Synthetic Methods

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Asymmetric Hydrogenation of α- and β-Enamido Phosphonates: Rhodium(I)/Monodentate Phosphoramidite Catalyst**

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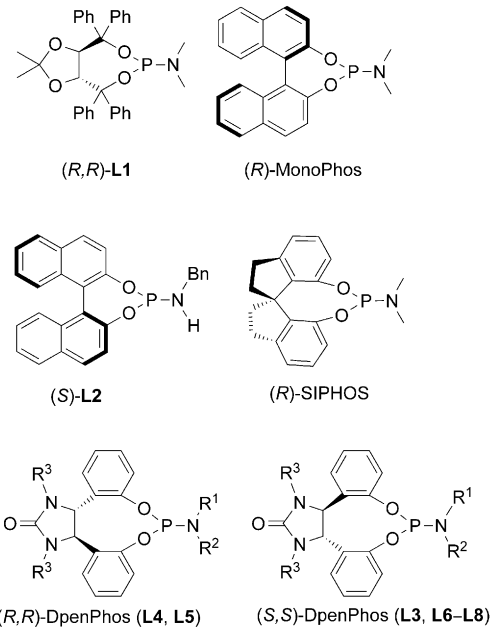
Optically active α- and β-amino phosphonic acid derivatives are bio-isosteric analogues of the corresponding amino acids, and have found widespread use in biochemistry and pharmaceuticals as active substances in anticancer drugs, enzyme inhibitors, catalytic antibodies, herbicides, bactericides, and antibiotics.[1] Consequently, considerable research efforts have been devoted to the asymmetric synthesis of these compounds over the past decades.[2] Several catalytic asymmetric methods involving different types of bond-forming processes have been developed in recent years for the synthesis of the α-amino phosphonic acid derivatives.[3] Among these protocols, catalytic asymmetric hydrogenation (AH) is particularly attractive and potentially practical when considering both atom efficiency and environmental concerns.[4] In spite of the great potential, however, so far the AH of α-enamino phosphonic acid derivatives has only received limited attention. Since the first report by Schöllkopf and coworkers in 1985,[5] a couple of catalytic systems based on Rh^I- or Ru^{II}/bisphospines have been developed for the AH of α-enamido phosphonates, thus affording the α-amino phosphonic acid derivatives in good efficiency and varying levels of enantioselectivity.[3b,6] In contrast, catalytic asymmetric protocols that can provide direct access to β-amino phosphonic acid derivatives are remarkably scarce.[3a,7] Specifically, catalytic AH of β-enamido phosphonates remains less explored despite some notable achievements made very recently for the AH of β-aryl-substituted β-enamido phosphonates by using rhodium- or iridium/diphosphine catalysts.[8–10] It seems somewhat surprising that to date no successful use of readily available monodentate chiral phosphine ligands in the Rh^I-catalyzed AH of α- or β-enamido phosphonates has been achieved, despite the great successes in the AH of their dehydroamino acid analogues.[11] Apart from easy preparation and good stability, an important advantage of using monodentate phosphine ligands is that they may allow the use of ligand mixtures for rapid generation of a chiral catalyst library and hence high-throughput screening for a targeted reaction.[12] Herein, we present our results on the use of a monodentate phosphoramidite ligand, DpenPhos,[13a–b] for the efficient Rh^I-catalyzed AH of a wide variety of α- and β-enamido phosphonates to give the corresponding α- and β-amino phosphonates in excellent optical purities.

The study was initiated by screening the Rh^I complexes of some well-established phosphoramidite ligands[11b,13–14] (Scheme 1) using (*E*)-dimethyl 1-benzamido-2-phenylvinylphosphonate (**1a**), a benchmark substrate for AH of α-enamido phosphonates (see Table 1 for reaction equation). The reactions were performed in dichloromethane at an ambient pressure of hydrogen with 1 mol% of the catalyst, which was made in situ by reacting $[Rh(cod)_2]BF_4$ (cod = cycloocta-1,5-diene) with the corresponding phosphoramidite ligand in a 1:2 molar ratio. Under such reaction conditions, this class of complexes demonstrated a distinct behavior in catalytic activity, that is, either active or inactive depending on



(*S*,*S*)-**L3** : R^3 = Bn, R^1 = R^2 = Me
(*R*,*R*)-**L4** : R^3 = Bn, R^1,R^2 = $-(CH_2)_5-$
(*R*,*R*)-**L5** : R^3 = Bn, R^1,R^2 = $-(CH_2)_2O(CH_2)_2-$
(*S*,*S*)-**L6** : R^3 = Bn, R^1 = Bn, R^2 = H
(*S*,*S*)-**L7** : R^3 = Et, R^1 = Bn, R^2 = H
(*S*,*S*)-**L8** : R^3 = Bn, R^1 = *i*Pr, R^2 = H

Scheme 1. Chiral monodentate phosphoramidites used in this study.

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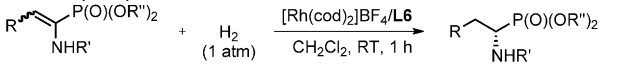
whether or not the relevant phosphoramidite ligand carried a P–N–H moiety within its structure. Whereas full conversions could be achieved within 1 hour when using (*S*)-**L2** and (*S*,*S*)-**L6**–**L8**, no product was detected under analogous reaction conditions when using (*R*,*R*)-**L1**, MonoPhos, SIPHOS, (*S*,*S*)-**L3**, or (*R*,*R*)-**L4**–**L5** (see the Supporting Information). All these experimental facts clearly indicate the importance of the P–N–H moiety of the ligand for catalytic activity, and may provide a suitable platform for either multicomponent catalyst assemblies or substrate organizations through hydrogen-bonding interactions in the catalysis.[13b–c] Catalysts of the DpenPhos series [(*S*,*S*)-**L6**–**L8**] gave the best results, thus yielding **2a** in 97–98% *ee* irrespective of the variation in either R^1 or R^3. The solvent effect is also dramatic in terms of reactivity and enantioselectivity (see the Supporting Information). For the AH of **1a** using the Rh/(*S*,*S*)-**L6** catalyst, CH_2Cl_2, $ClCH_2CH_2Cl$, toluene, or *i*PrOH yielded full conversions with *ee* values above 96%, whereas the protic solvent methanol only resulted in poor conversion (29%) and a significantly reduced *ee* value (40%) under otherwise identical reaction conditions. Under optimized reaction conditions, hydrogenation of a number of β-aryl-substituted (*E*)-dimethyl α-benzamido phosphonates catalyzed by Rh/(*S*,*S*)-**L6** afforded the corresponding α-amino phosphonate esters with high *ee* values (Table 1, entries 1–5). Considering that Cbz is an amine protecting group that is easier to remove than Bz, we next turned to the N-Cbz-protected α-enamido phosphonate esters **3a**–**q** to investigate the substrate scope. Gratifyingly, the hydrogenation turned out to be quite general and the Rh/(*S*,*S*)-**L6** catalyst worked very well with a variety of substrates (Table 1, entries 6–22). All the reactions were accomplished within 1 hour at room temperature with an ambient pressure of hydrogen, thus providing the corresponding chiral phosphonates **4** in quantitative conversion with high *ee* values (97–>99%) in most cases. Neither the electronic nature nor the steric hindrance of the β substituent (R) had any obvious influence upon the enantioselectivity and reactivity (Table 1, entries 6–21), and consistently high *ee* values were obtained for substrates with aromatic (Table 1, entries 6–17), heteroaromatic (entry 18), and alkyl (entries 19–21) substituents at the β positions. An exception was found in the case of the β-styryl-substituted substrate **3q**, wherein the double bond in proximity to the N-Cbz group was selectively hydrogenated with full conversion, albeit with a slightly lower *ee* value (Table 1, entry 22). It is noteworthy that the productivity of the Rh/(*S*,*S*)-**L6** catalyst can be very high under elevated hydrogen pressures, as shown in the case of the hydrogenation product **4o**, whose *R* isomer is the synthetic precursor of the potent aminopeptidase inhibitor (*R*)-phospholeucine.[15] After a prolonged reaction at 40 atm of H_2 with a catalyst loading of 0.01 mol% (S/C = 10000), (*S*)-**4o** was isolated in high yield (95%) on gram scale with excellent enantioselectivity (Table 1, entry 23). Finally, the Rh/(*S*,*S*)-**L6** system was also efficient in the catalytic AH of the terminal N-Cbz enamido phosphonate **5**, to give (*S*)-**6** (whose *R* isomer is the synthetic precursor to the potent antibacterial agent Alafosfalin)[16] in high optical purity (Table 1, entry 24). To verify the tolerance of the catalyst system for the *E*- or *Z*-isomeric substrate, both *E* and *Z* isomers of ethyl β-phenyl-α-enamido phosphonates [(*E*)-**7** and (*Z*)-**7**] were prepared and submitted to the hydrogenation. It was found that the reactions proceeded with complete conversion of the substrates and afforded the corresponding α-amino phosphonate ester **8** in 99 and 88% *ee*, respectively, with the same sense of asymmetric induction (Table 1, entries 25 and 26). For the AH of an *E*/*Z*-isomeric mixture of **7** (*E*/*Z* = 2.88:1), a satisfactory *ee* value (95%) of the product **8** was obtained upon full conversion of the substrate (Table 1, entry 27), thus attesting to the robustness of the protocol.

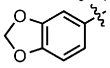
To further demonstrate the efficiency of the present catalysis, we carried out a series of reaction profile studies on the hydrogenation of **3o** using the catalyst [Rh-

Table 1: Rh^I/(*S*,*S*)-**L6** catalyst used for the AH of β-substituted α-enamido phosphonates.[a]



(*E*)-**1a-e**: R' = Bz, R'' = Me
(*E*)-**3a-q**: R' = Cbz, R'' = Et
5: R' = Cbz, R'' = Me
(*E*)- or (*Z*)-**7**: R' = Ac, R'' = Me

2a-e: R' = Bz, R'' = Me
4a-q: R' = Cbz, R'' = Et
6: R' = Cbz, R'' = Me
8: R' = Ac, R'' = Me

Entry	R	Product	S/C[b]	*ee* [%][c]
1	Ph (**1a**)	**2a**	100	>99 (*S*)
2	4-FC_6H_4 (**1b**)	**2b**	100	>99 (*S*)
3	4-ClC_6H_4 (**1c**)	**2c**	100	>99 (*S*)
4	4-BrC_6H_4 (**1d**)	**2d**	100	>99 (*S*)
5	3-ClC_6H_4 (**1e**)	**2e**	100	>99 (*S*)
6	Ph (**3a**)	**4a**	100	98 (*S*)
7	2-MeC_6H_4 (**3b**)	**4b**	100	97(*S*)
8	3-ClC_6H_4 (**3c**)	**4c**	100	98 (*S*)
9	3-BrC_6H_4 (**3d**)	**4d**	100	98 (*S*)
10	3-$MeOC_6H_4$ (**3e**)	**4e**	100	98 (*S*)
11	4-FC_6H_4 (**3f**)	**4f**	100	98 (*S*)
12	4-ClC_6H_4 (**3g**)	**4g**	100	>99 (*S*)
13	4-BrC_6H_4 (**3h**)	**4h**	100	97 (*S*)
14	4-$NO_2C_6H_4$ (**3i**)	**4i**	100	98 (*S*)
15	4-$MeOC_6H_4$ (**3j**)	**4j**	100	98 (*S*)
16	 (**3k**)	**4k**	100	>99 (*S*)
17	2-naphthyl (**3l**)	**4l**	100	98 (*S*)
18	2-thienyl (**3m**)	**4m**	100	97 (*S*)
19	*c*-hexyl (**3n**)	**4n**	100	>99 (*S*)
20	*i*Pr (**3o**)	**4o**	100	98 (*S*)
21	*t*Bu (**3p**)	**4p**	100	98 (*S*)
22	styryl (**3q**)	**4q**	100	86 (*S*)
23[d]	*i*Pr (**3o**)	**4o**	10000	98 (*S*)
24	H (**5**)	**6**	100	>99 (*S*)
25[e]	Ph [(*E*)-**7**]	**8**	100	99 (+)
26[e]	Ph [(*Z*)-**7**]	**8**	100	88 (+)
27[e]	Ph [(*E*)/(*Z*)-**7**] (*E*/*Z* = 2.88:1)	**8**	100	95 (+)

[a] Reaction conditions: [**1a-e**] = 0.1 M; [**3a-q**] = 0.2 M, [**5**] = 0.2 M; [Rh(cod)$_2$]BF_4 = 1 mol%, Rh^I/(*S*,*S*)-**L6** = 1:2. Conversion always >99% (^{31}P NMR). [b] Substrate/catalyst (S/C) molar ratio. [c] Determined by chiral HPLC analysis using a chiral stationary phase. Absolute configurations of **2a**–**c** were assigned by comparison of $[\alpha]_D$ with the literature values, **4c** and **4o** by X-ray analysis (see the Supporting Information), and **4a** by derivatizing to a known compound; absolute configurations of **2d**–**e**, **4b**, **4d**–**n**, **4p**–**q** determined by CD analysis (see the Supporting Information). [d] P_{H_2} = 40 atm, 16 h. The yield of the isolated **4o** is 95%. [e] With catalyst Rh^I/(*R*,*R*)-**L6**, P_{H_2} = 5 atm, 3 h. Bz = benzoyl, Cbz = benzyloxycarbonyl.

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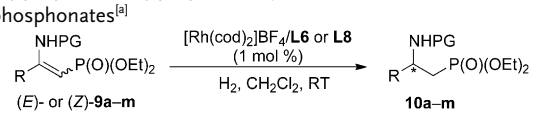
$(cod)_2]BF_4$/(*S*,*S*)-**L6**. The effects of the substrate concentration, catalyst concentration, and hydrogen pressure on the reaction rates were examined. The consumption of **3o** was evaluated by ^1H NMR analysis of aliquots taken from the active hydrogenation mixture, and the reaction profiles, which were measured under standard conditions (molar ratio Rh/(*S*,*S*)-**L6** = 1:2, $T = 26\,^\circ C$, CH_2Cl_2 solvent), are shown in Figure S5 in the Supporting Information. There is no apparent incubation period shown in the profiles in Figure S5(a), thus suggesting a fast activation of the precatalyst by hydrogenation of the cod ligand. In most cases the initial rates are almost maintained until approximately 50–70% conversion. The reactions proceed at nearly the same rates for all the tested substrate concentrations (see Figure S6 in the Supporting Information), thus indicating a zero-order dependence of the hydrogenation rate on substrate concentration. There is a consistent enhancement in the initial reaction rates with the catalyst concentrations from 0.25 to 1.0 mM, although the profile at [Rh] = 0.25 mM demonstrates a complex behavior at the early stage of the reaction [Figure S5(b)]. As shown in Figure S5(c), the catalytic activity increases significantly with ascending hydrogen pressures, with a TOF value of 1800 h^{-1} being achieved at 4 atm hydrogen (60% conversion within 2 min). Altogether, the Rh^I/(*S*,*S*)-**L6** system demonstrates high efficiency and excellent enantioselectivity in the AH of a broad range of α-enamido phosphonates, thus suggesting its potential utility in the synthesis of optically active α-amino phosphonates.

Table 2: Rh^I/(*S*,*S*)-**L6** or Rh^I/(*S*,*S*)-**L8** catalyst used for the AH of *Z* or *E* isomers of β-enamido phosphonates[a]



(*E*)- or (*Z*)-**9a–m** → **10a–m**

Entry	Substrate	R	PG	Ligand	P_{H_2} [atm]	*t* [h]	*ee* [%][b]
1	(*Z*)-**9a**	C_6H_5	Bz	(*S*,*S*)-**L6**	10	16	>99 (*R*)
2	(*Z*)-**9b**	4-MeC_6H_4	Bz	(*S*,*S*)-**L6**	5	12	98 (*R*)
3	(*Z*)-**9c**	4-$MeOC_6H_4$	Bz	(*S*,*S*)-**L6**	5	12	96 (*R*)
4	(*Z*)-**9d**	4-FC_6H_4	Bz	(*S*,*S*)-**L6**	10	16	98 (*R*)
5	(*Z*)-**9e**	4-ClC_6H_4	Bz	(*S*,*S*)-**L6**	10	16	98 (*R*)
6	(*Z*)-**9f**	4-BrC_6H_4	Bz	(*S*,*S*)-**L6**	10	16	>99 (*R*)
7	(*Z*)-**9g**	2-ClC_6H_4	Bz	(*S*,*S*)-**L6**	10	16	>99 (*R*)
8	(*Z*)-**9h**	2-naphthyl	Bz	(*S*,*S*)-**L6**	10	16	95 (*R*)
9	(*Z*)-**9i**	3-thienyl	Bz	(*S*,*S*)-**L6**	10	16	>99 (*R*)
10	(*Z*)-**9j**	cyclohexyl	Bz	(*S*,*S*)-**L6**	10	16	>99 (*R*)
11[c]	(*Z*)-**9k**	2-pyridyl	Bz	(*S*,*S*)-**L6**	45	24	46 (*R*)
12	(*Z*)-**9l**	2-$CF_3C_6H_4$	Bz	(*S*,*S*)-**L6**	10	16	n.r.
13	(*E*)-**9g**	2-ClC_6H_4	Bz	(*S*,*S*)-**L6**	10	16	81 (*R*)
14	**9g** (*E*/*Z* = 1:4)	2-ClC_6H_4	Bz	(*S*,*S*)-**L6**	10	16	93 (*R*)
15	(*E*)-**9m**	4-MeC_6H_4	Ac	(*S*,*S*)-**L8**	10	16	88 (−)
16	(*Z*)-**9m**	4-MeC_6H_4	Ac	(*S*,*S*)-**L8**	10	16	96 (−)
17[d]	(*Z*)-**9f**	4-BrC_6H_4	Bz	(*S*,*S*)-**L6**	40	24	>99 (*R*)

[a] Unless otherwise specified, the conversions were >99% as determined by ^{31}P NMR analysis. Reaction conditions: [**9a–m**] = 125 mM, [Rh-$(cod)_2]BF_4$ = 1.25 mM, Rh/(*S*,*S*)-**L6** (or (*S*,*S*)-**L8**) = 1:2. [b] Determined by chiral HPLC analysis using a chiral stationary phase. Absolute configuration of **10e** was determined by X-ray crystal structure analysis, while those of **10a–d** and **10f–k** were assigned by comparison of their CD spectra to that of (*R*)-**10e** (see the Supporting Information), [c] 15% conversion. [d] 0.1 mol% catalyst loading, 95% conversion. n.r. = no reaction, PG = protecting group.

Encouraged by these results, we moved to examine the catalytic efficiency of Rh^I/(*S*,*S*)-**L6**-type complexes in the AH of the more demanding β-enamido phosphonate esters. Compound (*Z*)-**9b** was used as the model substrate for optimization of the reaction conditions and ligand screening. Rh^I/(*S*,*S*)-**L6** was again found to be optimal in terms of both reactivity and enantioselectivity, and effected complete conversion into **10b** (98% *ee*) after 12 hours in CH_2Cl_2 under 5 atm H_2 (see the Supporting Information). Extension of the protocol to the AH of a series of β-enamido phosphonate esters was also generally successful, and the results are summarized in Table 2. For the (*Z*)-β-enamido phosphonates having an aromatic substituent, the reactions proceeded smoothly to full conversions and the enantioselectivities were generally excellent, ranging from 95 to greater than 99% *ee* (Table 2, entries 1–8). An exception is the reaction involving the substrate with a strongly electron-withdrawing 2-CF_3-substituted phenyl group [(*Z*)-**9l**]; in this case no product was detected under similar reaction conditions (Table 2, entry 12). It is also noteworthy that by using this protocol, for the first time, (*Z*)-β-enamido phosphonates bearing a β-heteroaryl or an β-alkyl substitutent can be hydrogenated with excellent enantioselectivity (Table 2, entries 9 and 10, respectively). However, the system is substantially less efficient for the substrate with a β-2-pyridyl substituent as the reaction proceeds sluggishly even under a higher hydrogen pressure (45 atm; Table 2, entry 11). The Rh^I/Dpenphos catalytic system Rh^I/(*S*,*S*)-**L6** or Rh^I/(*S*,*S*)-**L8** also gave satisfactory results in the AH of (*E*)-β-enamido phosphonates, albeit with a somewhat lower enantioselectivity compared to their *Z* isomers (Table 2, entries 13 versus 7, and 15 versus 16). The catalyst can therefore tolerate the use of an *E*/*Z* = 1:4 isomeric mixture of substrate **9g** to afford the corresponding product with a compromised enantioselectivity (Table 2, entry 14). It is noteworthy that so far not a single catalyst has been reported to be efficient for the hydrogenation of *Z*/*E* mixtures of β-enamido phosphonates. Finally, under a reduced catalyst loading of 0.1 mol%, the AH of (*Z*)-**9f** under 40 atm of H_2 afforded 95% conversion into **10f** with a greater than 99% *ee* after 24 hours (Table 2, entry 17).

To understand the structural details of the catalyst precursor, a single crystal of the complex [Rh(cod){(*S*,*S*)-**L6**)}$_2$]BF_4 was grown from the CH_2Cl_2/acetone/*n*-hexane (1:1:1) solvent mixture and characterized by X-ray crystallography. As shown in Figure 1, the complex contains two phosphoramidite ligands, (*S*,*S*)-**L6**, coordinated to rhodium through the P atom, with a square-planar coordination arrangement around the metal center. Such a pattern is typical for closely related Rh/phosphoramidite complexes reported previously by the groups of Reetz[17] and Zhou[18] as well as ourselves.[13a] The Rh–P bond lengths of [Rh(cod)-{(*S*,*S*)-**L6**)}$_2$]BF_4 (2.2679(12) and 2.2727(13) Å) are essentially in keeping with the literature values of these complexes,

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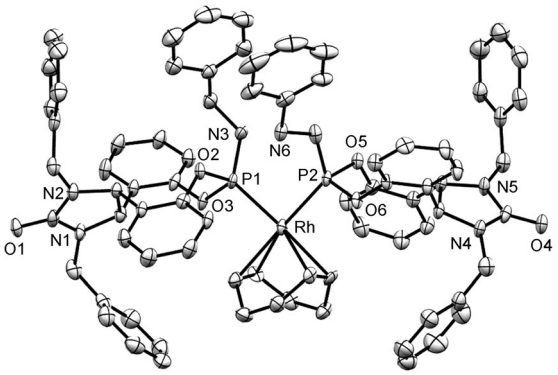

Figure 1. Crystal structure of $[Rh(cod)\{(S,S)\text{-}\mathbf{L6}\}_2]BF_4\cdot(CH_3COCH_3)_4\text{-}(CH_2Cl_2)$. The hydrogen atoms, solvent molecules, and the BF_4^- counteranion have been omitted for clarity. The thermal ellipsoids are shown at 50% probability.

whereas the P-Rh-P bite angle [93.78(4)°] is distinctly smaller. There is a hydrogen bond formed between one of the (*S*,*S*)-**L6** ligands and a lattice enclathrated acetone molecule in the complex (see the Supporting Information). The hydrogenation of the substrate **3o** using this isolated Rh/(*S*,*S*)-**L6** complex afforded **4o** in 99% *ee*, which is essentially the same as that attained using the corresponding in situ prepared complex, thus suggesting that $[Rh(cod)\{(S,S)\text{-}\mathbf{L6}\}_2]BF_4$ should indeed be the catalyst precursor in the reaction. Furthermore, ^{31}P NMR spectroscopy of the in situ prepared Rh/(*S*,*S*)-**L6** (1:2 molar ratio) complex indicated the clean formation of a single species in the solution (see the Supporting Information). Moreover, the nonlinear effect (NLE)[19] of the $[Rh(cod)_2]BF_4$/(*S*,*S*)-**L6** catalyzed hydrogenation of **3a** was examined using (*S*,*S*)-**L6** with varying *ee* values under the reaction conditions shown in Table 1. A positive NLE was observed for this catalytic system (see Figure S6 in the Supporting Information), thus indicating that the Rh species involved in the catalysis should contain more than one monodentate phosphoramidite ligand within or at the periphery of the catalytic cycle. Finally, investigation of the effect of the Rh/L ratio on rate and *ee* value, in combination with the some preliminary ^{31}P and ^1H NMR studies on the $[Rh(cod)_2BF_4]$/**L6** systems generated in situ with Rh/**L** molar ratios of 1:1, 1:2, 1:3, and 1:4, shows that a $[Rh(\mathbf{L6})_2]$ species should be responsible for the catalysis (see the Supporting Information).

In conclusion, chiral monodentate phosphoramidite DpenPhos ligands bearing a primary amine moiety [(*S*,*S*)-**L6**–**L8**] have been found to be highly efficient in the Rh^I-catalyzed AH of α- and β-enamido phosphonates, including a wide variety of β-aryl-, β-heteroaryl-, and β-alkyl-substituted substrates. For the Rh^I/(*S*,*S*)-**L6**-catalyzed AH of α-enamido phosphonates, *ee* values ranging from 96% to greater than 99% were obtained in most cases under an ambient pressure of H_2 at room temperature. The resulting catalyst is very reactive (turnover frequency of up to 1800 h^{-1} at 4 atm hydrogen), and the *S* enantiomer of the potent aminopeptidase inhibitor (*R*)-phospholeucine could be obtained on gram scale with 98% *ee* under a very low catalyst loading (S/C = 10000). The *S* enantiomer of a synthetic precursor to the potent antibacterial agent Alafosfalin could also be obtained in high enantioselectivity (> 99% *ee*) by using this procedure. Moreover, the catalyst was also successful in the AH of a variety of β-substituted (*Z*)- or (*E*)-β-enamido phosphonate esters, with *ee* values ranging from 95% to greater than 99% in most cases. The X-ray crystallographic analysis reveals that the catalyst precursor contains two ligand moieties in its structure, and an NLE study demonstrates that the rhodium species involved in the catalysis contains more than one monodentate phosphoramidite ligand within or at the periphery of the catalytic cycle. These salient features suggest that the present approach is likely to find use in the synthesis of optically active α- or β-amino phosphonic acid derivatives.

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