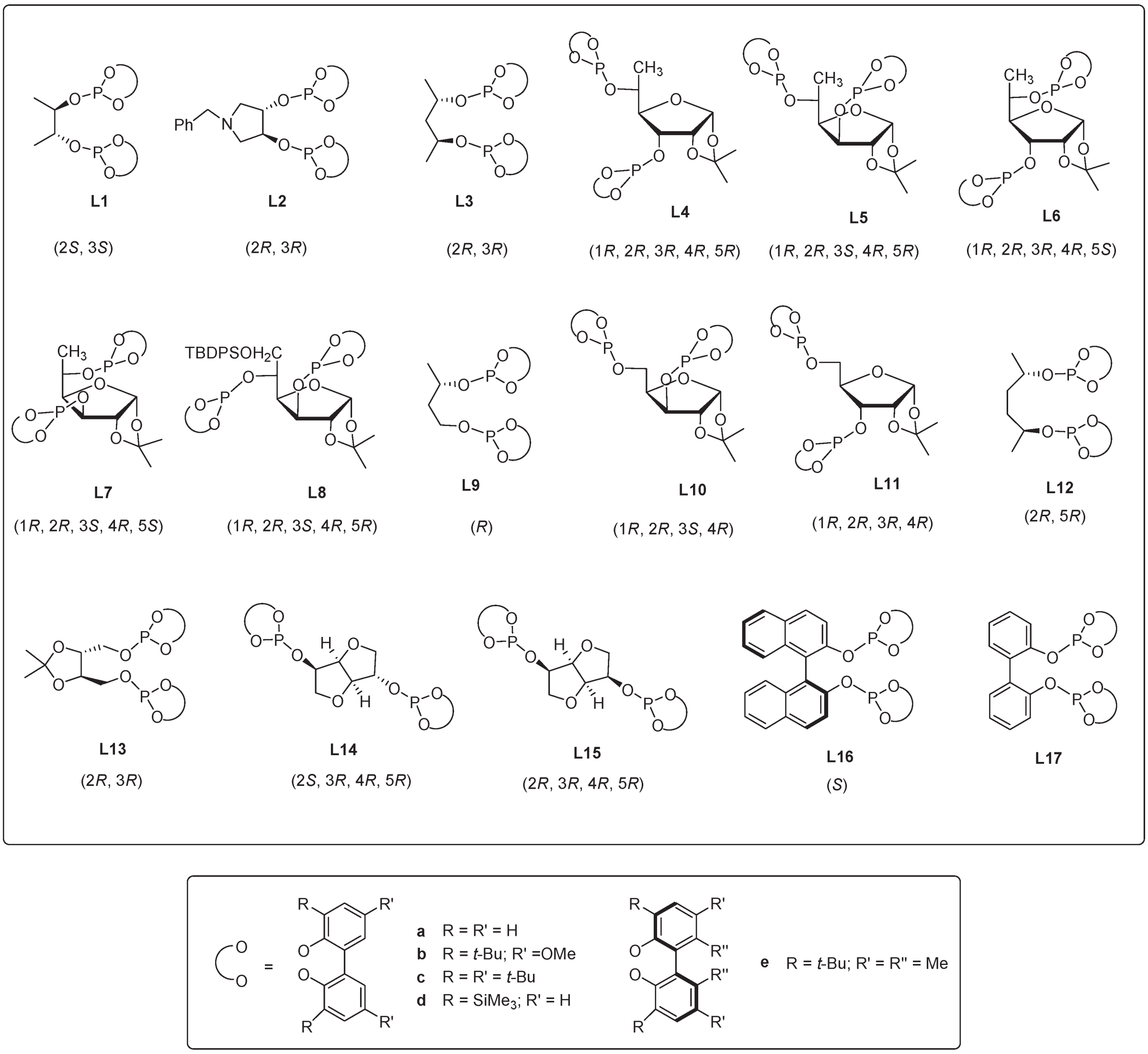


FIGURE 1. Disphosphite ligands **L1**−**L17a**−**e** used in the Rh-catalyzed asymmetric hydroformylation of heterocyclic olefins.

prolonged reaction time was due to the hydroformylation of the 2,3-dihydrofuran **3** formed under reaction conditions. This also caused a loss of enantioselectivity because the absolute configuration of the predominant enantiomer of **2** obtained from **3** is *R*, which is opposite to that which is obtained from **1**. These results show that the absence of isomerization of the substrate is important for achieving high enantioselectivity from the reaction of **1**. Indeed, the ee of **2** dropped when the hydroformylation of **3** (which is formed from the isomerization of **1**) took place at a low ligand-to-rhodium ratio (Table 1, entry 1). Accordingly, a decrease in the substrate-to-rhodium ratio had a negative effect on regio- and enantioselectivity because of the hydroformylation of the isomerization product **3** (Table 1, entry 7).

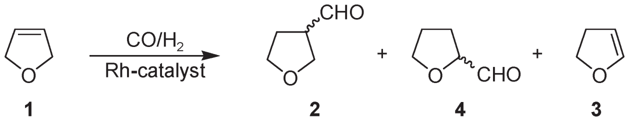
Varying the temperature strongly affects chemo- and regioselectivity (Table 1, entries 2, 8, and 9). Increasing the temperature negatively affected regioselectivity, whereas lowering the temperature to 25 °C negatively affected activity and chemoselectivity. This is because at high temperature hydroformylation of the isomerized 2,3-dihydrofuran **3** takes place. The best trade-off between chemo- and regioselectivities was therefore achieved at 45 °C.

For the purpose of comparison, the other ligands were tested under optimized conditions (i.e., ligand-to-rhodium ratio of 2, $P_{CO/H2} = 1$, 24 h reaction time at 45 °C). Our results indicate that selectivity is affected by the length of the bridge, the backbone of the ligand, and the substituents of the biphenyl moieties (see Table 2). In no cases were hydrogenated or polymerized products of 2,5-dihydrofuran observed.

The influence of the bridge length indicates that the use of 1,3-diphosphites provided a better catalytic performance than 1,2- and 1,4-diphosphites. Ligands **L3**−**L11**, which have three carbon atoms in the bridge (Table 2, entries 3−18), therefore provided higher regio- and enantioselectivities than ligands **L1**−**L2** (Table 2, entries 1 and 2), which have two carbon atoms in the bridge, and ligands **L12**−**L17** (Table 2, entries 19−24), which have four carbon atoms in the bridge.

The influence of the ligand backbone indicates that increasing the rigidity of the ligand is beneficial. Our results with ligands **L3c** and **L9c** are therefore worse than those with the corresponding ligands **L4c** and **L11c**, which have the same configuration of carbons adjacent to the phosphite

TABLE 1. Rh-Catalyzed Asymmetric Hydroformylation of 1 Using Ligand L10c. Optimization of the Reaction Conditions[a]



entry	ligand	L/Rh	CO/H_2	% conv[b]	% aldehyde (**2**:**4**)[c]	% **3**[d]	% ee of **2**[e]
1	**L10c**	1.1	1	100	82 (89:11)	18	31 (*S*)
2	**L10c**	2	1	100	88 (100:0)	12	53 (*S*)
3	**L10c**	4	1	100	75 (100:0)	25	53 (*S*)
4[f]	**L10c**	2	1	100	98 (95:5)	2	37 (*S*)
5	**L10c**	2	2	100	87 (100:0)	13	53 (*S*)
6	**L10c**	2	0.5	91	59 (100:0)	32	52 (*S*)
7[f,g]	**L10c**	2	1	100	100 (92:8)	0	34 (*S*)
8[h]	**L10c**	2	1	26	13 (100:0)	13	54 (*S*)
9[i]	**L10c**	2	1	100	94 (98:2)	6	51 (*S*)

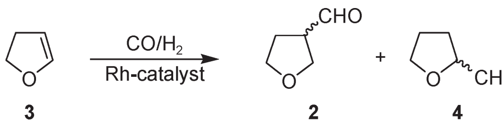
[a] P = 18 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **1**/Rh = 400, toluene (5 mL). T = 45 °C, t = 24 h. [b] Total conversion measured by ^1H NMR. [c] Conversion into aldehydes determined by ^1H NMR. [d] Isomerization measured by ^1H NMR. [e] Enantioselectivity of **2** measured by ^1H NMR using $Eu(hfc)_3$ on the corresponding methyl ester. [f] t = 48 h. [g] **1**/Rh= 200. [h] T = 25 °C. [i] T = 65 °C.

TABLE 2. Rh-Catalyzed Asymmetric Hydroformylation of 1 Using Ligands L1−L16a−d[a]

entry	ligand	% conv[b]	% aldehyde (**2**:**4**)[c]	% **3**[d]	% ee of **2**[e]
1	**L1c**	100	100 (72:28)	0	> 5
2	**L2c**	100	70 (97:3)	30	6 (*S*)
3	**L3c**	100	99 (95:5)	1	23 (*R*)
4	**L4c**	100	92 (98:2)	8	47 (*R*)
5	**L5a**	76	64 (99:1)	8	> 5
6	**L5b**	98	86 (98:2)	12	43 (*S*)
7	**L5c**	100	99 (99:1)	1	74 (*S*)
8	**L5d**	100	98 (99:1)	2	63 (*S*)
9	**L6c**	90	75 (96:4)	15	27 (*R*)
10	**L7c**	100	94 (98:2)	6	25 (*R*)
11	**L8c**	100	92 (97:3)	8	61 (*S*)
12	**L9c**	100	100 (85:15)	0	14 (*R*)
13	**L10a**	61	55 (99:1)	6	> 5
14	**L10b**	73	66 (98:2)	7	15 (*S*)
15	**L10c**	100	88 (100:0)	12	53 (*S*)
16	**L10d**	100	89 (99:1)	11	34 (*S*)
17	**L11b**	100	100 (77:23)	0	5 (*S*)
18	**L11c**	100	91 (95:5)	9	24 (*R*)
19	**L12c**	100	100 (64:36)	0	> 5
20	**L13c**	100	100 (99:1)	0	> 5
21	**L14c**	100	100 (78:22)	0	7 (*S*)
22	**L15c**	100	100 (82:18)	0	> 5
23	**L16c**	100	100 (96:4)	0	15 (*R*)
24	**L17e**	100	100 (100:0)	0	24 (*R*)
25[f]	**binaphos**	100	100 (100:0)	0	64 (*R*)

[a] P = 18 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **1**/Rh = 400, toluene (5 mL), T = 45 °C, t = 24 h. [b] Total conversion measured by ^1H NMR. [c] Conversion into aldehydes determined by ^1H NMR. [d] Isomerization measured by ^1H NMR. [e] Enantioselectivity of **2** measured by ^1H NMR using $Eu(hfc)_3$ on the corresponding methyl ester. [f] P=20 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **1**/Rh = 400, benzene (1.5 mL), ligand/Rh = 4, T = 40 °C, t = 24 h (see ref 6b).

TABLE 3. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of 3[a]



entry	ligand	% conv[b]	% aldehyde (**2**:**4**)[c]	% ee of **2**[d]
1	**L1c**	100	100 (54:46)	< 5
2	**L3c**	100	100 (68:32)	43 (*S*)
3	**L4c**	100	100 (73:27)	48 (*S*)
4	**L5a**	80	80 (75:25)	< 5
5	**L5b**	100	100 (74:26)	49 (*R*)
6	**L5c**	100	100 (76:24)	75 (*R*)
7	**L5d**	100	100 (73:27)	61 (*R*)
8	**L6c**	100	97 (70:30)	29 (*S*)
9	**L7c**	100	92 (69:31)	21 (*S*)
10	**L8c**	100	100 (72:28)	58 (*R*)
11	**L10c**	88	88 (78:22)	48 (*R*)
12	**L12c**	100	100 (55:45)	< 5
13	**L13c**	100	100 (50:50)	< 5
14[e]	**binaphos**	100	100 (50:50)	38 (*S*)

[a] P = 18 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **3**/Rh = 400, toluene (5 mL), T = 45 °C, t = 48 h. [b] Total conversion measured by ^1H NMR. [c] Conversion into aldehydes determined by ^1H NMR. [d] Enantioselectivity of **2** measured by ^1H NMR using $Eu(hfc)_3$ on the corresponding methyl ester. [e] P = 100 bar, [Rh(acac)$(CO)_2$] (0.012 mmol), **3**/Rh = 400, benzene (1.5 mL), ligand/Rh = 4, T = 40 °C, t = 24 h (see ref 6b).

groups but also a more rigid furanoside backbone (Table 2, entries 3 and 12 vs 4 and 18, respectively). We also found that both carbon atoms adjacent to the phosphite moieties must be substituted if regio-, chemo-, and enantioselectivity need to be high. Accordingly, ligands **L3**−**L5**, substituted at both carbon atoms adjacent to the phosphite, provided higher selectivities than ligands **L9**−**L11**, which are substituted only at one carbon atom (Table 2, entries 3, 4, and 7 vs 12, 15, and 18). For disubstituted ligands, we also found that the presence of a methyl substituent is more effective at transferring the chiral information than the presence of a *tert*-butyldimethylsilyl group (Table 2, entries 7 vs 11). Finally, our results with ligands **L4**−**L7** indicate that there is a cooperative effect between stereocenters C-3 and C-5 of the furanoside backbone that resulted in a matched combination for ligand **L5** (Table 2, entries 7 vs 4, 9 and 10).

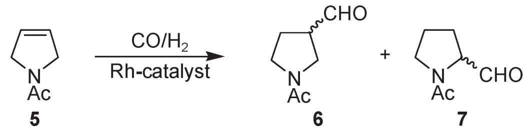
We investigated the effect of the biphenyl substituents with ligands **L5**, **L10**, and **L11** (Table 2, entries 5−8, 13−18) and found that these moieties affect catalytic performance. Bulky substituents in the *ortho* and *para* positions of the biphenyl moieties are needed for high enantioselectivity. Therefore, ligand **L5c** provided the highest enantioselectivity (Table 2, entry 7).

In summary, if chemo-, regio-, and enantioselectivities are to be high, the length of the bridge and the rigidity of the ligand backbone need to be correctly combined and bulky *tert*-butyl groups in both the *ortho* and *para* positions of the biphenyl phosphite moieties need to be present. Accordingly, ligand **L5c** showed practically no isomerization with excellent regioselectivity (99%) and unprecedently high enantioselectivity (ee's of 74%). Ligand **L5c** therefore competes favorably with the binaphos ligand, which so far has provided the best enantioselectivities for this substrate (Table 2, entry 7 vs 25).

Next we applied diphosphite ligands **L1**−**L17a**−**e** in the Rh-catalyzed asymmetric hydroformylation of 2,3-dihydrofuran **3**. Our results are summarized in Table 3. In no cases were isomerized (product **1**), hydrogenated, or polymerized products of 2,3-dihydrofuran observed.

Our results followed the same trend as for the hydroformylation of **1**. The selectivities of the process were affected by the length of the bridge, the backbone of the ligand, and the substituents of the biphenyl moieties. Accordingly, 1,3-diphosphites (Table 3, entries 2−11) were superior in terms of regio- and enantioselectivities to the 1,2- and 1,4-diphosphites (Table 3, entries 1 and 12−13, respectively). Again, ligand **L5c**, with a methyl substituent at the C-5 position, provided unprecedented enantioselectivities in favor of the tetrahydrofuran-3-carbaldehyde **2** (Table 3, entry 6). Note, however, that the sense of the enantioselectivity was opposite to that in the hydroformylation of 2,5-dihydrofuran **1** (Table 2, entry 7 vs Table 3, entry 6). Using the same ligand **L5c**, therefore, both enantiomers of tetrahydrofuran-3-carbaldehyde **2** can be accessed in high enantioselectivity by simple substrate change. Again, these results compete favorably with the best of those reported using the binaphos ligand (Table 3, entry 6 vs 14).

TABLE 4. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of 5 Using Ligands L1−L17a−e[a]

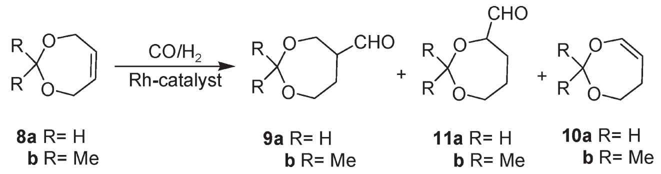


entry	ligand	% conv[b]	% aldehyde (**6**:**7**)[c]	% ee of **6**[d]
1	**L1c**	100	100 (98:2)	< 5
2	**L3c**	100	100 (100:0)	19 (−)
3	**L5c**	100	100 (100:0)	71 (+)
4	**L10c**	100	100 (99:1)	49 (+)
5	**L12c**	100	100 (98:2)	< 5
6[e]	**binaphos**	92	92 (100:0)	66 (−)

[a] P = 18 bar, [Rh(acac)(CO)$_2$] (0.012 mmol), **5**/Rh = 400, toluene (5 mL), T = 45 °C, t = 72 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Enantioselectivity of **6**. [e] P = 100 bar, [Rh(acac)(CO)$_2$] (0.012 mmol), 1/Rh = 400, benzene (1.5 mL), ligand/Rh = 4, T = 40 °C, t = 24 h (see ref 6b).

Encouraged by our excellent results in the Rh-catalyzed asymmetric hydroformylation of substrates **1** and **3**, we examined the hydroformylation of *N*-acetyl-3-pyrroline (**5**). These results, which are summarized in Table 4, follow the same trend as in the hydroformylation of **1** and **3**. As expected, activities were lower than in the hydroformylation of **1**.[6b] Again, using ligand **L5c** is highly advantageous as it provides the highest enantioselectivities obtained so far (Table 4, entry 3 vs 6).

TABLE 5. Selected Results for the Rh-Catalyzed Asymmetric Hydroformylation of 8a,b Using Ligands L1−L17a−e[a]



entry	ligand	substrate	% conv[b]	% aldehyde (**9**:**11**)[c]	% **10**[d]	% ee of **9**[e]
1	**L1c**	**8a**	100	100 (100:0)	0	8 (−)
2[f]	**L1c**	**8a**	89	89 (100:0)	0	8 (−)
3[g]	**L1c**	**8a**	88	88 (100:0)	0	7 (−)
4	**L2c**	**8a**	88	88 (100:0)	0	9 (+)
5	**L3c**	**8a**	100	100 (100:0)	0	13 (−)
6	**L4c**	**8a**	79	79 (100:0)	0	37 (−)
7	**L5a**	**8a**	54	54 (100:0)	0	< 5
8	**L5b**	**8a**	75	75 (100:0)	0	18 (+)
9	**L5c**	**8a**	85	85 (100:0)	0	23 (+)
10	**L5d**	**8a**	83	83 (100:0)	0	22 (+)
11	**L6c**	**8a**	78	51 (100:0)	27	30 (+)
12	**L7c**	**8a**	90	90 (100:0)	0	35 (+)
13	**L8c**	**8a**	93	93 (100:0)	0	47 (+)
14	**L9c**	**8a**	91	91 (100:0)	0	8 (+)
15	**L10c**	**8a**	59	59 (100:0)	0	40 (+)
16	**L11c**	**8a**	74	48 (100:0)	26	30 (+)
17	**L13c**	**8a**	100	100 (100:0)	0	5 (−)
18	**L14c**	**8a**	96	96 (100:0)	0	15 (+)
19	**L15c**	**8a**	100	100 (100:0)	0	14 (+)
20	**L16c**	**8a**	56	56 (100:0)	0	56 (−)
21	**L17e**	**8a**	98	98 (99:1)	0	37 (+)
22[h]	**L16c**	**8a**	7	7 (100:0)	0	60 (−)
23[h]	**L10c**	**8a**	12	12 (100:0)	0	60 (+)
24[h]	**L8c**	**8a**	18	18 (100:0)	0	68 (+)
25[i]	**binaphos**	**8a**	> 99	> 99 (100:0)	0	76 (−)
26[j]	**L8c**	**8b**	94	94 (100:0)	0	55 (*S*)
27[j]	**L10c**	**8b**	86	86 (100:0)	0	51 (*S*)
28[j]	**L16c**	**8b**	73	73 (100:0)	0	59 (*R*)
29[i]	**binaphos**	**8b**	98	98 (100:0)	0	69 (*R*)

[a] P = 18 bar, CO/H$_2$ = 1/2, [Rh(acac)(CO)$_2$] (0.012 mmol), L/Rh = 2, **8**/Rh = 400, toluene (5 mL), T = 45 °C, t = 4 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Isomerization measured by ^{1}H NMR. [e] Enantioselectivity of **9**. [f] CO/H$_2$ = 1. [g] CO/H$_2$ = 2. [h] T = 25 °C. t = 24 h. [i] See ref 6b. [j] t = 24 h.

2.2. Asymmetric Hydroformylation of Seven-Membered Heterocyclic Olefins. To further study the potential of these diphosphite ligands, we then tested them in the hydroformylation of *cis*-4,7-dihydro-1,3-dioxepin (**8a**) and *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepin (**8b**).

Our most important results are shown in Table 5. Again, the selectivities of the process were affected by the length of the bridge, the backbone of the ligand, and the substituents of the biphenyl moieties. However, the effect of these parameters was different from their effect on the hydroformylation of the previous substrates (**1**, **3**, and **5**). In contrast to **1**, **3**, and **5**, therefore, both 1,3- and 1,4-diphosphites can provide good regio- and enantioselectivities if the appropriate rigidity of the ligand's backbone is chosen. Accordingly, not only 1,3-diphosphite ligands **L8c** and **L10c** were shown to be effective, but the 1,4-diphosphite ligand **L16c** also provided good results. Also, and in contrast to the previous substrates, for disubstituted furanoside 1,3-diphosphites the presence of a *tert*-butyldimethylsilyl group is more effective than the presence of a methyl substituent (Table 5; entries 13 vs 9). Interestingly, both enantiomers of the hydroformylation products **9** can be obtained by using pseudoenantiomer ligands (i.e., ligands **L4** and **L7**; Table 5, entries 6 and 12) or by carefully tuning the ligand parameters (i.e., ligands **L8c** and **L10c** vs **L16c**; Table 5; entries 23 and 24 vs 22 for substrate **9a**, and entries 26 and 27 vs 28 for substrate **9b**).

We also observed an important effect of the temperature, and this was more pronounced for the furanoside-based ligands **L8c** and **L10c**; therefore, lowering the temperature to 25 °C substantially increased enantioselectivity (up to 68%) and provided an excellent regioselectivity.

3. Conclusions

We have screened a library of modular diphosphite ligands **L1−L17a−e** in the Rh-catalyzed asymmetric hydroformylation of several hetereocylic olefins. Using this library we studied how the backbone of the ligand, the length of the bridge and the substituents of the biphenyl moieties affected the catalytic performance and determined the scope of diphosphite ligands. By carefully selecting the ligand components, we achieved high chemo-, regio- and enantioselectivities in different substrate types. Unprecedentedly high enantioselectivities for five-membered heterocyclic olefins were obtained using the furanoside diphosphite ligand **L5c**. Note that both enantiomers of the hydroformylation products can be synthesized using the same ligand by simple substrate change.[6b] For the seven-membered heterocyclic dioxepines, our results are among the best obtained. Also, both enantiomers of the hydroformylation products can be obtained by using pseudoenantiomer ligands or by carefully tuning the ligand parameters. These results open up the hydroformylation of heterocyclic compounds to the potentially effective use of readily available and highly modular diphosphite ligands.

4. Experimental Section

4.1. General Considerations. All experiments were carried out under argon atmosphere. All solvents were dried using standard methods and distilled prior to use. Ligands **L1**,[12] **L2**,[13] **L3**,[12] **L4−L7**,[14] **L8**,[15] **L9**,[12] **L10**,[16] **L11**,[17] **L12**,[12] **L13**,[13] **L14**,[18] and **L15−L16**[13] were prepared by previously described methods. Kelliphite (**L17e**) and commercial substrates **1**, **3**, and **8a** and were used without further purification. *N*-Acetyl-2-pyrroline (**5**)[6b] and *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepine (**8b**)[19] were prepared according to the methods in the literature. The formation of **10a** was confirmed on the basis of the NMR assignments.[20] ^{1}H and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer. Hydroformylation reactions were carried out in a Parr series 4593 stainless steel autoclave.

4.2. Typical Hydroformylation Procedure. The autoclave was purged three times with carbon monoxide. The solution of [Rh(acac)(CO)$_2$] (3.1 mg, 0.012 mmol), diphosphite (0.024 mmol), and substrate (4.8 mmol) in toluene (5 mL) was transferred to the stainless-steel autoclave. After pressurizing to 18 bar of syngas and heating the autoclave to 45 °C, the reaction was stirred for 24 h. Conversions and selectivities of the reaction were determined immediately by ^{1}H NMR analysis of the crude reaction without evaporation of the solvent. The determination of the enantiomeric excesses and absolute configurations was carried out using the procedures described in ref 6b.

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