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Ferrocene-based bidentate phosphonite ligands for rhodium(I)-catalyzed enantioselective hydroformylation

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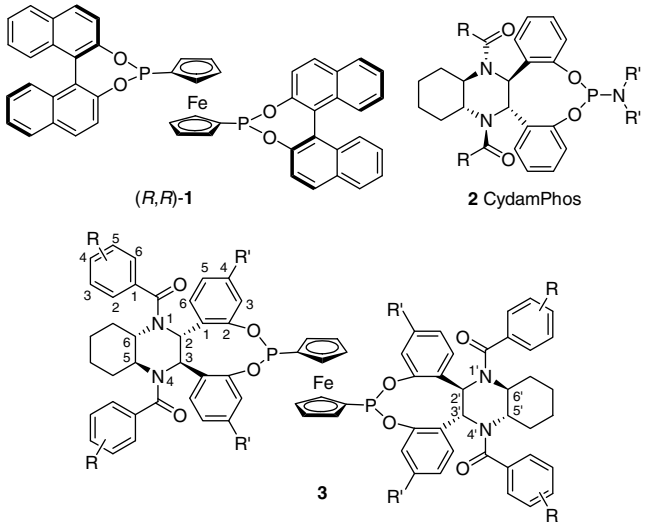
ABSTRACT

A new class of chiral modular bidentate phosphonite ligands has been synthesized in good overall yields by using cheap *trans*-1,2-diaminocyclohexane and ferrocene as starting materials, and applied in the Rh(I)-catalyzed asymmetric hydroformylation of vinyl acetate and styrene to afford the corresponding optically active aldehydes with good regioselectivity (up to 16.9 *b*/*l* ratio) and moderate to good enantioselectivity (up to 83% ee). The substituents on the backbone of the ligands are found to exhibit a remarkable effect on both the regio- and enantioselectivity of the catalysis.

Catalytic asymmetric hydroformylation (AHF) of olefins is one of the most important approaches for C–C bond formation to provide optically active aldehydes,[1] which can be readily transformed into a number of high-value-added chiral chemicals, such as amines, alcohols, and acids.[2] Although remarkable progresses in the area of AHF have been made during the last fifteen years with the development of rhodium-based catalyst systems bearing diphosphite ligand,[3] the phosphine–phosphite ligand (BINAPHOS),[4] and the diazaphospholane ligand,[5] it is still a challenging research topic in the area of asymmetric catalysis. One of the major problems involved in the catalyst design is how to control both the regio- and enantioselectivities, while maintaining a reasonable reaction rates at moderately high temperatures. In this respect, the chiral ligands often play a crucial role in catalytic activity and selectivity control. Therefore, the development of well-designed chiral ligands with new skeletons for the title reaction is highly desirable. Inspired by the excellent results obtained with some of the chiral diphosphite ligands,[3] we have developed a new class of ferrocene-bearing chiral bidentate phosphonite ligands that allow good control of regio- and enantioselectivities via facile structural manipulation. Herein we report our preliminary results on the synthesis of these modular ligands and their application in Rh(I)-catalyzed asymmetric hydroformylation of vinyl acetate and styrene.



The bidentate phosphonite ligand **1**[6] and monodentate phosphoramide ligands **2** (CydamPhos)[7] have been reported to possess excellent enantiocontrol capability in Rh(I)-catalyzed asymmetric hydrogenation of olefin derivatives. In particular, the modular structure of the latter allows for fine-tuning of stereo or electronic properties of substituents on the ligands, and the substituents at the backbone exhibit significant impact on the stereocontrol of

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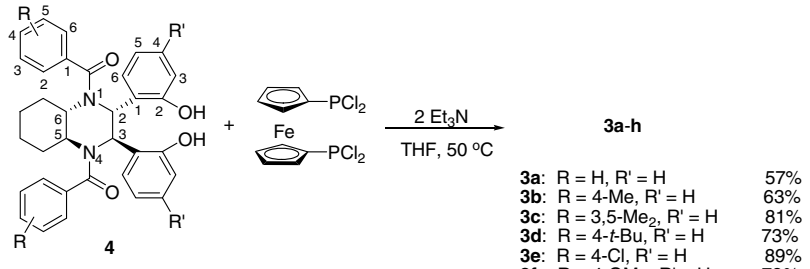


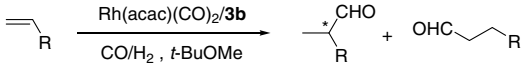
Scheme 1. The synthesis of diphosphonite ligands **3a**–**h**.

the catalysis. By taking together the structural features of ligands **1** and **2**, a new class of ferrocene-based modular chiral bidentate phosphonite ligands **3** was designed. As depicted in Scheme 1, the synthesis of bidentate phosphonite ligands **3a–h** is quite straightforward. The key intermediates **4a**–**h** were readily prepared in high yields via a three-step transformation sequence developed by our group using cheap *trans*-1,2-diaminocyclohexane and salicylaldehyde derivatives as starting materials.[7] The condensation of **4a**–**h** with 0.5 equiv of 1,1′-bis(dichlorophosphino)ferrocene[6] in the presence of 2 equiv of NEt_3 in THF at 50 °C afforded the corresponding bidentate phosphonite ligands **3a–h** in moderate to good yields (57–89%). These ligands are stable enough to allow manipulation in open air and can be stored under argon atmosphere over several months without any appreciable degradation. For comparison purpose, the enantiopure diphosphonite ligand **1** was also prepared according to the literature procedure starting from (*R*)-BINOL and 1,1′-bis(dichlorophosphino)ferrocene as the building blocks. [6]

Ligands **3** were then examined in the Rh(I)-catalyzed asymmetric hydroformylation of vinyl acetate and styrene. The catalyst prepared by in situ mixing ligand **3b** with $Rh(acac)(CO)_2$ was used for a preliminary optimization of reaction conditions, including solvents, ligand to metal ratios, CO/H_2 pressures, and reaction temperature. The results are summarized in Table 1. The conversions, regio- and enantioselectivities of the reactions were evaluated by GC analysis with dodecane as the internal standard. As shown Table 1, *t*-BuOMe is superior to either benzene or toluene in terms of both activity and enantioselectivity (entries 1–3). Variation in the **3b**/Rh(I) ratio also resulted in a change in the enantioselectivities for the reactions of both substrates. An overall assessment of the results indicated that **3b**/Rh = 2:1 is optimal in terms of both regio- and enantioselectivities (entries 3–6). Lowering the hydrogen pressure (from 40 to 20 bar, entries 5, 7, and 8) or increasing the CO partial pressure (5–20 bar, entries 5, 9, and 10) was unfavorable for the catalytic activities, and a gas pressure of 40 bar (H_2/CO 3:1) turned out to be optimal. The regio- and enantioselectivity of the reaction did not alter significantly within the examined temperature range (40–70 °C, entries 8, 11, and 12). Taken together, the optimized reaction conditions for AHF of styrene/vinyl acetate were found to be 40 bar (3:1) H_2/CO at 60 °C in the presence of 0.2 mol % of $Rh(acac)(CO)_2$/**3b** (1:2) for 2 h in *t*-BuOMe (entry 8).

With ligands **3a–h** in hand, we then examined their asymmetric induction ability in Rh(I)-catalyzed asymmetric hydroformylation of vinyl acetate and styrene under the optimized reaction conditions mentioned above. As shown in Table 2, increase of the steric bulkiness of R on the *N*-arylacyl substituents of the ligand to a certain extent was found to be beneficial to the enantioselectivities of

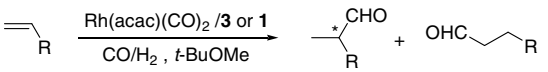
Table 1
Optimization of reaction conditions for the asymmetric hydroformylation of vinyl acetate and styrene[a]



Entry	L:Rh	P (H_2) (bar)	P (CO) (bar)	T (°C)	Vinyl acetate			Styrene		
					Conv. (%)	ee (%)	*b*/*l*	Conv. (%)	ee (%)	*b*/*l*
1[b]	1.5:1	40	10	60	78	45	17.2	99	11	5.7
2[c]	1.5:1	40	10	60	84	45	15.7	99	13	5.0
3	1.5:1	40	10	60	99	54	12.5	99	33	8.3
4	1.0:1	40	10	60	99	39	16.2	99	16	9.0
5	2.0:1	40	10	60	99	54	16.9	99	33	8.3
6	4.0:1	40	10	60	99	59	15.1	99	31	7.1
7	2.0:1	20	10	60	88	63	13.9	99	36	8.1
8	2.0:1	30	10	60	90	64	13.1	98	38	8.6
9	2.0:1	30	5	60	97	63	14.4	99	37	8.3
10	2.0:1	30	20	60	85	51	14.4	99	26	8.2
11	2.0:1	30	10	40	67	64	20.3	82	29	10.9
12	2.0:1	30	10	70	90	59	17.2	99	29	6.9

[a] Unless otherwise noted, all reaction were carried out with substrate:Rh(I) = 500:1 in *t*-BuOMe for 2 h. Conversion, branched-to-linear ratio and ee value were determined based on GC analysis (Supelco's Beta Dex 225) with dodecane as internal standard. The absolute configuration was *S* for the product of vinyl acetate and *R* for the product of styrene, which were assigned by comparing the optical rotations with those reported in the literature.[8]
[b] The solvent was benzene.
[c] The solvent was toluene.

Table 2
The effect of different ligands for the asymmetric hydroformylation of vinyl acetate and styrene[a]



Run	Ligand	Vinyl acetate			Styrene		
		Conv. (%)	ee (%)	*b*/*l*	Conv. (%)	ee (%)	*b*/*l*
1[b]	(2*R*,3*R*,5*S*,6*S*,2′*R*,3′*R*,5′*S*,6′*S*)-**3a**	64	55(*S*)	13.9	83	7(*R*)	12.2
2	(2*R*,3*R*,5*S*,6*S*,2′*R*,3′*R*,5′*S*,6′*S*)-**3b**	90	64(*S*)	13.1	98	38(*R*)	8.6
3	(2*R*,3*R*,5*S*,6*S*,2′*R*,3′*R*,5′*S*,6′*S*)-**3c**	**75**	**83**(***S***)	**15.1**	87	55(*R*)	7.5
4	(2*R*,3*R*,5*S*,6*S*,2′*R*,3′*R*,5′*S*,6′*S*)-**3d**	93	32(*S*)	10.6	99	1(*S*)	8.7
5	(2*R*,3*R*,5*S*,6*S*,2′*R*,3′*R*,5′*S*,6′*S*)-**3e**	91	62(*S*)	12.7	99	26(*R*)	8.6
6	(2*R*,3*R*,5*S*,6*S*,2′*R*,3′*R*,5′*S*,6′*S*)-**3f**	64	70(*S*)	13.3	84	49(*R*)	12.2
7	(2*S*,3*S*,5*R*,6*R*,2′*S*,3′*S*,5′*R*,6′*R*)-**3g**	84	35(*R*)	19.0	99	30(*S*)	15.7
8	(2*S*,3*S*,5*R*,6*R*,2′*S*,3′*S*,5′*R*,6′*R*)-**3h**	84	66(*R*)	14.6	**99**	**55**(***S***)	**16.9**
9	(*R*,*R*)-**1**	78	9(*S*)	5.3	98	25(*R*)	6.9

[a] All reaction were carried out with substrate:[Rh] = 500:1 in *t*-BuOMe for 2 h at 60 °C under 30 bar of H_2 and 10 bar of CO with **3**:[Rh] = 2.0:1.
[b] The solvent was toluene.

the reactions for both vinyl acetate and styrene (entries 1–3). However, the sterically more demanding *N*-arylacyl substituents (R = 4-*t*-Bu) in ligand **3d** are obviously unfavorable to the control of enantioselectivity. In fact, virturally racemic hydroformylation product was obtained in the reaction of styrene (entry 4). Ligands **3e** and **3f** exhibited a catalytic performance similar to that of **3b** (entries 5 and 6 vs 2). Remarkably, changing the substituent R′ of phenoxy moieties from H to methyl group can also lead to the dramatic changes of regio- and enantioselectivities, as ligands **3g** and **3h** exhibited decreased *ee*s but improved *b*/*l* ratios relative to those of **3b** and **3c** (entries 2 vs 7 and 3 vs 8, respectively). Ligand **1** was also tested in the reactions under the above-optimized conditions, with relatively poor enantioselectivity and regioselectivity being observed in the asymmetric hydroformylation of both substrates (entry 9).

These observations suggested that the stereocontrol capabilities of ligand **3** are highly sensitive to the subtle changes in the substituents on the ligand backbone, and the *N*-arylacyl substituents remote from the catalytic center can also exert a control of the enantioselectivity to some extent.[7] These facts along with the modular nature of this type of ligands suggest that their asymmetric induction capabilities could in principle be fine tuned by appropriate modifications of the R and R′ substituents on the skeleton of the ligands, which represents a valuable feature for ligand optimization. Within the ligand series **3a–h** and **1**, **3c** afforded the best enantiocontrol (83% ee) and moderate regioselectivity (*b*/*l* 15.1) for asymmetric hydroformylation of vinyl acetate, while **3h** gave the optimal enantioselectivity (55% ee) and good regioselectivity (*b*/*l* 16.9) for asymmetric hydroformylation of styrene.

In summary, we have developed a new class of ferrocene-based modular chiral diphosphonite ligands, which exhibited moderate to good enantioselectivities and regioselectivities in the Rh(I)-catalyzed asymmetric hydroformylations of vinyl acetate (up to 83% ee and 15.1 *b*/*l* ratio) and styrene (up to 55% ee and 16.9 *b*/*l* ratio), respectively. This type of ligands has salient features such as cheap starting material and facile preparation, structural tunability, as well as remote stereocontrol capability of backbone substituents. Further work on modifying the ligand structure for improvement of the regio- and enantioselectivity[9] as well as broadening the substrate scope of the asymmetric hydroformylation is undergoing in this lab.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.012.

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