Phosphorus Ligands

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Modular Monodentate Oxaphospholane Ligands: Utility in Highly Efficient and Enantioselective 1,4-Diboration of 1,3-Dienes**

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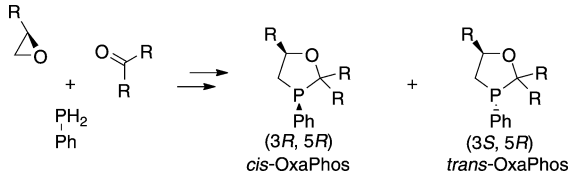
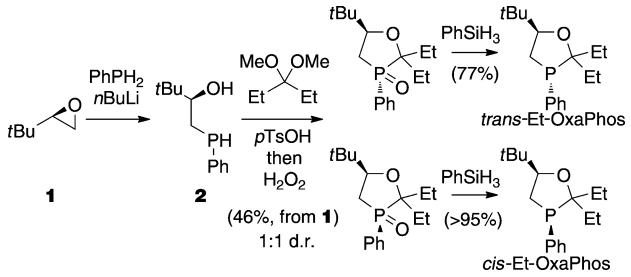
Chiral monodentate ligands are important tools for the control of enantioselectivity in catalytic reactions. These compounds are particularly important when transition-metal catalysts lack sufficient coordination sites to bind a bidentate ligand and still retain activity. Along these lines, modular, tunable chiral carbenes[1] and phosphoramidites[2] have found particular prominence in the field of asymmetric catalysis. Aside from these compound classes, however, there is a relative paucity of effective, tunable monodentate chiral ligands that have found widespread utility. In recent studies on the platinum-catalyzed enantioselective diboration of dienes, we achieved limited success when optimizing chiral phosphoramidite and phosphonite ligands for certain substrates.[3,4] Because catalytic diboration benefits from the presence of electron-rich monodentate phosphines,[5] we considered that solutions to problematic substrates might arise from the availability of a readily preparable, tunable, chiral, Lewis basic phosphine ligand.[6] Herein, we describe the synthesis and properties of enantiomerically enriched modular 1,3-oxaphospholanes (termed OxaPhos ligands, Scheme 1). These ligands are readily available from the



Scheme 1. Modular assembly of OxaPhos ligands.

combination of an enantiopure epoxide, a primary phosphine, and a ketone or the derived ketal.[7] In addition to describing their synthesis and properties, we also describe their use in the catalytic 1,4-diboration of challenging diene substrates.

The OxaPhos ligands possess two stereocenters, one at carbon and one at phosphorus, and are therefore available in two epimeric forms. The preparation of both epimers of the Et-OxaPhos ligand is described in Scheme 2 and is representative of the synthesis of this ligand class. Enantiomerically enriched terminal epoxide **1** was treated with phenylphosphide to furnish ring-opened secondary phosphine **2**. Without purification, phosphine **2** was subjected to transketalization with the dimethyl ketal of the reacting ketone. This synthesis sequence delivered a 1:1 mixture of tertiary phosphines that were directly oxidized with hydrogen peroxide. The stable phosphine oxides were easily separated by silica gel chromatography and subsequent stereoretentive reduction with phenylsilane[8] cleanly delivered the isomerically pure tertiary phosphines in good yield.



Scheme 2. Synthesis of Et-OxaPhos ligands.

The crystal structures of the phosphine oxide derivates of both *cis*- and *trans*-Et-OxaPhos ligands are depicted in Figure 1.[9] A notable feature of these structures is the invariant nature of the five-membered ring with the *tert*-butyl substituent adopting an equatorial position in each. Assuming similar conformations predominate in the reduced phosphine derivatives, one can anticipate that the phosphorus

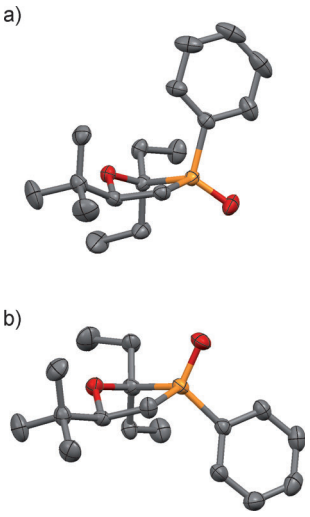


Figure 1. ORTEP representation of *cis* (a) and *trans* (b) Et-OxaPhos phosphine oxides (ellipsoids at the 60% probability level). C gray, O red, P yellow.

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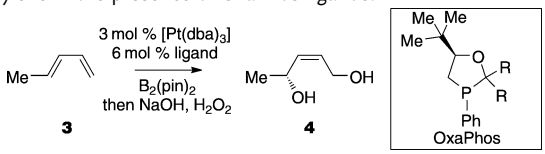
lone pair in the *cis*-OxaPhos ligand is better aligned with the adjacent C–O σ* orbital (OPCO dihedral angle = 151°) compared to the *trans*-OxaPhos ligand (OPCO dihedral = 99°). However, this alignment appears to have little consequence on the ligand electronic properties; after reduction, the derived *trans*-[L_2Rh(CO)Cl] complexes exhibit nearly identical CO stretching frequencies (1961 cm^{-1} for the *cis* ligand and 1962 cm^{-1} for the *trans*).[10] Of note, the CO stretching frequencies also suggest that the phosphorus atom in the OxaPhos ligands is relatively basic, comparable to $PhPCy_2$ (CO stretching frequency for *trans*-[$(PhPCy_2)_2$Rh(CO)Cl] = 1964 cm^{-1}).[10b]

To study the utility of oxaphospholanes in catalytic diboration, diene **3** was chosen for analysis (Table 1). Previous studies from our laboratory documented the efficacy of chiral

Table 1: Pt-catalyzed enantioselective diboration/oxidation of *trans*-piperylene in the presence of OxaPhos ligands.[a]



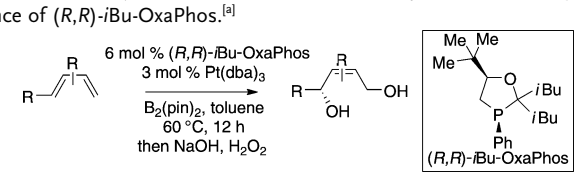
Ligand	Yield [%][b]	e.r.[c]
cis-Me-OxaPhos	83	85.5:14.5
trans-Me-OxaPhos	62	20.2:79.8
cis-Et-OxaPhos	85	94.5:5.5
trans-Et-OxaPhos	86	22.8:77.2
***cis-i*Bu-OxaPhos**	**86**	**97.0:3.0**
*trans-i*Bu-OxaPhos	88	38.9:61.1

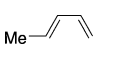
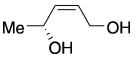
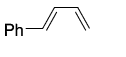
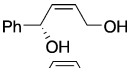
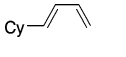
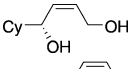
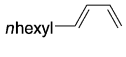
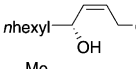
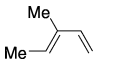
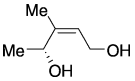
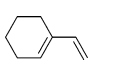
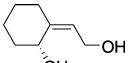
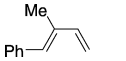
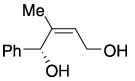
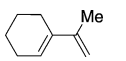
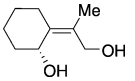
[a] Reactions employed 1.05 equivalents of $B_2(pin)_2$ and were carried out at 60 °C for 12 h. [b] Yield of isolated purified product; value is an average of two experiments. [c] Determined by GC with a chiral stationary phase; error ≤ ±0.2%. pin = pinacolato, dba = dibenzylideneacetone.

α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derived phosphonite ligands in diene diboration reactions, and with the most optimal ligand (xylyl-TADDOL-derived phenyl phosphonite) this substrate underwent diboration in only 70% *ee*.[3] As shown in Table 1 and discussed in the following, diboration under the influence of oxaphospholane ligands can be much more selective, and reactivity is outstanding. While diborations with propylene oxide derived ligands and ligands derived from aldehydes were not highly selective (data not shown), when the *tert*-butyl-substituted ligands were employed, elevated levels of enantiomeric enrichment were obtained. As depicted in Table 1, the *cis* and *trans* isomers of the OxaPhos ligands favor opposite product enantiomers. Significantly, the enantioselectivity with the *cis* ligand isomer is markedly enhanced as the size of the ketal substituents is increased, (substituents larger than isobutyl could not be incorporated with the current synthesis route), whereas the opposite trend occurs with the *trans* epimer. Importantly, with the *cis-i*Bu-OxaPhos ligand, the selectivity in the diboration of *trans*-1,3-pentadiene (Table 1) far surpasses that obtained with (xylyl)TADDOL-derived phosphonite ligand (97:3 e.r. versus 85:15 e.r.).

To survey the utility of *cis-i*Bu-OxaPhos in the diboration of other dienes, the collection of substrates in Table 2 was examined. As shown by the data, *cis-i*Bu-OxaPhos is useful

Table 2: Pt-catalyzed enantioselective diboration/oxidation in the presence of (*R*,*R*)-*i*Bu-OxaPhos.[a]



Entry	Substrate	Product	Yield [%][b]	e.r.[c]
1			86	97.0:3.0
2			65	96.1:3.9
3			>95	98.2:1.8
4			>95 (>95)[d]	97.5:2.5
5			82	99.0:1.0
6			>95	98.8:1.2
7			61[e]	98.1:1.9
8			82	82.5:17.5

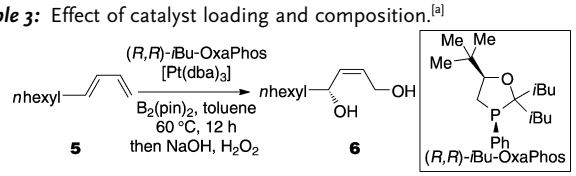
[a] Reactions employed 1.05 equivalents of $B_2(pin)_2$ and were carried out at 60 °C for 12 h. [b] Yield of isolated purified product; value is an average of two experiments. [c] Determined by GC, HPLC, or SFC analysis on a chiral stationary phase; error ≤ ±0.2%. With (xylyl)TADDOL-PPh, the enantioselectivities of the reactions corresponding to entries 1–5 are 70, 84, 91, 84, and 45% *ee*, respectively. [d] Yield in parentheses is for the purified 1,4-bis(boronate) intermediate. [e] 2:1 ratio of 1,4-/1,2-diboration products obtained; yield is for the purified 1,4 product. Cy = cyclohexyl.

for a range of aromatic and aliphatic terminal dienes, affording the derived 1,4-diol in excellent yield and enantioselectivity upon oxidative workup. The selective diboration reaction could be extended to 3,4-disubstituted dienes (Table 2, entries 5–7). The diboration of these substrates occurs in low selectivity with TADDOL-derived ligands, but with *cis-i*Bu-OxaPhos, enantiomeric purities of 96–98% *ee* were observed. A particularly noteworthy feature is that these substrates deliver difficult-to-access trisubstituted alkene products in a highly diastereo- and enantioselective fashion. The result in entry 8 suggests that the diboration strategy with *cis-i*Bu-OxaPhos can deliver chiral, tetrasubstituted alkene products with synthetically useful levels of selectivity. Lastly, it was demonstrated that the intermediate 1,4-bis(boronate) could be isolated in excellent yield and fully characterized (Table 2, entry 4).

The *cis*-butene-1,4-diols obtained by diene diboration can be readily oxidized[11] to butenolides and therefore represent

valuable synthetic intermediates.[12] However, if these structures are to be accessed on large scale using Pt catalysis, the amount of catalyst employed in the reaction can be a concern. To address this issue, the effects of catalyst composition and loading were examined (Table 3). Similar to the reactions described above, these reactions were carried out with rigorously dried and deoxygenated solvents and were conducted under argon. However, in contrast to the previous studies, the substrate for these experiments was also rigorously deoxygenated. As indicated in entry 1 (Table 3), very little reaction occurred when a ligand(L)/metal(M) ratio of 2:1 was employed. Suspecting that PtL_2 complexes might be inactive and that trace oxygen in the substrate might serve to oxidize a portion of the ligand and provide an active ML_1 complex, we repeated the experiment (Table 3, entry 2). After 4 h (no reaction, TLC analysis) the mixture was briefly exposed (< 5 s) to air, sealed, and allowed to react for 2 more hours. This experiment provided diol **6** in excellent yield and enantiomeric purity. Also consistent with the hypothesis that the active species may be an ML_1 complex is the fact that with 1.95:1 L/M and degassed substrate (Table 3, entry 3), the reaction proceeds normally. Notably, L/M ratios of 1.1:1 and 0.5:1 (Table 3, entries 4 and 5) provide reasonable yields and selectivity in the diboration of **5**, with the latter experiment indicating that a significant level of ligand-accelerated catalysis occurs. Expecting that at lower catalyst loading trace oxygen may be more problematic, we employed an L/M ratio of 2:1 when the amount of catalyst used in experiments was decreased to 0.1 mol% and 0.02 mol% (Table 3, entries 6–8). These reactions used nondegassed substrate and even at a 0.02 mol% loading of Pt^0, the diene diboration proceeds in excellent yields and enantioselectivity (Table 3, entry 8). This level of reactivity is in marked contrast to diborations with TADDOL-derived phosphonite ligands which proceed in < 5% conversion at 0.02 mol% loading and in 23% conversion at the 0.1% loading level.

Table 3: Effect of catalyst loading and composition.[a]



Entry	L [mol%]	M [mol%]	Yield [%][b]	ton[c]	e.r.[d]
1[e]	2.0	1.0	< 5	–	–
2[f]	2.0	1.0	90	90	96.4:3.6
3[e]	1.95	1.0	97	97	97.4:2.6
4[e]	1.1	1.0	98	98	97.3:2.7
5[e]	0.5	1.0	71	71	95.4:4.6
6	0.2	0.1	98	980	97.3:2.7
7	0.1	0.05	95	1900	97.2:2.8
8	0.04	0.02	95	4750	97.1:2.9

[a] Reactions were conducted under Ar atmosphere with anhydrous deoxygenated solvent and 1.05 equivalents of $B_2(pin)_2$ and were carried out at 60 °C for 12 h. [b] Yield of isolated purified product. [c] Turnover number = yield [%]/Pt [mol%]. [d] Determined by GC on a chiral stationary phase; error $\leq \pm 0.2$%. [e] Substrate was degassed. [f] Substrate was degassed substrate and the reaction mixture was briefly exposed to air (< 5 s) after a reaction time of 4 h.

The remarkable diboration activity of Pt catalysts derived from *cis*-*i*Bu-OxaPhos raises the concern that the presence of trace amounts of stereoisomeric catalysts (i.e. from incomplete chromatographic resolution during synthesis) might erode selectivity. To study this feature, we examined catalysts of varying diastereomeric purity in the diboration of 1,3-pentadiene. As depicted in Figure 2, these experiments revealed a substantial nonlinear effect that favors the more selective *cis* diastereomer of the *i*Bu-OxaPhos ligand.[13] Remarkably, even a 1:1 mixture of *cis* and *trans* *i*Bu-OxaPhos ligands delivers the product with synthetically useful levels of selectivity. Furthermore, the more selective *cis* ligand, even when contaminated with the less selective *trans* isomer (25%), provides the product in levels of selectivity nearly indistinguishable from that derived from a ligand sample that is > 97% pure *cis* isomer. Thus, not only is trace contamination by the *trans* stereoisomer of catalyst of little consequence, it is also not necessarily important to achieve substantial resolution during the synthesis outlined in Scheme 1.

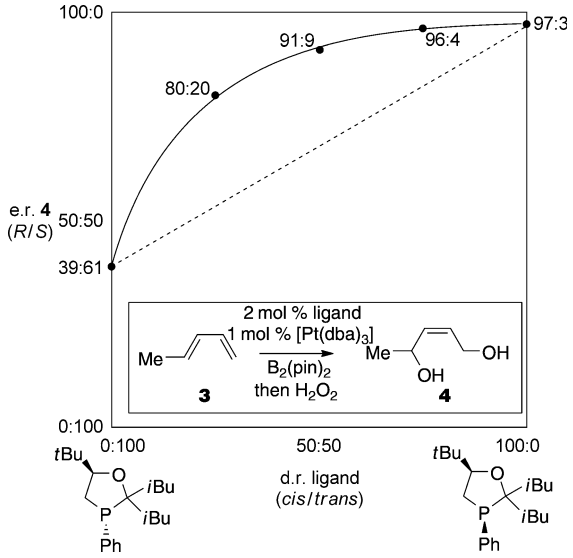


Figure 2. Correlation between catalyst diastereomer ratio and product enantiomer ratio.

In conclusion, OxaPhos ligands are tunable, chiral, monodentate phosphines that can offer very high enantioselectivity in catalytic diboration. Of particular note is that at the 0.02 mol% level of catalyst loading with which these catalysts can be effective, the cost of the catalyst becomes meaningless relative to the substrates and reagents in the diboration reaction.[14] Considering the impact that phosphoramidite ligands have had on asymmetric catalysis and the observation that OxaPhos ligands can offer advantages, it is anticipated that the latter ligand class may find significant use in catalysis.

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Keywords: asymmetric catalysis · boron · ligand design · oxidation

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[14] $[Pt(dba)_3]$ can be prepared from K_2PtCl_4 in one step (85% yield). At a price of roughly US$20000 per mole for K_2PtCl_4, a 1-mol-scale diboration reaction at a catalyst loading of 0.02 mol% Pt requires about $4 worth of catalyst. The current price of $B_2(pin)_2$ from AllyChemUSA, Inc. is approximately US$200 per mole.

