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High regioselectivity in propylene hydroformylation using rhodium-bisphosphite catalysts is due to properties of the *SRS* diastereomer

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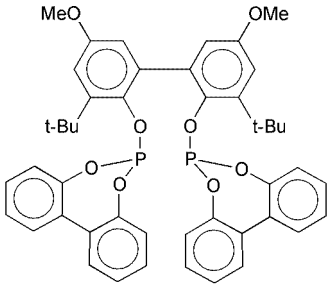
The large cone angle and bite angle of the *SRS* ligand diastereomer in biphenol-based Rh-bisphosphite catalysts lead to high linear regioselectivity in the hydroformylation of propylene.

Rhodium-catalyzed hydroformylation of α-olefins is widely used for the industrial synthesis of alcohols and carboxylic acid derivatives.[1] Biphenol-based bisphosphite ligands, such as **1**,



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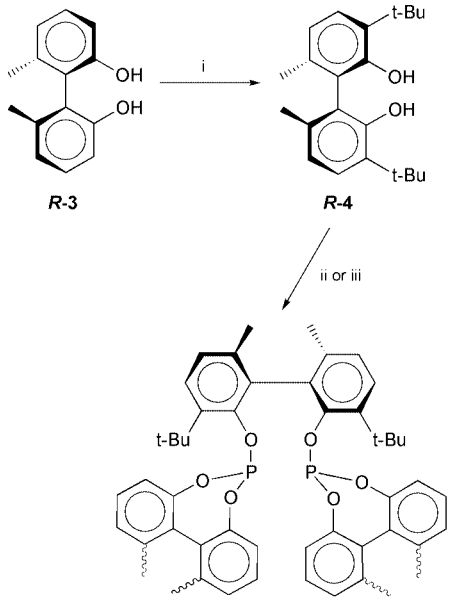
offer increased reaction rates and dramatic improvements in linear/branched regioselectivity (l/b) and chemoselectivity over conventional phosphine ligands in rhodium-catalyzed hydroformylation.[2] Unfortunately, a comprehensive mechanistic explanation of the factors that control hydroformylation regioselectivity has remained elusive. Several ligand structural features have been identified to be important in determining regiochemistry in hydroformylation, including steric bulk,[3] electrophilicity,[4] and, in bidentate ligands, bite angle.[5] In this communication we show that in this class of bisphosphite ligands, diastereomeric configuration can also have a profound effect on catalytic hydroformylation regiochemistry and activity.

Rhodium-catalyzed hydroformylation of α-olefins using **1** produces linear aldehydes with high regioselectivities while tolerating a wide variety of functional groups.[6] Structurally related optically-active bisphosphites have been developed which result in high regio- and enantioselectivities for asymmetric hydroformylation.[7] Due to the presence of three axial elements of chirality, bisphosphite **1** can potentially adopt three diastereomeric forms. The notation for these diastereomers (*RRR, SRR, SRS*) uses the middle descriptor for the central bridging biphenoxide moiety. Interconversion of these diastereomers can occur by rotations about the biaryl axes. Previous NMR studies have demonstrated facile epimerization of the cyclic dibenzo[*d*,*f*][1,3,2]dioxaphosphepin moiety in related bisphosphites.[8] This rotational process can interconvert all three possible diastereomers (*RRR, SRR, SRS*).

Rotation about the central *tert*-butyl substituted biphenyl axis could also interconvert *RRR* and *RSR* diastereomers, however, chiral HPLC studies reveal this process is slow. Analytical chiral stationary phase HPLC (Chiralcel OD, 99 : 1 hexane–propan-2-ol) separated **1** into two fractions (1 : 1 ratio) which exhibited identical UV spectra. When the column eluent was monitored using a polarimetric detector, the first peak exhibited a negative optical rotation; the second peak had a positive optical rotation. These enantiomers were physically separated by preparative chiral HPLC and then re-analyzed. Slow racemization of these enantiomers occurred ($t_{\frac{1}{2}}$ = 53 min) at 34 °C by rotation about the central bridging biaryl bond. Interconversion of diastereomers of **1**, therefore, most often occurs *via* dibenzo[*d*,*f*][1,3,2]dioxaphosphepin epimerization with a rate faster than the rate of hydroformylation.

Given the possibility that diastereomeric forms of **1** could contribute to the observed catalytic behavior, we sought to study the effect of isolated configurationally-stable bisphosphite diastereomers in propylene hydroformylation. Bisphosphite **2** was selected for study due to the presence of 6,6′-methyl substituents which prevent biaryl rotation. In addition, bisphosphite **2** contains 3,3′-*tert*-butyl substituents, which are necessary for high hydroformylation regioselectivity using ligands such as **1**. The synthesis of two of the three possible diastereomeric bisphosphites, **2**, is depicted in Scheme 1. Acid-catalyzed alkylation of enantiomerically-pure[9] (*R*)-**3** led to (*R*)-**4**. Synthesis of (*RRR*)-**2** and (*SRS*)-**2** as pure enantiomers was performed by reaction of (*R*)-**4** with the phosphorochloridite prepared by reaction of PCl_3 with the requisite enantiomer of **3**.

Rhodium-catalyzed propylene hydroformylation† was performed using (*RRR*)-**2** and (*SRS*)-**2** to investigate the effects of relative ligand stereochemistry. Hydroformylation using Rh–(*SRS*)-**2** resulted in a high regioselectivity (l/b = 46) with an



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Scheme 1 *Reagents and conditions*: (i) isobutylene, nitrobenzene, triflic acid (5 mol%); (ii) for (*RRR*)-**2**: *R*-6,6′-dimethylbiphenylphosphochloridite (2 equiv.), NEt_3, THF; (iii) for (*SRS*)-**2**: *S*-6,6′- dimethylbiphenylphosphochloridite (2 equiv.), nBuLi, THF.

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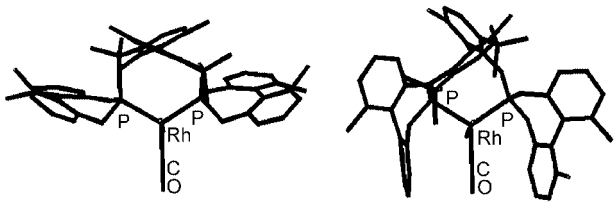

Fig. 1 Molecular mechanics structures of [(*RRR*)-**2**]Rh(CO)$_2$H (left) and [(*SRS*)-**2**]Rh(CO)$_2$H (right). Hydrogen atoms are omitted for clarity.

average rate of 513 turnovers h^{-1} over the course of 6 h. Under identical conditions, Rh–(*RRR*)-**2** gave a much lower rate (110 turnovers h^{-1}) and regioselectivity (l/b = 4) than the *SRS* diastereomer. Bisphosphite **1** exhibited a rate (434 turnovers h^{-1}) and regioselectivity (l/b = 53)[2] which was very similar to that observed with (*SRS*)-**2**. These results demonstrate that rhodium complexes of the *RRR* and *SRS* diastereomers of ligand **2** lead to inherently different regioselectivities and rates for propylene hydroformylation. The similarity between the catalytic performance of (*SRS*)-**2** and **1** suggests that during catalysis, **1** exists predominantly in the *SRS* configuration. Similar differences between bisphosphite diastereomers have been reported by van Leeuwen for asymmetric styrene hydroformylation, where the branched isomer predominates.[10] Reetz has recently reported that asymmetric alkene hydrogenation with biphenyl-based bisphosphite ligands displays an analogous difference between ligand diastereomers.[11] Our results obtained using diastereomeric structures of **2** indicate that achiral transformations mediated by bisphosphites are likewise effected by ligand structure.

Molecular mechanics calculations‡ of [(*SRS*)-**2**]Rh(CO)$_2$H and [(*RRR*)-**2**]Rh(CO)$_2$H were performed to identify the factors which could lead to their dramatically different hydroformylation behavior. The strain energies calculated for these two diastereomeric complexes were essentially identical (within 2 kcal mol^{-1}). The natural bite angle[12] for the *SRS* diastereomer was calculated to be 117°, whereas the *RRR* diastereomer was calculated to have a natural bite angle of 111°. Consistent with previous correlations[5] between hydroformylation regioselectivity and chelate natural bite angle, the more regioselective *SRS* diastereomer of **2** exhibits a larger natural bite angle than the less regioselective *RRR* diastereomer. In addition to differences in natural bite angle, these calculations also revealed a significant difference in cone angle between these two diastereomeric catalysts (Fig. 1). The cone angles at each phosphorus atom in (*RRR*)-**2** and (*SRS*)-**2** were calculated to be 104° and 157°, respectively. The *RRR* (low l/b) catalyst adopts an open geometry around the equatorial CO ligand, which should result in minimal energy differences between linear and branched alkyl or acyl intermediates. The *SRS* diastereomer, which dominates hydroformylation catalysis, is calculated to form a more crowded complex in which the two dibenzo[*d*,*f*]-[1,3,2]dioxaphosphepin moieties flank the equatorial CO ligand. This arrangement should result in large energy differences between linear and branched alkyl or acyl intermediates and could account for the high regioselectivity for linear aldehyde observed with ligands such as **1**.

Previous observations of increased hydroformylation regioselectivity with increased natural bite angle have been complicated by the relationship between cone angle and bite angle for chelating ligands.[5,12] Since large bite angle diphosphines and bisphosphites typically have larger cone angles than their smaller bite angle analogs, the inherent effect of the natural bite angle on hydroformylation regioselectivity is unclear. Recent calculations by Bo and van Leeuwen suggest that steric effects play the dominant role in determining hydroformylation regioselectivity.[13] Although the natural bite angles of (*RRR*)-**2** and (*SRS*)-**2** correlate with their hydroformylation regioselectivity, the very large difference in cone angles for these two diastereomers suggests that the high hydroformylation regioselectivity of (*SRS*)-**2** is predominantly due to an increase in steric influence of the bisphosphite ligand.

Notes and references

† Propylene hydroformylation experiments were performed in tetraglyme solution in a stirred autoclave at constant pressure (148 ppm Rh (1.4 mM), L:Rh(CO)$_2$(acac) = 2.0, 82 °C, 85 psi propylene, 45 psi 1:1 H$_2$–CO).
‡ Molecular mechanics calculations were performed using the augmented MM3 force field implemented in the CAChe software package. Natural bite angles were calculated by using a P–Rh–P bending force constant of 0 kcal mol^{-1} deg^{-2}. The authors are indebted to the reviewers for insight regarding these calculations.

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