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Rigid P-Chiral Phosphine Ligands with *tert*-Butylmethylphosphino Groups for Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Alkenes

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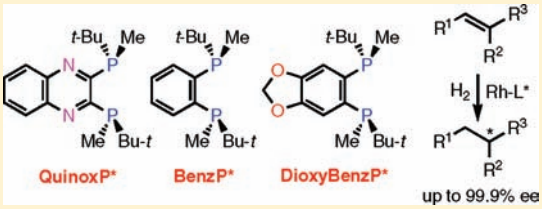
Supporting Information

ABSTRACT: Both enantiomers of 2,3-bis(*tert*-butylmethylphosphino)-quinoxaline (QuinoxP*), 1,2-bis(*tert*-butylmethylphosphino)benzene (BenzP*), and 1,2-bis(*tert*-butylmethylphosphino)-4,5-(methylenedioxy)-benzene (DioxyBenzP*) were prepared in short steps from enantiopure (*S*)- and (*R*)-*tert*-butylmethylphosphine–boranes as the key intermediates. All of these ligands were crystalline solids and were not readily oxidized on exposure to air. Their rhodium complexes exhibited excellent enantioselectivities and high catalytic activities in the asymmetric hydrogenation of functionalized alkenes, such as dehydroamino acid derivatives and enamides. The practical utility of these catalysts was demonstrated by the efficient preparation of several chiral pharmaceutical ingredients having an amino acid or a secondary amine component. A rhodium complex of the structurally simple ligand BenzP* was used for the mechanistic study of asymmetric hydrogenation. Low-temperature NMR studies together with DFT calculations using methyl α-acetamidocinnamate as the standard model substrate revealed new aspects of the reaction pathways and the enantioselection mechanism.



INTRODUCTION

Chiral phosphine ligands have played an important role in transition-metal-catalyzed asymmetric reactions, and an enormous number of ligands have been designed and synthesized over the past four decades.[1] Owing to unrelenting effort including the development of new catalytic asymmetric transformations, many chiral ligands have been proven to exhibit excellent enantioselectivities and some outstanding ligands have been employed in the industrial production of useful optically active compounds.[2,3] However, there are no "almighty" ligands, and hence, the exploration of more efficient and widely applicable chiral phosphine ligands is still a vital research topic in the field of asymmetric catalysis.[4]

Chiral phosphine ligands are largely classified into two categories. One category consists of ligands with chirality in their backbones. Representative examples are DIOP,[5] CHIRAPHOS,[6] BINAP,[7] DuPHOS,[8] Josiphos,[9] SEGPHOS,[10] and SDP,[11] in which the same two substituents, aryl groups in most cases, on the phosphorus atom are diastereotopic, influenced by stereogenic carbon centers or chirality based on the axial or planar molecular framework. Another category consists of chiral phosphine ligands exemplified by DIPAMP,[12] BisP*,[13] MiniPHOS,[14] TangPhos,[15] Trichickenfootphos,[16] DuanPhos,[17] SMSPhos,[4g,q,r] and ZhangPhos,[4v] all of which possess their chiral centers at phosphorus atoms. The most prominent is DIPAMP developed by Knowles et al. in 1975.[12a] This ligand has played a very important role in the development of asymmetric catalysis, and quite notable is the fact that it was employed for the first time in industry for the production of L-DOPA by rhodium-catalyzed asymmetric hydrogenation.[12c,d] Unfortunately, despite the landmark success of the discovery of DIPAMP, relatively little attention had been paid to this class of P-chiral phosphine ligands for more than 20 years, mainly because of synthetic difficulty and apprehension about the possible stereomutation at P-stereogenic centers.

We have long been interested in furthering the potential utility of P-chiral phosphine ligands and, to this end, have tried to explore new and efficient methods for their synthesis. In our initial approach published in 1985, we used phosphine–boranes having a methyl group, where the boranato group of the phosphine–boranes was considered to be a protecting group of phosphine and also an activating group to facilitate the deprotonation from the methyl group.[18] Consequently, the usefulness of the protocol was proven in the synthesis of DIPAMP and its analogous ligands.[18,19] In 1998, we prepared for the first time a P-chiral bidentate trialkylphosphine ligand, (*S*,*S*)-1,2-bis(*tert*-butylmethylphosphino)ethane ((*S*,*S*)-*t*-Bu-BisP*),

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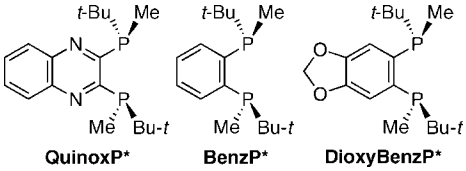
from *tert*-butyl(dimethyl)phosphine–borane by utilizing our phosphine–borane methodology and Evans' procedure that employed (−)-sparteine/*s*-BuLi as the enantioselective deprotonation reagent.[13,20] A similar ligand, (*R*,*R*)-bis(*tert*-butylmethylphosphino)methane ((*R*,*R*)-*t*-Bu-MiniPHOS), was also prepared in the following year.[14a] These two ligands exhibited almost perfect enantioselectivities in the rhodium-catalyzed asymmetric hydrogenation of some α-dehydroamino acids and related substrates, although the molecular structures of the catalysts are quite simple. Nevertheless, these ligands have seen little use in asymmetric catalyses because they are waxy or oily air-sensitive substances and cannot be conveniently handled in air. Another problem is that only single enantiomer ligands are obtained by the use of naturally occurring (−)-sparteine and the opposite enantiomers cannot be prepared by the straightforward procedure.[21,22]

Based on the facts mentioned above, we intended to prepare new ligands that are practically useful for various catalytic asymmetric transformations. The newly designed ligands are 2,3-bis(*tert*-butylmethylphosphino)quinoxaline (QuinoxP*), 1,2-bis(*tert*-butylmethylphosphino)benzene (BenzP*), and 1,2-bis(*tert*-butylmethylphosphino)-4,5-(methylenedioxy)-benzene (DioxyBenzP*). A common feature of these ligands is that two stereochemically equivalent *tert*-butylmethylphosphino groups are attached to the 1,2-positions of the aryl group. This molecular framework would lead to the formation of a C_2-symmetric five-membered chelate that is more rigid than the metal complex of *t*-Bu-BisP* and hence would further enhance enantioselectivity. The electron-attracting quinoxaline and the electron-donating (methylenedioxy)benzene backbones may affect the chemical properties of the ligands as well as the catalytic activity and the enantioselectivity. The anticipated electronic effects have attracted our interest and inspired us to prepare these ligands.[23] Herein we report the preparation of these ligands and their application to the rhodium-catalyzed asymmetric hydrogenation of prochiral functionalized alkenes.

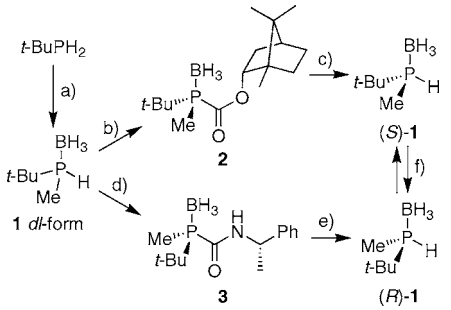


The mechanism of rhodium-catalyzed asymmetric hydrogenation is one of our continuing research subjects.[24−26] We have studied the mechanism by using a rhodium complex of the structurally simple BenzP* and methyl α-acetamidocinnamate (MAC) as a typical probing substrate with the expectation that unprecedented mechanistic aspects will be revealed by NMR studies coupled with DFT calculations.

RESULTS AND DISCUSSION

Preparation of Enantiopure (*S*)- and (*R*)-*tert*-Butylmethylphosphine–Boranes. In order to prepare the target ligands, we needed both enantiopure *tert*-butylmethylphosphine–boranes (*S*)-**1** and (*R*)-**1**. After searching for protocols that are capable of preparing both enantiomers (*S*)-**1** and (*R*)-**1** in large scale, we eventually used diastereomerically pure (R_P)-((−)-bornyloxy)(*tert*-butyl)methylphosphine–borane (**2**) and (S_P,*S*)-*tert*-butyl(methyl)(1-phenylethylcarbamoyl)phosphine–borane (**3**) as the intermediates (Scheme 1).[22] Here, *tert*-butylphosphine was reacted successively with iodomethane and $NaBH_4$ to give racemic *tert*-butylmethylphosphine–borane (**1**)

Scheme 1. Preparation of (*S*)- and (*R*)-*tert*-Butylmethylphosphine–Boranes from *tert*-Butylphosphines[a]



[a]Reagents and conditions: (a) (i) MeI, (ii) $NaBH_4$; (b) (i) *n*-BuLi, (ii) (−)-bornyl chloroformate; (c) KOH, H_2O/MeOH; (d) (*S*)-PhCH(Me)NCO, *n*-BuLi (10 mol %); (e) KOH, H_2O/THF; (f) (i) *n*-BuLi, (ii) $Br(CH_2)_2Br$, (iii) $LiAlH_4$.

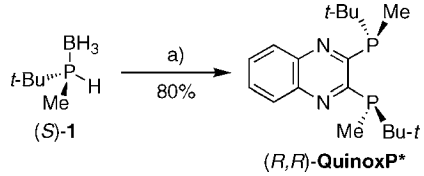
in high yield. This racemate was reacted with *n*-BuLi and (−)-bornyl chloroformate and the resulting diastereomeric mixture was recrystallized to give diastereomerically pure **2**. On the other hand, the reaction of **1** with (*S*)-1-phenylethyl isocyanate, followed by recrystallization, afforded diastereomerically pure **3**. Compounds **2** and **3** were subjected to hydrolysis to afford (*S*)-**1** and (*R*)-**1**, respectively, in satisfactory yields.

We then looked into the possibility of converting the single enantiomer secondary phosphine–borane into its opposite enantiomer. After several trials, it was found that (*S*)-**1** was converted into (*R*)-**1** in 90% yield and 97% enantioselectivity on successive treatments with *n*-BuLi, 1,2-dibromoethane, and $LiAlH_4$ in ether at low temperature.[22] This result indicates that the reverse transformation is also possible and hence, we can supply (*S*)-**1** or (*R*)-**1** from each opposite enantiomer.

Through the reactions mentioned above, we were able to obtain sufficient quantities of both enantiopure secondary phosphine–boranes (*S*)-**1** and (*R*)-**1** for the preparation of QuinoxP*, BenzP*, and DioxyBenzP*.

Synthesis of P-Chiral Phosphine Ligands and Their Rhodium Complexes. 2,3-Bis(*tert*-butylmethylphosphino)-quinoxaline (QuinoxP*). Our initial trial for the synthesis of QuinoxP* was conducted with the use of (*S*)-**1**. The method is shown in Scheme 2. The overall reaction sequence consists of

Scheme 2. Preparation of (*R*,*R*)-QuinoxP* from (*S*)-1[a]



[a]Reagents and conditions: (a) (i) *n*-BuLi, THF, −80 °C, (ii) 2,3-dichloroquinoxaline, −80 °C to rt, (iii) TMEDA, rt.

three steps: (1) lithiation of (*S*)-**1** with *n*-BuLi, (2) addition/elimination reaction with 2,3-dichloroquinoxaline, and (3) deboranation with tetramethylethylenediamine (TMEDA). It should be noted that the three steps were carried out in one pot and the product QuinoxP* was obtained in 80% yield as an orange crystalline solid.[27] Recrystallization of the crude product from methanol gave pure (*R*,*R*)-QuinoxP*. The opposite enantiomer ligand (*S*,*S*)-QuinoxP* was also prepared by the

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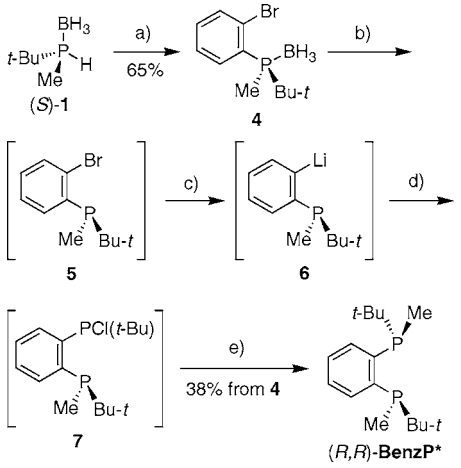
same method but using (*R*)-**1**. Notable is that crystalline QuinoxP* was neither oxidized nor epimerized at the stereogenic phosphorus atoms on exposure to air at room temperature for more than 1 month.[28]

1,2-Bis(*tert*-butylmethylphosphino)benzene (BenzP*). Ligand BenzP* possessing an *ortho*-phenylene backbone has long caught our attention because it looks quite simple and structurally fundamental. We have expected that the ligand would form an imposed five-membered chelate ring and the steric contrast between the *tert*-butyl group and the methyl group would induce excellent enantioselectivities in various asymmetric catalyses.

Our initial attempt to prepare BenzP* was conducted through transition-metal-catalyzed cross-coupling reactions of *o*-dibromobenzene or *o*-diiodobenzene with (*S*)-**1** in the presence of a base. Unfortunately, in most cases, monosubstituted compounds were produced in low to moderate yields and the desired disubstituted compound was not isolated at all. Subsequent trials led to the finding of a route to the target BenzP* (Scheme 3). The reaction of the lithium derivative of

Scheme 3. Preparation of (*R*,*R*)-BenzP* from (*S*)-1[a]



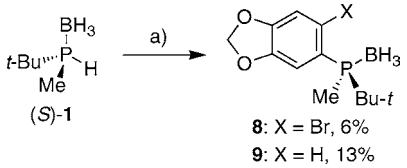
[a]Reagents and conditions: (a) (i) *n*-BuLi, THF, −80 °C, (ii) *o*-$C_6H_4Br_2$, −80 °C ∼ 0 °C; (b) DABCO, THF, reflux; (c) *s*-BuLi, −80 °C; (d) *t*-$BuPCl_2$, −80 °C ∼ 0 °C; (e) MeMgBr, 0 °C ∼ rt.

(*S*)-**1** with *o*-dibromobenzene afforded (*R*)-(2-bromophenyl)-(*tert*-butyl)methylphosphine−borane (**4**) as a crystalline compound with complete retention of configuration at the phosphorus atom in 65% yield.[29,30] This compound was reacted successively with 1,4-diazabicyclo[2.2.2]octane (DABCO), *sec*-butyllithium, *tert*-butyldichlorophosphine, and methylmagnesium bromide to give desired ligand (*R*,*R*)-BenzP* in 38% yield. It should be noted that these four reaction steps were carried out in one pot without having to isolate intermediates **5**−**7** and fortunately, (*R*,*R*)-BenzP* was readily separated as a crystalline solid from other byproducts, such as a *meso*-diphosphine isomer. The overall yield from (*S*)-**1** may be unsatisfactory (25%), but one great merit of this process is the concise reaction pathway with no requirement of chromatography. In the same manner, the counter enantiomer ligand (*S*,*S*)-BenzP* was prepared from (*R*)-**1**.

We anticipated the high sensitivity of BenzP* to air as the electron density at the phosphorus atom was considered to be higher than that of QuinoxP*. Contrary to this anticipation, crystalline BenzP* was not oxidized when exposed to air for more than one week. This operationally convenient property of BenzP* is potentially useful for various asymmetric catalyzes.[31]

1,2-Bis(*tert*-butylmethylphosphino)-4,5-(methylenedioxy)benzene (DioxyBenzP*). Our first choice for the preparation of DioxyBenzP* was above-mentioned reaction sequence, using 1,2-dibromo-4,5-(methylenedioxy)benzene and (*S*)-**1** as the starting materials. However, the first step resulted in the formation of a complex reaction mixture containing a small amount of desired compound **8** and undesired **9** (Scheme 4).

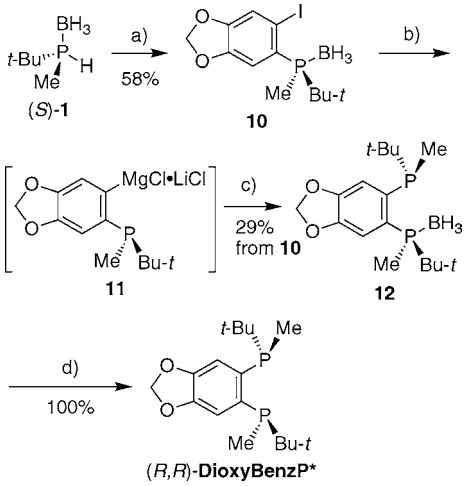
Scheme 4. Formation of Compounds 8 and 9[a]



[a]Reagents and conditions: (a) (i) *n*-BuLi, THF, −80 °C, (ii) 1,2-dibromo-3,4-(methylenedioxy)benzene, −80 °C ∼ 0 °C.

The use of 1,2-diiodo-4,5-(methylenedioxy)benzene significantly improved the reaction to provide the desired compound **10** in 58% yield (Scheme 5). This compound was reacted

Scheme 5. Preparation of (*R*,*R*)-DioxyBenzP*[a]



[a]Reagents and conditions: (a) (i) *s*-BuLi (3 equiv), −80 °C, (ii) 1,2-diiodo-4,5-(methylenedioxy)benzene, (iii) I_2, THF, −80 °C; (b) (i) DABCO, THF, reflux, (ii) *i*-PrMgCl•LiCl; (c) (i) *t*-$BuPCl_2$, (ii) MgMgBr, (iii) BH_3•THF; (d) DABCO, THF, reflux.

subsequently with DABCO and *i*-PrMgCl·LiCl[32,33] to form organomagnesium intermediate **11**, which was further reacted with *tert*-butyldichlorophosphine and methylmagnesium bromide. The reaction mixture was worked-up in a manner similar to the preparation of BenzP*, but the product (*R*,*R*)-DioxyBenzP* did not crystallize out from the solution containing the other byproducts. We next tried to isolate the ligand as a borane adduct by the addition of borane−THF complex to the reaction mixture. Through this procedure and subsequent column chromatography, we obtained monoborane adduct **12** as an air-stable crystalline solid,[34] and this was finally converted to (*R*,*R*)-DioxyBenzP* on treatment with DABCO in refluxing THF (Scheme 5).

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In a similar manner, (*S*,*S*)-DioxyBenzP* was prepared from (*R*)-**1** and 1,2-diiodo-4,5-(methylenedioxy)benzene. Thus obtained DioxyBenzP* was a colorless crystalline solid. This ligand is not so stable in air compared with QuinoxP* and BenzP*, but can be handled in air for as long as a few hours.

Rhodium Complexes of QuinoxP*, BenzP*, and DioxyBenzP*. The above-mentioned P-chiral phosphine ligands were reacted with cationic rhodium diene complexes ($[Rh(cod)_2]SbF_6$ (cod: 1,5-cyclooctadiene), $[Rh(cod)_2]PF_6$, $[Rh(cod)_2]BF_4$, ($[Rh(nbd)_2]SbF_6$, (nbd: norbornadiene), and $[Rh(nbd)_2]BF_4$) to prepare catalyst precursors for asymmetric hydrogenation. Among these diene complexes, $[Rh(cod)_2]SbF_6$ was found to be most suitable for the preparation of the catalyst precursors. Thus, [Rh(QuinoxP*)(cod)]SbF_6, [Rh(BenzP*)-(cod)]SbF_6, and [Rh(DioxyBenzP*)(cod)]SbF_6 were obtained as wine red or orange crystalline solids in good to high yields. The rhodium complex [Rh((*R*,*R*)-BenzP*)(nbd)]SbF_6 for mechanistic study was also prepared by reacting (*R*,*R*)-BenzP* with [Rh(nbd)]SbF_6, the latter of which was generated in situ by mixing $[RhCl(nbd)]_2$ and silver hexafluoroantimonate in acetone.

The molecular structures of [Rh(QuinoxP*)(cod)]SbF_6 and [Rh(BenzP*)(cod)]SbF_6 were determined by single-crystal X-ray analysis. Respective ORTEP drawings are shown in Figures 1 and 2.

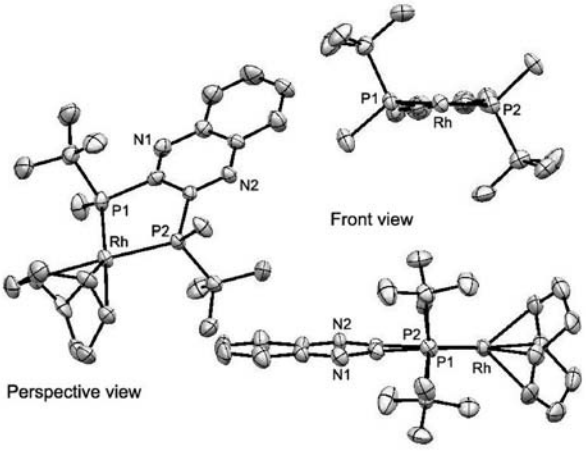

Figure 1. ORTEP drawing of [Rh((*R*,*R*)-QuinoxP*)(cod)]SbF_6. All hydrogen atoms and counteranion (SbF_6) are omitted for clarity.

The two structures closely resemble each other, particularly for the asymmetric environment around rhodium and phosphorus atoms. The five-membered chelate rings are slightly distorted from the P1−Rh−P2 plane. Thus, the dihedral angles between the P1−Rh−P2 plane and the backbone C−C bond of QuinoxP*-Rh and BenzP*-Rh complexes are 7.2° and 12.0°, respectively. The front views and the side views clearly show that the aromatic rings are inclined from the plane to form δ-type chelate structures, whereby the bulky *tert*-butyl groups occupy the quasi-axial positions and the methyl groups are located at the quasi-equatorial positions. It is interesting to compare these crystal structures with that of the rhodium complex of (*S*,*S*)-bis(*tert*-butylmethylphosphino)ethane (*t*-Bu-BisP*).[13,14b] Figure 3 shows three ORTEP views of [Rh((*S*,*S*)-*t*-Bu-BisP*)(nbd)]BF_4. In contrast to the former complexes, this complex forms a λ-type chelate structure with a larger dihedral angle (27.0°) between the P1−Rh−P2 plane and the backbone C−C bond, where the *tert*-butyl groups occupy the quasi-equatorial positions and the methyl groups are located at

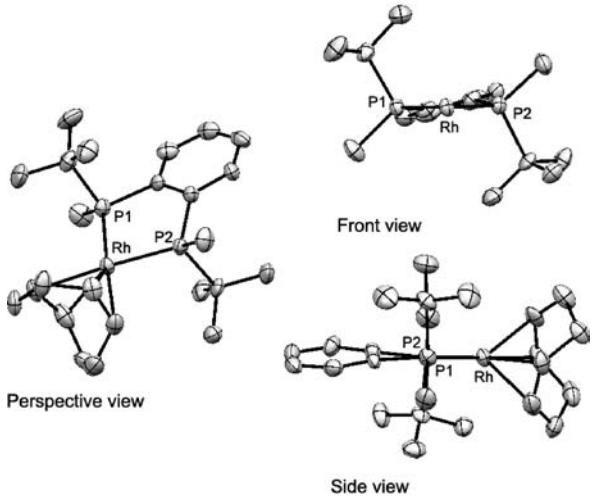

Figure 2. ORTEP drawing of [Rh((*R*,*R*)-BenzP*)(cod)]SbF_6. All hydrogen atoms and counteranion (SbF_6) are omitted for clarity.

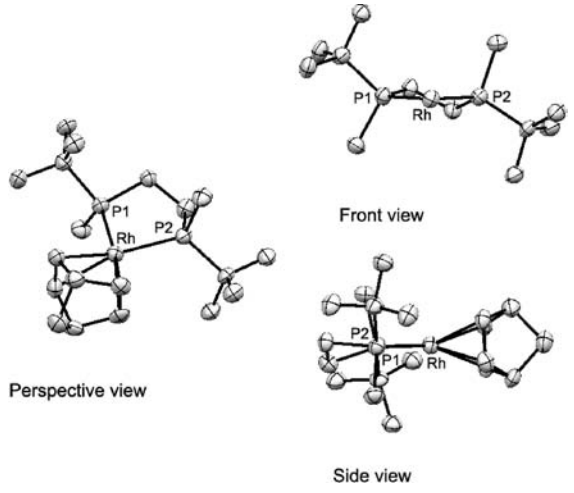

Figure 3. ORTEP drawing of [Rh((*S*,*S*)-BisP*)(nbd)]BF_4. All hydrogen atoms and counteranion (BF_4) are omitted for clarity.

the quasi-axial positions. It is apparent that QuinoxP* and BenzP* form more rigid rhodium complexes owing to the aryl backbones than *t*-Bu-BisP* having a two-methylene backbone. In addition, the *tert*-butyl groups shield the north−northwestern area of the second quadrant and the south−southeastern area of the fourth quadrant. These strictly imposed asymmetric environments lead us to anticipate higher enantioselectivities than the use of the rhodium complex of *t*-Bu-BisP*.

Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Alkenes. The enantioinduction ability and the catalytic activity of the rhodium complexes of QuinoxP*, BenzP*, and DioxyBenzP* were examined in the asymmetric hydrogenation of prochiral functionalized alkenes. We focused our attention on the hydrogenation of α- and β-dehydroamino acids derivatives and enamides. This is because they are three fundamental sets of nitrogen-functionalized alkenes for asymmetric hydrogenation and the produced optically active compounds feature versatile utility in industry as well as in many scientific areas.[35]

1. Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives. The rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives is one of the most

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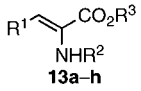
Table 1. Asymmetric Hydrogenation of α-Dehydroamino Acid Derivatives

entry[a]	substrate	ligand	S/C	H_2 (atm)	time (h)	ee (%) of product (conf.)	conversion[b]
	 **13a–h**						
1	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*R*,*R*)-QuinoxP*	1000	3	0.3	99.9 (*R*)	
2	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*S*,*S*)-QuinoxP*	1000	3	0.3	99.9 (*S*)	
3	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*R*,*R*)-QuinoxP*	10000	5	18	99.7 (*R*)	36%
4	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*R*,*R*)-BenzP*	1000	3	0.3	99.9 (*R*)	
5	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*S*,*S*)-BenzP*	1000	3	0.3	99.9 (*S*)	
6	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*R*,*R*)-BenzP*	10000	5	5	99.8 (*R*)	
7	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*R*,*R*)-DioxyBenzP*	1000	3	0.4	99.9 (*R*)	
8	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*S*,*S*)-DioxyBenzP*	1000	3	0.6	99.9 (*S*)	
9	**13a**: R^1 = Ph, R^2 = Ac, R^3 = Me	(*R*,*R*)-DioxyBenzP*	10000	5	24	95.1 (*R*)	
10	**13b**: R^1 = H, R^2 = Ac, R^3 = Me	(*R*,*R*)-QuinoxP*	1000	3	0.2	99.9 (*R*)	
11	**13b**: R^1 = H, R^2 = Ac, R^3 = Me	(*R*,*R*)-QuinoxP*	10000	5	3	99.9 (*R*)	
12	**13b**: R^1 = H, R^2 = Ac, R^3 = Me	(*R*,*R*)-BenzP*	1000	3	0.3	99.9 (*R*)	
13	**13b**: R^1 = H, R^2 = Ac, R^3 = Me	(*R*,*R*)-BenzP*	10000	5	1	99.8 (*R*)	
14	**13b**: R^1 = H, R^2 = Ac, R^3 = Me	(*R*,*R*)-DioxyBenzP*	1000	3	0.3	99.9 (*R*)	
15	**13b**: R^1 = H, R^2 = Ac, R^3 = Me	(*R*,*R*)-DioxyBenzP*	10000	5	24	94.9 (*R*)	
16	**13c**: R^1 = 3-MeO-4-AcOC_6H_3, R^2 = Ac, R^3 = Me	(*R*,*R*)-QuinoxP*	1000	3	0.3	99.9 (*R*)	
17	**13c**: R^1 = 3-MeO-4-AcOC_6H_3, R^2 = Ac, R^3 = Me	(*R*,*R*)-BenzP*	1000	3	0.3	99.9 (*R*)	
18	**13c**: R^1 = 3-MeO-4-AcOC_6H_3, R^2 = Ac, R^3 = Me	(*R*,*R*)-DioxyBenzP*	1000	3	0.4	99.9 (*R*)	
19	**13d**: R^1 = 2-Naph, R^2 = Ac, R^3 = Me	(*R*,*R*)-QuinoxP*	1000	5	0.2	99.6 (*R*)	
20	**13d**: R^1 = 2-Naph, R^2 = Ac, R^3 = Me	(*R*,*R*)-BenzP*	1000	5	0.5	97.2 (*R*)	
21	**13e**: R^1 = Ph, R^2 = Ac, R^3 = H	(*R*,*R*)-QuinoxP*	1000	3	0.2	99.9 (*R*)	
22	**13e**: R^1 = Ph, R^2 = Ac, R^3 = H	(*R*,*R*)-BenzP*	1000	3	0.5	99.5 (*R*)	
23	**13e**: R^1 = Ph, R^2 = Ac, R^3 = H	(*R*,*R*)-DioxyBenzP*	1000	3	1	99.2 (*R*)	
24	**13f**: R^1 = *m*-FC_6H_4, R^2 = Ac, R^3 = H	(*R*,*R*)-QuinoxP*	200	3	0.1	99.7 (*R*)	
25	**13f**: R^1 = *m*-FC_6H_4, R^2 = Ac, R^3 = H	(*R*,*R*)-BenzP*	1000	3	0.7	99.4 (*R*)	
26	**13f**: R^1 = *m*-FC_6H_4, R^2 = Ac, R^3 = H	(*R*,*R*)-DioxyBenzP*	1000	3	1	99.3 (*R*)	
27	**13g**: R^1 = 2-Furyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-QuinoxP*	200	3	8	98.7 (*R*)	
28	**13g**: R^1 = 2-Furyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-BenzP*	200	3	3	99.1 (*R*)	
29[c]	**13g**: R^1 = 2-Furyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-BenzP*	1000	5	18	99.6 (*R*)	90%
30	**13g**: R^1 = 2-Furyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-DioxyBenzP*	200	3	3	97.9 (*R*)	
31	**13h**: R^1 = 2-Pyrrolyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-QuinoxP*	200	3	8	98.2 (*R*)	
32	**13h**: R^1 = 2-Pyrrolyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-BenzP*	200	3	3	94.1 (*R*)	
33[c]	**13h**: R^1 = 2-Pyrrolyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-BenzP*	1000	5	18	95.6 (*R*)	50%
34	**13h**: R^1 = 2-Pyrrolyl, R^2 = Cbz, R^3 = Me	(*R*,*R*)-DioxyBenzP*	200	3	4	95.2 (*R*)	23%

[a]All reactions were carried out in methanol at room temperature, unless otherwise noted. [b]All reactions were completed under the conditions, unless otherwise stated. The conversions were determined by ^{1}H NMR. [c]The reaction was carried out in dichloromethane.

frequently studied asymmetric catalyses. One major reason is that the reaction offers a straightforward way for the synthesis of optically active α-amino acids from inexpensive starting materials. Another reason is that this hydrogenation is utilized as a probing reaction to test the enantioinduction ability of newly synthesized chiral phosphine ligands.

With three sets of rhodium complexes in hand, we at first examined their enantioinduction abilities in the hydrogenation of α-dehydroamino acid derivatives. The results are summarized in Table 1.

Entries 1−9 show the results obtained by the use of a typical probing substrate, methyl α-acetamidocinnamate (MAC) (**13a**). The hydrogenation with S/C = 1000 under 3 atm H_2 pressure at room temperature was completed within 0.3−0.5 h to produce the corresponding product with 99.9% ee (entries 1, 2, 4, 5, 7, and 8). Both enantiomer catalysts afforded the same ee's, proving that they have the same catalytic efficiencies. The hydrogenation with S/C = 10000 under 5 atm H_2 pressure was also examined. The use of QuinoxP*-Rh complex resulted in a low chemical yield under these conditions, whereas the ee of the product was quite high (99.7%) (entry 3). Complete conversion was observed when BenzP*-Rh and DioxyBenzP*-Rh were used; BenzP*-Rh afforded the product with 99.8% ee after 5 h (entry 6) whereas DioxyBenzP*-Rh required a longer reaction time to give the product with significantly lower ee (95.1%) (entry 9). β-Unsubstituted derivative **13b** was also hydrogenated (entries 10−15). Except for entry 15, the reactions proceeded rapidly to yield the product with 99.8−99.9% ee, even when 10000 S/C ratio was employed. Application to the hydrogenation of **13c** leading to the precursor to L-DOPA provided notable results. All the three catalysts were quite efficient to give products with 99.9% ee (entries 16−18). These results, together with the catalytic efficiencies, are favorable compared with the highest values hitherto reported for this transformation.[3a] Compound **13d** was also readily subjected to hydrogenation to give optically active 2-naphthylalanine, which is a versatile precursor to such pharmaceutically important compounds as SDZ NKT 343, a

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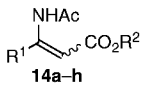
potent human NK_1 tachykinin receptor antagonist (entries 19 and 20).[36,37] Free α-dehydroamino acids **13e,f** were also readily reduced under similar conditions (entries 21−26). The enantioinduction abilities were tested also for the hydrogenation of compounds possessing a 2-furyl or a 2-pyrrolyl group (entries 27−34). The reactions were completed in methanol under 3 atm H_2 pressure to give products with considerably high enantioselectivities when 200 S/C ratio was employed. The reactions with S/C = 1000 in dichloromethane resulted in incomplete conversion (entries 29 and 33).

2. Hydrogenation of β-Dehydroamino Acids Derivatives. The rhodium-catalyzed asymmetric hydrogenation of β-dehydroamino acid derivatives is one of the most efficient methods for the production of chiral β-amino acids, and considerable effort has been made in this area.[38] In most cases, the hydrogenation of (*E*) derivatives gives rise to high enantioselectivities compared with that of (*Z*) derivatives; the latter reactions require higher H_2 pressure and/or a longer reaction time to yield products with lower enantioselectivities,[39] while in some cases, comparatively high enantioselectivities are observed.[4n,v,40]

We employed rhodium catalysts in the hydrogenation of several β-substituted β-(acetylamino)acrylates **14a−h**. The results are shown in Table 2. The hydrogenation of methyl (*E*)-3-acetamido-2-butenoate ((*E*)-**14a**) in the presence of 0.1 mol % (*R,R*)-QuinoxP*-Rh under 3 atm H_2 pressure was completed within 1 h to give the product with 99.9% ee (entry 1). The corresponding (*Z*)-isomer was also smoothly subjected to hydrogenation under the same conditions to give the product with slightly lower ee (99.0%) (entry 2). Use of (*R,R*)-BenzP*-Rh provided almost the same results (entries 3 and 4). A 1:1 mixture of (*E*)-**14a** and (*Z*)-**14a** was also subjected to hydrogenation to show the mean ee value (98.7%) (entry 5) and lower catalyst loading (S/C = 5000) resulted in slightly lower ee (97.9%) (entry 6). (*R,R*)-DioxyBenzP*-Rh was also effective for both (*E*)-**14a** and (*Z*)-**14a**, giving the product with 99.5% ee and 98.5% ee, respectively (entries 7 and 8). Compound (*E*)-**14b** (R^1 = Pr) was similarly hydrogenated

Table 2. Asymmetric Hydrogenation of β-Dehydroamino Acid Derivatives

entry[a]	substrate	ligand	S/C	H_2 (atm)	time (h)	ee (%) of product (config.)	conversion[b]
	 **14a−h**						
1	(*E*)-**14a**: R^1 = Me, R^2 = Me	(*R,R*)-QuinoxP*	1000	3	1	99.9 (*R*)	
2	(*Z*)-**14a**: R^1 = Me, R^2 = Me	(*R,R*)-QuinoxP*	1000	3	0.8	99.0 (*R*)	
3	(*E*)-**14a**: R^1 = Me, R^2 = Me	(*R,R*)-BenzP*	1000	3	0.8	99.6 (*R*)	
4	(*Z*)-**14a**: R^1 = Me, R^2 = Me	(*R,R*)-BenzP*	1000	3	0.8	97.6 (*R*)	
5	(*E*)-**14a**:(*Z*)-**14a** = 1:1	(*R,R*)-BenzP*	1000	3	0.8	98.7 (*R*)	
6	(*E*)-**14a**:(*Z*)-**14a** = 1:1	(*R,R*)-BenzP*	5000	5	20	97.9 (*R*)	
7	(*E*)-**14a**: R^1 = Me, R^2 = Me	(*R,R*)-DioxyBenzP*	1000	3	0.7	99.5 (*R*)	
8	(*Z*)-**14a**: R^1 = Me, R^2 = Me	(*R,R*)-DioxyBenzP*	1000	3	0.6	98.5 (*R*)	
9	(*E*)-**14b**: R^1 = Pr, R^2 = Et	(*R,R*)-QuinoxP*	1000	3	6	99.9 (*R*)	
10	(*Z*)-**14b**: R^1 = Pr, R^2 = Et	(*R,R*)-QuinoxP*	1000	3	6	97.6 (*R*)	90%
11	(*E*)-**14b**: R^1 = Pr, R^2 = Et	(*R,R*)-BenzP*	1000	3	4	99.9 (*R*)	
12	(*Z*)-**14b**: R^1 = Pr, R^2 = Et	(*R,R*)-BenzP*	1000	3	3	94.0 (*R*)	
13	(*E*)-**14b**: R^1 = Pr, R^2 = Et	(*R,R*)-DioxyBenzP*	1000	3	5	99.1 (*R*)	
14	(*Z*)-**14b**: R^1 = Pr, R^2 = Et	(*R,R*)-DioxyBenzP*	1000	3	3	96.8 (*R*)	53%
15	(*Z*)-**14c**: R^1 = *i*-Pr, R^2 = Et	(*R,R*)-QuinoxP*	1000	3	18	89.9 (*S*)	41%
16	(*Z*)-**14c**: R^1 = *i*-Pr, R^2 = Et	(*R,R*)-BenzP*	1000	3	12	86.3 (*S*)	
17	(*Z*)-**14c**: R^1 = *i*-Pr, R^2 = Et	(*R,R*)-DioxyBenzP*	1000	3	24	93.1 (*S*)	
18	(*Z*)-**14d**: R^1 = Ph, R^2 = Me	(*R,R*)-QuinoxP*	1000	3	0.8	98.1 (*S*)	
19	(*Z*)-**14d**: R^1 = Ph, R^2 = Me	(*R,R*)-BenzP*	1000	3	0.5	97.2 (*S*)	
20	(*Z*)-**14d**: R^1 = Ph, R^2 = Me	(*R,R*)-DioxyBenzP*	1000	3	0.6	95.4 (*S*)	
21	(*Z*)-**14e**: R^1 = *p*-$MeOC_6H_4$, R^2 = Et	(*R,R*)-QuinoxP*	1000	3	8	99.1 (*S*)	
22	(*Z*)-**14e**: R^1 = *p*-$MeOC_6H_4$, R^2 = Et	(*R,R*)-BenzP*	1000	3	2	98.5 (*S*)	
23	(*Z*)-**14e**: R^1 = *p*-$MeOC_6H_4$, R^2 = Et	(*R,R*)-DioxyBenzP*	1000	3	3	97.7 (*S*)	
24	(*Z*)-**14f**: R^1 = *p*-FC_6H_4, R^2 = Et	(*R,R*)-QuinoxP*	1000	4	1	96.5 (*S*)	
25	(*Z*)-**14f**: R^1 = *p*-FC_6H_4, R^2 = Et	(*R,R*)-BenzP*	1000	4	8	93.4 (*S*)	
26	(*Z*)-**14f**: R^1 = *p*-FC_6H_4, R^2 = Et	(*R,R*)-DioxyBenzP*	1000	4	18	94.9 (*S*)	
27	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-QuinoxP*	1000	3	2	59 (*S*)	
28[c]	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-QuinoxP*	100	3	1	73 (*S*)	
29	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-BenzP*	1000	3	1	71 (*S*)	
30[c]	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-BenzP*	100	3	1	77 (*S*)	
31	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-DioxyBenzP*	1000	3	0.6	84 (*S*)	
32[c]	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-DioxyBenzP*	100	3	1	90 (*S*)	
33[d]	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-DioxyBenzP*	100	3	2	78 (*S*)	
34[e]	(*Z*)-**14g**: R^1 = 3,5-$Cl_2C_6H_3$, R^2 = Me	(*R,R*)-DioxyBenzP*	100	3	2.5	86 (*S*)	
35	(*Z*)-**14h**: R^1 = *o*-MeC_6H_4, R^2 = Et	(*R,R*)-QuinoxP*	200	5	8	94.9 (*S*)	
36	(*Z*)-**14h**: R^1 = *o*-MeC_6H_4, R^2 = Et	(*R,R*)-BenzP*	200	5	8	95.5 (*S*)	
37	(*Z*)-**14h**: R^1 = *o*-MeC_6H_4, R^2 = Et	(*R,R*)-DioxyBenzP*	200	5	8	92.8 (*S*)	

[a]All reactions were carried out in methanol at room temperature. [b]All reactions were completed under the conditions, unless otherwise stated. The conversions were determined by ^{1}H NMR. [c]The reaction was carried out in dichloromethane. [d]In THF. [e]In ethyl acetate.

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to yield the product with enantioselectivities of 99.1−99.9%, and its (*Z*)-isomer (*Z*)-**14b** underwent hydrogenation to yield the product with slightly lower selectivities (94.0−97.6%). Compound (*Z*)-**14c** (R^1 = *i*-Pr) was hydrogenated to furnish the product with significantly lower enantioselectivities (86−93.1% ee), whereas (*R,R*)-DioxyBenzP*-Rh gave the product that had the highest selectivity (93.1% ee) (entries 15−17). It should be noted that these results are superior to previously reported ones (MalPHOS: 69% ee;[39d] Me-DuPHOS: 4% ee;[39d] Et-FerroTANE: 31% ee;[40c] Trichickenfootphos: 69% ee[40d]).

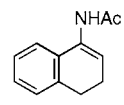
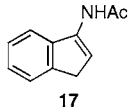
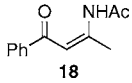
The asymmetric hydrogenation of aryl-substituted (*Z*)-*β*-dehydroamino acid esters ((*Z*)-**14d−h**) took place under 3−5 atm H_2 pressure. Model substrate (*Z*)-**14d** was rapidly converted into the corresponding *β*-amino acid derivative; the use of QuinoxP* gave the corresponding product with the highest ee (98.1%) whereas DioxyBenzP* afforded the product with the lowest ee (95.4%) (entries 18−20). Similarly, *p*-methoxyphenyl- or *p*-fluorophenyl-substituted compounds ((*Z*)-**14e,f**) were hydrogenated with complete conversion and excellent enantioselectivities (entries 21−26). In sharp contrast, 3,5-dichlorophenyl-substituted derivative (*Z*)-**14g** furnished the product with unexpectedly low ee under the same conditions in the presence of QuinoxP*-Rh (entry 27). Changing the solvent from methanol to dichloromethane improved the enantioselectivity from 59% ee to 73% ee (entry 28). A similar result was obtained when BenzP*-Rh was used (entry 30). When DioxyBenzP*-Rh was employed, high enantioselectivity was observed, and in dichloromethane 90% ee was achieved (entries 31 and 32). Further trials that involved changing of the solvent to THF and ethyl acetate resulted in rather lower enantioselectivities (entries 33 and 34). On the other hand, the hydrogenation of *ortho*-substituted compound (*Z*)-**14h** provided excellent results (entries 35−37). Thus, the enantioselectivity (95.5% ee) obtained by the use of (*R,R*)-BenzP*-Rh is comparable to the previously reported highest level selectivities (e.g., Binapine: >99% ee;[40c] ZhangPhos: 92% ee[4v]).

3. Hydrogenation of α-Substituted Enamides. Optically active secondary amines are frequently used as resolving agents, chiral auxiliaries, and intermediates in the synthesis of a wide range of biologically active compounds. The asymmetric hydrogenation of *α*-substituted enamides is considered to be one of the efficient preparative routes to this class of compounds, and many chiral phosphine ligands have been used for this transformation. Although very high enantioselectivities have been achieved by the use of such ligands as DuPHOS,[41] BPE,[41] *t*-Bu-BisP*,[42] BDPMI,[43] TangPhos,[15] R-SMS-Phos,[4g,q,r] and BIBOP,[4n] more efficient and practically useful methods with lower catalyst loading as well as mild reaction conditions are urgently required especially for practical applications.

We tested the applicability of the above-mentioned rhodium complexes in the asymmetric hydrogenation of some representative *α*-substituted enamides. The results are listed in Table 3.

The hydrogenation of *α*-arylenamides **15a−c** was run in methanol at room temperature in the presence of 0.1 mol % rhodium complex under 3 or 5 atm H_2 pressure. In the case of *N*-(1-phenylvinyl)acetamide (**15a**), the reaction times and enantioselectivities differed significantly depending on the

Table 3. Asymmetric Hydrogenation of *α*-Substitiuted Enamides

entry[a]	substrate	ligand	S/C	H_2 (atm)	time (h)	ee (%) of product (config.)	conversion[b]
	 **15a–d**						
1	**15a**: R^1 = Ph	(*R,R*)-QuinoxP*	1000	3	1.5	99.4 (*R*)	
2	**15a**: R^1 = Ph	(*R,R*)-BenzP*	1000	5	5	92.9 (*R*)	
3	**15a**: R^1 = Ph	(*R,R*)-DioxyBenzP*	1000	3	4	90 (*R*)	
4	**15b**: R^1 = 2-Naphthyl	(*R,R*)-QuinoxP*	1000	3	0.2	99.7 (*R*)	
5	**15b**: R^1 = 2-Naphthyl	(*R,R*)-BenzP*	1000	3	0.5	94.5 (*R*)	
6	**15b**: R^1 = 2-Naphthyl	(*R,R*)-DioxyBenzP*	1000	3	0.9	92.7 (*R*)	
7	**15c**: R^1 = *p*-$O_2NC_6H_4$	(*R,R*)-QuinoxP*	1000	3	0.3	99.9 (*R*)	
8	**15c**: R^1 = *p*-$O_2NC_6H_4$	(*R,R*)-BenzP*	1000	3	0.5	99.2 (*R*)	
9	**15c**: R^1 = *p*-$O_2NC_6H_4$	(*R,R*)-DioxyBenzP*	1000	3	0.7	99.6 (*R*)	
10	**15d**: R^1 = *t*-Bu	(*R,R*)-QuinoxP*	1000	5	0.3	99.0 (*S*)	
11	**15d**: R^1 = *t*-Bu	(*R,R*)-BenzP*	1000	5	0.3	96.6 (*S*)	
12	**15d**: R^1 = *t*-Bu	(*R,R*)-DioxyBenzP*	1000	5	0.6	95.1 (*S*)	
13	 **16**	(*R,R*)-QuinoxP*	200	20	19	33 (*R*)	
14		(*R,R*)-BenzP*	200	20	19	53 (*R*)	
15		(*R,R*)-DioxyBenzP*	200	20	19	58 (*R*)	
16[c]		(*R,R*)-DioxyBenzP*	200	20	19	50 (*R*)	
17	 **17**	(*R,R*)-QuinoxP*	200	20	18	91.7 (*R*)	
18		(*R,R*)-BenzP*	200	20	18	74 (*R*)	
19		(*R,R*)-DioxyBenzP*	200	20	18	82 (*R*)	
20	 **18**	(*R,R*)-QuinoxP*	200	3	7	96.6 (*S*)	60%
21		(*R,R*)-BenzP*	200	3	4	98.6 (*S*)	
22		(*R,R*)-DioxyBenzP*	200	3	12	98.6 (*S*)	

[a]All reactions were carried out in methanol at room temperature, unless otherwise stated. [b]All reactions were completed under the conditions, unless otherwise stated. The conversions were determined by ^{1}H NMR. [c]The reaction was carried out in dichloromethane.

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ligand (entries 1−3); when QuinoxP*-Rh complex was used, the reaction was completed within 1.5 h and the product had excellent enantioselectivity (99.4% ee), whereas BenzP*-Rh and DioxyBenzP*-Rh provided the product with 92.9% ee and 90% ee, respectively. Analogous results were obtained in the hydrogenation of *N*-(1-(2-naphthyl)vinyl)acetamide (**15b**). In contrast, all three complexes showed high catalytic efficiencies in the hydrogenation of *N*-(1-(4-nitrophenyl)vinyl)acetamide (**15c**) (entries 7−9).

Compound **15d**, which is an enamide having a bulky *tert*-butyl group at α-position, was readily subjected to hydrogenation to give a product with more than 95% ee (entries 10−12). Note that in this case, an (*S*)-configuration product was formed, in contrast to the hydrogenation of α-arylenamides that led to (*R*)-products. The dramatic difference in stereochemical outcome in this kind of reaction was previously observed when Me-DuPHOS or *t*-Bu-BisP* was used,[41b,42] and the opposite enantioselection mechanisms were explained in terms of steric and electronic effects.[42]

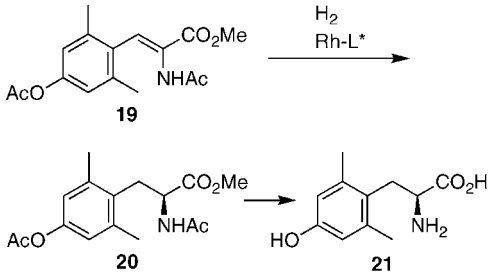
Cyclic enamides **16** and **17** were also used as probing substrates. Compared to acyclic enamides, these enamides are known to be reduced under high H_2 pressure and products with excellent enantioselectivities are hardly obtained except for a few examples.[35a,b] The hydrogenation in the presence of 0.5 mol % catalyst required 20 atm H_2 pressure and 18−19 h to complete, and the resulting products had enantiomeric excesses of 33−91.7% (entries 13−19). These ee values are comparable to most of the reported ones, but are significantly lower than the highest values (98−>99% ee) obtained by the use of Me-BPE or Me-PennPhos.[41b,44]

β-Keto enamides are useful prochiral compounds for the preparation of optically active β-amino ketones and 1,3-aminoalcohols.[45,46] We tested the utility of our rhodium complexes for the enantioselective synthesis of β-amino ketone using compound **18** as the standard substrate. As shown in entries 20−22, BenzP*-Rh and DioxyBenzP*-Rh provided 3-acetylamino-1-phenyl-1-butanone with 98.6% ee, which is comparable to the result obtained by the use of DuanPhos (96% ee).[45]

Preparation of Chiral Building Blocks for the Production of Optically Active Pharmaceuticals. As described above, the three rhodium complexes of QuinoxP*, BenzP*, and DioxyBenzP* were found to be highly efficient catalyst precursors for the asymmetric hydrogenation of α- and β-dehydroamino acid derivatives and enamides. On the basis of available data, we next employed these complexes for the preparation of chiral ingredients for several important pharmaceuticals in order to examine the practical utility of the catalysts.

At first, we focused our attention on the preparation of an optically active α-amino acid that has yet to be satisfactorily prepared with existing methods. As the target compound, (*S*)-2′,6′-dimethyltyrosine (**21**) was chosen because this unnatural amino acid is used as a component of the δ-opioid antagonist Dmt-Tic pharmacophore and its synthesis via the rhodium-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate (**19**) to **20** was not achieved with excellent enantioselectivitity due to the sterically congested nature of the prochiral alkene ((*R*,*R*)-DIPAMP: S/C = 100, H_2 4 atm, ethyl acetate, 60 °C, 24 h, 92% ee;[47] (*S*,*S*)-Et-FerroTANE: S/C = 500, H_2 5 atm, ethyl acetate, 60 °C, 16 h, 93% ee[48]). Our results are shown in Scheme 6. The initial screening reactions using DioxyBenzP* in ethyl acetate, THF, or methanol resulted in full conversion, but the enantioselectivities were disappointingly low. In contrast, the reaction in dichloromethane remarkably improved the ee to 98.2%. BenzP*-Rh provided the product with similarly high ee (98.7%). Use of QuinoxP* in ethyl acetate gave the product with higher ee (84%) than the use of DioxyBenzP* (68% ee). The reaction using QuinoxP*-Rh with S/C = 200 in dichloromethane afforded the product with 99.2% ee. Lowering the catalyst loading to 0.1 mol % also enabled full conversion into the product without any decrease of the enantioselectivity. These results indicate the potential utility of this rhodium-catalyzed hydrogenation for the production of this target amino acid and related substrates.

Scheme 6. Asymmetric Hydrogenation of α-Dehydroamino Acid Derivative 19



(*S*,*S*)-DioxyBenzP*: S/C = 100, AcOEt, 4 atm, 60 °C, 18 h, 68% ee
(*S*,*S*)-DioxyBenzP*: S/C = 200, THF, 4 atm, 60 °C, 18 h, 55% ee
(*S*,*S*)-DioxyBenzP*: S/C = 200, MeOH, 20 atm, rt, 23 h, 55% ee
(*S*,*S*)-DioxyBenzP*: S/C = 200, CH_2Cl_2, 20 atm, rt, 18 h, **98.2% ee**
(*S*,*S*)-BenzP*: S/C = 200, CH_2Cl_2, 20 atm, rt, 18 h, **98.7% ee**
(*S*,*S*)-QuinoxP: S/C = 200, AcOEt, 5 atm, 60 °C, 18 h, 84% ee
(*S*,*S*)-QuinoxP*: S/C = 200, CH_2Cl_2, 20 atm, rt, 18 h, **99.2% ee**
(*S*,*S*)-QuinoxP*: S/C = 1000, CH_2Cl_2, 20 atm, rt, 18 h, **99.1% ee**

Chiral β-amino acid derivatives are useful building blocks for the synthesis of biologically active compounds, such as β-peptides, β-lactam antibiotics, and taxol derivatives. In order to test the practical utility of our rhodium catalysts in the preparation of β-amino acid building blocks, we examined the asymmetric hydrogenation of a β-dehydroamino acid derivative **23** to prepare compound **24**, which is used for the synthesis of VLA-4 antagonist S9059 (**22**).[49] Similarly to the hydrogenation reactions mentioned above, the hydrogenation in the presence of 0.1 mol % catalyst under 3 atm H_2 pressure proceeded smoothly with full conversion within 1 h to provide compound **24** with excellent ee of up to 97.9% (Scheme 7). The high efficiency together with the excellent enantioselectivitity offers a valuable synthetic tool for the production of this chiral building block.

Schemes 8−11 illustrate four examples of the preparation of chiral secondary amine components of commercially available drugs or potentially useful compounds as pharmaceuticals. Scheme 8 shows the preparation of compound **26**, a precursor of acetylcholinesterase inhibitor SDZ-ENA-713 (**27**).[50] The asymmetric hydrogenation of enamide **25** using (*S*,*S*)-QuinoxP*-Rh or (*S*,*S*)-BenzP*-Rh with S/C = 1000 under 3 atm H_2 pressure proceeded rapidly at room temperature to give **26** with 99.4% ee and 93.9% ee, respectively. The result obtained using (*S*,*S*)-QuinoxP*-Rh was superior to the previous approach that used (*S*,*S*)-*t*-Bu-BisP*, which afforded the same product with 97% ee.[42]

Compound **28** is CGP-55845, a GAVA-B antagonist that has been investigated by Novartis as a potential treatment for epilepsy.[51] Previously, Harrison and Meek studied the preparation of a potential intermediate to **28** and carried out

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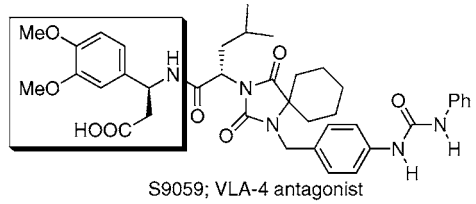
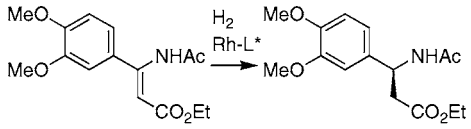
Scheme 7. Asymmetric Hydrogenation of β-Dehydroamino Acid Derivative 23



S9059; VLA-4 antagonist

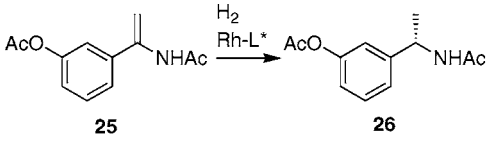
22



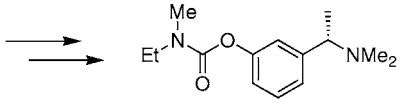
23 **24**

(*R,R*)-QuinoxP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.5 h, 97.7% ee
(*R,R*)-BenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 1 h, 96.2% ee
(*R,R*)-DioxyBenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.5 h, 97.9% ee

Scheme 8. Asymmetric Hydrogenation of Enamide 25



25 **26**

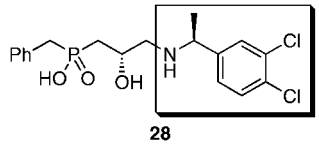


27

SDZ-ENA-713

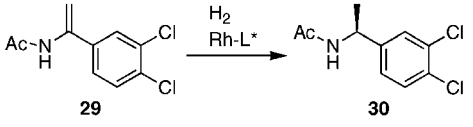
(*S,S*)-QuinoxP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.2 h, 99.4% ee
(*S,S*)-BenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.5 h, 93.9% ee
(*S,S*)-DioxyBenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.8 h, 94.1% ee

Scheme 9. Asymmetric Hydrogenation of Enamide 29



28

CGP-55845; GABA-B-antagonist

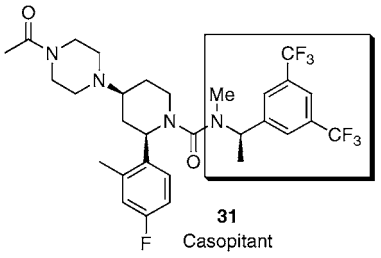


29 **30**

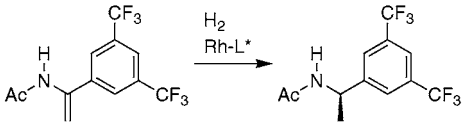
(*S,S*)-QuinoxP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.2 h, 98.7% ee
(*S,S*)-QuinoxP*: S/C = 10000, MeOH, 5 atm H_2, rt, 30 h, 97.7% ee (90% conversion)
(*S,S*)-BenzP*: S/C 1000, MeOH, 3 atm H_2, rt, 0.5 h, 96.4% ee
(*S,S*)-DioxyBenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.8 h, 95.8% ee

the asymmetric hydrogenation of **29** in the presence of (*S,S*)-Et-DuPhos-Rh (S/C = 5000) in methanol at 40 °C under 10 atm H_2 pressure to furnish **30** within 80 min with excellent enantioselectivity (97% ee).[52] We examined the same transformation using rhodium complexes of (*S,S*)-QuinoxP* and (*S,S*)-BenzP*. The results are included in Scheme 9. It should be noted that the hydrogenation using QuinoxP*-Rh with S/C = 1000 at room temperature was completed within 0.2 h to yield

Scheme 10. Asymmetric Hydrogenation of Enamide 32



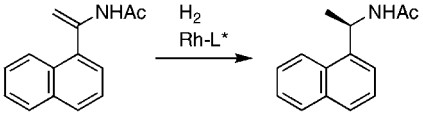
31 Casopitant



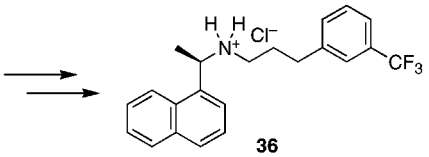
32 **33**

(*R,R*)-QuinoxP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.2 h, 99.9% ee
(*R,R*)-BenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.5 h, 99.9% ee
(*R,R*)-DioxyBenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 0.6 h, 98.1% ee
(*R,R*)-QuinoxP*: S/C = 10000, MeOH, 5 atm H_2, rt, 20 h, 99.9% ee

Scheme 11. Asymmetric Hydrogenation of Enamide 34



34 **35**



36

Cinacalcet hydrochloride

(*R,R*)-QuinoxP*: S/C = 1000, MeOH, 3 atm H_2, rt, 18 h, 85% ee
(*R,R*)-BenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 5 h, 95.1% ee
(*R,R*)-DioxyBenzP*: S/C = 1000, MeOH, 3 atm H_2, rt, 4 h, 97.1% ee

the product with 98.7% enantioselectivity. Lowering the catalyst loading to S/C = 10000 was also examined under 5 atm H_2 pressure and after 30 h, we obtained the product with 97.7% ee in 90% yield. These results compare favorably with the previously reported ones and indicate the potential utility for the production of intermediate **30**.

Casopitant (**31**) is a potent neurokinin 1 (NK_1) receptor antagonist developed by GlaxoSmithKline and its mesylate is effective for the treatment of chemotherapy-induced nausea and vomiting.[53] This compound contains an (*R*)-bis-(trifluoromethyl)phenylethylamine component that is used as a chiral building block for the manufacture of this drug. We tried to prepare building block **33** via the asymmetric hydrogenation of enamide **32**. The results are described in Scheme 10. The hydrogenation using QuinoxP*-Rh and BenzP*-Rh complexes proceeded rapidly to give the product in 99.9% ee, whereas use of DioxyBenzP*-Rh resulted in slightly decreased enantioselectivity (98.1%). It should be noted that the hydrogenation in the presence of QuinoxP*-Rh with S/C = 10000 proceeded under 5 atm H_2 pressure to lead to full conversion after 20 h without any decrease of enantioselectivity. The almost perfect enantioselectivity and

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the very high catalytic efficiency demonstrate the high utility of this hydrogenation method for the production of the chiral building block.

It has been reported that the asymmetric hydrogenation of most *ortho*-substituted aryl enamides is hardly achieved in high enantioselectivities compared with that of unhindered aryl enamides.[42,54] In 2006, Zhang and Zhang reported that triphosphorus bidentate phosphine−phosphoramide ligands exhibited excellent enantioselectivities even in the hydrogenation of *ortho*-substituted aryl enamides.[55] Furthermore, they employed the ligands in the asymmetric hydrogenation of 1-naphthylenamide **34** to prepare **35**, which is the key intermediate to Cinacalcet hydrochloride (**36**), a drug used for the treatment of hyperparathyroidism and hypercalcemia, and achieved very high enantioselectivities up to 93.8% ee. We applied our ligands to the same hydrogenation process to evaluate their practical utility. As shown in Scheme 11, whereas QuinoxP*-Rh did not exhibit very high selectivity (85% ee), the rhodium complexes of more electron-rich BenzP* and DioxyBenzP* furnished the product with remarkably high ee values (95.1% ee and 97.1% ee). The observed enantioselectivities are superior to the previously reported ones, and in conjunction with the catalytic efficiency and the mild reaction conditions, we believe that this method is practically useful.

Mechanistic Study Using Rhodium Complex of BenzP*. Interest in the details of the catalytic cycle and the mechanism of enantioselection in the rhodium-catalyzed asymmetric hydrogenation remains immense starting from the discovery of the reaction itself.[25,26] As the Rh-BenzP* complex demonstrated excellent results in the rhodium-catalyzed asymmetric hydrogenation, we decided to use it in our mechanistic study, together with the most conventional model substrate methyl α-acetamidocinnamate (MAC).

Hydrogenation of catalytic precursor [Rh((*R*,*R*)-BenzP*)(nbd)]SbF_6 (**37**) with 1 atm of H_2 at ambient temperature smoothly gave solvate complex **38** after approximately 10 min (Scheme 12). The addition of two equivalents of MAC to a solution of **38** in deuteriomethanol at ambient temperature led to immediate color change from pale yellow to dark red, indicating the formation of a catalyst−substrate complex **39a** (Scheme 12).

The structure of catalyst−substrate complex **39a** was elucidated from NMR data. The signal for CH═ proton of the coordinated double bond resonates at δ 6.38 and is coupled to Rh and phosphorus (3.1 and 4.8 Hz). The signals of both carbon atoms of the double bond are strongly shifted to the high-field region compared to the same signals in the free substrate MAC and exhibit characteristic coupling to Rh and phosphorus (Figure 4a). Both carbonyls in the ^{13}C NMR spectrum are shifted to the low-field region and coupled to Rh. These data unequivocally characterize **39a** as chelated catalyst−substrate complex.

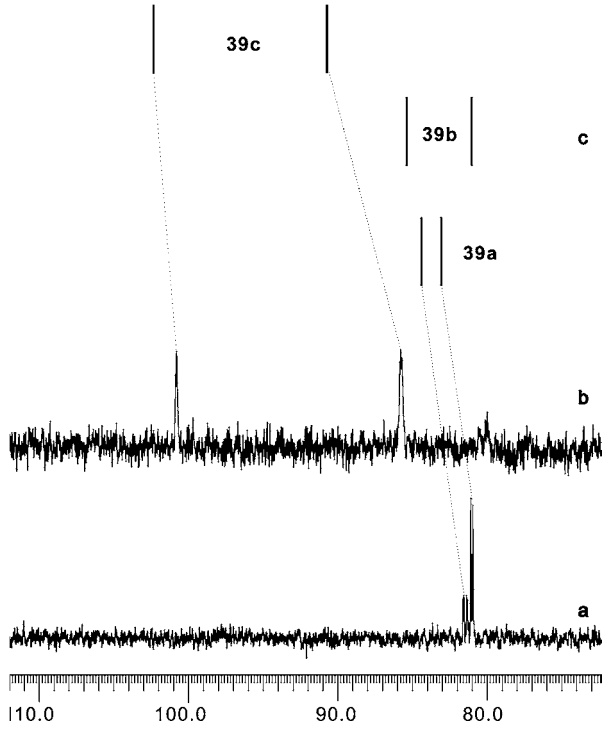
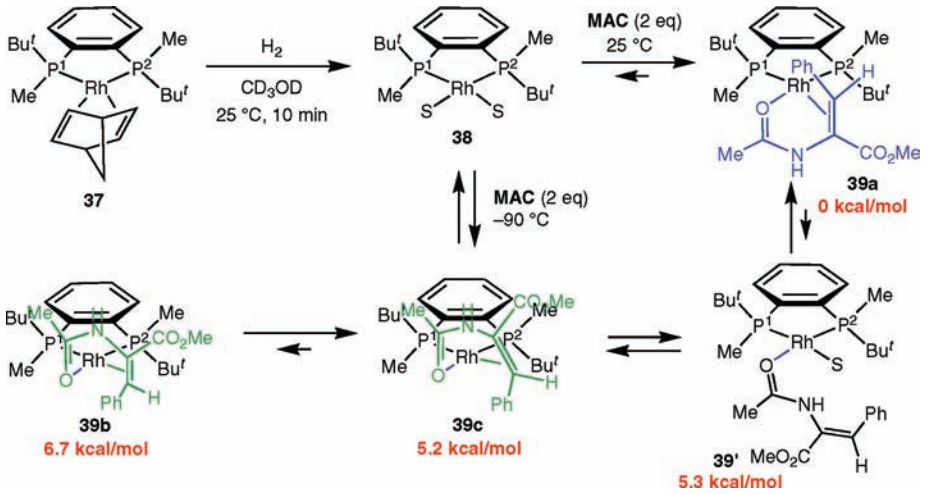


Figure 4. Section plots of ^{13}C NMR spectra (100 MHz, CD_3OD) showing signals from carbon atoms of the coordinated double bond. (a) Solution obtained by the addition of 2 eq of MAC to a deuteriomethanol solution of **38** at 25 °C. Spectrum measured at 25 °C. (b) The same reagents were mixed at −100 °C and the sample was put into the precooled probe of the NMR spectrometer. Spectrum measured at −90 °C. (c) Computed spectra (BLYP/SDD(Rh)6-31G+(2d,2p)/CPCM(methanol)).

Scheme 12. Generation of Solvate Complex and Formation of Catalyst−Substrate Complexes



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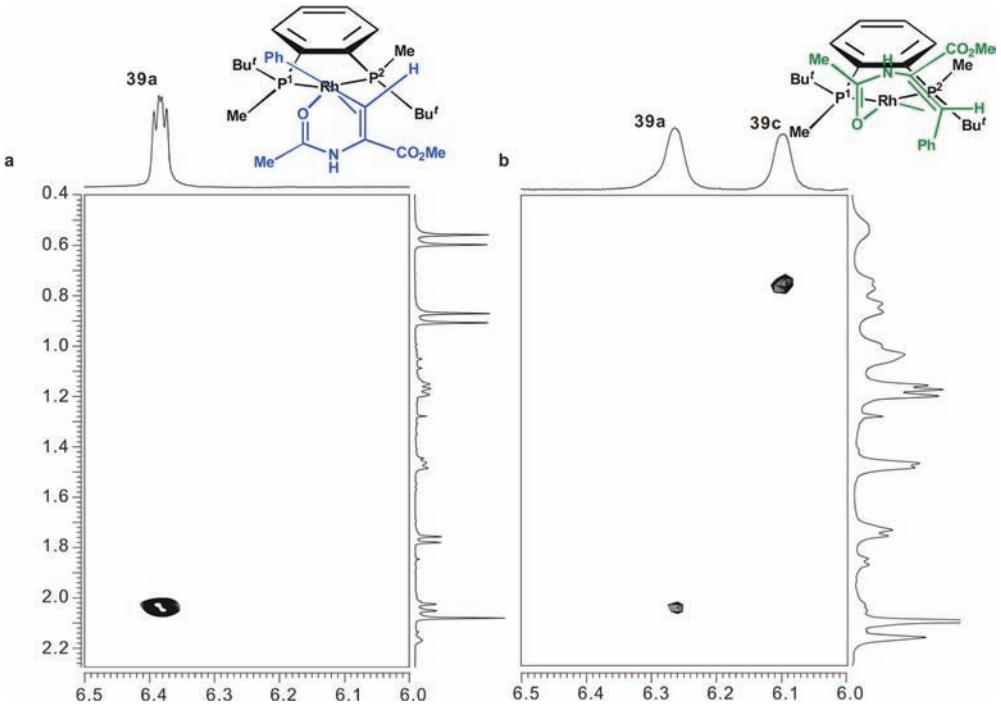

Figure 5. Section plots of phase-sensitive 2D NOESY spectra (400 MHz, CD_3OD). (a) Solution obtained by the addition of 2 eq of MAC to a deuteriomethanol solution of **38** at 25 °C. Spectrum measured at 25 °C. (b) The same reagents were mixed at −100 °C and the sample was put into the precooled probe of the NMR spectrometer. Spectrum measured at −90 °C. The olefinic proton of **39a** gives NOE only with the methyl group, whereas in **39c**, NOE between the olefinic proton and the *tert*-butyl group is observed. These data confirm the coordination modes in **39a** and **39c**.

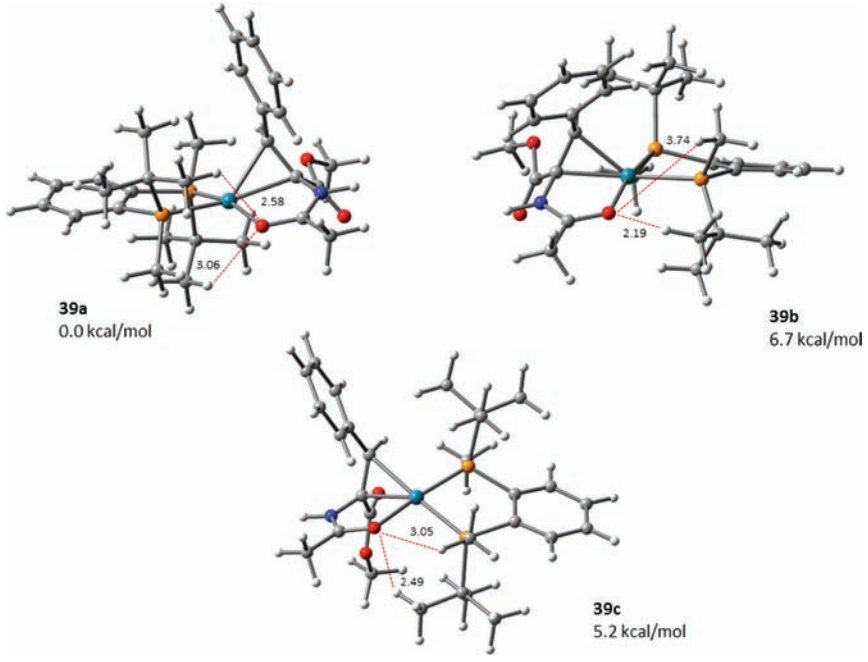

Figure 6. Structures and relative free energies (25 °C) of catalyst-substrate complexes **39a–c** optimized on the BLYP/SDD(Rh)6-31G+(2d,2p)/CPCM(methanol) level of theory.

Furthermore, from the phase-sensitive 2D $^1H-^1H$ NOESY spectrum of complex **39a** taken at 298 K, it was possible to determine the mode of coordination of the double bond in this complex. The CH═ proton had only one NOE cross-peak in the aliphatic region of the spectrum (Figure 5a), i.e., with the methyl group of the adjacent phosphorus atom. As such NOE is only possible in the case of *re*-coordination, this observation enabled us to complete the structure elucidation of **39a**. Other NOEs observed in the spectrum confirmed this structural assignment. (Details are described in the Supporting Information.)

We tried to reproduce these results computationally by optimizing of the structures of **39a** and *si*-coordinated catalyst–substrate complexes **39b** and **39c** on the BLYP/SDD(Rh)6-31G+(2d,2p)/CPCM(methanol) level of theory (Figure 6). The computed relative stabilities of **39a** and **39c** are in good

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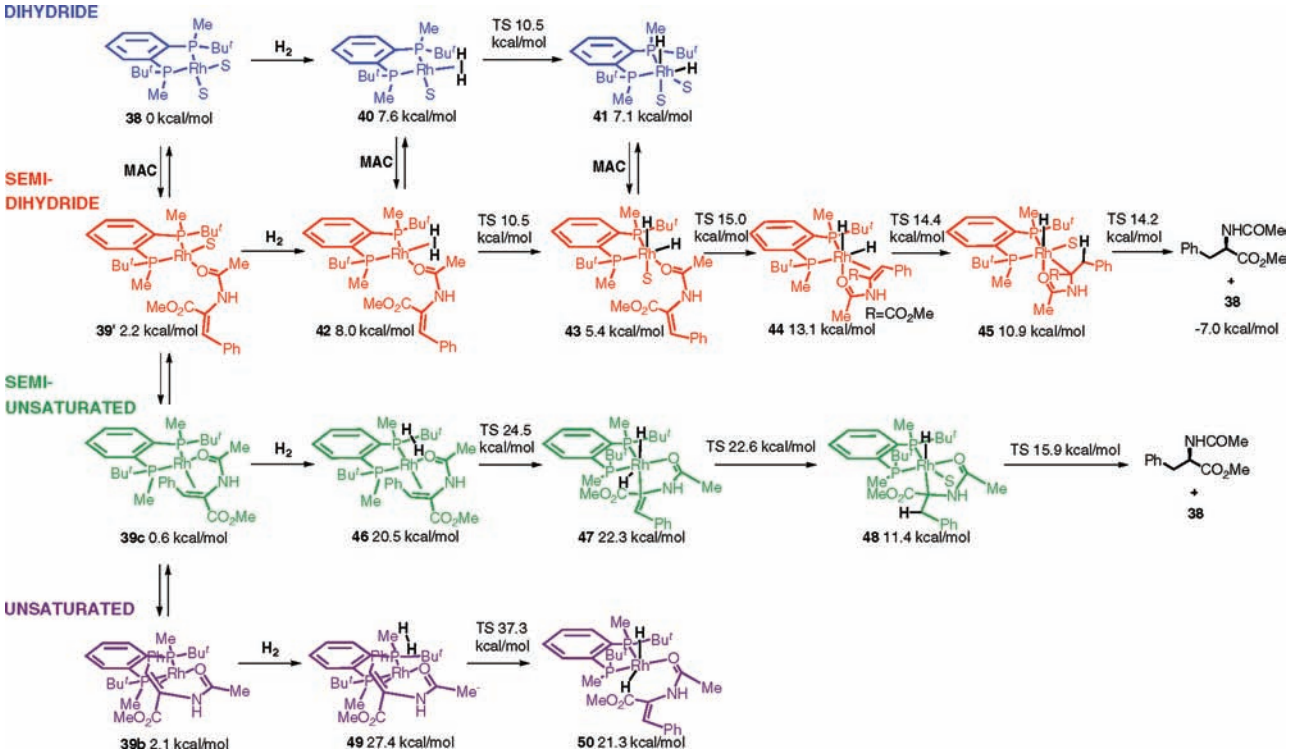
Scheme 13. Computational Results for Four Different Hydrogenation Pathways Leading to (*R*)-Product



accord with the experimental data, as the equilibrium concentration of **39b** that is destabilized by 6.7 kcal/mol would be negligible.

It should be noted that although **39a** is evidently more stable than **39b**, its "quadrant diagram" would show both methoxycarbonyl and phenyl substituents residing in the "hindered quadrants" near the *tert*-butyl groups. This fact demonstrates that qualitative speculations on the relative stabilities of the intermediates based on the quadrant diagram approach are often nonproductive. This has been already noticed by the inventor of the quadrant diagram himself.[12d] As can be seen from Figure 6, the methoxycarbonyl group of **39a** effectively escapes from the steric hindrance of the nearby *tert*-butyl group via bending of the coordinated double bond, and the phenyl group also escapes from the steric hindrance by taking a face-to-*tert*-butyl conformation. The main factor contributing to the relative instability of **39b** is the necessity to form the substrate chelate cycle with the oxygen atom of the amido carbonyl group in close proximity to the *tert*-butyl substituent. Thus, the corresponding Rh−O bond lengths are practically equal in the optimized structures of **39a** and **39b** (2.15 Å). However, if the closest distance between the NC=*O* atom and the hydrogen atom of the adjacent methyl group in **39a** is 3.06 Å, one of the hydrogen atoms of the *tert*-butyl group in **39b**, is as close as 2.19 Å to the oxygen atom of the amido carbonyl. Hence, we are certainly capable of distinguishing the relative hindrance from a methyl group and a *tert*-butyl group, and correctly assigning the "hindered quadrants". However, without detailed analysis of the structure, our conclusions on what these quadrants actually "hinder" may be misleading.

To check if there are any kinetic products that might precede the formation of **39a**, we prepared a sample by adding MAC to a solution of **38** at −90 °C and then set the sample in the precooled probe of the NMR spectrometer. This led to the detection of complex **39c**. The ^{31}P NMR spectra of **39a** and **39c** are very similar. The signal of the olefinic proton of **39c** resonates at δ6.55 and shows NOE with the signal of the *tert*-butyl group, effectively confirming the *si*-coordination of the double bond. On the other hand, the appearance of signals of the coordinated double bond in the ^{13}C NMR spectra of **39a** and **39b** is markedly different (Figure 4). The chemical shifts of CH= and C^{tert} in **39a** are almost the same; they exhibit characteristic couplings with Rh and phosphorus. In the ^{13}C NMR spectrum of **39c**, the signals of CH= (δ = 85.7) and C^{tert} (δ = 100.8) are far from each other and both are significantly shifted to the low-field region compared to the corresponding signals of **39a**.

We conducted a computational screening for the possible structures that would exhibit the characteristic ^{13}C chemical shifts of the coordinated double bond. As can be seen from Figure 4, our computations reasonably well reproduce the chemical shifts of the carbons of the coordinated double bond in **39a** and show convincingly that **39b** is not the intermediate observed at decreased temperatures. On the other hand, the computed chemical shifts for catalyst-substrate complex **39c** (Figure 6, bottom) are in qualitative agreement with the experimentally observed values. The coordination mode of the double bond is changed from roughly orthogonal to the chelate cycle in **39b** to almost coplanar in **39c**, which is 1.6 kcal/mol more stable than **39b**. A structure similar to **39c** was previously computed by Feldgus and Landis[56] for the catalyst-substrate complex of (*R*,*R*)-MeDuPHOS and α-acetamidocinnamonitrile, but this is the first experimental observation of such species.

In order to gain a further insight into the mechanism of enantioselection in the asymmetric hydrogenation catalyzed by the BenzP*-Rh complex, we carried out two low-temperature hydrogenation experiments.

First, we attempted the low-temperature hydrogenation of **39a**. Hydrogenation for 30 min at 2−3 atm H_2 at −90 °C did not result in the formation of any hydrogenation product.

dx.doi.org/10.1021/ja209700j | *J. Am. Chem.Soc.* 2012, 134, 1754−1769

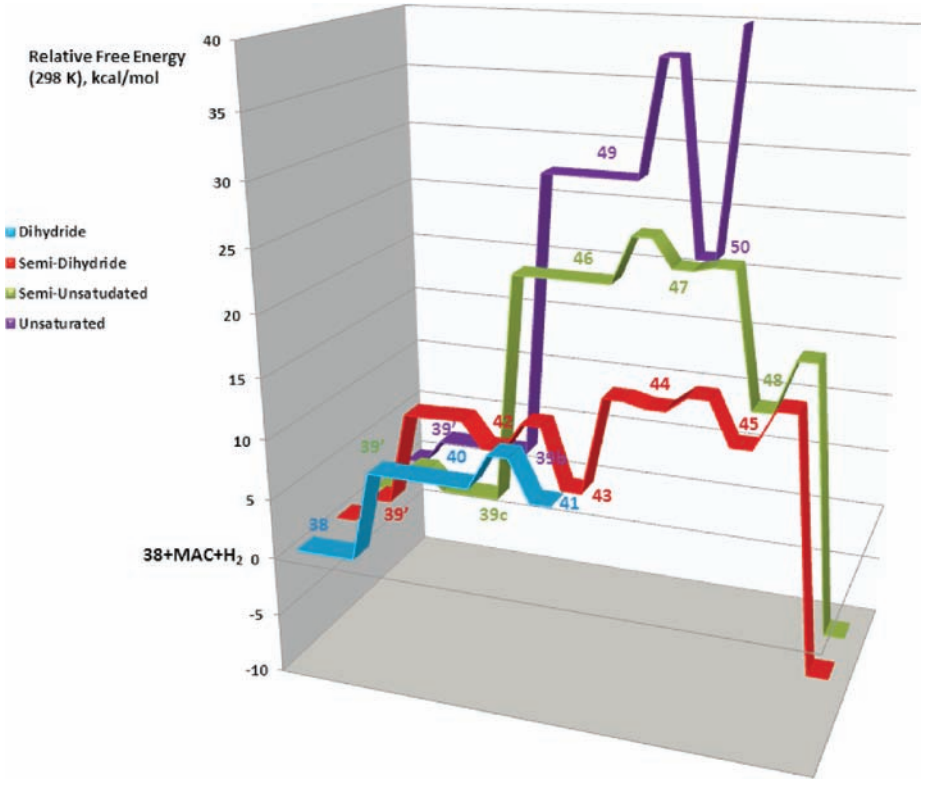


Figure 7. Profiles of the relative energies along four reaction pathways computed on the B3LYP/SDD(Rh)6-31G+(2d,2p)/CPCM(methanol) level of theory with additional diffuse function for phosphorus. Relative free energies at 298 K are shown.

When the temperature was raised to −50 °C, hydrogenation was completed after 30 min, and no intermediates were detected. The hydrogenation product recovered from this sample had 99.5% ee (*R*).

In the second experiment, an equilibrium mixture of **39c**, **38**, and MAC was hydrogenated at −90 °C. In this case, the hydrogenation of **39c** was completed in 10 min at −90 °C, whereas **39a** formed during the hydrogenation. The ee of the hydrogenation product was 99.7% (*R*).

These two experiments clearly show that **39a** cannot be directly hydrogenated; it must first dissociate its double bond to form **39′**, which is also in fast equilibrium with **39c**. Calculations show that the stabilities of **39b**, **39c**, and **39′** and the mixture of **38** and MAC are comparable. Hence, several reaction pathways are conceivable in the catalytic cycle and more detailed computations are necessary to confirm these possibilities.

We have studied the oxidative addition of H_2 to catalyst-substrate complexes **39b, 39c**, and **39′** and solvate complex **38** computationally (Scheme 13). Further reactions essential for the completion of the catalytic cycle were also computed in each case to compare the energetics of the corresponding catalytic pathways. Computations were performed for the unabridged molecules using the CPCM method (MeOH) for modeling solvation effects.

The results are shown in Figure 7. The oxidative addition of H_2 to solvate complex **38** or nonchelating complex **39′** occurs with very similar low activation barriers. These reactions involve the coordination of the dihydrogen molecule at the vacant coordination site, yielding molecular hydrogen complexes **40** and **42**, respectively. As **38** and **39′**, **40** and **42**, and **41** and **43** are easily interconvertible via the nonchelating coordination of the substrate, these two pathways are hardly distinguishable and merge in one low-energy pathway that leads to the formation of the hydrogenation product upon coordination of the double bond in **43** that yields dihydride intermediate **44**, which in turn undergoes migratory insertion to give monohydride intermediate **45**.

As there are no free coordination sites in chelating complex **39c**, the dihydrogen molecule must coordinate above one of the Rh−P bonds to form a molecular hydrogen complex that serves as the initial species in the oxidative addition step. Landis et al. looked into all four possible pathways for the oxidative addition of dihydrogen to an analogue of **39c**, the catalyst-substrate complex of Rh-(*R*,*R*)-Me-DuPHOS and *α*-acetamidocinnamonitrile.[56−58] However, only two of those pathways were found to have realistically low activation barriers. In the case of **39c**, the presence of the phenyl substituent at the *β*-position of the prochiral substrate leaves only one possibility for the formation of the molecular hydrogen complex (**46**), as all other pathways are effectively blocked by the coordinated substrate. Moreover, **46** is quite unstable: the reaction of **39c** with dihydrogen to yield **46** is endothermic by 20.5 kcal/mol. Although the activation energy for the oxidative addition itself is not high, the overall effective barrier for the formation of dihydride intermediate **47** (rate limiting step: oxidative addition) was computed to be 10.1 kcal/mol higher than that for the formation of dihydride intermediate **44** (rate limiting step: coordination of the double bond in **43**). Thus, the coordination of the double bond can hardly be expected to be kept during the oxidative addition of hydrogen to **39c**: most probably, it would dissociate on the way to molecular hydrogen complex **46**, yielding much more stable (by 12.5 kcal/mol) nonchelating molecular hydrogen complex **42**.

The oxidative addition to the complex **39b** was computed to be still more demanding: the transition state for the oxidative

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addition is 12.8 kcal/mol higher in energy than that for **39c**. Moreover, the structure of resulting dihydride intermediate **50** is strongly distorted and the double bond is only weakly bound to Rh (Rh−C and Rh−CH distances are 3.81 and 3.85 Å, respectively). As a result, we were unable to find a pathway for the migratory insertion in that case.

Thus, the computational analysis suggests that the hydrogenation takes place either via the dihydride pathway through the solvate complex **38** or via nonchelating complex **39′**, because dihydrogen is readily coordinated to the vacant site of these complexes. That means that the enantioselection must take place at a later stage of the catalytic cycle, i.e., during the recoordination of the double bond that leads to dihydride intermediate **44**.[25,26] Intuitively, it is clear that the formation of the chelate cycle should be more facile in the nonhindered quadrant, that will result in a product with correct absolute configuration. However, accurate computational analysis of this step is difficult due to the involvement of solvent molecules and the numerous possibilities for crossover of the reaction pathways. We will describe these computations in future publications.

CONCLUSIONS

In summary, we have prepared three conformationally rigid P-chiral phosphine ligands named QuinoxP*, BenzP*, and DioxyBenzP*. Their rhodium complexes exhibited excellent enantioselectivities of up to 99.9% and activities of up to 10000 h^{-1} TOF in the asymmetric hydrogenation of dehydroamino acid derivatives and enamides. The practical utility of the asymmetric hydrogenation using these ligands was demonstrated in the efficient preparation of chiral ingredients of several important pharmaceuticals. In addition to the catalytic efficiency, the ease of handling in air indicates the versatile utility of the ligands in a wide range of transition-metal-catalyzed asymmetric reactions.

The structurally simple and rigid ligand BenzP* was used for the mechanistic study of rhodium-catalyzed asymmetric hydrogenation. New aspects of the reaction pathways and the enantioselection mechanism were revealed by NMR studies and DFT calculations.

ASSOCIATED CONTENT

Supporting Information

Detailed descriptions of experimental procedures, X-ray crystallographic data (CIF), spectral data of all new compounds, HPLC and GC data for the determination of enantiomeric excesses, data for NMR study, and summary of for the calculation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Both enantiomers of QuinoxP* are now commercially available from Aldrich and Strem.

(29) The success of this transformation is largely indebted to the private communication from Professor Sylvain Jugé, the University of Bourgogne.

(30) It is noted that the use of *o*-dichlorobenzene in place of *o*-dibromobenzene provided not the desired compound (*R*)-1-(boranato-(*tert*-butyl)methylphosphino)-2-chlorobenzene but (*R,R*)-1,3-bis(boranato-(*tert*-butyl)methylphosphino)benzene in moderate yield.

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