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Remarkable Levels of Enantioswitching in Catalytic Asymmetric Hydroboration

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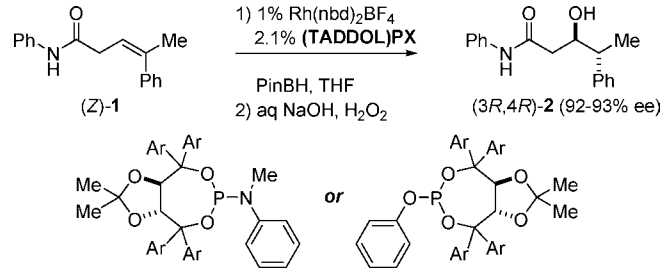
ABSTRACT



TADDOL-derived phosphites and phosphoramidites are effective ligands for rhodium-catalyzed asymmetric hydroborations of β,γ-unsaturated amides, achieving up to 99% ee. However, the sense of stereoinduction, *R* or *S*, is surprisingly dependent on rather subtle features of the ligand. For example, catalysts employing a TADDOL phenylphosphite and those using the closely related *N*-methylaniline-derived phosphoramidite of the same configuration give opposite enantiomers of the product. Those derived from optical antipodes give the same product with virtually the same enantioselectivity as illustrated above. The different stereochemical outcomes may reflect fundamental differences in catalyst structure, reactivity, or reaction mechanism.

Accessing either enantiomer of a chiral product via asymmetric catalysis is typically achieved by preparing both enantiomers of the catalyst. Occasionally, efficient enantioswitching, that is, producing each enantiomer using similar nonenantiomeric chiral catalysts, has been achieved by changing substituents on a ligand while preserving its absolute configuration.[1,2] Although the structural changes needed to effect enantioswitching are difficult to predict *a priori* or even rationalize after the fact, such processes are of special interest and hold the potential to yield fundamental insight into the origin of enantioselectivity in asymmetric catalysis. We now report striking examples of directed rhodium-catalyzed asymmetric hydroboration for which rather subtle changes in the structure of a TADDOL-derived ligand, for example, comparing a phenylphosphite to an *N*-methylaniline-derived phosphoramidite, lead to nearly complete reversal of stereochemistry. Several factors influencing the efficiency of enantioswitching and some surprising characteristics of the catalysts are found.

The catalyzed hydroboration reaction, first reported in 1985,[3] is of renewed interest.[4] Building upon the work of Evans[5] and Gevorgyan,[6] we reported that TADDOL-derived monophosphites are excellent ligands for carbonyl-directed

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(2) For several particularly impressive examples, see: (a) Wu, W.; Peng, Q.; Dong, D.; Hou, X.; Wu, Y. *J. Am. Chem. Soc.* **2008**, *130*, 9717–9725. (b) Zhang, W.; Shi, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3467–3476. (c) Hoarau, O.; Ait-Hadou, H.; Daran, J.; Cramailere, D.; Balavione, G. G. A. *Organometallics* **1999**, *18*, 4718–4723.

(3) (a) Männig, D.; Nöth, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 878–879. (b) The first highly selective asymmetric version was reported by Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426–3428.

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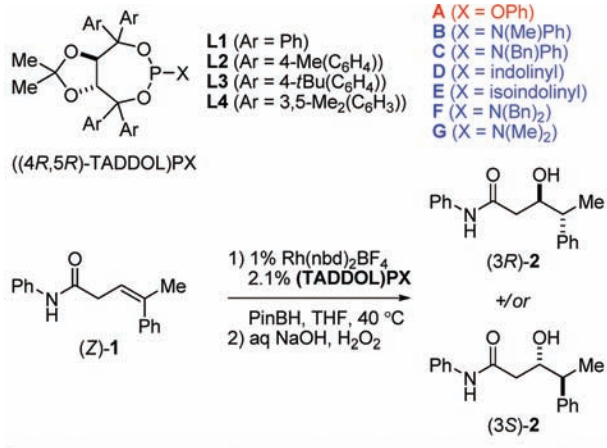
rhodium-catalyzed asymmetric hydroborations of (*E*)- and (*Z*)-trisubstituted-β,γ-unsaturated amides.[7] BINOL-derived phosphoramidites afford very selective catalysts for the related disubstituted alkenes and certain vinyl arene substrates.[8−10]

Several surprising observations were made while studying a series of TADDOL derivatives, (TADDOL)PX (**L1**−**L4**), in the reaction of amide **1**.[11] Small variations in the aryl substituents give rise to subtle changes in the shape of the phosphorus ligand.[7,8a,12,13] A series of phosphites, including phenylphosphites (i.e., **L1A**−**L4A**), and phosphoramidites (i.e., **L1**−**L4** with **B**−**G**) was used in conjunction with $Rh(nbd)_2BF_4$ to effect asymmetric hydroboration of **1** with pinacolborane (PinBH). The (3*R*)-**2**:(3*S*)-**2** enantiomeric ratios (er) determined after oxidative workup are summarized in Figure 1.



X	L1		L2		L3		L4	
	(3*R*)	(3*S*)	(3*R*)	(3*S*)	(3*R*)	(3*S*)	(3*R*)	(3*S*)
A	93	7	94	6	96.5	3.5	95	5
B	4.5	95.5	4	96	11.5	88.5	10	90
C	33.5	66.5	30	70	37	63	48	52
D	53	47	65	35	70	30	60	40
E	50	50	62.5	37.5	56.5	43.5	58.5	41.5
F	93	7	78.5	21.5	95.5	4.5	60	40
G	33	67	42.5	57.5	45	55	41.5	58.5

Figure 1. Enantiomeric ratio (er) for the formation of *R*/*S*-**2** varies as a function of the TADDOL subunit (i.e., **L1**−**L4**), while the sense of asymmetric induction (3*R* or 3*S*) is a function of the (TADDOL)PX substituent, X (X = **A**−**G**).

Phenylphosphites **L1A**−**L4A** afford predominantly the (3*R*)-β-hydroxyamide **2** (86−93% ee, 72−80% yield); **L3A** is the most selective among the ligands examined. In contrast, *N*-methylaniline-derived phosphoramidites **L1B**−**L4B** give the enantiomeric product, (3*S*)-**2** (77−92% ee); **L1B** and **L2B** perform nearly equivalently. It is not simply a consequence of phosphoramidite versus phosphite that determines the *R*/*S* stereochemical course of the reaction. The *N*,*N*-dibenzylamine-derived **L3F** affords (3*R*)-**2** in 91% ee. Other phosphoramidites give only modest levels of asymmetric induction. The *N*-benzylaniline-derived phosphoramidites **L1C**−**L4C** favor (3*S*)-**2** (4−40% ee). The indoline (i.e., **L1D**−**L4D**) and isoindoline (i.e., **L1E**−**L4E**) derivatives give near racemic product in the **L1** series and a modest excess of the (3*R*)-**2** for **L2**−**L4** derivatives (i.e., 13−40% ee). The *N*,*N*-dimethylamine derivative **L1G** affords (3*S*)-**2** in 34% ee.

Although the extent of enantioreversal is very high for (*Z*)-**1** with monophosphoramidites **L1B**−**L4B**, the isolated yields of **2** are significantly lower (35−45%) than those obtained using monophosphites **L1A**−**L4A** (72−80%). A side product, tentatively identified as an isomeric δ-hydroxyamide, is formed in substantial amounts (25−32%) but low enantiomeric excess from **1**. It presumably arises via rhodium-catalyzed alkene isomerization followed by hydroboration. Although rhodium-catalyzed alkene isomerization is well-known,[14] it has not generally been problematic with β,γ-unsaturated amides. For example, (*Z*)-**3** affords β-hydroxyamide **4** in 80% yield using either phosphite **L3A** or phosphoramidite **L4B**; alkene isomerization is apparently not a significant competing side reaction. Phenylphosphite **L3A** gives (3*R*)-**4** (96% ee). Phosphoramidite **L4B** exhibits the expected enantioreversal; however, the level of enantioselectivity favoring (3*S*)-**4** is somewhat lower, 80% ee (Figure 2). Other β,γ-unsaturated amides possessing trisubstituted alkenes bearing all alkyl substituents give similar results.

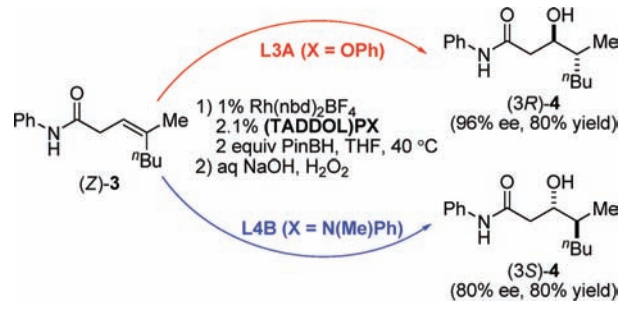


Figure 2. Other trisubstituted substrates, for example, (*Z*)-**3**, exhibit enantioreversal but to a somewhat lesser degree.

The disubstituted alkene, (*E*)-**5** (R = $(CH_2)_2$Ph), affords (3*S*)-**6** (90−99% ee) using monophosphites **L1**−**4A**; **L3A** and **L4A** give the highest enantioselectivity (Table 1). In contrast to the trisubstituted alkene substrates discussed above, the *N*-methylaniline-derived phosphoramidite ligands **L1**−**4B** afford poor to moderate levels of enantioselectivity varying from 33% ee favoring (3*S*)-**6** to 55% ee favoring

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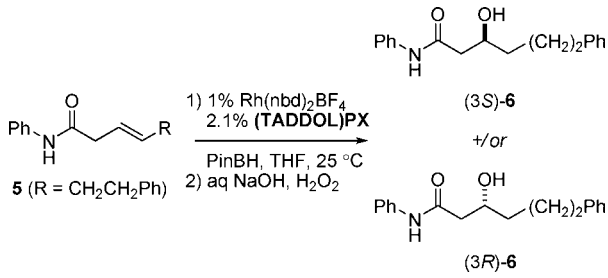
Table 1. Enantiomeric Ratio and Sense of Enantioselectivity (i.e., *R* or *S*) Vary Widely as a Function of the TADDOL Scaffold (i.e., **L1**−**L4**) and the Nature of X (i.e., **A**−**G**) with Unsaturated Amide **5**



X	L1		L2		L3		L4	
	(3*S*)	(3*R*)	(3*S*)	(3*R*)	(3*S*)	(3*R*)	(3*S*)	(3*R*)
A	99	1	95	5	99.5	0.5	99.5	0.5
B	22.5	77.5	30	70	60	40	66.5	33.5
C	15	85	50	50	50	50	50	50
D	1.5	98.5	1.5	98.5	75	25	95	5
E	5.5	94.5	6.5	93.5	28	72	50	50
F	91.5	8.5	91.5	8.5	98	2	70	30
G	15	85	25	75	20	80	38	62

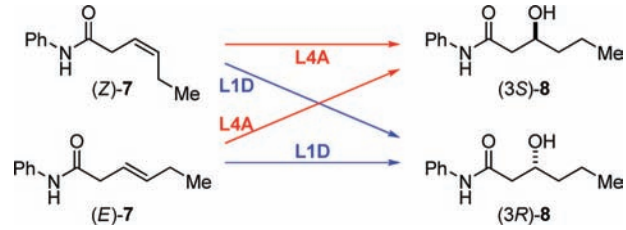
[a] The β-hydroxyamide is favored over the γ-regioisomer in all cases (2−15:1). The yield of **6** (R = CH_2CH_2Ph) is ligand-dependent and varies from 27% to 78%. The lowest yields generally reflect incomplete reaction and are not corrected for recovered starting material; the reaction conditions were not optimized. See Supporting Information for a complete summary of conversions and yields.

(3*R*)-**6**. The indolinyl (**D**) and isoindolinyl (**E**) derivatives are superior, giving (3*R*)-**6** in up to 97% ee with **L1D** or **L2D**. Furthermore, enantioswitching now strongly depends upon the TADDOL scaffold. In contrast to **L1D** and **L2D**, **L3D** and **L4D** give predominantly the enantiomeric product (3*S*)-**6**. Using **L4D** the enantioselectivity reaches 90% ee.

While computational studies have addressed the mechanism of rhodium-catalyzed hydroborations using rhodium chloride catalysts, the conclusions are not directly applicable to variants employing dissociable counterions (e.g., BF_4^-) or two point binding substrates.[15] Furthermore, prior studies suggest that several reaction pathways are close in energy and mechanistic details may vary depending on the exact conditions employed.[15b,16] It is, therefore, not feasible at this time to develop a complete mechanistic rationale accounting for the observed enantioreversal. Nonetheless, the (*Z*)- and (*E*)-isomers of unsaturated amide **7** prove useful in identifying several characteristics relevant to enantioswitching.

First, high levels of enantioselectivity and remarkably efficient enantioswitching are observed for either alkene geometry. Using phosphite **L4A**, (*Z*)- and (*E*)-**7** each afford (3*S*)-**8** in excellent enantiopurity (96% and 94% ee, respectively, Table 2, entries 1 and 2). Phosphoramidite **L1D**

Table 2. (*E*)- and (*Z*)-**7** Exhibit High Enantioswitching[a]



entry	7	ligand	8 (%ee) (3*S*)	8 (%ee) (3*R*)	% yld
1	Z	(4*R*,5*R*)-L4A (2.1 eq)	96		78
2	E	(4*R*,5*R*)-L4A (2.1 eq)	94		76
3	Z	(4*R*,5*R*)-L1D (2.1 eq)		97	83
4	E	(4*R*,5*R*)-L1D (2.1 eq)		96	81
5	Z	(4*S*,5*S*)-L4A + (4*R*,5*R*)-L1D		76	77
6	E	(4*S*,5*S*)-L4A + (4*R*,5*R*)-L1D		80	79
7	Z	(4*R*,5*R*)-L4A + (4*R*,5*R*)-L1D	46		70
8	E	(4*R*,5*R*)-L4A + (4*R*,5*R*)-L1D	50		73

[a] Reactions were run as follows: 1% $Rh(nbd)_2BF_4$, 2.1% ligand, 2.0 equiv of PinBH, rt, 24 h.

affords (3*R*)-**8** in 97% and 96% ee from (*Z*)- and (*E*)-**7**, respectively (entries 3 and 4). Using deuterated borane, PinBD, the isomeric (*Z*)- and (*E*)-**7** substrates afford diastereomeric products using either ligand, indicating that the catalyzed addition of boron and deuterium (hydrogen) across the double bond is overall stereospecific and *syn* for either ligand.[17]

Matched and mismatched combinations of **L4A** and **L1D** were examined (Table 2, entries 5−8). Recognizing of course that these heterocombinations could give rise to a mixture of three distinct 2:1 L:Rh complexes,[18] the "matched" pair is a pseudoracemate consisting of 1 equiv of the indolinyl phosphoramidite derived from the *L* or (4*R*,5*R*)-isomer of tartaric acid (i.e., (4*R*,5*R*)-**L1D**) with 1 equiv of the phe-

(10) Chiral monophosphoramidites are effective in rhodium-catalyzed asymmetric hydrogenations; for example, see: Minnaard, A. J.; Feringa, B. L.; Lefort, L.; De Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267–1277, and references therein.

(11) Unless noted otherwise, the results reported are obtained using the (4*R*,5*R*)-TADDOL derivative. See Supporting Information for complete details.

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(17) Approximately 70−76% γ-monodeuteration obtained in each case.

(18) A 2:1 L:Rh ratio is required for efficient asymmetric hydroboration using **L4A** or **L1D**. At lower L:Rh ratios, the level of enantioselectivity is decreased using either ligand.

nylphosphite derived from (4*S*,5*S*)-tartrate (i.e., (4*S*,5*S*)-**L4A**). Surprisingly, the matched pseudoracemate combination is only moderately less selective than either enantiopure ligand used separately. (3*R*)-**8** is produced in 76−80% ee (Table 2, entries 5 and 6), more selective than the homochiral (i.e., mismatched) combination, (4*R*,5*R*)-**L4A** plus (4*R*,5*R*)-**L1D**. The latter affords the opposite enantiomer, (3*S*)-**8**, albeit in only 46−50% ee (entries 7 and 8).

The phenylphosphite **L4A**, indolinyl phosphoramidite **L1D**, and the matched/mismatched combination catalysts were evaluated for nonlinear effects[19] in the catalyzed reaction of (*E*)-**7** with PinBH. The surprising results are shown in Figure 3. Graph A shows the change in enantiomeric purity of **8** as a function of the enantiomeric purity of phenyl phosphite **L4A**. The dashed line serves as a reference for a purely linear relationship. Viewing left-to-right, pure (4*R*,5*R*)-**L4A** to pure (4*S*,5*S*)-**L4A**, the data show a negative nonlinear effect for **L4A**. In contrast, indolinyl phosphoramidite **L1D** (Graph B) exhibits a strong positive nonlinear effect. Graph C shows two sets of data obtained by holding one component of the matched/mismatched combination catalysts constant while varying the enantiomeric purity of the second component. The red data points are obtained varying **L4A**; the blue data reflect varying **L1D**. The data for each show little deviation from linearity, suggesting that the mixed "(**L4A**)(**L1D**)Rh(I)" complex, rather than "(**L4A**)$_2$Rh(I)" or "(**L1D**)$_2$Rh(I)", dominates the reaction.

In summary, amide-directed rhodium catalyzed asymmetric hydroboration exhibits remarkable levels of enantioswitching. Relatively small changes in ligand substituents result in complete enantioreversal without changing the absolute stereochemistry of the ligand. Comparing nonlinear effects for the phenylphosphite **L4A**, indolinyl phosphoramidite **L1D**, and the apparent matched/mismatched combination catalysts suggests that although the ligands employed are structurally quite similar, the reactivity of each catalyst differs substantially from the others. The different stereochemical outcomes therefore may reflect significant and fundamental differences in catalyst structure, reactivity, and/or perhaps reaction mechanism leading to enantioreversal. Further work is in progress to gain a better understanding of the mechanistic basis for enantioswitching.

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Supporting Information Available: Experimental procedures and selected spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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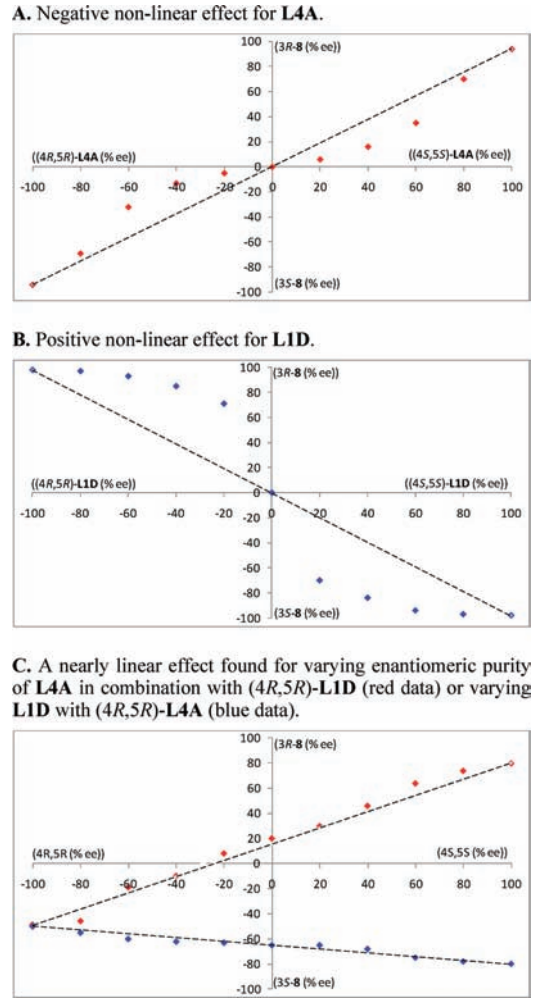

Figure 3. Nonlinear effects in the catalyzed hydroboration of (*E*)-**7** with PinBH. Negative and positive nonlinear effects for the catalysts using phosphite **L4A** (graph A) and phosphoramidite **L1D** (graph B), respectively, contrast with the largely linear effects found for equimolar combinations of **L4A** and **L1D** (graph C). The dashed lines are for reference only. (A) Negative nonlinear effect for **L4A**. (B) Positive nonlinear effect for **L1D**. (C) A nearly linear effect found for varying enantiomeric purity of **L4A** in combination with (4*R*,5*R*)-**L1D** (red data) or varying **L1D** with (4*R*,5*R*)-**L4A** (blue data).

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