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Catalytic asymmetric transformations with fine-tunable biphenol-based monodentate ligands

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Abstract—A library of new fine-tunable monodentate phosphite and phosphoramidite ligands based on chiral biphenol have been designed and developed. These monodentate phosphorus ligands have exhibited excellent enantioselectivity in the Pd-catalyzed asymmetric allylic alkylation and Rh-catalyzed asymmetric hydrogenation.

1. Introduction

Recently, chiral monodentate phosphorus ligands have been attracting increasing interest because of their structural simplicity as well as excellent efficiency in a variety of catalytic asymmetric transformations. The emergence of chiral monodentate ligands comes after three decades of predominance by chiral bidentate ligands with C_2-symmetry, which was often considered as a prerequisite for efficient asymmetric induction. Currently, the simplicity and ease of the synthesis and structural modification of chiral monodentate ligands can be considered as highly advantageous because these characteristics fit very well to a combinatorial approach to finding the most suitable ligand for a particular catalytic asymmetric transformation. Thus, this approach is now considered most practical as opposed to developing one universal and almighty ligand for different types of catalytic asymmetric reactions. Moreover, it has recently been demonstrated that using a mixture of chiral monodentate ligands, through a combinatorial approach, can offer superior results than the use of single ligand.[1–6]

Chiral monodentate phosphorus ligands have been successfully applied to a variety of catalytic asymmetric reactions such as hydrogenation,[2,4,7–13] 1,4-addition of dialkylzinc,[14–18] and boronic acids[5,19] to α,β-conjugated systems, hydrovinylation,[20] hydrosilylation,[21] hydroformylation,[22] allylation of aldehydes,[23] intramolecular Heck reaction,[24] allylic alkylation,[25,26] amination, and etherification.[27,28] It is worth mentioning that the large majority of these ligands are based on BINOL, TADDOL, spiroindanediol, or achiral biphenol bearing a chiral alcohol moiety or amine. We have been developing a new class of chiral monodentate phosphite and phosphoramidite ligands derived from readily accessible enantiopure axially chiral biphenol units (Fig. 1).[13,17,22] One of the salient features of these novel monodentate phosphorus ligands is their fine-tuning capability through modifications of the R^1, R^2, and R^3 groups. This feature is of critical importance because it allows a combinatorial approach to finding the most efficient ligand for a specific reaction or process.

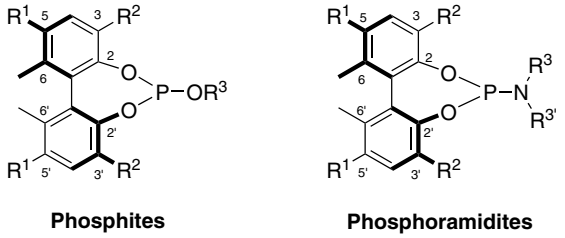

Figure 1. Biphenol based phosphites and phosphoramidites.

We describe here the applications of these novel monodentate phosphorus ligands with transition metal catalyst precursors to catalytic asymmetric transformations, which demonstrate the remarkable advantages that their fine-tuning capability can offer for achieving high catalyst efficiency and enantioselectivity. The catalytic asymmetric transformations that are discussed here are Pd-catalyzed asymmetric allylic alkylation and its

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application to the total synthesis of enantiopure (+)-γ-lycorane and Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate.

2. Results and discussion

2.1. Synthesis of monodentate phosphorus ligands

We designed and synthesized a library of chiral monophosphite and monophosphoramidite ligands having various substituents at the 3,3′-positions of the enantiopure 6,6′-dimethylbiphenol skeleton as well as different alkoxy, aryloxy, and dialkylamine moieties (Fig. 2). The enantiopure 6,6′-dimethylbiphenols were synthesized following the literature procedure.[29] Substituents at the 3,3′-positions were introduced according to the methods described previously.[13] Up to five different substituents, that is, H, Me, Br, *t*-Bu, and Ph, have been introduced onto the biphenol skeleton (Scheme 1). In general, a biphenol is reacted with an alkoxyphosphorous dichloride or a dialkylaminophosphorous dichloride in the presence of Et_3N in THF at room temperature for 12 h. The amines and alcohols used are commercially available with the exception of chiral bis[(1-aryl)ethyl]-amines, which were prepared by a literature method.[30,31]

2.2. Total synthesis of enantiopure (+)-γ-lycorane using Pd-catalyzed asymmetric allylic alkylation in the key step

Catalytic asymmetric allylic substitution provides one of the most powerful methods for the stereo-controlled formation of carbon–carbon or carbon–heteroatom bonds. This reaction serves as a reliable method for the synthesis of enantiopure natural and unnatural products.[32–35] Extensive studies have been performed to address mechanistic issues relevant to the regio- and stereoselectivity of this reaction.[32,36–40] Trost et al. pioneered asymmetric allylic alkylation reactions using modular ligands based on C_2-symmetrical chiral diamines bearing bis(diarylphosphino)benzoic acid units.[41] These ligands have achieved high efficiency in various systems through rational modification of the C_2-symmetrical diphosphine ligand module.[33,36] Catalytic asymmetric allylic substitution reactions have found a wide range of applications in organic syntheses, to date, along with the design and development of a variety of chiral ligands for these reactions.

The use of chiral monodentate phosphorus ligands in catalytic asymmetric allylic alkylation has been reported with an Ir-complex precursor, which generally leads to the formation of branched products with excellent

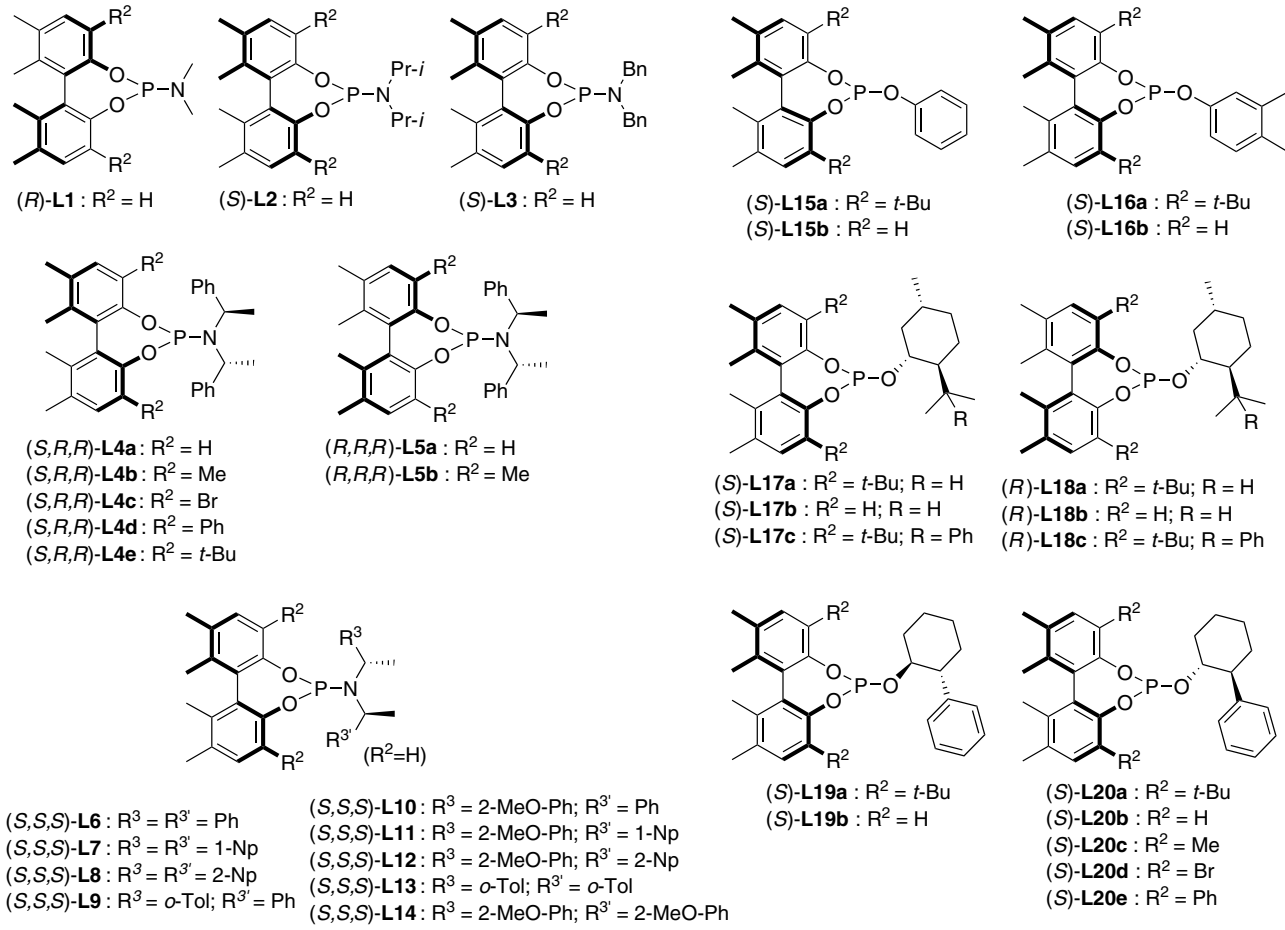
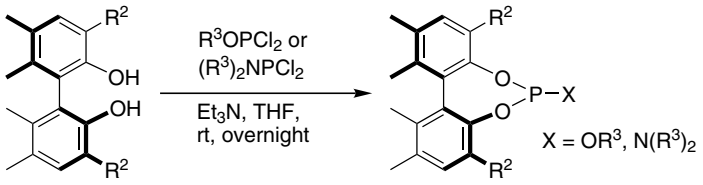


Figure 2. Library of chiral monodentate phosphoramidite and phosphite ligands.



Scheme 1. Synthesis of chiral monodentate phosphorus ligands.

regioselectivity.[42] However, the corresponding Pd-catalyzed reactions with chiral monodentate phosphorous ligands have only been poorly explored in spite of the fact that palladium is the metal of choice for asymmetric allylic substitution reactions in general.[26,43,44] Accordingly, we set out to explore the use of our novel monodentate phosphoramidite ligands in Pd-catalyzed asymmetric allylic alkylation reactions, especially for the asymmetric synthesis of a pentacyclic alkaloid, (+)-γ-lycorane.

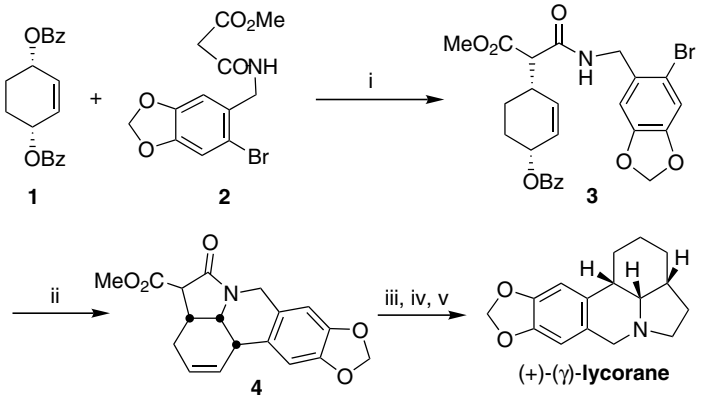
(+)-γ-Lycorane isolated from the plants of *Amaryllidacae* family belongs to a class of alkaloids that exhibit a variety of biological activities.[44] Due to its unique pentacyclic structure, (+)-γ-lycorane has inspired many synthetic chemists to develop a number of innovative approaches toward its total synthesis.[44–49] However, very few approaches to the asymmetric synthesis of this compound have been reported so far.[45,49] In 1995, Mori et al. reported the first asymmetric synthesis of (+)-γ-lycorane, featuring a Pd-catalyzed allylic alkylation in the key step, wherein a sequential allylic alkylation, allylic amination, and Heck reaction led to the target pentacyclic system (Scheme 2).[49] However, the best enantioselectivity achieved in this key step (step i in Scheme 2) using (*S*)-BINAPO was 54% ee, giving **3** in 30% yield (using 2.6 equiv of **2** and LDA). The yield and enantiopurity of **3** were dependent on the amounts of **2** and LDA used. Thus, **3** was obtained in 66% yield and 40% ee on using 1.1 equiv of **2** and LDA. This product (40% ee) was used to complete the total synthesis in 17% overall yield. The expedited five-step total synthesis, incorporating one-pot protocol, gave (+)-γ-lycorane with 46% ee in 23% overall yield.

This short total synthesis appears to have a lot of room for improvement. Thus, we decided to revisit this process by applying a library of our new chiral monodentate phosphoramidite ligands for optimization of the enantioselectivity and chemical yield and then accomplish a highly efficient total synthesis of (+)-γ-lycorane.

Prior to investigation into the key step in the (+)-γ-lycorane synthesis, we performed a preliminary study on the desymmetrization of a *meso*-dibenzoate, *cis*-1,4-dibenzoyloxycyclohex-2-ene, using dibenzyl malonate as simple nucleophile. Trost et al. previously investigated the desymmetrization of this *meso*-dibenzoate,[50] which provided useful insights into the mechanism of this reaction as well as the critical enantio-discrimination that a chiral ligand could exert during the ionization step of the catalytic cycle.[41,50]

First, a molecular modeling study (Spartan Program, MM2/PM3) was performed in order to see, which ligand moiety would play a crucial role in the enantio-discrimination step. It has been shown that the stereo-differentiation of a leaving group occurs before the ionization step in the catalytic cycle.[41,50] Accordingly, we examined the molecular arrangements of a Pd(0) complex bearing two molecules of monodentate phosphorous ligand **L1** and the *meso*-dibenzoate. Figure 3 shows the energy minimized structure of $Pd(L^*)_2$(olefin) [$L^* = (R)$-**L1**; olefin = *cis*-1,4-dibenzoyloxycyclohex-2-ene].

As Figure 3 illustrates, the $Pd(L^*)_2$(olefin) complex adopts two **L1** ligands with C_2-symmetrical arrangement around the Pd metal, and the two dimethylamine moieties are pointing toward the coordination site of the ole-



Scheme 2. Reagents and conditions:[49] (i) $Pd(OAc)_2$, (*S*)-BINAPO, **2** (2.6 equiv), LDA (2.6 equiv), THF/CH_3CN, 0 °C, 1 h; (ii) $Pd(OAc)_2$–dppb, NaH, DMF, 50 °C, 3 h then Et(*i*-Pr)$_2$N, 100 °C, 5 h; (iii) NaCl (1 equiv), DMSO/H_2O; (iv) Pd/C, H_2, MeOH; (v) $LiAlH_4$, reflux, 1 h.

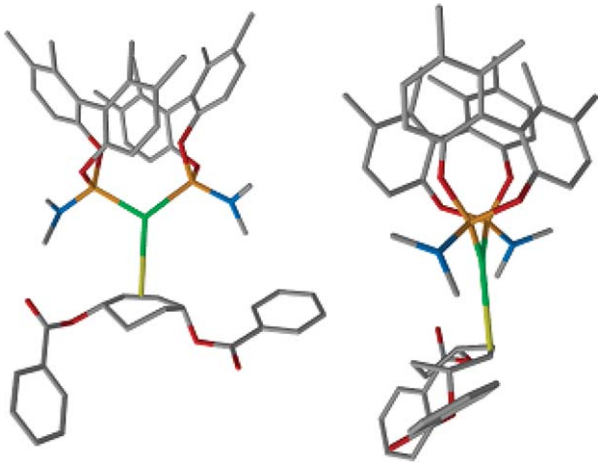
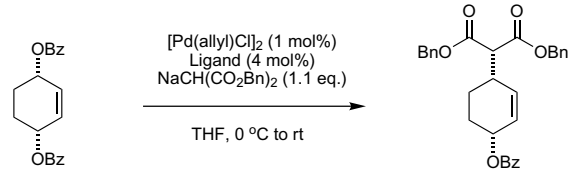


Figure 3. Energy minimized structure of $Pd(L^*)_2$(olefin) complex.

Table 1. Pd-catalyzed asymmetric allylic alkylation–desymmetrization of **1** with dibenzyl malonate



1 **5**

Entry	Ligand	Conv.[a] (%)	**5** (% ee)[b]
1	(*R*)-**L1**	80	28.7 (−)
2	(*S*)-**L2**	82	48.1 (+)
3	(*S*,*R*,*R*)-**L4a**	70	68.4 (+)
4	(*R*,*R*,*R*)-**L5a**	82	81.3 (−)
5	(*R*,*R*,*R*)-**L5b**	50	10.8 (−)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using a Daicel Chiralpak AD column.

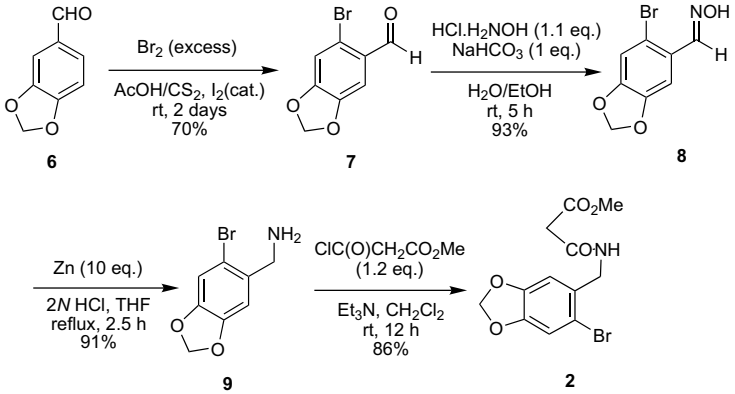
fin. It is clearly indicated that the dimethylamine moiety would play a key role in differentiating the two benzoate groups. Accordingly, we hypothesized that the stereoelectronic nature of the amine moiety of our phosphoramidite ligands would exert a critical effect on the enantioselectivity of the desymmetrization reaction.

With this hypothesis in mind, the Pd-catalyzed asymmetric allylic alkylation–desymmetrization of **1** with dibenzyl malonate, as a model study, was carried out for preliminary screening of effective phosphoramidite ligands. The results are summarized in Table 1. Since $[Pd(allyl)Cl]_2$ gave better results than $Pd(OAc)_2$ as the Pd-catalyst precursor, only the results with the use of $[Pd(allyl)Cl]_2$ are presented.

As Table 1 shows, a substantial increase in enantioselectivity for the formation of **5** is observed as the size of the amine moiety of the phosphoramidite ligand increases, that is, from **L1** with the smallest Me_2N moiety (28.7% ee) to **L5a** with the bulkiest $(PhMeCH)_2N$ moiety (81.3% ee) (R^2 = H in all cases). It is noteworthy that (i) the ligands with a (*S*)-biphenol moiety give the (+)-enantiomer of **5** as the major product, while that with a (*R*)-biphenol moiety affords (−)-**5** as the major product, that is, the axial chirality of the ligand controls the direction of enantio-discrimination of the two benzoate leaving groups, and (ii) introduction of methyl groups at the 3,3′-positions of the biphenyl moiety of **L5a** (i.e., **L5b**, R^2 = Me) causes a detrimental effect on the enantioselectivity as well as the conversion of the reaction. These observations are consistent with indications based on the molecular modeling of the complex shown in Figure 3. These preliminary results served as the starting point of our total synthesis of enantiopure (+)-γ-lycorane.

According to our planned route to (+)-γ-lycorane through revisiting Mori's first asymmetric synthesis, it was necessary to prepare nucleophile **2**, which is a malonate half amide. Since the synthesis of **2** was not reported in Mori's paper, or anywhere else by literature search, we synthesized **2** from commercially available piperonal **6** through the steps shown in Scheme 3. All attempted reductive amination of **7** to **9** failed because of a very facile coupling of aldehyde **7** with amine **9** formed in the reaction. Thus, we had to convert **7** to oxime **8** first, followed by reduction with zinc/HCl, to obtain **9** in excellent yield. Amine **9** was reacted with methyl malonyl chloride to give **2** in 86% yield.

Next, the efficacy of phosphoramidite ligands **L4a** and **L5a**, which gave promising results in the model study (Table 1), as well as **L3** was evaluated in the asymmetric



Scheme 3. Synthesis of nucleophile **2**.

allylic alkylation–desymmetrization reaction of **1** with 'real' nucleophile **2**. The reactions of **1** were run using 2.6 equiv of **2** and LDA in the presence of Pd-catalyst, prepared by mixing $[Pd(allyl)Cl]_2$ (2 mol %) with a ligand (8 mol %), in THF/CH_3CN (1:1) at 0 °C. The reactions gave a 54/46 diastereomer mixture of **3** due to epimerization of the acidic methine of the malonate half amide moiety. Thus, the additional two steps, leading to **10**, were necessary to determine the enantioselectivity of the reaction. The enantiopurity of **10** was unambiguously determined by chiral HPLC analysis using a Daicel Chiralpak AD-RH column. As Table 2 shows, **L5a** gave the best results (68% ee) among the three ligands examined (entries 1–3) under these conditions. The use of ligand **L5b** (R^2 = Me) led to almost no conversion, indicating a detrimental effect of the methyl groups at the 3,3′-positions of the biphenol moiety on the reaction (entry 4). Accordingly, we carried out the optimization of reaction conditions using **L5a** as the ligand. The reaction in THF at −78 to 0 °C for 12 h (started at −78 °C using 1.2 equiv of **2** and LDA, followed by warming up to 0 °C) gave **3** with 84.4% ee in 95% isolated yield (entry 5). Thus, the solvent and the reaction temperature appear to have dramatic effects on the reaction. When the reaction temperature was kept constant at −60 °C, the reaction completed in 15 h to give **3** in 93% yield and 86.2% ee (entry 6). We also examined the effects of the amounts of **2** and LDA on the reaction in THF at −60 °C. The reactions with 2.0 and 2.6 equiv of **2** and LDA gave **3** with 89.5% ee and 92.6% ee, respectively (entries 7 and 8). [Note: **L6** (*S*,*S*,*S*) is the enantiomer of **L5a**.] The results indicate that the use of excess amounts of **2** and LDA increases the enantioselectivity of the reaction. However, the observed increase in enantioselectivity is accompanied by a significant decrease in the yield of **3**.

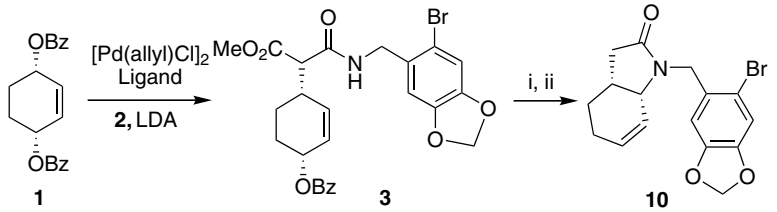
We found that the observed decrease in the yield of **3** was associated with the formation of dialkylated product **11**. This side product **11** was obviously obtained from the second allylic alkylation reaction of **3** with **2**. Naturally, the amount of **11** increases on using excess **2** and LDA. However, how is the increase in the enantiopurity of **3** related to the formation of **11**? We believe that enantiomer-selective kinetic resolution by the chiral Pd catalyst is taking place in the second allylic alkylation of **3** with **2**. A proposed mechanism is illustrated in Figure 4.

It is reasonable to hypothesize that the minor enantiomer of **3** yielded in the first asymmetric allylic alkylation, *ent*-**3**, reacts with chiral Pd complex much faster than **3** to form the corresponding π-allylic Pd-complex, which reacts with **2** to afford the dialkylated product **11**. This is because the remaining benzoate group in *ent*-**3** is the preferred leaving group for the chiral Pd-catalyst. Accordingly, enrichment of **3** may occur through selective conversion of *ent*-**3** to **11**, but decrease in the yield of **3** would be inevitably accompanied.

Although it was already a remarkable improvement that **3** was obtained in 93% isolated yield and 86.2% ee as compared with Mori's original work (40% ee in 66% yield or 54% ee in 30% yield),[49] we strongly felt that more improvement would be possible through systematic optimization of **L6** (*S*,*S*,*S*), which gives **3** with the correct absolute configuration for the total synthesis of (+)-γ-lycorane. Accordingly, we designed and synthesized a new optimization library of phosphoramidite ligand **L6** by introducing various C_2-symmetric, pseudo-C_2-symmetric and non-symmetrical *N*,*N*-bis(1-arylethyl)amine moieties bearing different aryl groups, including those with an *ortho* substituent (ligands **L7**–**14**, Fig. 2).

For the introduction of *ortho* substituents to the C_2- and pseudo-C_2-symmetric *N*,*N*-bis(1-arylethyl)amine moiety of BINOL-based phosphoramidite ligands, Alexakis et al. recently reported the markedly favorable effects of such substituents on the enantioselectivity as well as

Table 2. Pd-catalyzed asymmetric allylic alkylation–desymmetrization of **1** with nucleophile **2** using ligands **L3**, **L4a**, **L5a**, **L5b**, and **L6**



1 **3** **10**

Entry	Ligand	**2** (equiv)	Conditions	Yield[a] (%)	**10** (% ee)[b]
1	**L4a**	2.6	THF/CH_3CN, 0 °C to rt, 1.5 h	46	31.3 (+)
2	**L3**	2.6	THF/CH_3CN, 0 °C to rt, 1.5 h	58	42.1 (+)
3	**L5a**	2.6	THF/CH_3CN, 0 °C to rt, 1.5 h	62	68.0 (−)
4	**L5b**	2.6	THF/CH_3CN, 0 °C to rt, 1.5 h	Low conv.	NA
5	**L5a**	1.2	THF, −78 to 0 °C, 12 h	95	84.4 (−)
6	**L5a**	1.2	THF, −60 °C, 15 h	93	86.0 (−)
7	**L6**	2.0	THF, −60 °C, 15 h	63	89.5 (+)
8	**L5a**	2.6	THF, −60 °C, 20 min	27	92.6 (−)

(i) $[Pd(allyl)Cl]_2$, dppb, LDA, CH_3CN–THF, −50 °C to rt, 2.5 h; (ii) NaCl, DMSO–H_2O, 175 °C, 2.5 h.

[a] Isolated yield of **3**.

[b] Determined by chiral HPLC analysis using a Daicel Chiralpak AD-RH column.

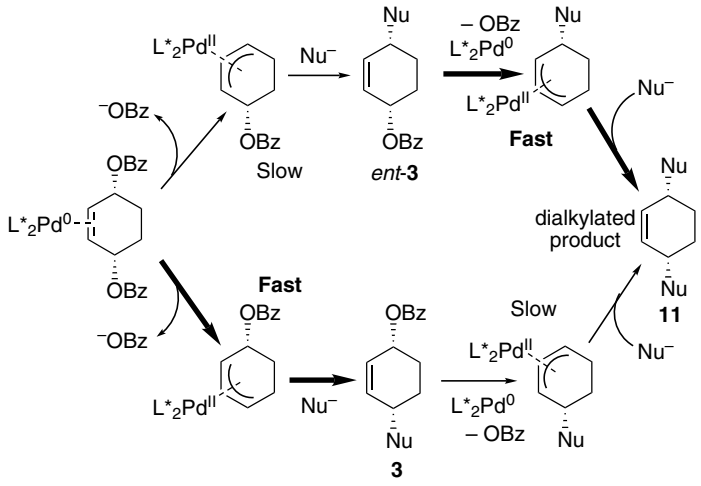


Figure 4. Proposed mechanism for the formation of the dialkylated product.

reaction rate in their Ir-catalyzed asymmetric allylic substitution reactions.[25,51] Thus, we set out to examine the *ortho* substitution effect in our biphenol-based ligand–Pd-catalyst system. In addition, we also designed non-symmetrical *N*,*N*-bis(1-arylethyl)amine moieties based on a combination of different aryl groups, that is, phenyl, *o*-tolyl, *o*-methoxyphenyl, 1-naphthyl, and 2-naphthyl groups.

The efficacy of **L6** congeners was examined in the Pd-catalyzed reaction of **1** with **2** using $[Pd(allyl)Cl]_2$ and 1.2 equiv of **2** and LDA in THF at −60 °C for 15 h. In each case, the amount of the dialkylated product was also determined. The separation of **3** and the dialkylated product **11** was performed. The enantioselectivity of the reaction was determined by converting **3** to **10** in the same manner as that described above (see Table 2). The results are summarized in Table 3.

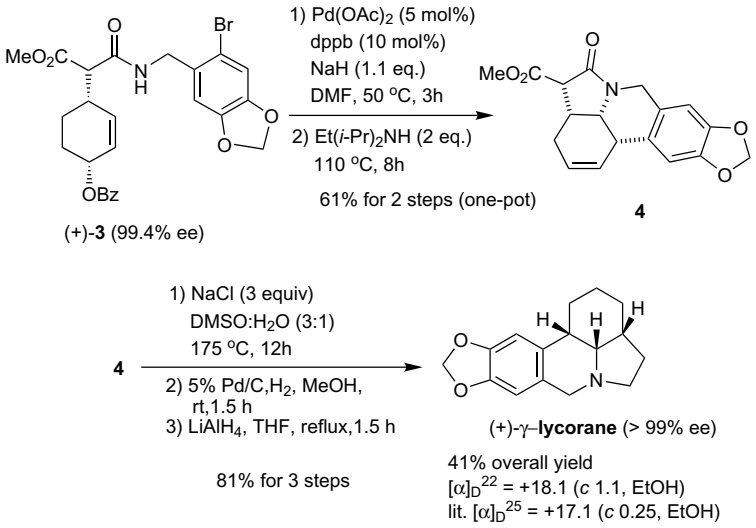
Table 3. Pd-catalyzed asymmetric allylic alkylation–desymmetrization of **1** with **2** using a focused library of **L6** congeners[a]

Entry	Ligand	**3** (%)[b]	**11** (%)[b]	**3** (% ee)[c]
1	**L5a**	93	6	86.2 (−)
2	**L7**	<5% conv.	—	—
3	**L8**	92	7	85.5 (+)
4	**L9**	85	13	83.0 (+)
5[d]	**L10**	**76**	19	**99.7** (+)
6	**L11**	<5% conv.	—	—
7[d]	**L12**	**83**	16	**99.4** (+)
8	**L13**	0% conv.	—	—
9	**L14**	<5% conv.	—	—
10[e]	**L14**	43 (72% conv.)	29	n.d.[f]

[a] Reactions were run with 100 mg (0.31 mmol) of **1**, $[Pd(allyl)Cl]_2$ (2 mol %), a ligand (8 mol %), **2** (1.2 equiv), LDA (1.2 equiv) in THF at −60 °C for 15 h unless otherwise noted.
[b] Isolated yield.
[c] Estimated based on the enantiopurity of **10** determined by chiral HPLC analysis using a Daicel Chiralpak AD-RH column.
[d] Reaction time was 8 h.
[e] Reaction was run at −30 °C for 24 h.
[f] n.d. = not determined.

As Table 3 shows, a very interesting and rather unanticipated substituent effect of the aryl groups of the amine moiety on the enantioselectivity as well as catalytic activity is observed. First of all, the markedly contrasting results for the use of **L7** ($R^3 = R^{3'} =$ 1-Np) and **L8** ($R^3 = R^{3'} =$ 2-Np) are worth mentioning (entries 2 and 3). The result for **L8** is similar to that for **L6** with 85.5% ee (entries 3 and 1), while the reaction with **L7** almost did not proceed under the same conditions and no change was observed even when forcing the reaction at room temperature. The result for **L7** appears to indicate that the reaction is very sensitive to the bulkiness and arrangement of the aryl moiety at the coordination site. Even one 1-naphthyl group seems sufficient to kill the Pd-catalyst activity. Thus, the reaction using **L11** ($R^3 =$ 1-Np, $R^{3'} =$ 2-MeO–Ph) virtually did not proceed (entry 6). To our surprise, ligands **L13** and **L14**, bearing C_2-symmetric *N*,*N*-bis(1-arylethyl)amine moieties, behaved very poorly, resulting in no conversion (entry 8) and <5% conversion (entry 9), respectively. Even when the reaction with **L14** was carried out at −30 °C for 24 h, the reaction did not complete (72% conversion) and formed a large quantity of the dialkylated side product **11** (entry 10). These results are unanticipated, since the same amine moieties were reported to give excellent results in the Ir-catalyzed reactions with BINOL-based ligands.[25,31]

A breakthrough in the enantioselectivity was achieved by ligands **L10** ($R^3 =$ 2-MeO–Ph, $R^{3'} =$ Ph) and **L12** ($R^3 =$ 2-MeO–Ph, $R^{3'} =$ 2-Np), bearing non-symmetrical *N*,*N*-bis(1-arylethyl)amine moieties wherein one of the aryl groups is 2-MeO-phenyl. The reactions with **L10** and **L12** gave **3** with 99.7% ee (76% yield) and 99.4% ee (83% yield), respectively (entries 5 and 7). Both reactions reached 100% conversion in 8 h. Formation of **11** was 19% for the reaction with **L10** and 16% for that with **L12**. Accordingly, a certain level of enantiomer enrichment, mentioned above, may have taken place in these cases, which has contributed to the achievement of extremely high enantioselectivity observed. It appears that 2-methoxyphenyl group in the non-symmetrical



Scheme 4. Completion of the total synthesis of enantiopure (+)-γ-lycorane from (+)-**3**.

N,*N*-bis(1-arylethyl)amine moiety has a profound effect on the enantioselectivity and reaction rate. It is possible to hypothesize that the oxygen of 2-methoxyphenyl group interacts with the Pd metal to fix the orientation of the phenyl ring, which has a crucial effect on the enantio-differentiation (desymmetrization) of the two benzoate groups in *meso*-**1**. Since the isolation of **3** from the reaction mixture is very easy, the reaction with **L12** provides a highly practical process for the total synthesis of enantiopure (+)-γ-lycorane.

The total synthesis of (+)-γ-lycorane was completed, following Mori's procedure with some modifications as shown in Scheme 4. As Scheme 4 illustrates, **3** (99.4% ee) was converted to pentacyclic oxo-lycorane **4** in 61% yield through one-pot tandem allylic amination–intramolecular Heck reaction. Then, **4** was subjected to the sequential demethoxycarbonylation, hydrogenation, and $LiAlH_4$-reduction to give the desired (+)-γ-lycorane (>99% ee) in 41% overall yield (six steps) from **1**.

This successful total synthesis of enantiopure (+)-γ-lycorane demonstrates the advantage of the fine-tuning capability of our novel phosphoramidite ligands in developing extremely efficient ligand for a specific asymmetric transformation through optimization of a lead ligand by rational design.

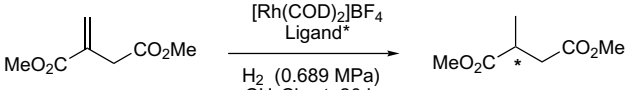
2.3. Asymmetric hydrogenation of dimethyl itaconate

Recently, chiral monodentate phosphorus ligands have shown high efficiency in the asymmetric hydrogenation of prochiral olefins.[7–9,13] Since the early work of Reetz and Mehler,[51] Feringa and co-workers,[7,52] and Claver et al.,[53] a number of new monodentate phosphorus ligands have been developed.[4,7–13,54] However, newer and more efficient chiral ligands along this line are clearly needed to achieve excellent enantiopurity and high catalyst efficiency for particular substrates and reactions. We describe here the application of a new class of chiral biphenol-based monophosphite ligands[13] to the Rh(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate and discussions about the possible active catalyst species.

As shown in Figure 2, we have designed and synthesized a library of novel biphenol-based monophosphite ligands bearing different alkoxy and aryloxy moieties along with different substituents at the 3,3′-positions (**L15**–**L20**).[13]

First, the reactions were carried out using ligands **L15**–**L19**, **L20a** and $[Rh(COD)_2]BF_4$ in CH_2Cl_2 at room temperature and 0.689 MPa of H_2 for 20 h. The results are summarized in Table 4.

Table 4. Asymmetric hydrogenation of dimethyl itaconate catalyzed by monodentate phosphite–$[Rh(COD)_2]BF_4$[a]



Entry	Ligand	Conv. (%)[b]	% ee[b,c]
1	**L15a**	90	14.0 (*R*)
2	**L15b**	100	96.5 (*S*)
3	**L16a**	97	19.0 (*R*)
4	**L16b**	100	96.4 (*S*)
5	**L17a**	100	25.0 (*R*)
6	**L17b**	100	92.0 (*S*)
7	**L18a**	100	44.0 (*S*)
8	**L18b**	100	93.0 (*R*)
9	**L17c**	3.5	24.3 (*R*)
10	**L18c**	4.3	32.0 (*S*)
11	**L19a**	<1	—
12	**L19b**	<1	—
13	**L20a**	<1	—

[a] Reactions were run in CH_2Cl_2 at 23 °C and 0.689 MPa of H_2 for 20 h [substrate (0.5 mmol, 0.1 M)/$[Rh(COD)_2]BF_4$/ligand = 200:1:2].
[b] Conversion and enantiopurity were determined by GC analysis.
[c] The absolute configuration was determined by comparing the chiral GC spectra with those of authentic samples.

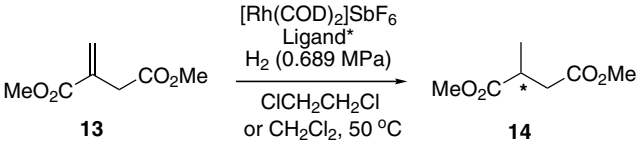
As Table 4 shows, the Rh catalysts with ligands **L15b**–**L18b** ($R^2 = H$) exhibited excellent enantioselectivity (92–96.5% ee) along with complete conversion (entries 2, 4, 6, and 8). However, the Rh-catalyst with ligands bearing a *tert*-butyl group at the 3,3′-positions of the biphenol moiety (**L15**–**L19**, **L20a**, **L17c**, and **L18c**) exhibited poor to excellent catalyst activity and low to moderate enantioselectivity (entries 1, 3, 5, 7, 9–11, and 13). The introduction of (−)-menthol as a chiral alkoxy moiety (**L17b** and **L18b**) did not improve the enantioselectivity as compared to that achieved by the use of **L15b** and **L16b**, which contain an achiral aryloxy moiety (entries 6 and 8 vs entries 2 and 4). Furthermore, the diastereomeric ligands **L17b** (*S*-biphenyl) and **L18b** (*R*-biphenyl) bearing the same (−)-menthol moiety gave virtually the same level of enantioselectivity (entries 6 and 8). Accordingly, it appears that the chiral alkoxy moiety has little effect on the enantioselectivity. In sharp contrast, substitution at the 3,3′-positions of the biphenol moiety exerts a critical influence on the direction and the extent of the asymmetric induction. Thus, the ligands bearing a hydrogen at the 3,3′-positions (**L15b**, **L16b**, **L17b**, and **L18b**) show excellent enantioselectivity (92.0–96.5% ee), giving (*S*)-methylsuccinate [(*R*) for **L18b**] (entries 2, 4, 6, and 8). However, the ligands with a *tert*-butyl group at the 3,3′-positions (**L15a**, **L16a**, **L17a**, and **L18a**) show a reversal in the direction of asymmetric induction to afford (*R*)-dimethylsuccinate with low to moderate enantiopurity (14–44% ee) [(*S*) for **L18a**] (entries 1, 3, 5, and 7). The ligands, **L17c** and **L18c**, bearing a phenylmenthyloxy group exhibited very low conversion and enantioselectivity, but the ligands bearing a bulky 2-phenylcyclohexyloxy group (**L19a**, **L19b**, and **L20a**) did not show any appreciable activity under the same conditions (entries 9–13).

Next, we examined the effects of Rh-catalyst precursor species and solvents on the catalytic activity and enantioselectivity. The reaction temperature was increased to 50 °C by taking into account the poor catalyst activity on using bulky ligands. As Rh-catalyst precursors, $[Rh(COD)_2]SbF_6$, $[Rh(NBD)_2]ClO_4$, and $[Rh(COD)_2]OTf$ were examined in place of $[Rh(COD)_2]BF_4$.

It is worth mentioning that the reactions using $[Rh(COD)_2]SbF_6$ gave markedly different results from those using $[Rh(COD)_2]BF_4$ as shown in Table 4, especially when bulky ligands bearing a *tert*-butyl group at the 3,3′-positions (**L17c**, **L18c**, **L19a**, and **L20a**) were used. The results are listed in Table 5. As Table 5 shows, these bulky ligands achieved excellent enantioselectivity (94.4–99.6% ee) and complete conversion when the reactions were carried out in CH_2Cl_2 or $ClCH_2CH_2Cl$ at 50 °C (entries 5–12). On the contrary, the ligands bearing an aryloxy moiety (**L15a** and **L16a**) or (−)-menthyloxy moiety (**L17a** and **L18a**) did not show any improvement (entries 1–4). Nevertheless, in all cases, the catalytic activity was greatly improved, affording the product in quantitative yield.

These results clearly indicate a remarkable effect of the counteranion of the cationic Rh catalyst species on the catalytic activity as well as enantioselectivity. Accordingly, we examined the effect of other counterions, using $[Rh(NBD)_2]ClO_4$ and $[Rh(COD)_2]OTf$ as catalyst precursors and **L20a** as the chiral ligand in CH_2Cl_2 under the same conditions (see footnote a of Table 5). To our surprise, no enantioselectivity was observed although the reaction proceeded in 100% conversion in each case. Moreover, the reactions using $[Rh(COD)_2]BF_4$ with **L19a** and **L20a** under the same conditions gave racemic methylsuccinate in 100% and 3.8% yields, respectively. These results confirmed the remarkable and unanticipated effect of counterions in this asymmetric catalysis.

Table 5. Asymmetric hydrogenation of dimethyl itaconate using $[Rh(COD)_2]SbF_6$ with monodentate phosphite ligands[a]



Entry	Ligand	Solvent	Conv. (%)[b]	% ee[b,c]
1	**L15a**	CH_2Cl_2	100	16.4 (*R*)
2	**L16a**	CH_2Cl_2	100	22.5 (*R*)
3	**L17a**	CH_2Cl_2	100	14.5 (*R*)
4	**L18a**	CH_2Cl_2	100	9.3 (*S*)
5	**L17c**	CH_2Cl_2	100	94.4 (*R*)
6	**L18c**	CH_2Cl_2	100	97.6 (*S*)
7	**L19a**	CH_2Cl_2	100	97.8 (*R*)
8	**L20a**	CH_2Cl_2	100	**99.0** (*R*)
9	**L17c**	$ClCH_2CH_2Cl$	100	98.9 (*R*)
10	**L18c**	$ClCH_2CH_2Cl$	100	98.7 (*S*)
11	**L19a**	$ClCH_2CH_2Cl$	100	**99.6** (*R*)
12	**L20a**	$ClCH_2CH_2Cl$	100	**99.1** (*R*)

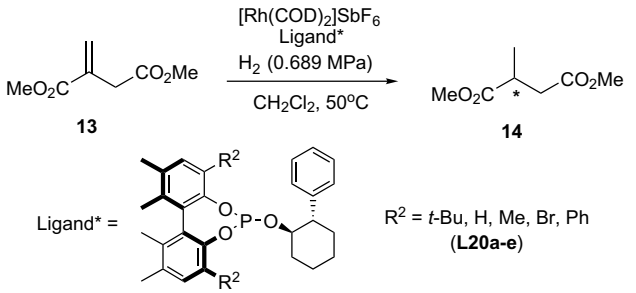
[a] The reaction was performed at 50 °C and 0.689 MPa of H_2 for 20 h [substrate (0.5 mmol, 0.1 M)/$[Rh(COD)_2]SbF_6$/ligand = 200:1:2].
[b] Conversion and enantiopurity were determined by GC analysis.
[c] The absolute configuration was determined by comparing chiral GC spectra with those of authentic samples.

We also examined the effect of solvents on the reaction using $[Rh(COD)_2]SbF_6$ and **L20a** and **L19a** (only for $CHCl_3$). To our surprise, the reactions under the same conditions mentioned above in MeOH (82.3% conv.), THF (100% conv.), toluene (30.7% conv.), EtOAc (91.2% conv.), and $CHCl_3$ (1.2% conv. using **L19a**) did not exhibit any enantioselectivity, yielding racemic product. Thus, it appears that this process using $[Rh(COD)_2]SbF_6$ as the catalyst precursor with chiral monodentate phosphite ligands is effective only in chlorine-containing solvents, that is, CH_2Cl_2 and $ClCH_2CH_2Cl$. Similar solvent effects were recently reported for BINOL-based phosphoramidite ligands.[7] These results would provide us with very important information about the nature of active catalyst species.

Next, we investigated the effect of the substituent at the 3,3′-positions of the biphenol moiety on the enantioselectivity and catalytic activity, using **L20** series. Thus, in addition to a *t*-Bu group (**L20a**), H (**L20b**), Me (**L20c**), Br (**L20d**), and Ph (**L20e**) were introduced as R^2 (Fig. 2). The reactions were carried out in CH_2Cl_2 under the same conditions mentioned above. The results

are listed in Table 6. As Table 6 shows, the bulkiness of R^2 exerts a critical effect on the enantioselectivity as well as the direction of asymmetric induction. Thus, the enantioselectivity decreases in accordance with the change in the size of the substituent from large to small, that is, in the order *t*-Bu, Ph, Br, Me, and H. In the case of **L20b** (R^2 = H), the reaction did not complete and the other enantiomer, that is, (*S*)-methylsuccinate, was obtained with only 2.7% ee. These results reconfirm the salient feature of our chiral monodentate phosphorus ligands that have a fine-tuning capability.

Table 6. Asymmetric hydrogenation of dimethyl itaconate using $[Rh(COD)_2]SbF_6$ with ligands **L20a–e**[a]



Entry	Ligand	R^2	Conv.[b] (%)	% ee[b,c]
1	**L20a**	*t*-Bu	100	99.0 (*R*)
2	**L20b**	H	81	2.7 (*S*)
3	**L20c**	CH_3	100	76.9 (*R*)
4	**L20d**	Br	100	97.1 (*R*)
5	**L20e**	C_6H_5	100	97.8 (*R*)

[a,b,c] See the footnotes of Table 5.

Since the emergence of chiral monodentate phosphorus ligands in asymmetric catalytic transformations, several studies have been performed by means of X-ray crystallography,[7,12,53,54] NMR,[53,55] and mass spectrometric analyses.[7] It is believed that two chiral monodentate phosphorus ligands would bind to the Rh metal to form an active catalyst species.[53,54] In order to shed light on the possible structure of active catalyst species, we examined the ligand to Rh ratio on the enantioselectivity of this reaction and also analyzed their structures by ^{31}P NMR. For these experiments, two ligands, **L18b** (R^2 = R = H) and **L18c** (R^2 = *t*-Bu, R = Ph), possessing very different bulkiness to each other, were used. The reaction with Rh-**L18b** catalyst was run using $[Rh(COD)_2]BF_4$ as the catalyst precursor in CH_2Cl_2 at room temperature for 20 h, while that with Rh-**L18c** was carried out using $[Rh(COD)_2]SbF_6$ as the catalyst precursor in CH_2Cl_2 at 50 °C for 20 h. The results of the asymmetric hydrogenation of dimethyl itaconate with different ligand/Rh ratios are listed in Table 7.

As Table 7 shows, the reactions using 1 or 2 equiv of **L18b** to Rh gave (*R*)-methylsuccinate with the same enantiopurity (93% ee) in quantitative yield (entries 1 and 2). However, both catalyst activity and enantioselectivity decreased considerably when 3 equiv of **L18b** to Rh was used (7.0% conversion, 57.8% ee) (entry 3). A similar phenomenon has recently been reported in the hydrogenation of a dehydroamino acid using a

Table 7. Effect of ligand/Rh ratio on the enantioselectivity and conversion of the asymmetric hydrogenation of dimethyl itaconate

Entry	Ligand	L/Rh	Conv. (%)[c]	% ee[c,d]
1	**L18b**[a]	1	100	93.0 (*R*)
2	**L18b**[a]	2	100	93.0 (*R*)
3	**L18b**[a]	3	7.0	57.8 (*R*)
4	**L18c**[b]	1	100	98.7 (*S*)
5	**L18c**[b]	2	100	98.8 (*S*)
6	**L18c**[b]	3	100	98.6 (*S*)

[a] See footnote a of Table 4.
[b] See footnote a of Table 5.
[c] Conversion and enantiopurity were determined by GC analysis.
[d] The absolute configuration was determined by comparing chiral GC spectra with those of authentic samples.

BINOL-based monodentate phosphoramidite ligand.[7] In sharp contrast to the **L18b** case, the ligand/Rh ratio did not have any appreciable influence on the enantioselectivity and conversion when the bulky ligand **L18c** was used. Thus, the reactions gave (*S*)-methylsuccinate with 98.6–98.8% ee in quantitative yield.

These results are intriguing in that two ligand–Rh complex systems show very different behaviors that may be arising from the bulkiness of the chiral ligands as well as the nature of the counterions. Accordingly, we set out to investigate the Rh-ligand species in solution by means of ^{31}P NMR analysis. Figures 5 and 6 show the ^{31}P NMR spectra of **L18b**–$[Rh(COD)_2]BF_4$ complexes and **L19a**–$[Rh(COD)_2]SbF_6$ complexes, respectively, with different Rh/ligand ratios in CD_2Cl_2 at room temperature.

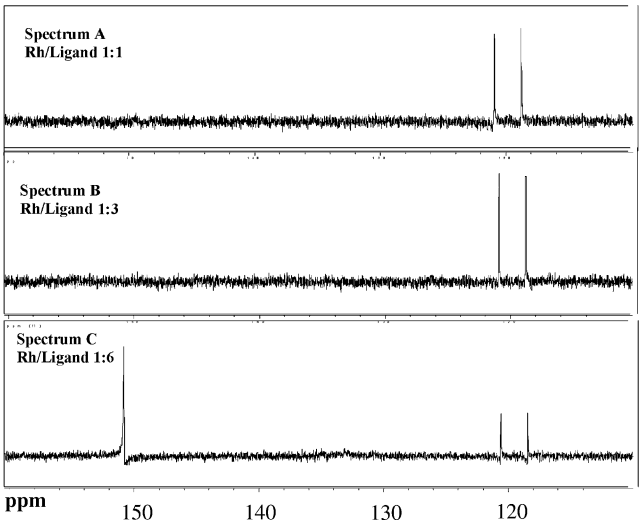


Figure 5. ^{31}P NMR of rhodium complexes with **L18b**. The samples were prepared by mixing $[Rh(COD)_2]BF_4$ with **L18b** at different ratios in CD_2Cl_2. ^{31}P NMR spectra were measured at rt.

As shown in Figure 5, only one doublet (δ 120 ppm, J = 259 Hz) for a **L18b**–$[Rh(COD)_2]BF_4$ complex appeared with the ligand/Rh ratio of 1 (Spectrum A) and 3 (Spectrum B). A tiny peak of the free ligand was observed at δ 151 ppm at the ratio of 4 and became clearly visible when the ratio was increased to 6 (Spectrum C).

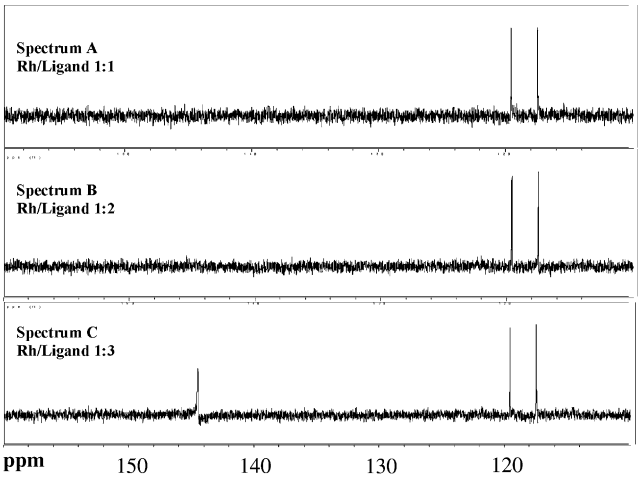


Figure 6. ^{31}P NMR of rhodium complexes with ligand **L19a**. The samples were prepared by mixing $[Rh(COD)_2]SbF_6$ with ligand **L19a** at different ratios in CD_2Cl_2. ^{31}P NMR spectra were measured at rt.

As shown in Figure 6, in the case of **L19a**–$[Rh(COD)_2]$-SbF_6 combinations, only one doublet appeared at almost the same position as that shown in Figure 5 (δ 118.5 ppm, $J = 255$ Hz) when the ligand/Rh ratio was 1 (Spectrum A) or 2 (Spectrum B). However, the peak of the free ligand was clearly observed at δ 144.5 ppm when the ratio was increased to 3.

The results for the **L19a**–$[Rh(COD)_2]SbF_6$ system seem straightforward in that a $(ligand)_2Rh^+$ species is formed selectively even when 1 equiv of the ligand to Rh is used, and a $(ligand)_3Rh^+$ species is not formed when 3 equiv of the ligand to Rh is present in the system because of the bulkiness of the ligand. Thus, it is reasonable to assume that $[(\mathbf{L19a})_2Rh(S)]^+SbF_6^-$ (S = solvent or COD) is formed. This complex should have a C_2-symmetry with two magnetically equivalent phosphorus nuclei, since no P–Rh–P coupling is observed.

The results for the **L18b**–$[Rh(COD)_2]BF_4$ system are, however, more complicated. From the result presented in Table 7, it is clear that a $(ligand)_3Rh^+$ species is generated in this system in the presence of molecular hydrogen, which has much less catalytic activity than the corresponding $(ligand)_2Rh^+$ species because of excessive congestion in the coordination site for this reaction. The enantioselectivity is also markedly decreased. Nevertheless, Spectrum B in Figure 5 does not show the formation of such $(ligand)_3Rh^+$ species. The existence of free ligand becomes clear only after adding 6 equiv of the ligand to Rh (Spectrum C, Fig. 5). The possible interpretations of the phenomena are as follows: (i) The $[(ligand)_2Rh(S)]^+BF_4^-$ species is formed as a stable complex in the same way as that in the **L19a**–$[Rh(COD)_2]SbF_6$ system. (ii) The $(ligand)_3Rh^+$ species is partially formed at the ligand/Rh ratio of 3, but this species is in equilibrium with the $(ligand)_2Rh^+$ species and free ligand at room temperature, which may be near the coalescence temperature of this equilibrium. This is why the $(ligand)_3Rh^+$ species is not visible. (iii) The equilibrium between the $(ligand)_2Rh^+$ species and the $(ligand)_3Rh^+$ species is slow or the formation of the $(ligand)_3Rh^+$ species is unfavorable in the absence of molecular hydrogen that would eliminate COD from the Rh coordination site. (iv) An appreciable bump appears around δ 133 ppm, which might be attributed to the $(ligand)_4Rh^+$ or $(ligand)_3Rh^+$ species in equilibrium with free ligand. Although these interpretations are still speculative in nature, these findings and interpretations warrant further mechanistic studies in these catalyst systems.

3. Conclusion

A series of novel monodentate phosphite and phosphoramidite ligands based on axially chiral biphenol have been developed and applied to asymmetric allylic alkylation and hydrogenation reactions. The salient features of these ligands include easy preparation and modification, enabling de facto fine-tuning capability of these ligand systems. The advantage of the fine-tuning capability has been demonstrated in the two asymmetric transformations presented here, that is, the best-fit ligands for particular reaction-types and their substrates have been successfully developed through rational optimization of lead ligands. It is worth mentioning that the substituents at the 3,3′-positions of the biphenol moiety exert a critical influence on the enantioselectivity and catalyst activity. The alcohol and amine moieties for phosphites and phosphoramidites, respectively, are also of critical importance for the efficacy of the chiral ligands. A short total synthesis of enantiopure (+)-γ-lycorane was successfully completed using highly efficient asymmetric allylic alkylation–desymmetrization reaction in the key step. Some insight into the active catalyst species in the asymmetric hydrogenation was obtained though more studies are necessary. Further investigations into the expansion of the ligand library as well as its applications to a variety of catalytic asymmetric transformations are actively underway in our laboratory.

4. Experimental

4.1. General method and material

^1H, ^{13}C, and ^{31}P NMR spectra were measured on a Varian Inova-400 NMR (400 MHz ^1H, 100 MHz ^{13}C, and 162 MHz ^{31}P), a Varian Inova-500 NMR (500 MHz ^1H), or a Varian Gemini-2300 (300 MHz ^1H, 75 MHz ^{13}C, and 121 MHz ^{31}P) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: 7.26 ppm ^1H, 77.0 ppm ^{13}C; C_6H_6: 7.15 ppm ^1H) as the internal standard or phosphoric acid as the external reference (0.0 ppm). Analytical gas chromatography was performed with a Hewlett–Packard 5890 Series II gas chromatograph (FID) system using a Supelco Beta Dex-225 chiral column. Analytical HPLC was carried out with a Shimadzu LC-2010A HPLC system using a Chiralpak ADRH column. Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured

on a Perkin–Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and flash chromatography was carried out on silica gel 60 (Silicyle; 40–63 μm particle size). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL. All reactions were carried out under argon or nitrogen atmosphere in oven-dried glassware using standard Schlenck techniques unless otherwise noted. The solvents were of reagent grade and were freshly distilled before use. Tetrahydrofuran was distilled from sodium/benzophenone under nitrogen. Acetonitrile and dichloromethane were distilled from calcium hydride. Anhydrous *N*,*N*-dimethyl formamide was purchased from DrySolv® and used without further purification. Enantiopure *N*,*N*-bis(1-arylethyl)amines were synthesized, following the reported procedure and were in full agreement with the reported data.[30,31] *N*,*N*-[(*S*)-1-(Naphthalen-2-yl)-ethyl][(*S*)-1-(2-methoxyphenyl)ethyl]-amine had not been previously reported and was synthesized using the same method.[31] 1,4-*cis*-Dibenzoyloxycyclohex-2-ene **1**[56] and 6-bromopiperonal **7**[57] were prepared by the literature methods.[57] Cationic rhodium complexes, $[Rh(COD)_2]$-BF_4 and $[Rh(COD)_2]SbF_6$, were prepared following the literature method.[58]

4.1.1. *N*,*N*-[(*S*)-1-(Naphthalen-2-yl)ethyl][(*S*)-1-(2-methoxy-phenyl)ethyl]amine. The crude amine was synthesized according to the literature procedure for this class of compounds,[31] starting from (*S*)-1-(naphthalen-2-yl)ethyl amine (99.0%) and 2-methoxyacetophenone. The crude amine, thus obtained, was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 10:1 then 8:1) to give diastereoisomerically pure amine as a light yellow oil (69% yield): $[\alpha]_D^{22} = -187$ (*c* 1.66, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, $J = 6.6$ Hz, 3H), 1.36 (d, $J = 6.6$ Hz, 3H), 1.92 (br s, 1H), 3.70 (q, $J = 6.6$ Hz, 1H), 3.74 (s, 3H), 3.79 (q, $J = 6.6$ Hz, 1H), 6.88–6.98 (m, 2H), 7.15 (dd, $J = 1.5$, 7.2 Hz, 1H), 7.14–7.27 (m, 1H), 7.43–7.49 (m, 3H), 7.62 (s, 1H), 7.78–7.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 25.07, 51.59, 55.10, 55.45, 110.69, 120.58, 125.22, 125.24, 125.50, 125.70, 127.52, 12761, 127.70, 127.92, 127.95, 132.79, 133.29, 133.47, 143.41, 157.53. HRMS (EI) calcd for $C_{21}H_{23}NO$ $[M]^+$ 305.1772; found 305.1779 ($\Delta = 2.2$ ppm).

4.2. General procedure for the preparation of phosphoramidite ligands

Phosphorous trichloride (87 μL, 1.0 mmol) was added dropwise to Et_3N (70 μL, 5 mmol) at 0 °C under N_2. To this mixture, a solution of amine (1.0 mmol) was added in THF (2 mL). The mixture was stirred at room temperature and monitored by ^{31}P NMR until the peak of the aminophosphorous dichloride was solely observed together with the disappearance of the peak of PCl_3. The mixture was then cooled to 0 °C and a solution of 5,5′,6,6′-tetramethylbiphenyl-2,2′-diol (1.0 mmol, 242 mg) in THF (3 mL) was added. The resulting mixture was stirred for 12 h at room temperature. After addition of ether (2 mL), the resulting solid was quickly filtered off on a short pad of silica gel and washed with ether. The combined solution was concentrated in vacuo to give a crude product. Purification of the crude product by flash chromatography on a short silica gel column using hexane/EtOAc as the eluent afforded the desired phosphoramidite ligand.

4.2.1. *O*,*O*′-(*S*)-(5,5′,6,6′-Tetramethyl-biphenyl-2,2′-diyl)-*N*,*N*-bis[(*S*)-1-(naphthalen-1-yl)ethyl]phosphoramidite L7. Purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 50:1 then 40:1); white solid; yield 60%; $R_f = 0.35$ (SiO_2, hexanes/EtOAc = 10:1); mp 222.5–224 °C; $[\alpha]_D^{22} = +168.2$ (*c* 1.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (d, $J = 6$ Hz, 6H), 1.98 (s, 6H), 2.07 (s, 3H), 2.31 (s, 3H), 5.42 (m, 2H), 6.58 (q, $J = 8.1$ Hz, 2H), 7.00 (t, $J = 7.8$ Hz, 2H), 7.14–7.41 (m, 8H), 7.64–7.73 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.29, 17.46, 19.99, 20.29, 23.04, 23.21, 52.91, 53.07, 118.36, 118.91, 118.95, 123.23, 123.26, 124.44, 124.51, 124.83, 124.92, 125.30, 126.87, 128.46, 129.26, 129.29, 129.88, 130.65, 131.69, 133.24, 133.46, 136.33, 135.36, 139.63, 139.67, 149.41, 149.60, 149.71; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 151.03. HRMS (ESI) calcd for $C_{40}H_{39}NO_2P$ $[M+H]^+$ 596.2718; found 596.2706 ($\Delta = -2.1$ ppm).

4.2.2. *O*,*O*′-(*S*)-(5,5′,6,6′-Tetramethylbiphenyl-2,2′-diyl)-*N*,*N*-bis[(*S*)-1-(naphthalen-2-yl)ethyl]phosphoramidite L8. Purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 40:1); white solid; yield 78%; $R_f = 0.36$ (SiO_2, hexanes/EtOAc = 10:1); mp 167–169.5 °C; $[\alpha]_D^{22} = -415.3$ (*c* 0.98, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.78 (d, $J = 7$ Hz, 6H), 1.97 (s, 3H), 2.02 (s, 3H), 2.19 (s, 3H), 2.30 (s, 3H), 4.56 (m, 2H), 6.84 (m, 2H), 7.11 (d, $J = 8$ Hz, 1H), 7.20 (d, $J = 8.5$ Hz, 1H), 7.33–7.42 (m, 5H), 7.46 (s, 2H), 7.54 (t, $J = 9$ Hz, 3H), 7.71 (d, $J = 8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.36, 17.62, 20.14, 20.26, 22.92, 23.08, 54.53, 54.67, 118.687, 118.93, 118.97, 125.49, 125.64, 126.42, 126.46, 126.94, 126.98, 127.08, 127.34, 127.87, 128.29, 129.28, 129.87, 129.89, 130.54, 131.73, 132.33, 132.97, 133.37, 133.39, 136.39, 137.27, 140.84, 149.31, 149.43, 149.67; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 145.75; HRMS (ESI) calcd for $C_{40}H_{39}NO_2P$ $[M+H]^+$ 596.2718; found 596.2739 ($\Delta = 3.4$ ppm).

4.2.3. *O*,*O*′-(*S*)-(5,5′,6,6′-Tetramethylbiphenyl-2,2′-diyl)-*N*,*N*-[(*S*)-1-phenylethyl][(*S*)-1-*o*-tolylethyl]phosphoramidite L9. Purified by flash chromatography on short silica gel column (hexanes/EtOAc = 40:1); white solid; yield 76%; $R_f = 0.45$ (SiO_2, hexanes/EtOAc = 20:1); mp 73–75 °C; $[\alpha]_D^{22} = -126$ (*c* 1.1, $CHCl_3$); ^1H NMR (500 Hz, $CDCl_3$) δ 1.54 (d, $J = 6.5$ Hz, 3H), 1.61 (d, $J = 6.5$ Hz, 3H), 1.67 (s, 3H), 2.01 (d, $J = 10.5$ Hz, 6H), 2.04 (s, 3H), 2.31 (s, 3H), 4.33 (m, 1H), 4.52 (m, 1H), 6.81–6.87 (m, 3H), 7.00–7.25 (m, 9H), 7.91 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.36, 17.58, 18.53, 20.13, 20.20, 20.25, 25.31, 25.65, 52.11, 52.39, 54.66, 118.54, 118.92, 118.96, 126.01, 126.12, 126.30, 126.58, 126.76, 127.19, 128.20, 129.28, 129.60, 129.82, 130.57, 130.63, 131.64, 133.31, 133.34, 134.19, 136.31, 137.23, 137.25, 141.71, 144.07, 149.49, 149.61; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 146.46. HRMS

(ESI) calculated for $C_{33}H_{36}NO_2P$ $[M+H]^+$ 510.2559; found 510.2558 ($\Delta = -0.2$ ppm).

4.2.4. *O,O′*-(*S*)-(5,5′,6,6′-Tetramethylbiphenyl-2,2′-diyl)-*N,N*-[(*S*)-1-phenylethyl][(*S*)-1-(2-methoxyphenyl)ethyl]-phosphoramidite L10. Purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 50:1); white solid; yield 65%; $R_f = 0.33$ (hexanes/EtOAc = 40:1); mp 77–78.5 °C; $[\alpha]_D^{22} = -102.4$ (*c* 1.25, $CHCl_3$); ^1H NMR (400 MHz, C_6D_6) δ 1.58 (d, $J = 6.8$ Hz, 6H), 1.82 (s, 3H), 1.85 (dd, $J = 2$, 7.6 Hz, 3H), 1.87 (s, 3H), 1.91 (s, 3H), 2.02 (s, 3H), 3.06 (s, 3H), 5.04 (m, 2H), 6.31 (dd, $J = 1.2$, 7.6 Hz, 1H), 6.76 (d, $J = 8.4$ Hz, 1H), 6.90–7.04 (m, $J = 6.8$ Hz, 6H), 7.26 (t, $J = 6.8$ Hz, 2H), 7.32 (d, $J = 8$ Hz, 2H), 8.06 (dt, $J = 1.6$, 7.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.36, 17.60, 20.15, 20.25, 20.46, 20.53, 24.63, 24.96, 48.80, 49.07, 54.52, 54.80, 109.55, 118.71, 189.94, 118.98, 120.13, 125.99, 126.84, 127.19, 127.74, 127.87, 128.30, 129.21, 129.77, 130.57, 130.68, 131.54, 133.20, 133.23, 134.11, 136.27, 137.20, 141.97, 149.55, 149.66, 149.72, 155.48; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 147.32. HRMS (ESI) calcd for $C_{33}H_{37}NO_3P$ $[M+H]^+$ 526.2511; found 526.2506 ($\Delta = 1.0$ ppm).

4.2.5. *O,O′*-(*S*)-(5,5′,6,6′-Tetramethylbiphenyl-2,2′-diyl)-*N,N*-[(*S*)-(naphthalen-1-yl)ethyl][(*S*)-1-(2-methoxy-phenyl)-ethyl]phosphoramidite L11. Purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 40:1); white solid; yield 53%; $R_f = 0.32$ (SiO_2, hexanes/EtOAc = 30:1); mp 92–94 °C; $[\alpha]_D^{22} = +96.7$ (*c* 1.23, $CHCl_3$); ^1H NMR (400 MHz, CD_2Cl_2) δ 1.4 (d, $J = 7.2$ Hz, 3H), 1.60 (d, $J = 7.2$ Hz, 3H), 1.98 (s, 6H), 2.12 (s, 3H), 2.32 (s, 3H), 3.58 (s, 3H), 3.75 (m, 1H), 5.37 (m, 1H), 6.49–6.67 (m, 4H), 6.89 (td, $J = 0.8$, 7.2 Hz, 1H), 7.10 (d, $J = 8$ Hz, 1H), 7.22 (d, $J = 8$ Hz, 1H), 7.29 (t, $J = 8$ Hz, 1H), 7.37 (m, 2H), 7.58 (d, $J = 8.4$ Hz, 1H), 7.66 (d, $J = 7.6$ Hz, 1H), 7.71 (m, 1H), 7.81 (m, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 17.62, 17.79, 20.32, 20.57, 22.89, 22.99, 23.17, 23.32, 51.67, 50.70, 55.29, 109.90, 119.01, 119.40, 120.37, 124.09, 124.12, 124.72, 124.76, 125.40, 125.45, 125.83, 127.61, 127.70, 128.36, 128.42, 128.93, 129.80, 130.31, 131.66, 132.35, 133.08, 134.02, 134.20, 136.95, 137.98, 140.72, 140.76, 150.14, 150.32, 150.39, 156.41; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 151.12; HRMS (ESI) calcd for $C_{37}H_{39}NO_3P$ $[M+H]^+$ 576.2668; found 576.2668 ($\Delta = 0.2$ ppm).

4.2.6. *O,O′*-(*S*)-(5,5′,6,6′-Tetramethylbiphenyl-2,2′-diyl)-*N,N*-[(*S*)-1-(naphthalen-2-yl)ethyl][(*S*)-1-(2-methoxy-phenyl)-ethyl]phosphoramidite L12. Purified by flash chromatography on silica gel (hexanes/EtOAc = 40:1); white solid; yield 77%; $R_f = 0.29$ (SiO_2, hexanes/EtOAC = 30:1); mp 103–105 °C; $[\alpha]_D^{22} = -246$ (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.63 (dd, $J = 7.5$, 16 Hz, 6H), 2.01 (d, $J = 13.5$ Hz, 6H), 2.20 (s, 3H), 2.31 (s, 3H), 2.99 (s, 3H), 4.66 (m, 1H), 4.71 (m, 1H), 6.26 (d, $J = 8$ Hz, 1H), 6.85–6.91 (m, 3H), 7.00 (t, $J = 8.5$ Hz, 1H), 7.10 (d, $J = 8$ Hz 1H), 7.20 (d, $J = 7.5$ Hz, 1H), 7.27 (m, 1H), 7.38 (m, 3H), 7.58 (s, 1H), 7.61–7.68 (m, 2H), 7.81 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.37, 17.61, 20.12, 20.24, 25.09, 25.29, 48.47, 48.64, 54.40, 109.29, 118.74, 118.96, 118.99, 120.13, 125.23, 125.78, 126.40, 127.15, 127.21, 127.51, 127.90, 127.98, 129.25, 129.82, 131.58, 132.13, 132.82, 133.25, 134.08, 136.33, 137.23, 139.63, 149.59, 149.72, 155.24; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 146.32. HRMS (ESI) calcd for $C_{37}H_{39}NO_3P$ $[M+H]^+$ 576.2668; found 576.2659 ($\Delta = -1.4$ ppm).

4.2.7. *O,O′*-(*S*)-(5,5′,6,6′-Tetramethylbiphenyl-2,2′-diyl)-*N,N*-bis[(*S*)-1-*o*-tolylethyl]phosphoramidite L13. Purified by flash chromatography on short silica gel column (eluent: hexanes/EtOAc = 40:1); white solid; yield 60%; $R_f = 0.35$ (SiO_2, hexanes/EtOAc = 30:1); mp 75–77 °C; $[\alpha]_D^{22} = +72$ (*c* 1.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (dd, $J = 1.5$, 6.9 Hz, 6H), 1.95 (s, 6H), 2.00 (s, 6H), 2.25 (s, 3H), 2.31 (s, 3H), 4.52 (m, 2H), 6.76 (d, $J = 8.1$ Hz, 1H), 6.92 (d, $J = 7.8$ Hz, 3H), 7.05 (dt, $J = 1.5$, 7.5 Hz, 2H), 7.15–7.22 (m, 4H), 7.75 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.28, 17.43, 18.85, 20.09, 20.27, 22.55, 22.78, 55.05, 55.21, 118.24, 118.92, 118.96, 126.03, 126.23, 126.28, 126.35, 129.41, 129.87, 129.98, 131,50, 134.94, 143.26, 143.28, 149.64, 150.01, 150.12; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 150.71. HRMS (ESI) calculated for $C_{34}H_{39}NO_2P$ $[M+H]^+$ 524.2718; found 524.2727 ($\Delta = 1.6$ ppm).

4.2.8. *O,O′*-(*S*)-(5,5′,6,6′-Tetramethylbiphenyl-2,2′-diyl)-*N,N*-bis[(*S*)-1-(2-methoxyphenyl)ethyl]phosphoramidite L14. Purified by flash chromatography on a short silica gel column (eluent: hexanes/EtOAc = 30:1); white solid; yield 68%; $R_f = 0.30$ (SiO_2, hexanes/EtOAc = 30:1); mp 149–150.5 °C; $[\alpha]_D^{22} = +34.4$ (*c* 0.64, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, $J = 7.5$ Hz, 6H), 2.01 (d, $J = 8$ Hz, 6H), 2.24 (s, 3H), 2.31 (s, 3H), 3.63 (s, 6H), 4.89 (m, 2H), 6.51 (d, $J = 8$ Hz, 2H), 6.72 (d, $J = 10$ Hz, 1H), 6.81 (m, 3H), 7.05 (m, 3H), 7.18 (d, $J = 8$ Hz, 1H), 7.53 (d, $J = 8$ Hz, 2H);. ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.31, 17.49, 20.14, 20.23, 22.16, 22.26, 50.43, 50.53, 54.63, 110.14, 118.70, 119.00, 119.55, 127.17, 127.72, 127.76, 129.13, 129.69, 131.13, 132.84, 133.07, 136.03, 137.13, 149.67, 156.09; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 151.20. HRMS (ESI) calcd for $C_{34}H_{39}NO_4P$ $[M+H]^+$ 556.2617; found 556.2707 ($\Delta = -1.7$ ppm).

4.3. Synthesis of nucleophile 2

4.3.1. 2-Bromo-4,5-(methylenedioxy)benzaldehyde oxime 8. Hydroxylamine hydrochloride (1.55 g, 22.3 mmol) was added in portions to a solution of $NaHCO_3$ (1.83 g, 21.8 mmol) in 50 mL of water at room temperature. The solution was added to a vigorously stirred suspension of **7** (5.0 g, 21.8 mmol) in ethanol (45 mL). The resulting mixture was stirred for 5 h and then left at −20 °C overnight. The suspension was filtered, washed with a few milliliters of cold ethanol, and dried under a vacuum to give **8** as a pure white solid (4.9 g, 93%): $R_f = 0.39$ (eluent: hexanes/EtOAc = 2:1); mp 153–155 °C; IR (KBr) 3463, 3325, 3101, 1500, 1473, 1249, 1041 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.11 (s, 2H) 7.24 (s, 1H), 7.27 (s, 1H), 8.22 (s, 1H), 11.48 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 102.38, 105.39, 112.45, 114.27, 125.12, 146.64, 147.60, 149.45.

HRMS (ESI) calcd for $C_8H_7BrNO_3$ $[M+H]^+$ 243.9609; found 243.9612 ($\Delta = 1.2$ ppm).

4.3.2. 1-Bromo-6-aminomethyl-3,4-(methylenedioxy)-benzene 9. To a solution of **8** (4.0 g, 16.3 mmol) in THF (200 mL) a 2 M HCl solution (80 mL) was added, followed by zinc (10.4 g, 160 mmol). The mixture was vigorously stirred under reflux for 2.5 h until the reaction was complete. The reaction mixture was cooled to room temperature, filtered on a Celite pad to remove the excess zinc, and condensed under reduced pressure to about 90 mL. The aqueous layer was extracted with EtOAc (50 mL) and then its pH adjusted to >10 by the addition of saturated ammonia solution. The resulting precipitate was filtered off through a Celite pad and washed with EtOAc (50 mL). The two layers were separated and the water layer was washed with EtOAc (4×75 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered, and evaporated in vacuo to give crude **9** as an oil. The oil was purified by passing through a short silica gel column (eluent: EtOAc/2% Et_3N). The combined fractions were concentrated in vacuo to afford amine **9** as a clear oil (3.4 g, 91% yield): $R_f = 0.4$ (SiO_2, EtOAc/10% Et_3N); ^1H NMR (300 MHz, $CDCl_3$) δ 1.62 (br s, 2H), 3.79 (s, 2H), 5.95 (s, 2H), 6.87 (s, 1H), 6.98 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.76, 101.62, 109.08, 112.78, 113.54, 135.46, 147.18, 147.46. HRMS (ESI) calcd for $C_8H_9BrNO_2$ $[M+H]^+$ 229.9817; found 229.9822 ($\Delta = 2.2$ ppm).

4.3.3. Methyl *N*-[6-bromo-3,4-(methylenedioxy)-benzyl]carbamoylacetate 2. To a solution of amine **9** (615 mg, 2.67 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (0.93 mL, 680 mg, 6.7 mmol) at 0 °C under N_2. Then, methyl malonyl chloride (0.35 mL, 440 mg, 3.2 mmol) in CH_2Cl_2 (5 mL) was slowly added. The mixture was stirred at room temperature for 12 h. Saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The resulting two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated in vacuo to give the crude product as yellow oil. The crude product was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 2:1 then 1:1) to afford pure **2** as a white solid (756 mg, 86% yield): mp 118–119 °C; IR (KBr) 3273, 3071, 1738, 1630, 1550, 1503, 1479, 1205, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 2H), 3.75 (s, 3H), 4.44 (d, 2H, $J = 6$ Hz), 5.96 (s, 2H), 6.85 (s, 1H), 7.00 (s, 1H), 7.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.76, 43.70, 52.44, 101.78, 110.25, 112.72, 114.20, 130.19, 147.45, 147.89, 164.68, 169.84. HRMS (ESI) calcd for $C_{12}H_{13}BrNO_5$ $[M+H]^+$ 329.9977; found 329.9977 ($\Delta = -0.2$ ppm).

4.4. General procedure for the Pd-catalyzed asymmetric allylic alkylation–desymmetrization reaction

4.4.1. Methyl (1′*S,4′*R**)-2-(4′-benzoyloxy-2′-cyclohexen-1′-yl)-2-*N*-[6″-bromo-3″,4″-(methylene-dioxy)benzyl]-carbamoylacetate 3.** To a solution of **2** (122 mg, 0.37 mmol) in THF (3 mL) LDA (2 N in THF, 0.186 mL, 0.37 mmol) was added at −78 °C under N_2. Separately, a solution of $[Pd(allyl)Cl]_2$ (2.24 mg, 0.006 mmol) and a ligand (0.024 mmol) in THF (3 mL) was stirred at room temperature for 10 min. Dibenzoate **1** (100 mg, 0.31 mmol) was added at once to this catalyst solution and the resulting mixture was cooled to −78 °C. The nucleophile (i.e, **2** + LDA) solution was then slowly cannulated into the substrate–catalyst solution. The mixture was stirred at the given temperature until TLC showed completion of the reaction or no more progress in the reaction. A saturated NH_4Cl solution was added (2 mL) to quench the reaction and the reaction mixture was extracted with CH_2Cl_2. The two layers were separated and the water layer was further extracted with CH_2Cl_2 (3×2 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude oil was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 3:1 then 2:1) to give **3** as a white foamy solid. Product **3** was obtained as a mixture of two diastereoisomers (dr = 54:46 by NMR). $R_f = 0.4$ (SiO_2, hexanes/EtOAc = 1:1): mp = 57–61 °C for a diastereoisomer mixture; IR (KBr): 3294, 3070, 1743, 1708, 1654, 1481, 1272, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.55–2.06 (m, 4H), 2.87 (m, 1H), 3.20 (d, $J = 10$ Hz, 0.54H), 3.26 (d, $J = 9.2$ Hz, 0.46H), 3.73 (s, 1.6H), 3.75 (s, 1.7H), 4.42 (m, 2H), 5.41 (m, 1H), 5.81–5.89 (m, 1H), 5.90–6.00 (m, 1H), 5.94 (s, 2H), 6.86 (s, 1H), 6.94 (m, NH, 0.51H), 6.99 (d, $J = 2.8$ Hz, 1H), 7.12 (m, NH, 0.47H), 7.42 (m, 2H), 7.54 (m, 1H), 8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, a mixture of two diastereoisomers) δ [22.23, 22.41], 27.01, [37.41, 37.55], 43.96, 44.07, [52.47, 52.55], [57.44, 57.76], [66.59, 66.84], [101.83, 101.86], [110.29, 110.45], 112.75, 114.22, [127.07, 127.26], 128.28, [129.57, 129.99], [130.03, 130.50], 132.86, [133.17, 133.36], 147.47, 148.01, 165.99, [166.67, 166.71], [171.81, 171.48]. HRMS (ESI) calcd for $C_{18}H_{19}BrNO_5$ $[M-PhCO_2H]^+$ 408.0447; found 408.0438 ($\Delta = -2.0$ ppm).

4.4.2. 1,4-Bis[{2-bromo-4,5-(methylenedioxy)benzyl}carbamoyl(methoxylcarbonyl)methyl]cyclohex-2-ene 11. $R_f = 0.29$ (SiO_2, EtOAc = 1:2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 2H), 1.64 (m, 2H), 2.80 (m, 2H), 3.08–3.18 (m, 2H), 3.71 (s, 3H), 3.18 (s, 3H), 4.39 (m, 4H), 5.61 (m, 2H), 5.96 (s, 4h), 6.85 (m, 2H), 6.91 (m, NH, 0.5H), 6.97 (m, 3H), 7.07 (m, NH, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.24, 24.41, 23.46, 23.55, 36.21, 36.44, 36.58, 43.89, 43.98, 52.39, 52.44, 52.46, 57.41, 57.48, 57.58, 57.84, 101.82, 101.84, 110.23, 110.26, 110.31, 110.35, 112.71, 112.74, 114.14, 129.64, 129.72, 129.78, 130.05, 130.09, 147.44, 147.90, 147.96, 166.85, 166.91, 166.99, 171.25, 171.27, 171.37, 171.41. HRMS (ESI) calcd for $C_{30}H_{31}Br_2N_2O_{10}$ $[M+H]^+$ 737.0345; found 737.0359 ($\Delta = 1.8$ ppm).

4.4.3. (3a*R,7a*S**)-1-[6′-Bromo-3,4-(methylenedioxy)-benzyl]-3-(methoxycarbonyl)-3a,4,5,7a-tetrahydro-indolin-2-one 3a.** A solution of $[Pd(allyl)Cl]_2$ (2.65 mg, 7.24 μmol) and dppb (6.2 mg, 15 μmol) was stirred in CH_3CN (2 mL) under N_2 for 1 h. Separately, a solution of **3** (156 mg, 0.294 mmol) in THF (2 mL) was cooled to −50 °C under N_2. LDA (0.154 mL, 2 M soln) was added

to this solution and the mixture was stirred for 5 min and warmed to room temperature. The Pd–dppb catalyst solution was then quickly added to the substrate solution and the mixture was stirred at rt for 2.5 h. TLC analysis showed that the reaction was complete. To the reaction mixture, saturated NH_4Cl solution was added (3 mL) to quench the reaction and the reaction mixture was extracted with CH_2Cl_2. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was purified by flash chromatography using hexanes/EtOAc (3:1) as the eluent to give **3a** as a colorless oil (85 mg, 71% yield): $R_f = 0.36$ (SiO_2, hexanes/EtOAc = 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.62 (m, 1H), 1.76 (m, 1H), 2.06 (m, 3H), 2.80 (m, 1H), 3.32 (d, 1H, $J = 6.8$ Hz), 3.79 (s, 3H), 3.99 (m, 1H), 4.27 (d, 1H, $J = 16$ Hz), 4.80 (d, 1H, $J = 16$ Hz), 5.70 (m, 1H), 5.93–5.97 (m, 1H), 5.95 (s, 2H), 6.82 (s, 1H), 6.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.81, 23.24, 35.83, 44.14, 52.35, 52.55, 53.40, 101.80, 109.21, 112.50, 113.54, 122.86, 128.49, 131.64, 147.85, 169.38, 170.12. HRMS (ESI) calcd for $C_{18}H_{19}BrNO_5$ $[M+H]^+$ 408.0447; found 408.0460 ($\Delta = 3.3$ ppm).

4.4.4. (3a*R,7a*S**)-1-[6′-Bromo-3,4-(methylenedioxy)-benzyl]-3a,4,5,7a-tetrahydroindolin-2-one 10.** To a solution of **3a** (37 mg, 0.09 mmol) in DMSO (1 mL), water (0.3 mL) and NaCl (15 mg) were added. The resulting solution was stirred at 175 °C for 2.5 h. TLC analysis showed the completion of the reaction. Water (2 mL) was added and the reaction mixture was extracted with Et_2O/CH_2Cl_2 (1:1) (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting oil was chromatographed on a silica gel column (eluent: hexanes/EtOAc = 5:3) to give **10** as a white crystalline solid (29 mg, 91% yield): $R_f = 0.25$ (SiO_2, hexanes/EtOAc = 1:1); mp 85–86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50–1.80 (m, 3H), 1.92–2.20 (m, 2H), 2.28 (m, 1H), 2.40–2.60 (m, 2H), 3.86 (m, 1H), 4.27 (d, 1H, $J = 20.8$ Hz), 4.74 (d, 1H, $J = 15.6$ Hz), 5.75 (m, 1H), 5.93–5.99 (m, 1H), 5.96 (s, 2H), 6.76 (s, 1H), 6.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 24.11, 31.02, 35.72, 43.98, 54.76, 101.78, 109.26, 112.58, 113.50, 123.22, 129.30, 131.82, 147.74, 174.44. HRMS (ESI) calcd for $C_{16}H_{17}NO_3Br$ $[M+H]^+$ 350.0392; found 350.0383 ($\Delta = -2.4$ ppm).

The determination of the enantiopurity of **10** was performed on a Shimadzu LC-2010A HPLC system using a Chiralpak ADRH column (eluent CH_3CN/H_2O 60:40, flow 0.5 mL/min).

4.5. Synthesis of (+)-γ-lycorane

4.5.1. (3a*R*,12b*S*,12c*S*)-1,2-Dehydro-4-(methoxycarbonyl)-5-oxo-γ-lycorane 4. A solution of **3** (70 mg, 0.132 mmol) in degassed dry DMF (0.5 mL) was slowly added to a suspension of NaH (60% oil, 5.8 mg, 0.145 mmol) in DMF (1 mL) under N_2 at −78 °C. The solution was slowly warmed to 0 °C. A stirred solution of $Pd(OAc)_2$ (1.7 mg, 7.5 μmol) and dppb (6.5 mg, 15 μmol) in DMF (0.5 mL) was prepared separately and cannulated to the reaction mixture of **3** and NaH in DMF at 0 °C. The temperature was raised to 50 °C and the reaction monitored until the disappearance of **3** and the clean formation of the allylic amination product **3a** was confirmed (3 h). Then, diisopropylethylamine (55 μL, 0.3 mmol) was added to the reaction mixture and the temperature was raised to 110 °C. The reaction mixture was stirred for 7 h and cooled to room temperature. Water (3 mL) was added to quench the reaction and the reaction mixture was extracted with ethyl acetate (5 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduce pressure to give crude Heck reaction product **4** as a brown oil. The crude oily product was purified by flash chromatography on silica gel (eluant: hexanes/EtOAc = 2:1) to yield pure **4** as a colorless oil (26 mg, 61% yield): $R_f = 0.27$ (SiO_2, hexanes/EtOAc = 2:3); $[\alpha]_D^{22} = -19.6$ (*c* 0.51, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.26 (m, 2H), 3.20 (d, $J = 5$ Hz, 1H) 3.28 (m, 2H), 3.80 (s, 3H), 4.16 (d, $J = 17.5$ Hz, 1H), 4.22 (dd, $J = 4.5$, 8 Hz, 1H), 4.85 (d, $J = 17.5$ Hz, 1H), 5.71 (d, $J = 9.5$ Hz, 1H), 5.92–5.95 (m, 1H), 5.96 (s, 2H), 6.58 (s, 1H), 6.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.71, 34.34, 38.29, 42.41, 52.74, 55.52, 55.71, 101.11, 105.96, 108.80, 124.02, 126.75, 129.25, 133.77, 146.93, 147.00, 168.61, 170.67. HRMS (ESI) calcd for $C_{18}H_{18}NO_5$ $[M+H]^+$ 328.1185; found 328.1185.($\Delta = 0.1$ ppm).

4.5.2. (3a*R*,12b*S*,12c*S*)-1,2-Dehydro-5-oxo-γ-lycorane 12a. To a solution of **4** (23 mg, 0.07 mmol) in DMSO (1.5 mL), water (0.5 mL) and NaCl (13 mg) was added. The mixture was stirred at 175 °C for 15 h. The reaction mixture was cooled to room temperature and 2 mL of water was added. The reaction mixture was extracted with ethyl acetate (5 × 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product. Purification of the crude product by flash chromatography on silica gel (eluant: hexanes/EtOAc = 1:1.5) afforded pure **12** as a white solid (18 mg, 93% yield): mp 174–177 °C (decomp.); $R_f = 0.21$ (SiO_2, hexanes/EtOAc = 1:5); ^1H NMR (500 MHz, $CDCl_3$) δ 2.10–2.21 (m, 3H), 2.66 (dd, $J = 9.5$, 17 Hz, 1H), 2.88 (m, 1H), 3.28 (m, 1H), 4.05 (m, 1H), 4.11 (d, $J = 17$ Hz, 1H), 4.79 (d, $J = 17$ Hz, 1H), 5.65 (d, $J = 9.5$ Hz, 1H), 5.88 (m, 1H), 5.94 (d, $J = 2.5$ Hz, 2H), 6.58 (s, 1H), 6.70 (s, 1H). HRMS (ESI) calcd for $C_{16}H_{16}NO_3P$ $[M+H]^+$ 270.1130; found 270.1118 ($\Delta = -1.3$ ppm).

4.5.3. (3a*R*,12b*S*,12c*S*)-5-Oxo-γ-lycorane 12b. 5-Oxodihydrolycorane **12a** (11 mg, 0.04 mmol) was dissolved in methanol (1.5 mL) and 5% Pd/C (10 mg) was added at once. The solution was stirred under ambient pressure of H_2 at room temperature for 1.5 h (TLC analysis showed that the reaction was completed). The catalyst was filtered off on a short Celite pad and the filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by flash chromatography on silica gel (eluent: hexane/

EtOAc = 1:1.5) to afford 5-oxo-lycorane **12b** (10.7 mg, 95% yield) as colorless crystals: mp 169–170 °C; $R_f = 0.31$ (SiO_2, hexanes/EtOAc = 1:5); $[\alpha]_D^{22} = +83.8$ (c 0.74, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.13–1.38 (m, 3H), 1.67–1.76 (m, 3H), 2.09 (d, 1H, $J = 26.5$ Hz), 2.41 (m, 1H), 2.57 (dd, 1H, $J = 11.5$, 27 Hz), 2.75 (td, 1H, $J = 7.5$, 14 Hz), 3.77 (t, 1H, $J = 7.5$ Hz), 4.32 (d, AB, $J = 29$ Hz), 4.54 (d, 1H, $J = 29$ Hz), 5.93 (dd, AB, 2H, $J = 2$, 7.5 Hz), 6.60 (d, 2H, $J = 9.5$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.64, 27.89, 30.27, 32.98, 39.85, 40.32, 42.71, 55.73, 101.03, 106.69, 108.49, 123.33, 131.61, 146.64, 146.72, 175.67. HRMS (ESI) calcd for $C_{16}H_{16}NO_3P$ $[M+H]^+$ 272.1287; found 272.1281 ($\Delta = -1.9$ ppm).

4.5.4. (+)-γ-Lycorane. To a suspension of $LiAlH_4$ (10 mg, 0.28 mmol) in THF (1 mL), a solution of 5-oxo-lycorane **12b** (15 mg, 0.055 mmol) was added in THF (2 mL) at 0 °C under N_2. The solution was refluxed for 1.5 h (TLC showed that the reaction was completed). A saturated Na_2SO_4 solution (1 mL) was carefully added at 0 °C and the reaction mixture was stirred for 2 h. After the addition of 1 N NaOH (2 mL), the two layers were separated and the aqueous layer was washed with EtOAc (4 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product as a yellow oil. Purification of the crude product through silica gel chromatography (eluent: hexanes/EtOAc = 1:2 then 1:4) afforded pure (+)-γ-lycorane as a colorless oil (13 mg, 92% yield): $R_f = 0.37$ (SiO_2, hexanes/EtOAc = 1:6); $[\alpha]_D^{22} = +18.1$ (c 1.1, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.27–1.35 (m, 3H), 1.43–1.52 (m, 3H), 1.62–1.64 (m, 1H), 1.69–1.71 (m, 1H), 1.74–1.77 (m, 1H), 2.00–2.03 (m, 1H), 2.13–2.20 (m, 1H), 2.38 (m, 1H), 2.74 (m, 1H), 3.21 (d, $J = 14.5$ Hz, 1H), 3.38 (m, 1H), 4.02 (d, $J = 14.5$ Hz, 1H), 5.89 (dd, $J = 3.5$, 5 Hz, 2H), 6.49 (s, 1H), 6.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.19, 29.28, 30.38, 31.69, 37.36, 39.46, 53.73, 57.11, 62.90, 100.65, 106.24, 108.33, (127.1), 133.16, 145.64, 146.04. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M+H^+]$ 258.1494; found 258.1487 ($\Delta = -2.7$ ppm).

4.5.5. General procedure for Rh(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate. The reaction of dimethyl itaconate using $[Rh(COD)_2]SbF_6$ and ligand (**19a**) is described as a typical example. In a 10 mL glass reaction vessel with a magnetic stirring bar under nitrogen, a mixture of $[Rh(COD)_2]SbF_6$ (1.4 mg, 0.0025 mmol) and **19a** (3.0 mg, 0.0050 mmol) was dissolved in 5 mL of 1,2-dichloroethane, and the solution was stirred at room temperature for 2 min. To this catalyst solution, dimethyl itaconate (0.08 mL, 0.5 mmol) was added. The reaction vessel was then placed in a 300 mL stainless steel autoclave, and the autoclave was pressurized and purged with hydrogen gas five times. The vessel was subsequently charged with hydrogen gas to 0.689 MPa. The autoclave was warmed to 50 °C and the reaction was carried out at this temperature for 20 h with stirring. The autoclave was allowed to cool to room temperature, and then the hydrogen gas was carefully released. The reaction mixture was filtered through a short pad of silica gel and the filtrate was subjected to gas chromatographic analysis using a Supelco Beta Dex-225 column for the determination of the conversion and enantiomeric purity of dimethyl methylsuccinate: the analysis showed that the conversion was 100% with 100% product selectivity and (*R*)-dimethyl methylsuccinate with 99.6% ee was formed.

Other reactions were performed practically in the same manner with variations in the reaction temperature, the Rh-catalyst precursor, and the solvent used.

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