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Letter

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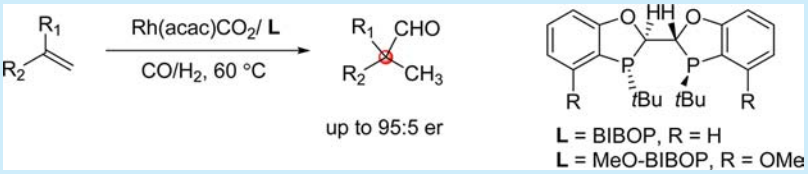
Tunable *P*-Chiral Bisdihydrobenzooxaphosphole Ligands for Enantioselective Hydroformylation

Renchang Tan,[†] Xin Zheng,[†] Bo Qu,[‡] C. Avery Sader,[‡] Keith R. Fandrick,[‡] Chris H. Senanayake,*[,‡] and Xumu Zhang*[,†]

[†]Department of Chemistry and Chemical Biology and Department of Medicinal Chemistry, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854, United States

[‡]Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, United States

Supporting Information



ABSTRACT: Air-stable and tunable chiral bisdihydrobenzooxaphosphole ligands (BIBOPs) were employed in rhodium-catalyzed asymmetric hydroformylation of various terminal olefins with excellent conversions (>99%), moderate-to-excellent enantioselectivities (up to 95:5 er), and branched to linear ratios (b:l) of up to 400.

Asymmetric hydroformylation (AHF) is a powerful homogeneous catalytic process that constructs optically active aldehydes by one-carbon homologation in a single step from olefins.[1] Since the discovery of the phosphine−phosphite Binaphos ligand for Rh-catalyzed AHF in 1993,[2] several P−O-based phosphite and phosphonite ligands have been developed, including Chiraphite,[3] Kelliphite,[4] Yanphos,[5] and Ding's phosphonite ligands.[6] Phosphites and phosphonites are good π acceptors, favoring CO dissociation in the catalytic cycle and accelerating the reaction rate.[7] As a result, phosphine ligands that are highly reactive for asymmetric hydrogenation are generally not effective for AHF. There has been an extensive search of chiral ligands from existing ones to join the family of the few ligands that are effective for AHF.[8] Recently, phosphorus ligands with a bisphospholane backbone have emerged as another effective ligand structure for this application, such as Esphos,[9] bis(diazaphospholane) (BDP) ligands,[10] Duanphos,[11] and Ph-BPE.[12] The development of efficient chiral phosphorus ligands has greatly enhanced the regio- and enantioselectivity in rhodium-catalyzed AHF. Structurally tunable and operationally convenient chiral phosphorus ligands remain of great interest in further broadening the applications of AHF reactions.

We recently reported a series of air-stable, white-crystalline, C_2-symmetric, *P*-chiral bisdihydrobenzooxaphosphole ligands (BIBOPs) (Figure 1) for highly enantioselective asymmetric hydrogenation of *N*-acetyl enamides, α-arylenamides, α-(acylamino)acrylic acids, and β-(acylamino)acrylate.[13] These crystalline dimeric ligands are stable in air and can be conveniently synthesized on a kilogram scale.[13a] The air-stability property results from the two benzene rings at the 4- and 5-positions adjacent to the phosphorus atoms, which is in direct contrast to the highly air-sensitive Tangphos ligand. Furthermore, these features greatly increase the conformational rigidity of the ligands, which is essentially important to affect the reactivity and selectivity of AHF. We envisioned that these ligands could be effective for rhodium-catalyzed AHF.

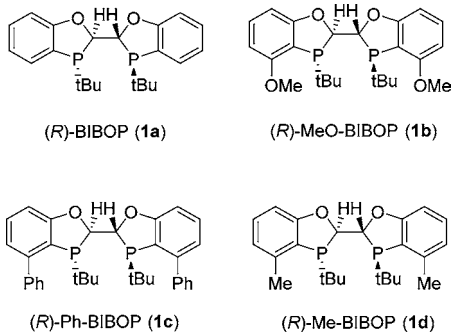


Figure 1. BIBOP ligands for AHF reactions.

Our initial investigation started with the classic vinyl acetate (**2**) as the model substrate. Excess ligand with a high L/Rh ratio is commonly required to stabilize the catalytically active complex under high-temperature conditions in hydroformylation reactions to maintain the catalyst activity and enantioselectivity.[7] A Rh/L ratio of 1:3.0 was applied at 60 °C for 20 h in toluene in the presence of 1.0 mol % $Rh(acac)(CO)_2$ and 3.0 mol % (*R*)-BIBOP (**1a**) under 20 bar syngas (CO/H_2 = 10/10). To our delight, vinyl acetate was fully hydroformylated

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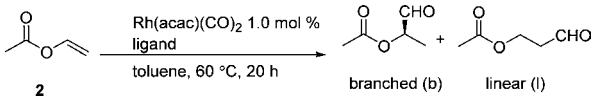
with a 25:1 branched to linear (b:l) regioisomeric ratio and 91:9 er of the branched isomer. Furthermore, the ligand was found to be stable under the reaction conditions, and no access ligand is required. The same conversion and enantioselectivity were obtained with a slight excess ligand loading at a Rh/**1a** ratio of 1:1.2 (Table 1, entry 3).

Table 1. AHF Screening of Vinyl Acetate 2[a]



entry	L	Rh/L	CO/H_2	conv (%)[b]	b:l[b]	er[c]
1	**1a**	1:3.0	10/10	>99	25:1	91.0:9.0
2	**1a**	1:2.0	10/10	>99	20.6:1	91.3:8.7
3	**1a**	1:1.2	10/10	>99	20:1	91.5:8.5
4	**1a**	1:0.9	10/10	>99	13:1	72.5:27.5
5	**1a**	1:1.2	5/15	>99	27:1	91.2:8.8
6	**1a**	1:1.2	15/5	>99	27:1	91.0:9.0
7	**1b**	1:1.2	10/10	>99	>200:1	95.3:4.7
8	**1c**	1:1.2	10/10	28	12:1	71.0:29.0
9	**1d**	1:1.2	10/10	96.4	20:1	51.0:49.0

[a]Reaction conditions: **2** (1.0 mmol) catalyzed by Rh−ligand in toluene (0.5 mL) at 60 °C for 20 h under a syngas pressure of 20 bar. [b]Conversions and branched to linear (b:l) ratios of the products were determined by ^{1}H NMR spectroscopy. [c]Determined by chiral GC.

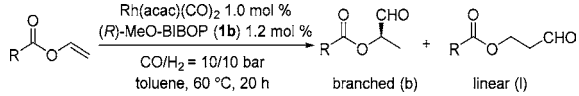
Next, the CO partial pressure was varied since it affects both the conversion and regio- and enantioselectivity of AHF.[7] The catalyst system turns out to be robust toward the CO pressure. When the CO partial pressure in CO/H_2 was decreased from 10/10 to 5/15 (Table 1, entry 5) or increased from 10/10 to 15/5 (Table 1, entry 6), the conversion remained >99%. Both the b:l ratios and the enantiomeric ratios were the same under different CO pressures (Table 1, entries 3, 5, and 6). A syngas pressure of CO/H_2 = 10/10 was selected for further studies.

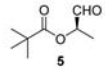
Among the BIBOP ligands, the Ph substituent (**1c**) led to low conversion and enantioselectivity (Table 1, entry 8). The Me substituent (**1d**) also led to a low enantiomeric ratio, although it provided almost full conversion (Table 1, entry 9). To our delight, (*R*)-MeO-BIBOP (**1b**) provided an increased regioselectivity with a b:l ratio of >200:1 and a higher enantioselectivity of 95.3:4.7 er (Table 1, entry 7). On the other hand, the structurally related Duanphos and Tangphos ligands produced poor reactivity and enantioselectivity.

With the optimized reaction conditions in hand, AHF of vinyl acetate derivatives was explored in the presence of the MeO-BIBOP ligand (Table 2). The conditions are applicable to both the aliphatic and aromatic substituents. All of the substrates were successfully converted to the desired aldehydes with excellent enantioselectivities of up to 95.3:4.7 er. It is noteworthy that the regioselectivities are outstanding, with aldehyde b:l ratios of up to 415:1 (entry 4).

To obtain a better understanding of the origin of the enantioselectivity, computational studies were conducted for the hydroformylation process of vinyl acetate in the presence of (*R*)-BIPOP (**1a**) as the ligand (Figure 2). All of the calculations were performed with Gaussian 09[14] using density functional theory (DFT) employing the UB3LYP functional[15] and the LANL2DZ basis set with the effective core potential for Rh[16] and UB3LYP-gCP-D3/6-31G(d) for all other atoms. The geometrical counterpoise (gCP)[17] and dispersion (D3)[18]

Table 2. AHF of Vinyl Acetate Derivatives



entry	substrate	product	conv (%)[a]	b:l[a]	er[b]
1	R = CH_3 (**2**)	 **3**	>99	285:1	95.3:4.7
2	R = *t*-Bu (**4**)	 **5**	>99	127:1	95.2:4.8
3	R = *n*-C_7H_{15} (**6**)	 **7**	>99	269:1	94.5:5.5
4	R = *n*-C_9H_{19} (**8**)	 **9**	>99	415:1	94.4:5.6
5	R = Ph (**10**)	 **11**	>99	37:1	95.0:5.0

[a]Conversions and b:l ratios were determined by ^{1}H NMR spectroscopy (see the Supporting Information). [b]Determined by chiral GC.

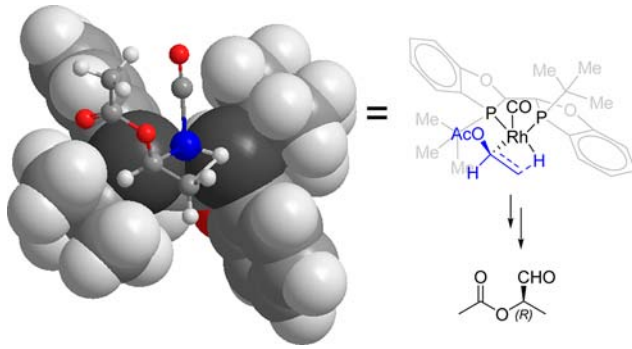
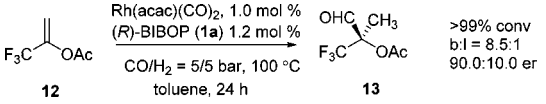


Figure 2. DFT (UB3LYP/LanL2DZ for Rh; UB3LYP-gCP-D3/6-31G(d) for all other atoms)-calculated transition state for the Rh−hydride olefin insertion and stereochemical model.

corrections of Grimme and co-workers were applied to all of the stationary points to correct for basis set superposition error with 6-31G(d) and missing van der Waals dispersion in B3LYP, respectively. On the basis of the reported mechanism,[19] the calculated rate-determining transition state of the stereochemically defining Rh−hydride olefin insertion shows that the vinyl group binds to the rhodium center to position the acetate away from the bulky *tert*-butyl group of the BIBOP ligand. In this orientation, the *Si* face of the olefin is bound to the rhodium center and ultimately receives the carbonyl functionality, generating the *R* configuration of the aldehyde. This result is consistent with the experimental data.

AHF of 1,1-disubstituted olefins has been a challenging task, and only a few ligands can deliver acceptable enantioselectivities.[11,20] BIBOPs were tested in the AHF of 1-(trifluoromethyl)vinyl acetate (**12**) (Scheme 1). BIBOP (**1a**)

Scheme 1. AHF of 1,1-Disubstituted Olefin 12



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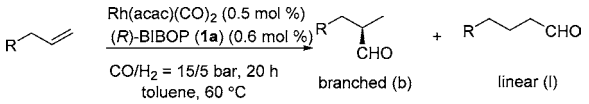
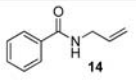
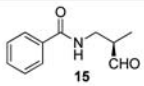
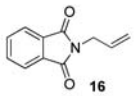
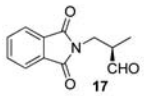
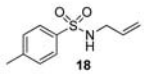
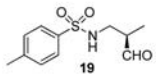
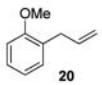
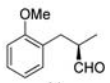
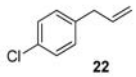
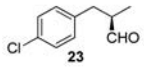
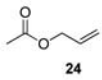
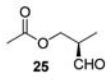
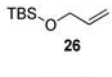
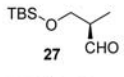
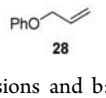
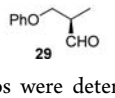
turned out to be an effective ligand. Chiral aldehyde **13** was produced with a 90:10 er and a b:l ratio of 8.5:1. **13** is a key precursor for enantiomerically pure 2-(trifluoromethyl)lactic acid, which is an important building block for many active pharmaceutical ingredients.[21]

To further expand the substrate scope, AHF was tested on a series of allylic derivatives (Table 3). Allylic compounds are particularly challenging for AHF because of the potential for double-bond migration[1b] and the difficulty of regioselectivity control.[22] To our delight, for benzoyl-, phthaloyl-, and *p*-$MePhSO_2$-protected allylic amines **14**, **16**, and **18**, enantiomeric ratios of 89.2:10.8, 87.3:12.7, and 92.2:7.8, respectively, were obtained in the presence of (*R*)-BIBOP as the ligand (Table 3, entries 1−3). The resulting amide-protected chiral β^2-amino aldehydes are useful synthons that can be transformed into important building blocks such as chiral β^2-amino acids and amino alcohols.[23] The protecting groups can then be removed according to the known procedures.[24] Encouraged by the success of the AHF of N-functionalized allyl substrates, Ph- and O-functionalized allylic substrates were also evaluated. For the aryl allyl substrates **20** and **22** that lack directing groups, 93.0:7.0 er and 88:12 er, respectively, were obtained for aldehydes **21** and **23**, although the b:l ratios were modest. Allyl acetate **24** gave an excellent enantioselectivity of 93.3:6.7 er and good regioselectivity with a b:l ratio of 7.7 (Table 3, entry 6).

In summary, bisdihydrobenzooxaphosphole (BIBOP) ligands were successfully applied in rhodium-catalyzed asymmetric hydroformylation reactions with excellent conversions and good to excellent enantioselectivities. The ease of synthesis and excellent air stability make BIBOP ligands stand out as a unique ligand structure in the field of hydroformylation. Computational studies have provided insights into the reaction mechanism, in particular the Rh−hydride olefin insertion process. Application of these ligands on other olefin substrates is currently ongoing.

Table 3. AHF of Allylic Substrates



entry	substrate	product	conv (%)[a]	b:l[a]	er[b]
1	 14	 15	>99	8.0:1	89.2 : 10.8
2	 16	 17	>99	11.2:1	87.3:12.7
3	 18	 19	>99	3.0:1	92.2:7.8
4	 20	 21	>99	1.2:1	93.0:7.0
5	 22	 23	>99	1.1:1	88.1:11.9
6	 24	 25	>99	7.7:1	93.3:6.7
7	 26	 27	>99	2.0:1	88.8:11.2
8	 28	 29	>99	4.1:1	86.8:13.2

[a]Conversions and b:l ratios were determined by ^{1}H NMR spectroscopy. [b]Determined by Chiral GC and HPLC.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01452.

Experimental procedures and characterization data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: chris.senanayake@boehringer-ingelheim.com.
*E-mail: xumu@rci.rutgers.edu.

Notes

The authors declare no competing financial interest.

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