JOC Article

Chiral C_2-Symmetric Ligands with 1,4-Dioxane Backbone Derived from Tartrates: Syntheses and Applications in Asymmetric Hydrogenation

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Chiral 1,4-diphenylphosphines **5**−**7** as well as thioether **8** were synthesized from tartrates employing Ley's "BDA" and "Dispoke" methodologies as the key step. Rhodium(I) complexes with **5**−**7** are efficient catalysts for the asymmetric hydrogenation of β-substituted enamides and MOM-protected β-hydroxyl enamides, which furnished chiral amines or β-amino alcohols with 94→99% ee. These results indicated that the 1,4-dioxane backbone in the ligands having the general structure **2** played an important role in stabilizing metal−ligand chelate conformation. Higher enantioselectivities with ligand **2** were achieved compared with the analogous ligands having the general structure **1**.

Introduction

It is well-known that transition metal-catalyzed asymmetric reactions are substrate- and ligand-dependent. For example, electron deficient ligands are required for asymmetric hydroformylation,[1] while electron rich and rigid chiral ligands are good for asymmetric hydrogenation.[2] Searching chiral ligands with ease of synthesis, high activity, and enantioselectivity is a continuing important task in this field. Recently, we introduced several classes of structurally innovative bisphosphines based on the conformational analysis of the chelating complexes. These ligands have shown excellent enantioselectivities in Rh- and Ru-catalyzed hydrogenation of olefins and ketones.[3]

Since Kagan's seminal work on Rh-DIOP **3** (the first chiral 1,4-diphosphine) catalyzed asymmetric hydrogenation,[4] several types of modified DIOP ligands have been reported for transition metal-catalyzed reactions. One such modification, (*R*,*S*,*S*,*R*)-DIOP* **4**,[5] afforded excellent results in the rhodium-catalyzed hydrogenation of β-substituted enamides. We reason that the equatorial orientation of all substituents in the metal−ligand seven-membered chelate ring is the key factor for such high enantioselectivities. These results gave us the insight that a chiral ligand with the general structure **2** may be more effective than those with the general structure **1** for Rh-catalyzed hydrogenation (Figures 1 and 2). The 1,4-dioxane six-membered ring in **2** is conformationally rigid compared with the flexible 1,3-dioxolane five-membered ring in **1**. High enantioselectivities for hydrogenation of simple enamides obtained with Rh-**4** (*R*,*S*,*S*,*R*)-DIOP* prompted us to investigate asymmetric hydrogenation with ligands **5**−**7**. The different enantioselectivities from DIOP **3** and ligands **2** in asymmetric hydrogenation could lead to insights in catalyst design. Herein we report the improved synthetic routes for making a bisphosphine **5** and several related ligands (**6**−**8**). Using "BDA"[6] and "Dispoke"[7] methodologies developed by Ley for 1,2-diol protections as the key step, ligands **2** with the six-membered ring were prepared. We are pleased to report that rhodium−phosphine **2** can be effective for hydrogenation of β-substituted enamides and MOM-protected β-hydroxyl enamides. A number of chiral amines and β-amino alcohols with 94→99% ee were achieved.

Results and Discussions

Tartaric acid is a very important starting material for making a variety of homochiral molecules. These com-

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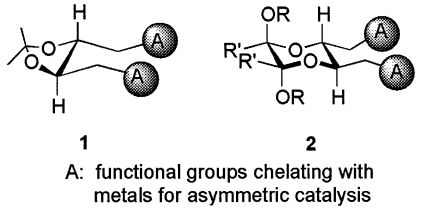


FIGURE 1.

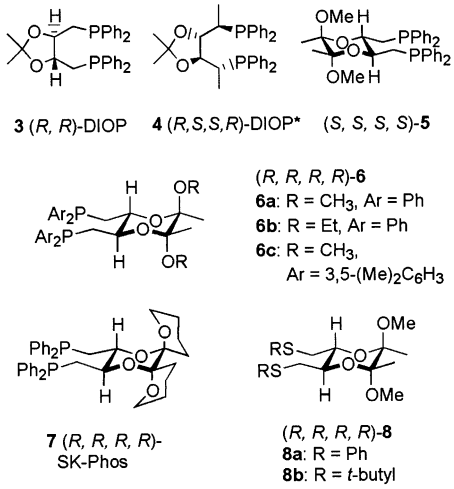
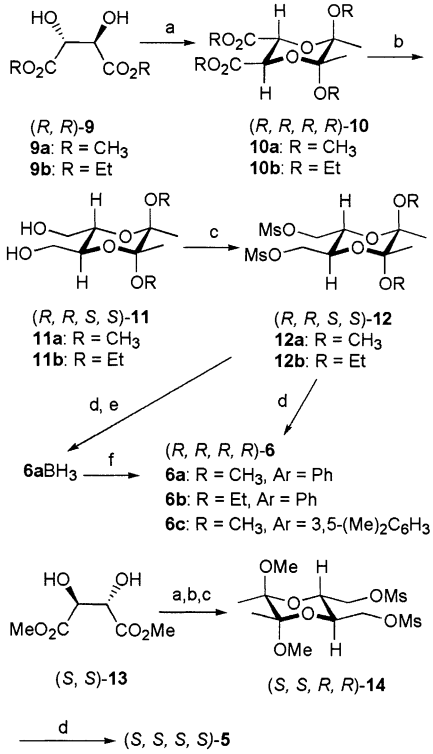


FIGURE 2.

pounds with C_2-symmetry can be used as ligands or auxiliaries in asymmetric synthesis. Bisphosphine ligands **6a**,**b** were originally prepared by Berens and co-workers from L-tartrate esters.[8,9] The protected tartrate derivatives **10a**,**b** were formed using an acetal exchange procedure in moderate yields. The ditosylates from diol **11** formed in 53 and 76% yield, respectively. The low yields are probably caused by an intramolecular reaction resulting in the formation of a tetrahydrofuran derivatives.[8] We modified this approach using Ley's one pot methodology to make the acetal **10a** (Scheme 1).[6b] The advantage of this approach is that only one stereoisomer is formed and the product can be easily isolated in high yield.[6b] We also extended this method to prepare the ethyl derivative **10b** by refluxing a mixture of **9b**, triethyl orthoformate in the presence of CSA (camphorsulfonic acid) in dry ethanol. We synthesized the bismesylates **12** in 95−97% yield and employed them as the key intermediates for the ligands syntheses. The bisphosphines **6a**,**b** were produced in this way smoothly in 76 and 73% yield, respectively. The other enantiomer (*S*,*S*,*S*,*S*)-**5** was also made in 73% yield via the same route from D-tartrate **13**. To simplify the operation, we purified the phosphine **6a** by transforming it in situ into its phosphine borane adduct. This was accomplished by treatment with a 1 M BH_3 solution in THF. The borane adduct **6a**·BH_3 can be easily crystallized from hexanes/ether. The desired phosphine **6a** was obtained by reacting **6a**·BH_3 with 1,4-diazabicyclo[2.2.2]octane (DABCO) in

SCHEME 1



[a] $CH_3COCOCH_3$ (1.2 equiv), CSA (0.1 equiv), $CH(OCH_3)_3$ (3.0 equiv) for **10a** and **14** [$CH(OEt)_3$ for **10b**], CH_3OH for **10a** and **14** (EtOH for **10b**), reflux, 14−18 h. [b] $LiAlH_4$ (1.1 equiv), THF, 0 °C to reflux 2 h. [c] MsCl, Et_3N, CH_2Cl_2, 0 °C to room temperature, 1 h. [d] Ph_2PH [(3,5-xylyl)$_2$PH for **6c**], *n*-BuLi, THF, 0 °C to room temperature, 12 h. [e] BH_3·THF, CH_2Cl_2, 0 °C to room temperature, 12 h. [f] DABCO, toluene, 50 °C, 12 h.

toluene. The bisphosphine (2*R*,3*R*,5*R*,6*R*)-5,6-bis((di(3,5-dimethylphenyl)phosphanyl)methyl)-2,3-dimethoxy-2,3-dimethyl[1,4]dioxane (**6c**) was prepared in a similar manner using bis((3,5-dimethyl)phenyl)phosphine as the nucleophile.

To introduce a more rigid ligand system, a new spiroketal phosphine **7** was designed. The new phosphine **7** (named as SK−Phos)[10] with dispiroketal chiral pocket was prepared from L-dimethyl tartrate by following the procedure described in Scheme 2. Reaction with excess dimethyl tartrate **9a** and 3,3′,3,3′-tetrahydro-6,6′-bi-2*H*-pyran (bis-DHP)[7c] in diethyl ether/CH_2Cl_2 (5:1) in the presence of hydrogen chloride gave a single diastereoisomer of dispiroketal **15** in 56% yield.[11] The strong anomeric effect plays an important role in this transformation.[6a,11] Subsequent reduction of **15** to the 1,4-diol **16** by $LiAlH_4$ was achieved in 85% yield. Reaction of **16** with methanesulfonyl chloride in the presence of triethylamine gave the mesylate **17** in 88% yield. Nucleophillic attack of **17** with lithium diphenylphosphine in THF afforded the desired phosphine **7**. The product was purified by a short silica gel column eluted with hexanes/ethyl ether (95:5) in a drybox to give a white solid in 53% yield.

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(9) (a) Berens, U.; Selke, R. *Tetrahedron: Asymmetry* **1996**, *7*, 2055. (b) Haag, D.; Scharf, H.-D. *J. Org. Chem.* **1996**, *61*, 6127. (c) Haag, D.; Runsink, J.; Scharf, H.-D. *Organometallics* **1998**, *17*, 398. (d) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Holz, J.; Borner, A. *Tetrahedron Lett.* **2000**, *41*, 2351. (e) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Borner, A. *Chem. Commun.* **2000**, 1867.

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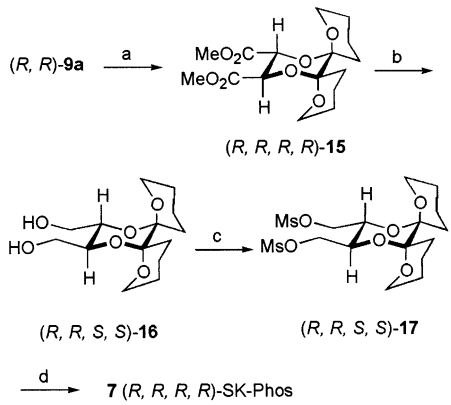
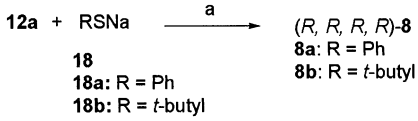
SCHEME 2



[a] Bis-DHP, HCl, Et_2O/CH_2Cl_2, 0 °C to room temperature, 12 h. [b] $LiAlH_4$, THF, 0 °C to reflux, 2 h. [c] MsCl, Et_3N, CH_2Cl_2, 0 °C to room temperature, 1 h. [d] Ph_2PH, *n*-BuLi, THF, 0 °C to room temperature, 12 h.

SCHEME 3



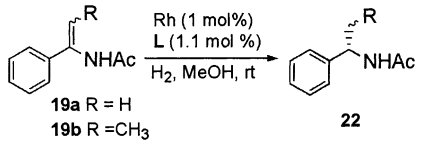
[a] NaH, THF, RSH, 0 °C to room temperature, 6 h.

In addition to synthesizing chiral bisphosphines, we made some sulfur derivatives having the 1,4-dioxane backbone. Recently, a number of disulfur ligands[12] and sulfur−phosphinite and sulfur−phosphine[13] ligands have been developed. Some of these ligands gave high selectivities in rhodium-catalyzed asymmetric hydrogenations. In our investigations, sulfur derivatives **8a**,**b** were synthesized from the corresponding sodium thiolate reacting with mesylate **12a** in THF in good yields (Scheme 3).

The 1,4-bisdiphenylphosphines **5**, **6a**−**c**, and **7** and sulfur compounds **8a**,**b** have been prepared in moderate to good yields. These syntheses depend on Ley's 1,2-diol protection methodologies.[6,7] The advantages of these synthetic routes are ease of operation and scalability for industrial applications.

Chiral amines are often used as resolving agents and chiral auxiliaries or have served as critical components of pharmaceutical agents.[14] Recently, much progress has been made in generating optically active cyclic and acyclic amines through the rhodium(I)-catalyzed hydrogenation of simple enamides.[15] In 1996, Burk and co-workers reported the first breakthrough on the enantioselective hydrogenation of arylenamides with Rh−DuPhos and Rh−BPE catalysts.[15a] Imamoto investigated the mechanism for this transformation using his Rh−BisP* and Rh−MiniPHOS catalysts.[15f] Most recently, Lee et al. introduced a DIOP analogue which showed high enantioselectivity.[15g] We have made major advances in hydrogenation of both acyclic and cyclic amide systems using chiral phosphine ligands such as BICP,[15d] PennPhos,[3d] Binaphane,[15e] and DIOP*.[5a] On the basis of our study and work carried out by other groups,[15,16] we found that rhodium complexes with 1,4-bis(diphenylphosphines) were especially effective for the enantioselective hydrogenation of acyclic enamides (see Supporting Information). These results prompted us to apply simple chiral ligands **5**−**7** possessing a 1,4-dioxane backbone for rhodium-catalyzed asymmetric hydrogenation of enamides (Table 1).

TABLE 1. Hydrogenation of 19 by a Rh/L Complex[a]



entry	Rh[b]	L	sub	ee (%) (config)[c]
1	A	**6a**	**19a**	90 (S)
2	B	**6a**	**19a**	92 (S)
3	C	**6a**	**19a**	93 (S)
4	D	**6a**	**19a**	92 (S)
5	E	**6a**	**19a**	93 (S)
6	E	**6b**	**19a**	94 (S)
7	E	**6c**	**19a**	83 (S)
8	E	**7**	**19a**	93 (S)
9	E	**5**	**19a**	93 (R)
10	E	**6a**	**19b**	98 (S)
11	E	**6b**	**19b**	98 (S)
12	E	**6c**	**19b**	71 (S)
13	E	**7**	**19b**	97 (S)
14	E	**5**	**19b**	97 (R)
15[d]	E	**8a**	**19b**	21 (S)
16[d]	E	**8b**	**19b**	18 (S)

[a] The reaction was carried out at room temperature under 45 psi of H_2 for 24 h. The catalyst was prepared in situ by stirring a solution of Rh precursor and the bisphosphine ligand **L** in 4 mL of methanol {[substrate (0.5 mmol, 0.125 M)/[Rh]/L = 1:0.01:0.011]}. The reaction went with >99% conversion unless otherwise stated. [b] A = $[Rh(COD)Cl]_2$, B = $Rh(COD)_2PF_6$, C = $Rh(COD)_2SbF_6$, D = $Rh(NBD)_2BF_4$, E = $Rh(NBD)_2SbF_6$. [c] Enantiomeric excesses were determined by GC using a Supelco Chiral Select 1000 (0.25 mm × 15 m) column. The absolute configuration was assigned by comparison of optical rotation with reported data. [d] 95% and 37% conversions were determined by GC for runs 15 and 16, respectively.

We have employed *N*-acetyl-1-phenylethenamine as the typical substrate. The active catalyst rhodium complex was generated in situ by mixing 1.1 equiv of ligand

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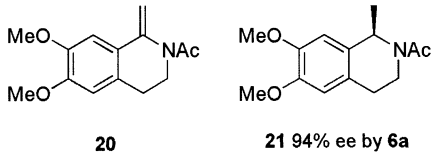


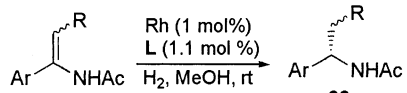
20 **21** 94% ee by **6a**

FIGURE 3.

and Rh (1 equiv) precursor. Systematic investigation showed that methanol and toluene were the best solvents for this transformation. Comparable results (93 and 94% ee) were obtained when $Rh(NBD)_2SbF_6$/**6a** was used as the catalyst. Enantioselectivities dropped down to 87 and 82% when methylene chloride and THF were used as solvents, respectively. We chose methanol as the solvent because substrate and catalyst have good solubility. Cationic Rh(I)/**L** complexes were found to be more selective than a neutral precursor $[Rh(COD)Cl]_2$ (Table 1, entry 1 vs entries 2−5), while counteranions do not affect the selectivity. Sterically hindered bisphosphines **6b** and **7** led to a slight change in the enantioselectivity from the result with **6a**. All three ligands produced the chiral amine with the same stereoselectivity (*S*). Enantioselectivities observed with these three ligands in hydrogenation of enamides are higher than the result with (*R*,*R*)-DIOP **3**. Importantly, the absolute configuration of the product with **6a**,**b** and **7** is opposite from that observed with (*R*,*R*)-DIOP! This opposite induction of chirality was also found in rhodium-catalyzed hydrogenation with other modified DIOP analogues. The diverse ee values reported in the literature and here can be explained as results of changes of the metal−ligand chelate conformation.[17] Replacing the flexible five-membered ring in **3** by a rigid six-membered ring in **6a** rearranges the conformation dramatically and enantioselectivities of **19a** reversed from 68% ee (*R*)[16f] to 93% ee (*S*). By comparing results from various 1,4-bisphosphine ligands with different backbones, it is clear that the conformational properties of the ligand backbone are crucial for effective chirality transfer. When the phenyl groups were changed to 3,5-dimethylphenyl (**6c**), the ee in hydrogenation of **19a** dropped to 83% (entry 7).

To further explore the utility of the reaction, we examined the asymmetric hydrogenation of cyclic enamide **20**. Under the same reaction conditions, hydrogenation of cyclic enamide **20** gave the corresponding tetrahydroisoquinoline **21** in 94% ee. To the best of our knowledge, this is the highest ee reported for this transformation using a Rh(I) catalyst. We have achieved an excellent result in hydrogenation of an α-aryl enamide (**19b**) with a β-methyl group. Generally, hydrogenation of a β-substituted enamide gives higher enantioselectivity than the corresponding terminal enamide (Table 2). Several β-substituted enamides were reduced with Rh catalysts, and

TABLE 2. Hydrogenation of 19 by Rh/6b or Rh/7[a]



19 **22**

entry	Ar/R	L	ee(%) (S)[b]
1	C_6H_5/isopropyl	**6b**	98
2	C_6H_5/isopropyl	**7**	98
3	C_6H_5/Bn	**6b**	98
4	C_6H_5/Bn	**7**	97
5	*p*-$CF_3C_6H_4/CH_3$	**6b**	95
6	*p*-$CF_3C_6H_4/CH_3$	**7**	94
7[c]	*p*-$MeOC_6H_4/CH_3$	**6b**	98
8[c]	*p*-$MeOC_6H_4/CH_3$	**7**	98
9[c]	2-naphthyl/CH_3	**6b**	97
10[c]	2-naphthyl/CH_3	**7**	97

[a] The reaction was carried out at room temperature under 45 psi of H_2 for 24 h. The catalyst was prepared in situ by stirring a solution of $Rh(NBD)_2SbF_6$ and the bisphosphine ligand **L** in 4 mL of methanol {[substrate (0.5 mmol, 0.125 M)/[Rh]/**L** = 1:0.01:0.011]}. The reaction went with >99% conversion unless otherwise stated. [b] Enantiomeric excesses were determined by GC using a Supelco Chiral Select 1000 (0.25 mm × 15 m) column. The absolute configuration was assigned by comparison of optical rotation with reported data. [c] Enantiomeric excesses were determined by HPLC using a (*S*,*S*)-Whelk-O1 column.

enantiomerically enriched α-arylamine derivatives can be furnished. Like Rh−DuPhos and Rh−BICP systems, this hydrogenation is not so sensitive to the geometry of the substrate.[15] A *E*/*Z* mixture of β-substituted enamides was employed in all cases. Substrate **19b** with a 2:1 *E*/*Z* mixture was hydrogenated with 98% ee. This result is higher than those obtained with DIOP (87% ee)[16a,g] or Py*−DIOP (84% ee).[16a] When R is a bulky group such as isopropyl and benzyl, high selectivities are observed (up to 97% ee). Sulfur compounds **8a**,**b** were also tried to catalyze this hydrogenation. The phenyl thioether **8a**−Rh(I) complex showed a reasonable activity (95% conversion) and moderate enantioselectivity (21% ee, Table 1, entry 15). When a *tert*-butyl derivative **8b** was used as the ligand, only 37% conversion and 18% ee (Table 1, entry 16) were achieved. Since separation of *E*/*Z* isomers of enamides is extremely difficult, hydrogenation of these *E*/*Z* mixtures in high enantioselectivity is crucial for making chiral amines.

The β-amino alcohol moiety is a common building block in naturally occurring and synthetic molecules, and many synthetic methods are well-documented.[18] Chiral amino alcohols have been widely used as pharmaceutical components[19] and chiral ligands or auxiliaries.[20,21] We are interested in developing asymmetric hydrogenation methods[22] for the synthesis of amino alcohols.[23] Hydrogenation of MOM-protected β-hydroxyl enamides with Rh−BICP and Rh−Me−DuPhos lead to amino alcohols in high ees.[23] Since the MOM-protected β-hydroxyl enamides are

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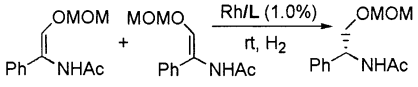
TABLE 3. Hydrogenation of 23a by a Rh/L Complex[a]

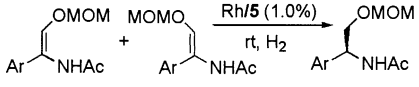


(*Z*)-**23a** (*E*)-**23a** (*R*)-**24a**

entry	Rh/**L**[b]	solv	H_2 (bar)	ee (%) (config)[c]
1	A/**6a**	MeOH	15	97 (*R*)
2	A/**6a**	CH_2Cl_2	15	97 (*R*)
3	A/**6a**	toluene	15	98 (*R*)
4	A/**6a**	THF	15	94 (*R*)
5	A/**6a**	toluene	20	98 (*R*)
6	A/**6a**	toluene	10	97 (*R*)
7	A/**6a**	CH_2Cl_2	20	95 (*R*)
8	A/**6a**	CH_2Cl_2	10	94 (*R*)
9	B/**6a**	CH_2Cl_2	15	97 (*R*)
10	C/**6a**	CH_2Cl_2	15	95 (*R*)
11	D/**6a**	CH_2Cl_2	15	98 (*R*)
12	D/**6b**	CH_2Cl_2	15	96 (*R*)
13	D/**6c**	CH_2Cl_2	15	87 (*R*)
14	D/**7**	CH_2Cl_2	15	97 (*R*)
15	D/**5**	CH_2Cl_2	15	98 (*S*)

[a] The reaction was carried out at room temperature under the selected pressure of H_2 for 24 h. The catalyst was prepared in situ by stirring a solution of Rh precursor and the bisphosphine ligand **L** in solvent 4 mL{[substrate (0.5 mmol, 0.125 M)/[Rh]/**L** = 1:0.01:0.011]}. The reaction went with >99% conversion unless otherwise stated. [b] A = $Rh(COD)_2PF_6$, B = $Rh(COD)_2SbF_6$, C = $Rh(NBD)_2BF_4$, D = $Rh(NBD)_2SbF_6$. [c] Enantiomeric excesses were determined by HPLC using a Chiralpak AS column. The absolute configuration was assigned by comparison of optical rotation with reported data.

TABLE 4. Hydrogenation of 23 by a Rh/5 Complex[a]



(*Z*)-**23** (*E*)-**23** (*S*)-**24**

entry	Ar	ee[b] (%)
1	**23b**/*p*-$CH_3C_6H_4$	99
2	**23c**/*p*-$MeOC_6H_4$	96
3	**23d**/*p*-ClC_6H_4	97
4	**23e**/*p*-FC_6H_4	99
5	**23f**/2,4-$F_2C_6H_3$	96
6	**23g**/*p*-PhC_6H_4	98
7	**23h**/2-naphthyl	>99

[a] The reaction was carried out at room temperature under 15 bar of H_2 for 24 h. The catalyst was prepared in situ by stirring a solution of $Rh(NBD)_2SbF_6$ and ligand **5** in 4 mL of CH_2Cl_2 {[substrate (0.5 mmol, 0.125 M)/[Rh]/**L** = 1:0.01:0.011]}. The reaction went with >99% conversion unless otherwise stated. [b] Enantiomeric excesses were determined by HPLC using a Chiralpak AS column. The absolute configuration was assigned by comparison of optical rotation with reported data.

β-substituted enamides, we expected the Rh catalysts with chiral ligands **5**−**7** should be highly enantioselective for hydrogenation of this class of substrates.

To optimize the reaction conditions, a α-phenylenamide **23a** was chosen as a model substrate in asymmetric hydrogenation. The results were summarized in Table 3. This reaction is not very sensitive to the solvents (entries 1−4) or hydrogen pressure (entries 2, 3, and 5−8). Taking into account the solubility of the catalyst and substrate, methylene chloride was chosen as the solvent and the hydrogenation was carried out at 15 bar of H_2. Like hydrogenation of other β-substituted enamides, the change of counteranions did not affect the selectivity. Hydrogenation of **23a** with rhodium catalysts with ligands **5**, **6a**,**b,** and **7** gave the chiral amino MOM-protected alcohol **24a** in 96−98% ee. These results are comparable to those obtained from BICP and Me−DuPhos ligands. The significant advantage in these new catalytic systems is that both enantiomers of the 1,4-bisphosphine ligands are readily accessible from inexpensive and commercially available tartrates.

Under the standard reaction conditions, a variety of α-arylenamides **23** with a MOM-protected β-hydroxyl group were subjected to the hydrogenation with Rh−**5** catalyst (Table 4). All substrates were hydrogenated with high ees (95→99%). These results demonstrate that this Rh catalytic system can be highly efficient for making chiral β-amino alcohols.

Summary

In conclusion, chiral ligands with a 1,4-dioxane backbone can be prepared easily using Ley's "BDA" and "Dispoke" methodologies. Rhodium catalysts with chiral 1,4-diphenylphosphines **5**, **6a**,**b,** and **7** are highly effective for the asymmetric hydrogenation of enamides and MOM-protected β-hydroxyl enamides, providing a wide range of chiral amines and β-amino alcohols. Further investigation of these ligands to asymmetric synthesis and the roles of the 1,4-dioxane backbone in stabilizing the metal−ligand chelate conformation is in progress. These results will be reported in due course.

Experimental Section

General Methods. All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. Toluene, diethyl ether, and tetrahydrofuran were distilled from sodium benzophenone ketyl under nitrogen. Methylene chloride was distilled from CaH_2. Methanol and ethanol were distilled from Mg under nitrogen.

Compounds **10a**, **11a**, and **15** were prepared according to the reported methods.[6b,11]

(2*R*,3*R*,5*S*,6*S*)-2,3-Diethoxy-2,3-dimethyl-5,6-bis(hydroxymethyl)[1,4]dioxane (11b). (±)-10-Camphorsulfonic acid (1.1 g, 4.9 mmol) was added to a solution of L-diethyl tartrate (10.1 g, 49 mmol), 2,3-dibutanone (5.1 g, 59 mmol), and dry triethyl orthoformate (30 mL, 180 mmol) in dry ethanol (200 mL). The reaction was heated under reflux for 16 h. The mixture was neutralized with triethylamine (5 mL), and the solvent was removed under reduced pressure. The residue was purified by a short silica gel plug to give an oil. This oily intermediate was reduced using $LiAlH_4$ in THF. Recrystallization from hexanes/ether gave a white solid in 68% yield. The analytical data were identical to the sample prepared earlier by the different route.[8]

(2*R*,3*R*,5*S*,6*S*)-2,3-Dimethoxy-2,3-dimethyl-5,6-bis(((methanesulfonyl)oxy)methyl)[1,4]dioxane (12a). To a solution of diol **11a** (2.36 g, 10.0 mmol) and triethylamine (4.9 mL, 35.0 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of methanesulfonyl chloride (2.4 mL, 30.0 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 30 min at 0 °C, the reaction

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mixture was stirred for additional 30 min at room temperature. This mixture was quenched by saturated aqueous ammonium chloride solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic solution was dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by a flash chromatography on silica gel eluted with hexanes/CH_2Cl_2/ethyl ether (50:35:15) to give a white solid 3.80 g in 97% yield: mp 90−2 °C. $[\alpha]^{24}_D = -121.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 4.40−4.28 (m, 4H), 4.01−3.90 (m, 2H), 3.22 (s, 6H), 3.08 (s, 6H), 1.25 (s, 6H). ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 99.1, 68.7, 66.4, 48.1, 37.6, 17.1. HRMS. Calcd for $C_{11}H_{21}O_9S_2$ (M-OCH_3): 361.0627. Found: 361.0612.

(6*R*,7*R*,14*S*,15*S*)-1,8,13,16-Tetraoxadispiro[5,0,5,4]-14,15-dihydroxymethylhexadecane (16). A solution of ester **15** (1.45 g, 4.21 mmol) in THF (30 mL) was added dropwise to a suspension of $LiAlH_4$ (670 mg, 17.6 mmol) in THF (100 mL) under stirring at 0 °C. After 1 h stirring at room temperature, the suspension was heated for 1 h under reflux. After the mixture was cooled to room temperature, excess $LiAlH_4$ was decomposed by careful addition of water (0.7 mL), 15% aqueous NaOH (0.7 mL), and water (2.1 mL). The inorganic compounds were filtered off, and the residue was extracted with CH_2Cl_2 by means of a Soxhlet. The combined extracts were evaporated and purification by a silica gel column (hexanes/EtOAc = 1) provided a white solid in 85% yield: mp 88−90 °C. $[\alpha]^{24}_D = -107.1$ (*c* 0.88, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 3.87−3.65 (m, 10H), 2.60 (br, 2H), 1.82−1.50 (m, 12H). ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 96.1, 68.6, 62.3, 60.8, 28.2, 24.9, 18.1. HRMS. Calcd for $C_{14}H_{25}O_6$ (MH^+) and $C_{14}H_{24}O_6Na$ (MNa^+): 289.1651 and 311.1471. Found: 289.1624 and 311.1477.

(2*S*,3*S*,5*S*,6*S*)-5,6-Bis((diphenylphosphanyl)methyl)-2,3-dimethoxy-2,3-dimethyl[1,4]dioxane (5). To a solution of diphenylphosphine (1.90 mL, 11.0 mmol) in THF (80 mL) was added *n*-BuLi in hexane (6.9 mL, 11.0 mmol) at −78 °C over 5 min via a syringe. The resulting orange solution was warmed to room temperature and stirred for 1 h. After the mixture was cooled to −78 °C, bismesylate **15** (1.96 g, 5.0 mmol) in THF (20 mL) was added over 20 min. The resulting orange solution was warmed to room temperature and stirred overnight. The white suspension was hydrolyzed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl ether , and the combined organic solution was dried over Na_2SO_4. After removal of the solvents under reduced pressure, the residue was purified by a flash chromatography on a silica gel column eluted with hexanes/ethyl ether (95/5) to give a white solid (2.1 g in 73% yield): mp 70−71 °C. $[\alpha]^{24}_D = +124.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.37−7.14 (m, 20H), 3.63−3.58 (m, 2H), 2.94 (s, 6H), 2.17−2.01 (m, 4H), 1.08 (s, 6H). ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 139.3 (d, J = 13.8 Hz), 138.2 (d, J = 14.3 Hz), 133.3 (d, J = 20.1 Hz), 132.3 (d, J = 18.6 Hz), 128.9−128.1 (m, aromatic), 98.9, 70.4 (m), 48.0, 30.7 (d, J = 13.3 Hz), 17.4; ^{31}P NMR ($CDCl_3$) δ −20.1 ppm. HRMS. Calcd for $C_{34}H_{39}O_4P_2$ $(MH)^+$ and $C_{34}H_{38}O_4P_2Na$: 573.2324 and 595.2143. Found: 573.2378 and 595.2159.

(2*R*,3*R*,5*R*,6*R*)-5,6-Bis((phenylthio)methyl)-2,3-dimethoxy-2,3-dimethyl[1,4]dioxane (8a). A suspension of NaH (300 mg, 12.5 mmol) in 10 mL of THF was cooled to 0 °C. To this suspension was added thiophenol (1.51 g, 13.8 mmol) over 10 min. The mixture was warmed to room temperature and was stirred for 1 h. The sodium thiophenolate suspension was cooled to 0 °C, and a solution of **12a** (5.76 g, 1.47 mmol) in 10 mL of THF was added over 5 min. After stirring at room temperature for 4 h, the reaction mixture was poured into 10 mL of NH_4Cl at 0 °C. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The excess thiol was removed under high vacuum. The residue was subjected to a silica gel column with 10:1 hexanes/ethyl acetate, which furnished **8a** as a faint yellow oil in 88% yield. $[\alpha]^{20}_D = -99.2$ (*c* 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.30−7.28 (m, 4H), 7.21−7.16 (m, 4H), 7.13−7.09 (m, 2H), 3.76−3.74 (m, 2H), 3.12 (s, 6H), 3.06−2.91 (m, 0.4H), 1.19 (s, 6H). ^{13}C NMR($CDCl_3$, 90.56 MHz): δ 136.3, 129.6, 128.9, 126.2, 99.1, 70.7, 48.0, 35.5, 17.4. HRMS. Calcd for $C_{21}H_{24}O_3S_2$ (M-MeOH): 389.1245. Found: 389.1273.

General Procedure for Asymmetric Hydrogenation. To a solution of $[Rh(COD)_2]PF_6$ (2.1 mg, 0.0045 mmol) in methanol (4 mL) in a glovebox was added bisphosphine **5** (0.10 mL of 0.05 M solution in toluene, 0.005 mmol). After the mixture was stirred for 10 min, substrate (0.5 mmol) was added. The hydrogenation was performed at room temperature under 45 psi of hydrogen for 24 h. After the hydrogen was released, the reaction mixture was passed through a short silica gel column to remove the catalyst. The ee was measured by capillary GC or HPLC directly without any further modification.

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Supporting Information Available: Text characterizing data of compounds **6a**·BH_3, **6c**, **7**, **8b**, **12b**, **14**, and **17** and figures showing ^{31}P, ^{1}H, and ^{13}C NMR spectra of all new compounds and the results of asymmetric hydrogenation of some enamides catalyzed by a various of Rh/1,4-bisphosphines catalysts. This material is available free of charge via the Internet at http://pubs.acs.org.

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