First successful application of diphosphite ligands in the asymmetric hydroformylation of dihydrofurans

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Good enantioselectivities and excellent regioselectivities are achieved in the Rh-catalyzed asymmetric hydroformylation of 2,5- and 2,3-dihydrofuran using diphosphite ligands; whereby the backbone of the ligand is crucial to suppressing isomerization and obtaining high ee's.

The value of enantiopure heterocyclic compounds, *i.e.* tetrahydrofuran derivatives, lies mainly in their use as building blocks for the synthesis of natural products and pharmaceuticals. The asymmetric hydroformylation of heterocyclic olefins can provide a potential synthetic tool for preparing these compounds. However, there have been only a few reports on this topic.[1] So far, only phosphine–phosphite binaphos ligand has provided good regio- and enantio-control in the Rh-catalyzed asymmetric hydroformylation of heterocyclic compounds.[1b]

For this kind of substrate, as well as controlling the enantioselectivity of the process, the chemo- and regio-selectivity are often a problem.[1,2] 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** were present due to an isomerization process. This isomerization 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 the 2,3-dihydrofuran **3** *via* β-hydride elimination reaction. This new substrate can similarly evolve to produce the 2-alkyl and 3-alkyl intermediates. Although the formation of the 3-alkyl intermediate is thermodynamically favoured, the acylation occurs faster in the 2-alkyl intermediate. Regioselectivity is therefore dominated by the rate of formation of the acyl complex.

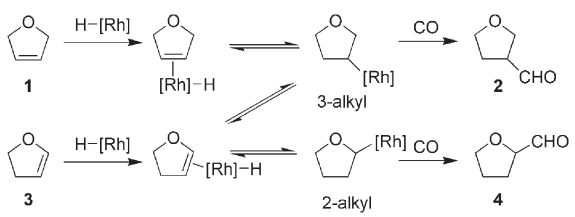
In recent years, diphosphites have emerged as suitable ligands for the Rh-asymmetric hydroformylation of vinylarenes, yielding comparable activities and enantioselectivities to the best ones in the literature using the binaphos ligand.[3] However, to the best of our knowledge, the use of diphosphite ligands for the asymmetric hydroformylation of heterocyclic substrates has not been reported. This is mainly because extensive isomerization has previously been observed when phosphite ligands were used.[2]

In this paper we report the first successful application of diphosphite ligands in the Rh-catalyzed asymmetric hydroformylation of 2,5- and 2,3-dihydrofuran. As ligands we have chosen representative examples of the two most successfully applied families of diphosphite ligands in the hydroformylation of vinyl arenes (Fig. 1).[3,4]

Diphosphite ligands **5–9** 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. The results are shown in Table 1.† In no cases were hydrogenated or polymerized products of 2,5-dihydrofuran observed.

Varying the ligand-to-rhodium ratio showed that the combination of chemo-, regio- and enantioselectivities was best when 2 equiv of ligand was used (entry 1 *vs* 2 and 3). A lower ligand-to-rhodium ratio therefore decreased the regio- and enantioselectivities in aldehyde **2** (entry 2), while a higher ligand-to-rhodium ratio had a negative effect on chemoselectivity, increasing the formation of the isomerized product **3** (entry 3).

A prolonged reaction time increased conversion into aldehydes (entry 4). However, the regio- and enantioselectivity in the desired product **2** decreased (entry 4 *vs* 1). 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 2, entry 1). If we compare all of these results, we can conclude that the loss in regioselectivity with the prolonged reaction time is due to the hydroformylation of the 2,3-dihydrofuran **3** formed under reaction conditions. This fact also causes a loss in enantioselectivity. The reason is that the



Scheme 1 Proposed mechanism for the isomerization process.

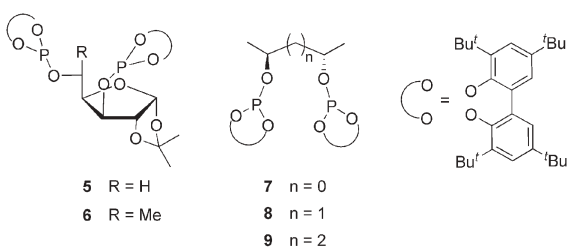


Fig. 1 Diphosphite ligands used in the Rh-catalyzed asymmetric hydroformylation of 2,5- and 2,3-dihydrofuran.

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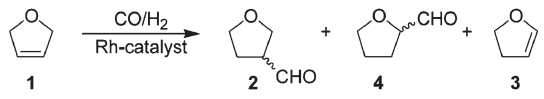
Table 1 Rh-catalyzed asymmetric hydroformylation of **1** using diphosphite ligands **5–9**[a]

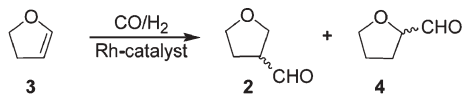


1 **2** **4** **3**

Entry	Ligand	% Conv[b]	% Ald. (**2**/**4**)[c]	% **3**[d]	% ee of **2**[e]
1	**5**	100	88 (100/0)	12	53 (*S*)
2[f]	**5**	100	82 (89/11)	18	31 (*S*)
3[g]	**5**	100	75 (100/0)	25	53 (*S*)
4[h]	**5**	100	98 (95/5)	2	37 (*S*)
5[i]	**5**	100	87 (100/0)	13	53 (*S*)
6	**6**	100	99 (99/1)	1	74 (*S*)
7	**7**	100	100 (72/28)	0	<5
8	**8**	100	99 (95/5)	1	23 (*R*)
9	**9**	100	100 (64/36)	0	<5
10[j]	binaphos	100	100 (100/0)	0	64 (*R*)

[a] P = 18 bar, p_{CO}/p_{H2} = 1, [Rh(acac)(CO)$_2$] (0.012 mmol), **1**/Rh = 400, toluene (5 mL), Ligand/Rh = 2, T = 45 °C, t = 24 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 **2** measured by ^{1}H NMR using Eu(hfc)$_3$. [f] Ligand/Rh = 1. [g] Ligand/Rh = 4. [h] t = 48 h. [i] p_{CO}/p_{H2} = 2. [j] 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.

Table 2 Selected results for the Rh-catalyzed asymmetric hydroformylation of **3** using diphosphite ligands[a]



3 **2** **4**

Entry	Ligand	% Conv[b]	% Ald. (**2**/**4**)[c]	% ee of **2**[d]
1	**5**	88	88 (78/22)	48 (*R*)
2	**6**	100	100 (76/24)	75 (*R*)
3	**8**	100	100 (68/32)	43 (*S*)
4[e]	binaphos	100	100 (50/50)	38 (*S*)

[a] P = 18 bar, p_{CO}/p_{H2} = 1, [Rh(acac)(CO)$_2$] (0.012 mmol), **3**/Rh = 400, toluene (5 mL), Ligand/Rh = 2, T = 45 °C, t = 48 h. [b] Total conversion measured by ^{1}H NMR. [c] Conversion into aldehydes determined by ^{1}H NMR. [d] Enantioselectivity of **2** measured by ^{1}H NMR using Eu(hfc)$_3$. [e] P = 20 bar, [Rh(acac)(CO)$_2$] (0.012 mmol), **3**/Rh = 400, benzene (1.5 mL), Ligand/Rh = 4, T = 40 °C, t = 24 h.

absolute configuration of the predominant enantiomer of **2** obtained from **3** is *R*, which is opposite to that 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 (entry 2).

It is generally accepted that isomerization occurs as a result of competition between the β-hydride elimination process and CO insertion (Scheme 1). Therefore, as a high CO pressure is necessary to suppress isomerization, we then performed an experiment by increasing the CO partial pressure. However, the rate of hydroformylation *vs.* isomerization was unaffected (entry 5 *vs.* 1).

The rest of ligands were compared under standard conditions (*i.e.* ligand-to-rhodium ratio of 2, 24 h reaction time and p_{CO}/p_{H2} = 1).

The use of ligand **6**, which differs from ligand **5** in that it has a methyl substituent at C-5, showed practically no isomerization combined with excellent regioselectivity and unprecedentedly high ee's (entry 6).

Ligands **7–9** showed lower regio- and enantioselectivities than ligands **5** and **6**. This can be attributed to the higher isomerization when this family of ligands is used than when the furanoside ligands **5** and **6** are used. The results also indicated that the bridge length affects the catalytic performance. Therefore, ligand **8**, which, like ligands **5** and **6**, has three carbon atoms in the bridge, provides higher regio- and enantioselectivites than ligands **7** and **9**, which have two and four carbon atoms in the bridge, respectively.

To sum up, these results indicate that the furanoside backbone is more effective in transferring the chirality to the tetrahydrofuran-3-carbaldehyde **2**. In particular, note the excellent positive effect of the presence of the methyl substituent at the C-5 position of the furanoside backbone (ligand **6**) in inhibiting the isomerization process and transferring the chiral information. Ligand **6** therefore competes favourably with the binaphos ligand, which so far has provided the best enantioselectivities for this substrate (entry 6 *vs.* 10).

Diphosphite ligands **5–9** were also tested in the Rh-catalyzed asymmetric hydroformylation of 2,3-dihydrofuran **3**. The results are summarized in Table 2. The catalysts were prepared as for the hydroformylation of **1**.† In no cases were isomerized (product **1**), hydrogenated or polymerized products of 2,3-dihydrofuran observed. The results followed the same trend as for the hydroformylation of **1**. The furanoside diphosphites were superior in terms of regio- and enantioselectivities to the pentanediol-based diphosphite and the binaphos ligands (entries 1 and 2 *vs.* entries 3 and 4). Again ligand **6**, with a methyl substituent at C-5 position, provided unprecedented enantioselectivities in favour of the tetrahydrofuran-3-carbaldehyde **2** (entry 2). Note, however, that the sense of enantioselectivity was opposite to that of the hydroformylation of 2,5-dihydrofuran **1** (entry 2, Table 2 *vs.* entry 6, Table 1). Using the same ligand **6**, this important feature enables the synthesis of both enantiomers of tetrahydrofuran-3-carbaldehyde **2** by simple substrate change.

In conclusion, we have shown that diphosphite ligands are suitable for the Rh-catalyzed hydroformylation of 2,5- and 2,3-dihydrofurans. We have found that the degree of isomerization and the effectiveness in transferring the chiral information in the product can be tuned by an appropriate choice of ligand. Unprecedentedly high enantioselectivities for both substrates have therefore been obtained using the furanoside diphosphite ligand **6**. Note that both enantiomers of tetrahydrofuran-3-carbaldehyde **2** can be synthesized using the same ligand **6** by simple substrate change. These results open up the hydroformylation of heterocyclic compounds to the potential effective use of readily available and highly modular diphosphite ligands.

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Notes and references

† Typical procedure. The autoclave (100 mL) 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 dihydrofuran (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. Conversion and selectivity 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 excess and absolute configuration were carried out using the procedure described in ref. 1*b*.

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