Highly enantioselective hydroformylation of dihydrofurans catalyzed by hybrid phosphine–phosphonite rhodium complexes†

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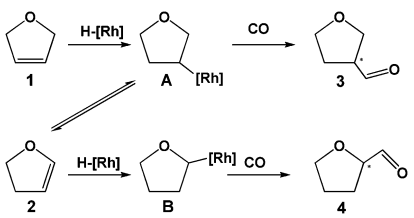
Unprecedented regio- and enantioselectivities (>91%) are reported for the Rh-catalyzed asymmetric hydroformylation of 2,3- and 2,5-dihydrofuran using tunable hybrid phosphine–phosphonite ligands.

Asymmetric hydroformylation is a powerful synthetic tool to construct a plethora of enantiomerically enriched compounds, and it has found several applications.[1] Traditionally, vinyl aromatics have been the most extensively explored substrates,[2] while asymmetric hydroformylation of heterocyclic olefins such as dihydrofuran, dihydropyran and pyrroline is scarcely investigated.[3] The carbaldehydes of dihydrofuran and pyrroline display a wide range of biological activities, functioning as antitumor and antibacterial agents, and are recognized as influential motifs in pharmaceutical compounds.[4] The asymmetric hydroformylation of these heterocyclic olefins would provide an efficient and atom economic protocol to prepare the respective carbaldehydes. Control over the stereo-selectivity is principally the key challenge in asymmetric hydroformylation reactions, but for the current dihydrofuran substrates also chemo- and regioselectivity are crucial issues to be addressed, as isomerization often takes place under hydroformylation conditions (Scheme 1). Although compound **3** is the expected hydroformylation product of 2,5-dihydrofuran **1**, generally significant amounts of compound **2** and **4** are also formed. The isomerization occurs *via* β-hydride elimination of the intermediate **A** to afford **2**, which subsequently hydroformylates to **4**.



Scheme 1 Proposed isomerization mechanism in hydroformylation of **1**.

So far non-C_2 symmetric bidentate ligands such as BINAPHOS[5] and sugar based diphosphites[5] provide the most selective rhodium catalysts for the hydroformylation of **1** and **2**. Based on these results, we anticipated that a tunable hybrid phosphine–phosphonite scaffold could result in an active and selective catalyst; so far such ligands have not been reported in the asymmetric hydroformylation of heterocyclic olefins. Herein we report on the syntheses and successful application of xanthene based hybrid phosphine–phosphonite ligands in the Rh-catalyzed asymmetric hydroformylation of 2,3- and 2,5-dihydrofuran, leading to unprecedented regioselectivities and the highest enantioselectivities (91%) ever reported for these challenging substrates.

Wide bite angle diphosphines such as xantphos have been successfully applied in *e.g.* Rh-catalyzed hydroformylation, leading to good regioselectivities whilst suppressing undesirable isomerization reactions.[6] We anticipated that chiral ligands with inequivalent P-donors[5,7] based on the xanthene backbone may address both the stereoselectivity and the chemoselectivity issues involved in the hydroformylation of dihydrofurans, and therefore we set out to prepare xanthene based phosphine–phosphonite ligands **7a–c**.‡ The σ-donating phosphine group and π-accepting phosphonite fragment, bearing a chiral auxiliary, are anticipated to induce a highly asymmetric environment around the catalytic center. Ligand modifications are relatively straightforward, giving rise to a set of similar ligands using analogous synthetic schemes.

Our approach involves a simple, two step synthetic protocol starting from the reported monophosphine **5**.[8] Lithiation of **5** followed by the addition of aminochlorophosphine yielded intermediate **6** (see Scheme 2) in 85% isolated yield.† The ^{31}P NMR spectrum of **6** in C_6D_6 at room temperature indicates an AB spin system with doublets at 92.4 and −15.1 ppm ($^6J_{P-P}$ coupling of 17.1 Hz), assigned to the aminophosphine and diphenyl phosphine moieties, respectively.[9] The desired hybrid phosphine–phosphonite ligands **7a–c** were readily prepared upon reaction of **6** with the BINOL derivatives **a–c** (Scheme 2).[10] The individual reactions were generally carried out in toluene at 120 °C and the products were isolated nearly quantitatively after purification by flash silica chromatography.[10] Typically, the ^{31}P NMR spectra of **7a–c** at ambient temperature displayed a doublet in the range of 181–167 ppm (phosphonite) and one between −13 and −18 ppm (phosphine) with $^6J_{P-P}$ couplings of approx. 30–34 Hz. The chemical shift of the phosphonite fragment is

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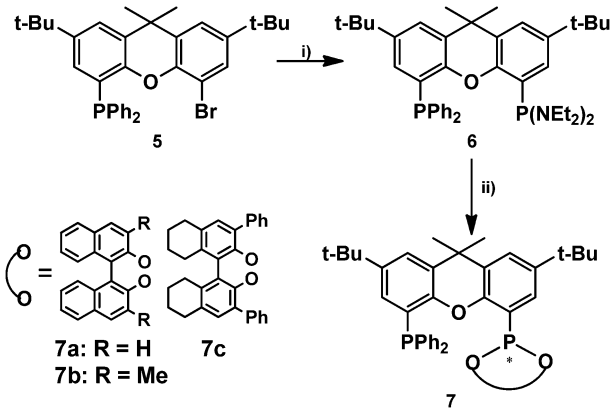


Scheme 2 General methodology displaying the synthesis of ligands **7a–c**; (i) −78 °C, 2 equiv. *tert*-BuLi, 1.1 equiv. $ClP(NEt_2)_2$; (ii) 1.1 equiv. BINOL derivatives **a–c**, 120 °C reflux in toluene.

similar to those reported previously.[9] All new ligands were characterized by a combination of analytical techniques (ESI†).

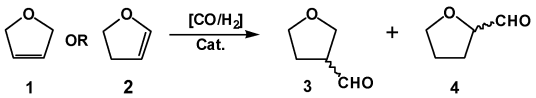
The coordination behaviour of the hybrid ligand **7c** was studied by mixing 2 equivalents of **7c** with 1 equivalent of $[Rh(\mu\text{-}Cl)(CO)_2]_2$ in dichloromethane, and the complex formation was monitored by ^{31}P NMR spectroscopy. The reaction proceeded readily at ambient temperature and after 2 h complex **8** [Rh(**7c**)(CO)Cl] was formed in quantitative yield. The ^{31}P NMR spectrum of **8** displays two doublets of doublets at 162.2 ppm ($^1J_{Rh-P}$ = 202 Hz, $^2J_{P-P}$ = 532 Hz) and 20.6 ppm ($^1J_{Rh-P}$ = 127.5 Hz, $^2J_{P-P}$ = 532 Hz), clearly indicating the coordination of two chemically inequivalent phosphorus atoms to the rhodium in mutual *trans*-disposition (ESI†).

In our pursuit to identify the catalytic species we investigated the coordination mode of **7c** under catalytic conditions. Stoichiometric amounts of **7c** and $Rh(acac)(CO)_2$ were mixed under 5 bars of syngas. The ^{31}P high pressure (HP) NMR spectrum of this solution revealed two doublets of doublets, centered at 173.9 ppm (with $^1J_{Rh-P}$ = 203 Hz, $^2J_{P-P}$ = 95 Hz) and 19.5 ppm (with $^1J_{Rh-P}$ = 130.6 Hz, $^2J_{P-P}$ = 95 Hz). The corresponding ^1H HP-NMR spectrum of this solution displayed a doublet of doublets of doublets in the hydride region, at −9.0 ppm ($^1J_{Rh-H}$ = 4.1 Hz, $^2J_{P^*-H}$ = 35 and $^2J_{P-H}$ = 8 Hz). Coupling patterns were verified with various 1D- and 2D-NMR spectroscopic techniques. The fairly small $^2J_{P-H}$ couplings are characteristic for a complex with predominantly bis-equatorial (ee) coordination mode of the two phosphorus donors, which is in line with data for xanthene based diphosphonites,[11] but is rather unusual for a hybrid bidentate bisphosphorus ligand (ESI†).[12] In the estimated 20% ea complex present in solution, the phosphonite is positioned *trans* to the hydride.

The performance of the phosphine–phosphonite ligands **7a–c** in the asymmetric hydroformylation of 2,5-dihydrofuran was evaluated and the representative catalytic data are summarized in Table 1. The catalysts were prepared *in situ* by mixing an appropriate amount of **7** and $Rh(acac)(CO)_2$ as a catalyst precursor. The catalyst based on the ligands with chiral binol derivatives **7a** and **7b** displayed very poor performance (runs 1–3). Only a moderate ee of 47% could be obtained using the ligand **7b**, even after extensive screening of various reaction conditions. Preliminary screening with **7c** pointed to a much better performance of the rhodium complexes based on this ligand as ee's around 90% were obtained. Increasing the reaction temperature from 25 °C to 40 °C led to significantly higher conversions without jeopardizing the selectivity (Table 1, run 6 *vs.* 7 and 8). Furthermore, prolonged reaction time increased the conversion to aldehyde **3**, whilst retaining high regio- and stereoselectivity (Table 1, run 10). At 45 °C regioselectivity reached >99.95% for 3-carbaldehyde **3** with 91% ee at 90% conversion (run 8). Performing the reaction at 50 °C led to a drop in both regio- and enantioselectivity and substantial isomerization (15%) to 2,3-dihydrofuran was observed (run 9). We attribute the dramatically decreased regio- and enantioselectivity to the parallel hydroformylation of 2,3-dihydrofuran, generated *in situ via* isomerization (Scheme 1), which results in the opposite enatiomer of carbaldehyde **3** (*vide infra*).

As can be seen from runs 13–19 (*vide infra*), hydroformylation of **2** by the same catalyst produces two regioisomeric products. Importantly the opposite enantiomer of carbaldehydes **3** is formed when this substrate is converted, indicating that isomerization of **1** to **2** and subsequent hydroformylation dramatically lowers the overall ee. We therefore performed an experiment at 30 bars of H_2/CO, to further suppress

Table 1 Rhodium catalyzed asymmetric hydroformylation of **1** and **2** using ligands **7a–c**[a]



Run	Ligand/sub	L/Rh ratio	Time/h	Temp/°C	Regio (**3**/**4**)[b]	% Conv[c]	%ee **3**
1[i]	7a/**1**	2.1	15	60	85 : 15	60	4
2[d]	7b/**1**	4.7	15	40	99 : 1	35	~5
3[e]	7b/**1**	4.7	18	40	100 : 00	20	47
4	7c/**1**	2	15	25	100 : 00	5–8	89 (*S*)
5	7c/**1**	3	15	25	100 : 00	5	90 (*S*)
6	7c/**1**	4.7	15	25	100 : 00	5	91 (*S*)
7	7c/**1**	4.7	15	40	100 : 00	40	91 (*S*)
8[f]	7c/**1**	4.7	40	45	100 : 00	90	91 (*S*)
9[g]	7c/**1**	4.7	15	50	96 : 4	75	32 (*S*)
10	7c/**1**	4.7	48	45	100 : 00	97	90 (*S*)
11	7c/**1**	5.5	48	45	100 : 00	86	90 (*S*)
12[h]	7c/**1**	4.7	16	25	93 : 7	n.d.	90 (*S*)
13[j]	7a/**2**	2.1	18	60	75 : 25	34	19
14[k]	7b/**2**	4.7	16	40	81 : 19	7	55 (*R*)
15	7c/**2**	4.7	15	50	75 : 25	18	87 (*R*)
16	7c/**2**	4.7	15	40	79 : 21	7	88 (*R*)
17[l]	7c/**2**	4.7	40	25	80 : 20	5	91 (*R*)
18[m]	7c/**2**	4.7	20	25	81 : 19	n.d.	90 (*R*)
19[n]	7c/**2**	4.7	60	45	77 : 23	69	81 (*R*)

[a] $Rh(acac)(CO)_2$ (1.9×10^{-6} mol), S/Rh = 200, $p(CO/H_2)$ = 20 bars, T = 25 °C, t = 15 h, toluene = 0.75 mL, no hydrogenation or isomerization product could be observed. [b] Regio- and enantioselectivity measured by chiral GC. [c] Total conversion determined by ^1H NMR. [d] S/Rh = 400. [e] $p(CO/H_2)$ = 55 bars, S/Rh = 400. [f] Isomerization to 2,3-dihydrofuran was detected by NMR (5%). [g] Isomerization to 2,3-dihydrofuran was detected by NMR (15%). [h] $p(CO/H_2)$ = 30 bars, S/Rh = 400. [i] S/Rh = 400. [j] L/Rh = 2.1, S/Rh = 400. [k] $p(CO/H_2)$ = 40 bars, S/Rh = 400. [l] $p(CO/H_2)$ = 25 bars. [m] $p(CO/H_2)$ = 15 bars, S/Rh = 400. [n] $Rh(acac)(CO)_2$ (3.9×10^{-6} mol).

isomerization,[5] but this instead decreased the regioselectivity while the enantioselectivity was retained (run 12). To our knowledge, the enantiomeric excess for the hydroformylation of 2,5-dihydrofuran obtained with ligand **7c** (91%) is the highest ever reported, and importantly, it coincides with excellent regioselectivity (>99.95%).

Riding high on the excellent catalyst performance, we set out to assess the ligands **7a–c** in the asymmetric hydroformylation of 2,3-dihydrofuran. The important findings are also summarized in Table 1. Overall, substrate **2** was found to be less reactive than **1** and the regioselectivity in all cases stayed almost constant at 80 : 20 (**3**/**4**). Ligands **7a** and **7b** were again outperformed by **7c** (runs 13–15). Further optimization was performed using ligand **7c**, and the conversion improved significantly at higher temperatures, although at the expense of a slightly lower enantioselectivity (runs 15–17). Next, the effect of syngas pressure was studied. An excellent enantioselectivity (91%) with the best regio-control (80 : 20) was achieved at 25 bars (run 17), while either lower or higher pressures resulted in decreased selectivities (runs 15, 16 and 18, 19). Prolonged reaction times at 45 °C improved the conversion to 69%, although the enantioselectivity dropped to 81% (run 19). Interestingly, the sense of enantioselection in **1** and **2** is opposite in nature, *i.e.* the absolute configuration of the predominant enantiomer obtained from **1** is *S*, while that obtained from **2** is *R* (ESI†). This is important as it explains why isomerization side reactions can directly deteriorate the ee of the product that is formed.

In conclusion, we report a new class of xanthene based, hybrid phosphine–phosphonite ligands that are easy to modify. *In situ* high pressure NMR spectroscopy showed that the two phosphorus nuclei predominantly occupy bis-equatorial positions, in contrast to most related chiral hybrid bidentate ligands such as BINAPHOS. On the other hand, this mode of coordination is in line with previous xanthene based ligands.[11] The performance of the novel ligands was evaluated in the asymmetric hydroformylation of notoriously difficult 2,3- and 2,5-dihydrofuran substrates. The hybrid ligand **7c** was undoubtedly the best among the three and displayed excellent performance. Employing **7c**, an unprecedented high enantiomeric excess (91%) was obtained in the hydroformylation of **1** along with excellent regio-selectivities. Similarly, an ee of 91% and good regioselectivity (80 : 20) was obtained in the asymmetric hydroformylation of **2** using ligand **7c**, which clearly outperforms other systems reported for this substrate. A remarkable observation is that both enantiomers of product **3** are accessible using the same catalyst, simply by changing the substrate from 2,5- to 2,3-dihydrofuran. In addition, this phenomenon implies the necessity to suppress isomerization, as this will lead to a dramatic decrease in selectivity. We are currently further exploring the substrate scope of this new class of catalysts.

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Notes and references

‡ A simple PM3 model suggested that the 3,3′ position on the (octahydro)binol in **7** should be the most influential position to control the selectivity and that increasing steric bulk around this position might induce high enantioselectivities. Based on these leads we designed the tuneable, hybrid phosphine–phosphonite ligands **7a–c**.

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10 Synthesis of **7a** and **7b** proceeds smoothly, whereas a catalytic amount of tetrazole as a protonating agent was necessary to prepare **7c**, see ESI†.

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