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Fine-tunable monodentate phosphoroamidite and aminophosphine ligands for Rh-catalyzed asymmetric hydroformylation

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ABSTRACT

A biaryl-based monophosphoroamidite **L1**–**L4a**–**f** and aminophosphine **L5**–**L7a**–**f** ligand library was screened in the Rh-catalyzed asymmetric hydroformylation of several vinylarenes and heterocyclic olefins. Our results indicate that the selectivity is strongly dependent on the ligand parameters and on the substrate type. Enantioselectivities (up to 46%) were moderate in the hydroformylation of several vinylarenes **S1**–**S5** and promising (up to 58%) for the more challenging heterocyclic olefins **S6**–**S9**.

1. Introduction

Asymmetric hydroformylation has attracted much attention as a potential tool for preparing enantiomerically pure aldehydes.[1] Despite its importance, asymmetric hydroformylation is less developed than other processes such as hydrogenation. Traditionally, vinylarenes have been the most studied substrates. Although Rh-diphosphites and Rh-phosphine-phosphite (Binaphos) have proven to be the most efficient catalytic systems,[2] recently diphospholane,[3] bis-(diazaphospholodine)[4] and phosphine-phosphoroamidite[5] have emerged as suitable alternative ligands for this process. These latter ligands have led to the successful Rh-catalyzed hydroformylation of other types of substrates, such as allyl cyanide, vinyl acetate and some bicyclic olefins.[3–5] However, further research is still needed if the range of substrates to be studied is to be extended. Most of the ligands reported to date for Rh-catalyzed hydroformylation have been designed with the advantages of bidentate ligands in mind. Although chiral monodentate ligands have recently proven to be highly efficient in several asymmetric catalytic transformations (i.e., hydrogenation,[6] 1,2-[7] and 1,4-additions[8]), they are rarely used in hydroformylation. In 2004, Ojima et al. reported the successful application of chiral biphenyl monophosphoroamidite ligands for the challenging Rh-catalyzed asymmetric hydroformylation of allyl cyanide (ees up to 80%).[9,10] Despite this success, to the best of our knowledge monophosphoroamidites have not been applied to other substrates and, therefore, the scope of the catalyst systems containing monodentate P-ligands needs to be verified.

Encouraged by the success of monophosphoroamidite ligands in the hydroformylation of allyl cyanide, we herein report the use of a biaryl-based monophosphoroamidite and aminophosphine ligand library **L1**–**L7a**–**f** (Fig. 1) in the Rh-catalyzed asymmetric hydroformylation of vinylarenes and heterocyclic olefins. These ligands have the advantage of being readily accessible, highly diverse, air stable and inexpensive compared to most bidentate ligands.[11] In addition, they are amenable to parallel synthesis.[12] With this library, we fully investigated the effect of systematically varying the substituents and configuration at both the biaryl moieties **L1**–**L4** and the substituents attached to the nitrogen group (R = **a**–**f**) and the type of functional group (phosphoroamidites **L1**–**L4** or aminophosphines **L5**–**L7**).

2. Results and discussion

2.1. Asymmetric hydroformylation of vinylarenes

As mentioned above, vinylarenes, especially styrene, have been the most popular substrates for asymmetric hydroformylation. This is largely because the hydroformylation of these substrates gives rise to important intermediates for the synthesis of chiral arylpropionic acids widely used as non-steroidal anti-inflammatory drugs.[1]

In the first set of experiments, we tested monodentate ligands **L1**–**L7a**–**f** in the rhodium-catalyzed hydroformylation of styrene **S1** (Eq. 1). The latter was chosen as a substrate because this reaction has been performed with a wide range of ligands with several donor groups, so the efficiency of the various ligand systems could be compared directly.[1] The catalytic system was generated in situ by adding the corresponding ligand to [Rh(acac)(CO)$_2$] as a catalyst

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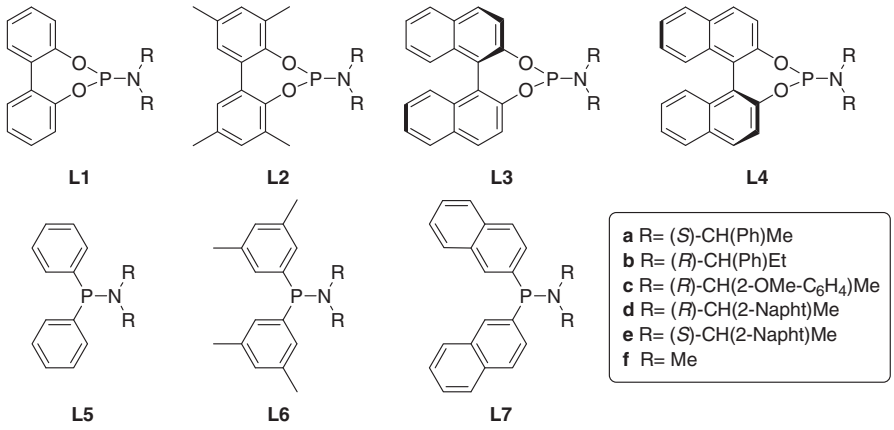
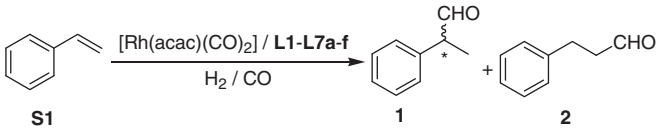


Figure 1. Monodentate phosphoroamidite and aminophosphine ligands **L1**–**L7a**–**f**.

precursor. Hydrogenated or polymerized products of styrene were not observed.



(1)

Initially, we determined the optimal reaction conditions by conducting a series of experiments with ligand **L1a** in which the ligand-to-rhodium ratio, temperature and CO/H_2 pressure ratio were varied (Table 1). As expected, varying the ligand-to-rhodium ratio showed that the best trade-off between activities and selectivities was obtained using a ligand-to-rhodium ratio of 2 (Table 1, entries 1-3). A higher ligand-to-rhodium ratio negatively affected the activity and regioselectivity. Varying the temperature had an important effect on regio- and enantioselectivity. Decreasing the temperature to 25 °C had a positive effect on the regio- and enantioselectivity, but decreased the activity (Table 1, entry 1 vs 4). After identical catalyst preparation, hydroformylation experiments were carried out under different CO and H_2 partial pressures (Table 1, entries 4–6). The results clearly show that higher partial pressures of H_2 lead to slightly higher initial turnover frequencies and, surprisingly, have an extremely positive effect on the enantioselectivity (Table 1, entry 5).

For comparative purposes, the rest of the ligands were tested under the conditions that gave the optimum trade-off between enantioselectivities and reaction rates: that is, a ligand-to-rhodium ratio of 2, a temperature of 25 °C and a CO-to-H_2 ratio of 0.5. The results are summarized in Table 2. We found that the regio- and enantioselectivities were highly affected by the type of functional group and the substituents and configurations at both the biaryl moiety and the amine group. The trade-off between regio- (up to 99%) and enantioselectivities (ees up to 40%) was best with ligand **L1a**, which combines a simple biphenyl group with a chiral bis[(*S*)-1-phenylethyl]amine moiety.

We first studied the effect of varying the steric properties at both the biphenyl group and the amino substituents with ligands **L1**–**L2a**–**d**. In general, we found that increasing the steric properties at both the biphenyl group (ligands **L1** vs **L2**; Table 2, entries 1 vs 4) and at the amino substituents (**a** vs **b**–**d**, Table 2) decreased the regio- and enantioselectivities. Introducing small non-chiral

Table 1
Rh-catalyzed asymmetric hydroformylation of **S1** using ligand **L1a**[a]

Entry	L/Rh	*T* (°C)	% Conv[b] (h)	%-**1**[c]	%ee[d]
1	2	45	99 (1)	95	6 (*S*)
2	5	45	99 (1)	84	8 (*S*)
3	10	45	60 (1)	91	10 (*S*)
4	2	25	15 (2)	99	10 (*S*)
5[e]	2	25	19 (2)	99	40 (*S*)
6[f]	2	25	4 (2)	99	21 (*S*)

Optimization of the reaction conditions.
[a] P = 25 bar, P_{CO}/P_{H2} = 1, [Rh(acac)(CO)$_2$] (0.013 mmol), styrene/Rh = 500, toluene (15 mL). Preactivation time 16 h.
[b] Conversion into aldehydes measured by GC. Reaction time in hours shown in parentheses.
[c] %-2PP measured by GC.
[d] Enantioselectivity measured by GC.
[e] P_{CO}/P_{H2} = ½.
[f] P_{CO}/P_{H2} = 2.

Table 2
Selected results for the Rh-catalyzed hydroformylation of **S1** using ligands **L1**–**L7a**–**f**[a]

Entry	Ligand	%Conv[b] (h)	%-**1**[c]	%ee[d]
1	**L1a**	16 (2)	99	40 (*S*)
2	**L1b**	20 (4)	95	8 (*R*)
3	**L1c**	30 (4)	95	0
4	**L2a**	20 (4)	94	3 (*R*)
5	**L2d**	8 (4)	96	7 (*S*)
6	**L3a**	25 (4)	92	10 (*S*)
7	**L3f**	30 (4)	97	12 (*S*)
8	**L4a**	10 (4)	94	20 (*R*)
9	**L5a**	12 (4)	>99.9	5 (*S*)
10	**L5e**	12 (4)	>99.9	5 (*S*)
11	**L6a**	10 (4)	>99.9	7 (*S*)
12	**L7a**	20 (4)	>99.9	12 (*S*)
13	**L1a/L1c**	18 (4)	95	5 (*S*)
14	**L1a/L2a**	18 (4)	93	15 (*S*)
15	**L1a/L3a**	20 (4)	95	23 (*S*)
16	**L1a/L4a**	21 (4)	95	4 (*R*)
17	**L1b/L1c**	16 (4)	96	4 (*S*)
18	**L1b/L3a**	13 (4)	93	2 (*S*)
19	**L1b/L4a**	18 (4)	94	22 (*R*)
20	**L2a/L2d**	12 (4)	96	5 (*S*)
21	**L2a/L3a**	17 (4)	92	4 (*S*)
22	**L2a/L4a**	19 (4)	93	13 (*R*)
23	**L3a/L4a**	21 (4)	92	0
24	**L5a/L6a**	12 (4)	>99.9	8 (*S*)
25	**L5a/L7a**	14 (4)	>99.9	15 (*S*)
26	**L5e/L7a**	18 (4)	>99.9	15 (*S*)

[a] P = 25 bar, P_{CO}/P_{H2} = 1/2, [Rh(acac)(CO)$_2$] (0.0125 mmol), styrene/Rh = 500, toluene (15 mL). Preactivation time 16 h. T = 25 °C.
[b] Conversion into aldehydes measured by GC. Reaction time in hours shown in parentheses.
[c] %-**1** measured by GC.
[d] Enantioselectivity measured by GC.

methyl substituents at the amine group (**f**) also decreased enantioselectivity (Table 2, entry 7).

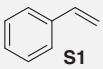
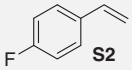
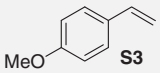
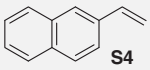
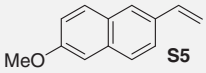
We also used ligands **L3a** and **L4a**, which contain opposite, enantiomerically pure binaphthyl moieties to investigate the possibility of a cooperative effect on the enantioselectivity of the configuration of the biaryl moiety and the amino group. The results indicated that there was a cooperative effect that led to a matched combination for ligand **L4a**, which contains an (*S*)-binaphthyl moiety. However, the enantioselectivity obtained using **L4a** is lower than that obtained with the biphenyl-based ligand **L1a** (Table 2, entries 6 and 8 vs 1).

Next, after comparing these results with those from the related aminophosphine ligands **L5**–**L7**, we found that replacing the biphenol or binaphthol moiety with simple aryl groups had a extremely positive effect on regioselectivity (up to >99.9%), although the enantioselectivities decreased (Table 2, entries 1–8 vs 9–12).

Finally, following the pioneering work of Reetz et al.,[13] we studied combining mixtures of two different monodentate P-ligands. Unfortunately, none of the combinations led to any improvements in either the regio- or enantioselectivity (i.e. Table 2, entries 13–26).

We next applied ligand **L1a** in the Rh-catalyzed hydroformylation of other vinyl arenes (Table 3). The presence of a fluoro substituent at the *para* position of the substrate hardly affected the conversion, or regio- or enantioselectivity (Table 3, entries 1 vs 2). However, the presence of *para*-methoxy and naphthyl substituents in the substrate had a positive effect on the enantioselectivity (Table 3, entries 1 vs 3–5).

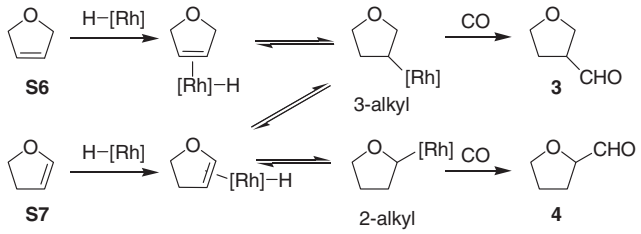
Table 3
Rh-catalyzed hydroformylation of several vinylarenes using ligand **L1a**[a]

Entry	Substrate	%Conv[b] (h)	%-Branched[c]	%ee[d]
1	 **S1**	99 (20)	99	40 (*S*)
2	 **S2**	100 (20)	98	39 (*S*)
3	 **S3**	84 (20)	99	45 (*S*)
4	 **S4**	78 (20)	99	46 (*S*)
5	 **S5**	66 (20)	99	49 (+)

[a] P = 25 bar, P_{CO}/P_{H2} = 1/2, [Rh(acac)(CO)$_2$] (0.0125 mmol), vinylarene/Rh = 500, toluene (15 mL). Preactivation time 16 h. T = 25 °C.
[b] Conversion into aldehydes measured by GC. Reaction time in hours shown in parentheses.
[c] %-Branched measured by GC.
[d] Enantioselectivity measured by GC.

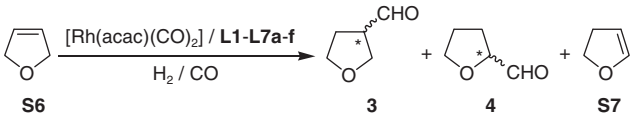
2.2. Asymmetric hydroformylation of heterocyclic olefins

The asymmetric hydroformylation of heterocyclic olefins gives access to important building blocks for the synthesis of natural products and pharmaceuticals. However, only a few studies had been reported on this topic.[14] 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.[14,15] For example, in the hydroformylation of 2,5-dihydrofuran **S6**, the expected product is tetrahydrofuran-3-carbaldehyde **3** (Scheme 1). However, considerable amounts of 2,3-dihydrofuran **S7** and tetrahydrofuran-2-carbaldehyde **4** can also be formed due to an isomerization process. This isomerization takes place simultaneously with the hydroformylation reaction (Scheme 1).



Scheme 1. Proposed mechanism for the isomerization process.

In an initial set of experiments, we tested monodentate ligands **L1**–**L7a**–**f** in the rhodium-catalyzed hydroformylation of 2,5-dihydrofuran **S6** (Eq. 2). In no cases were hydrogenated or polymerized products of 2,5-dihydrofuran observed.



(2)

We first determined the optimal reaction conditions by conducting a series of experiments with ligand **L1a** in which the ligand-to-rhodium ratio, CO/H_2 pressure ratio, reaction time and temperature were varied (Table 4).

Table 4
Rh-catalyzed asymmetric hydroformylation of **S6** using ligand **L1a**[a]

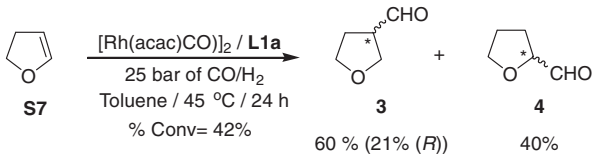
Entry	L/Rh	T (°C)	%Conv[b] (h)	%Aldeh.[c] (**3**:**4**)	%**S7**[d]	%ee of **3**[e]
1	2	45	94 (6)	80 (95:5)	14	45 (*S*)
2	5	45	86 (6)	80 (98:2)	6	18 (*S*)
3[f]	2	45	82 (6)	39 (88:12)	43	n.d.
4[g]	2	45	91 (6)	81 (97:3)	10	42 (*S*)
5	2	45	100 (24)	100 (93:7)	0	28 (*S*)
6	2	25	11 (8)	10 (99:1)	1	44 (*S*)

Optimization of the reaction conditions.
[a] P = 25 bar, P_{CO}/P_{H2} = 1, [Rh(acac)(CO)$_2$] (0.013 mmol), **S6**/Rh = 400, toluene (5 mL). Without preactivation of the catalyst.
[b] Total conversion measured by ^{1}H NMR. Reaction time in hours shown in parentheses.
[c] Conversion into aldehydes determined by ^{1}H NMR.
[d] Isomerization measured by ^{1}H NMR.
[e] Enantioselectivity of **3** measured by ^{1}H NMR using Eu(hfc)$_3$ on the corresponding methyl ester.
[f] P_{CO}/P_{H2} = 0.5
[g] P_{CO}/P_{H2} = 2.

Varying the ligand-to-rhodium ratio showed that the enantioselectivity was best when 2 equiv of ligand was used (Table 4, entries 1 and 2). A higher ligand-to-rhodium ratio negatively affected both activity and enantioselectivity.

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 hardly affected the rate of hydroformylation *vs* isomerization (Table 4, entries 1 vs 4), although decreasing the CO/H_2 pressure ratio negatively affected the chemoselectivity, which increased the formation of isomerized product **S7** (Table 4, entries 1 vs 3).

A prolonged reaction time increased the conversion into aldehydes (Table 4, entry 5) but decreased the regio- and enantioselectivity in the desired product **3** (Table 4, entry 1 vs 5). This decrease is due to the hydroformylation of the 2,3-dihydrofuran **S7** formed under the reaction conditions. The hydroformylation of **S7** leads to the formation of the opposite enantiomer of **3** (see Scheme 2) and



Scheme 2. Asymmetric hydroformylation of **S7** using the Rh–**L1a** catalytic system.

promotes the formation of undesired hydroformylation product **4**.[14d]

Lowering the temperature to 25 °C negatively affected activity, but had a positive effect on chemo- and regioselectivity (Table 1, entry 6).

We next applied the remaining ligands under the same reaction conditions. The results are summarized in Table 5. In general, enantioselectivities and activities followed the same trends as in the hydroformylation of styrene. The enantioselectivity was best when ligand **L1a** was used (ees up to 45%, Table 5, entry 1). However, in contrast to the hydroformylation of vinylarenes, the regioselectivity in product **3** is positively affected by the presence of bulky substituents at either the biaryl moiety or the amino group (Table 5, entry 1 vs 2–5). Although the cooperative effect between the configuration of the biaryl moiety and the amino group on the enantioselectivity was not very pronounced, it did have a strong effect on the chemo- and regioselectivity of the process. So, while ligand **L3a**, with an (*R*)-binaphthyl group, provided good chemo- and regiocontrol, ligand **L4a**, with an (*S*)-binaphthyl group, provided the lowest chemo- and regioselectivity of all the ligands tested. The 45% enantiomeric excess obtained when the simple readily available Rh–**L1a** catalytic system was used is very promising for the hydroformylation of heterocyclic compounds since only three catalytic systems have provided better enantioselectivities for substrate **S6**.[14f,14b,14d]

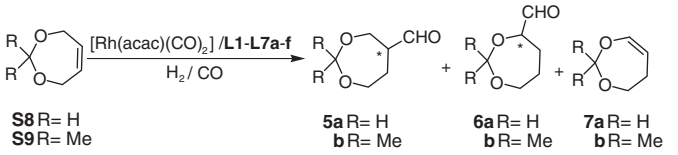
Table 5
Selected results for the Rh-catalyzed hydroformylation of **S6** using ligands **L1**–**L7a**–**f**[a]

Entry	L	%Conv[b] (h)	%Aldeh.[c] (**3**:**4**)	%**S7**[d]	%ee of **3**[e]
1	**L1a**	94 (6)	80 (93:7)	14	45 (*S*)
2	**L1b**	62 (4)	59 (99:1)	3	15 (*S*)
3	**L1c**	39 (4)	39 (100:0)	0	18 (*S*)
4	**L2a**	55 (4)	50 (100:0)	5	2 (*R*)
5	**L2d**	45 (4)	20 (100:0)	25	6 (*S*)
6	**L3a**	80 (4)	70 (100:0)	10	8 (*R*)
7	**L3f**	92 (4)	81 (96:4)	11	11 (*R*)
8	**L4a**	87 (4)	19 (70: 30)	68	14 (*R*)
9	**L5a**	63 (4)	58 (100:0)	5	2 (*R*)
10	**L6a**	34 (4)	34 (100:0)	0	6 (*R*)
11	**L7a**	42 (4)	42 (100:0)	0	8 (*R*)

[a] P = 25 bar, P_{CO}/P_{H2} = 1, [Rh(acac)(CO)$_2$] (0.0125 mmol), **S6**/Rh = 400, toluene (5 mL), L/Rh = 2. Without preactivation of the catalyst. T = 45 °C.
[b] Total conversion measured by ^{1}H NMR. Reaction time in hours shown in parentheses.
[c] Conversion into aldehydes determined by ^{1}H NMR.
[d] Isomerization measured by ^{1}H NMR.
[e] Enantioselectivity of **3** measured by ^{1}H NMR using Eu(hfc)$_3$ on the corresponding ester.

Next we applied ligand **L1a**, which provided the best results in the Rh-catalyzed asymmetric hydroformylation of 2,3-dihydrofuran **S7** (Scheme 2). The hydroformylation of this substrate is slower and provides lower levels of regio- and enantioselectivity than for substrate **S6**.[14b,14d–f] Low-to-moderate regio- and enantioselectivities were obtained. It should be pointed out that the hydroformylation of **S7** provided the opposite enantiomer on the desired aldehyde **3** than the hydroformylation of **S6**.

To further study the potential of ligands **L1**–**L7a**–**f**, we next tested them in the hydroformylation of *cis*-4,7-dihydro-1,3-dioxepin **S8** and *cis*-2,2-dimethyl-4,7-dihydro-1,3-dioxepin **S9** (Eq. 3). In all cases, these ligands exhibited high chemo- and regioselectivities for the desired aldehyde **5**. Therefore, except for ligand **L7a** (Table 6, entry 10) neither aldehyde **6** nor isomerized product **7** was detected.



(3)

Our most important results are shown in Table 6. Again, the selectivities of the process were affected by the type of functional group and the substituents and configurations at both the biaryl moiety and the amine group. However, the effect of these parameters was different from their effect on the hydroformylation of the previous substrates **S1**–**S6**. Therefore, activities and selectivities were best with ligand **L1b** (Table 6, entry 2). As for substrates **S1**–**S6**, none of the ligand combinations improved the enantioselectivity (Table 6, entries 11–17).

Table 6
Selected results for the Rh-catalyzed hydroformylation of **S8** and **S9** using ligands **L1**–**L7a**–**f**[a]

Entry	L	Substrate	T (°C)	%Conv[b] (h)	%Aldeh.[c] (**5**:**6**)	%ee of **5**[d]
1	**L1a**	**S8**	45	91 (2)	91 (100:0)	18 (+)
2	**L1b**	**S8**	45	100 (2)	100 (100:0)	36 (+)
3	**L1c**	**S8**	45	100 (2)	100 (100:0)	5 (+)
4	**L2a**	**S8**	45	83 (2)	83 (100:0)	0
5	**L2d**	**S8**	45	85 (2)	85 (100:0)	19 (+)
6	**L3a**	**S8**	45	72 (2)	72 (100:0)	2 (−)
7	**L3f**	**S8**	45	94 (2)	94 (100:0)	0
8	**L4a**	**S8**	45	96 (2)	96 (100:0)	16 (−)
9	**L5a**	**S8**	45	96 (2)	96 (100:0)	0
10	**L7a**	**S8**	45	93 (2)	78 (94:6)	0
11	**L1a**/**L1b**	**S8**	45	100 (2)	100 (100:0)	2 (+)
12	**L1a**/**L1c**	**S8**	45	100 (2)	100 (100:0)	4 (+)
13	**L1a**/**L2a**	**S8**	45	100 (2)	100 (100:0)	0
14	**L1a**/**L3a**	**S8**	45	100 (2)	100 (100:0)	10 (+)
15	**L1a**/**L4a**	**S8**	45	100 (2)	100 (100:0)	30 (−)
16	**L1b**/**L1c**	**S8**	45	100 (2)	100 (100:0)	27 (+)
17	**L3a**/**L4a**	**S8**	45	100 (2)	100 (100:0)	8 (−)
18	**L1b**	**S8**	25	96 (24)	96 (100:0)	58 (+)
19	**L1b**	**S9**	25	76 (24)	76 (100:0)	53 (*S*)

[a] P = 25 bar, P_{CO}/P_{H2} = 1/2, [Rh(acac)(CO)$_2$] (0.0125 mmol), substrate/Rh = 100, toluene (5 mL), L/Rh = 2. Without preactivation of the catalyst.
[b] Total conversion measured by ^{1}H NMR. Reaction time in hours shown in parentheses.
[c] Conversion into aldehydes determined by ^{1}H NMR.
[d] Enantioselectivity of **5** measured by ^{1}H NMR using Eu(hfc)$_3$ on the crude reaction mixture.

We also observed that temperature had an important effect. A decrease from 45 to 25 °C substantially increased the enantioselectivity (by as much as 58% and 53% for **S8** and **S9**, respectively) while maintaining the excellent chemo- and regioselectivity. It should be noted that the enantioselectivity obtained using the Rh–**L1b** catalytic system is very promising and not so far from the best ees obtained in the literature.[16]

3. Conclusions

A biaryl-based monophosphoroamidite **L1**–**L4a**–**f** and aminophosphine **L5**–**L7a**–**f** ligand library was tested to determine its effects on the asymmetric Rh-catalyzed hydroformylation of several vinylarenes and heterocyclic olefins. Our results indicated that selectivity strongly depended on the type of functional group, the substituents and the configurations at both the biaryl moiety and the amine group, and the substrate type. For vinylarenes **S1**–**S5** and the heterocyclic olefin 2,5-dihydrofuran **S6**, enantioselectivities (ees up to 46%) were best with ligand **L1a**, whereas for 4,7-dihydro-1,3-dioxepin substrates **S8** and **S9** enantioselectivities (ees up to 58%) were best with ligand **L1b**. These results extend the range of substrates for which monodentate phosphoroamidite ligands have proven to be promising and therefore open up new lines of research on the use of monophosphoroamidites for the asymmetric hydroformylation of more challenging substrates such as heterocyclic olefins.

4. Experimental section

4.1. General considerations

All experiments were carried out under an argon atmosphere. All solvents were dried using standard methods and distilled prior to use. Ligands were prepared by previously described methods.[17] Commercial substrates **S1**–**S8** were used without further purification. *cis*-2,2-Dimethyl-4,7-dihydro-1,3-dioxepin **S9** was prepared according to the method described in the literature.[18]

4.2. Typical hydroformylation procedure for vinylarenes S1–S5

In a typical experiment, the autoclave was purged three times with CO. The solution was formed from $[Rh(acac)(CO)_2]$ (3.1 mg, 0.0125 mmol) and ligand (0.025 mmol) in toluene (10 mL). After pressurizing to the desired pressure with syngas and heating the autoclave to the reaction temperature, the reaction mixture was stirred for 16 h to form the active catalyst. The autoclave was depressurized and a solution of substrate (6.25 mmol) in toluene (5 mL) was introduced into the autoclave, which was pressurized again. During the reaction several samples were taken from the autoclave. After the desired reaction time, the autoclave was cooled to room temperature and depressurized. The reaction mixture was analyzed by gas chromatography.[19]

4.3. Typical hydroformylation procedure for heterocyclic substrates S6–S9

The autoclave was purged three times with carbon monoxide. The solution of $[Rh(acac)(CO)_2]$ (3.1 mg, 0.0125 mmol), ligand (0.025 mmol) and substrate (5 mmol for **S6** and **S7** and 1.25 mmol for **S8** and **S9**) in toluene (5 mL) was transferred to the stainless-steel autoclave. After pressurizing to 25 bar of syngas and heating the autoclave to the desired temperature, the reaction mixture was stirred for the time shown in Tables 4–6. Conversions and selectivities of the reaction were determined immediately by ^{1}H NMR analysis of the crude reaction mixture without evaporation of the solvent. The enantiomeric excesses and absolute configurations were determined using the procedures described in Ref. 14b.

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