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Total Synthesis of Enantiopure (+)-γ-Lycorane Using Highly Efficient Pd-Catalyzed Asymmetric Allylic Alkylation

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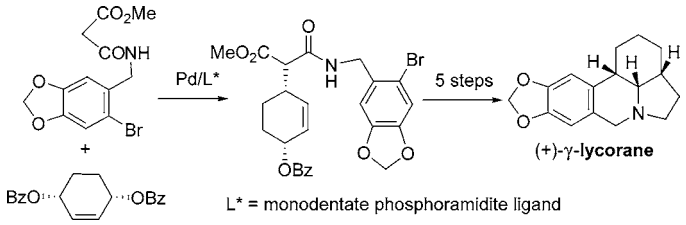
ABSTRACT



A highly efficient short total synthesis of (+)-γ-lycorane (>99% ee, 41% overall yield) was achieved by using the asymmetric allylic alkylation in the key step catalyzed by palladium complexes with novel chiral biphenol-based monodentate phosphoramidite ligands.

Catalytic asymmetric allylic substitution serves as one of the most powerful methods for the regio- and stereoselective formation of C−C, C−N, and C−O bonds. The high synthetic utility of this catalytic process is now well established through numerous efficient syntheses of enantiopure natural and unnatural products.[1] Trost et al. pioneered the asymmetric allylic alkylation using C_2-symmetric diamine-based modular diphosphine ligands, which achieved excellent enantioselectivity in various systems.[1−2] 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 regioselectivity.[3] In contrast, the corresponding Pd-catalyzed reactions with monodentate phosphorus ligands remain poorly explored.[4]

We have reported a new class of monodentate phosphorus ligands based on axially chiral biphenols.[5] One of the salient features of these ligands is their fine-tuning capability through modification of the R^1, R^2, and R^3 groups (Figure 1). Thus, high catalytic activity and enantioselectivity have been achieved in the hydrogenation of dimethyl itaconate (up to 99.6% ee), hydroformylation of allyl cyanide (up to 80%

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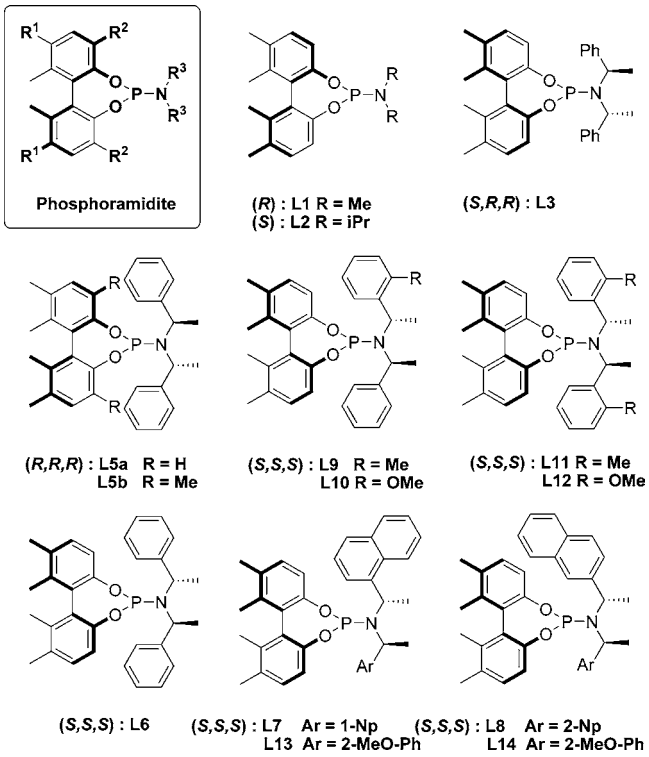

Figure 1. Phosphoramidite ligands library.

ee), and conjugate addition of diethylzinc to cycloalkenones and nitroolefins (up to 99% ee).[5]

We describe here the application of these ligands to the Pd-catalyzed asymmetric allylic alkylation reaction for the total synthesis of (+)-γ-lycorane, an alkaloid isolated from the plants of Amaryllidacae family. Because of its unique pentacyclic structure, (+)-γ-lycorane has attracted substantial attention for its total synthesis.[6] However, very few approaches to the asymmetric synthesis of this alkaloid have been reported so far.[6a,7] In 1995, Mori and co-workers reported the first asymmetric synthesis of (+)-γ-lycorane, featuring a Pd-catalyzed asymmetric allylic alkylation in the key step (Scheme 1).[7] However, the best enantioselectivity achieved in this key step (step 1 in Scheme 1) using (*S*)-BINAPO was 54% ee, giving **7a** in 30% yield (using 2.6 equiv of **6** and LDA). The yield and enantiopuiry of **7a** was dependent on the amounts of **6** and LDA used. Thus, **7a** was obtained in 66% yield and 40% ee on using 1.1 equiv of **6** and LDA. This product (40% ee) was used to complete the total synthesis in 17% overall yield. The expedited 5-step total synthesis, incorporating one-pot protocol, gave (+)-γ-lycorane with 46% ee in 23% overall yield.

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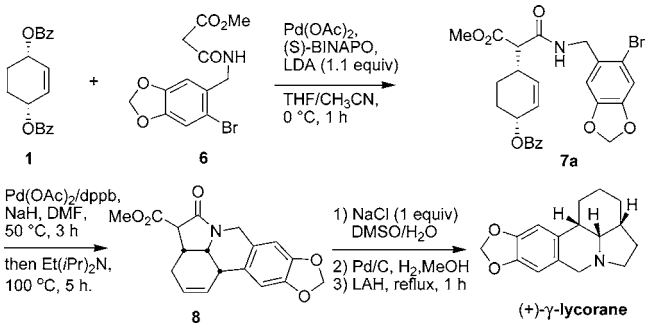
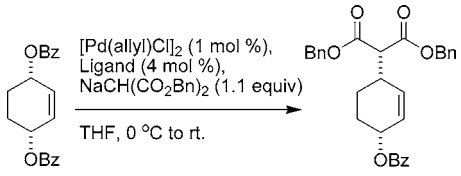
Scheme 1. Asymmetric Synthesis of (+)-γ-Lycorane



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.

First, we performed a model study on the desymmetrization of *cis*-1,4-dibenzoyloxycyclohex-2-ene (**1**) using dibenzyl malonate as a nucleophile. The aim of this model study was the preliminary screening of effective phosphoramidite ligands. Results are summarized in Table 1.

Table 1. Desymmetrization of *meso*-Diester **1**[a]



entry	ligand	conv[b](%)	% ee[c]
1	**L1**	80	28.7 (−)
2	**L2**	82	48.1 (+)
3	**L3**	70	68.4 (+)
4	**L5a**	82	81.3 (−)
5	**L5b**	50	10.8 (−)

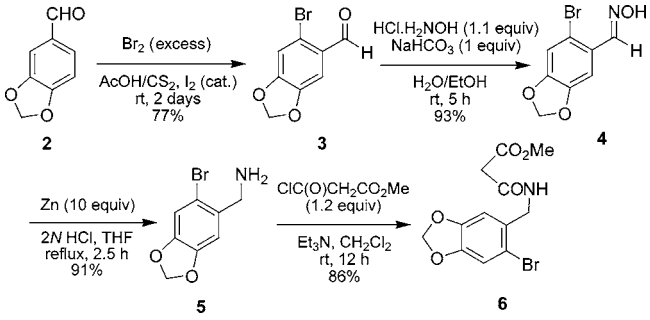
[a] Reactions were run using [Pd(allyl)Cl]$_2$ (1 mol %) with a monodentate ligand (4 mol %) in THF at 0 °C for 2 h. [b] Determined by ^{1}H NMR. [c] Determined using Daicel Chiralpak AD.

As Table 1 shows, a substantial increase of enantioselectivity for the formation of **7b** is observed as the size of the amine moiety of the ligand increases (entries 1 to 4). Thus, **L1** afforded **7b** with 28.7% ee while 81.3% ee was obtained with **L5a**. It is worthy of note that (i) (*S*)-biphenol-based ligands give (+)-**7b** as the major product, while (*R*)-biphenol-based ligands predominantly yield (−)-**7b** (i.e., the axial chirality of the ligand dictates the direction of the enantiodiscrimination of the two benzoate groups) and (ii) introduction of methyl groups at the 3,3′-positions of the biphenol moiety of **L5a** (i.e., **L5b**, R^2 = Me) causes a detrimental effect on the enantioselectivity as well as conversion of the

reaction (entry 5). These preliminary results served as the starting point for applying our ligands to the key step in the total synthesis of enantiopure (+)-γ-lycorane.

According to our planned route to (+)-γ-lycorane by revisiting Mori's first asymmetric synthesis, it was necessary to prepare the malonate half-amide **6**. Since the synthesis of **6** was not reported in Mori's paper nor anywhere else by literature search, we synthesized **6** from commercially available piperonal **2** through steps shown in Scheme 2.

Scheme 2. Synthesis of Nucleophile **6**

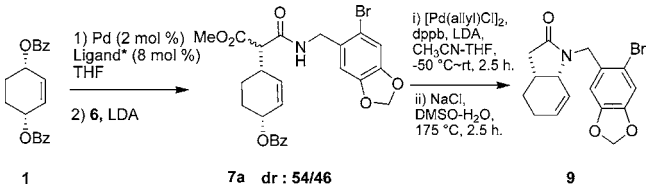


Next, the efficacy of phosphoramidite ligands **L3**, **L5a,** and **L5b** was evaluated in the reaction of **1** with "real" nucleophile **6** and LDA as base (**6**/LDA = 1). Consistent with the model study, **L5a** gave the best results among the three ligands examined. Also, it was found the solvent and the reaction temperature had critical effects on the reaction. Thus, after basic optimization of the reaction conditions using **L5a** as the ligand, the reactions in THF at −60 °C appeared optimal. The reactions gave a 54/46 diastereomer mixture of **7a** due to epimerization of the acidic methine of the malonate half amide moiety. Thus, it was necessary to convert **7a** to **9** in order to determine the enantioselectivity of the reaction. The enantiopuriy of **9** was unambiguously determined by chiral HPLC analysis using a Daicel Chiralpak AD-RH column (Table 2).

Under these conditions, the reaction of **1** with **6** (1.2 equiv) using **L5a** gave **7a** in 93% yield and 86.2% ee (Table 2, entry 1). We also examined the effects of the amounts of **6** and LDA on the reaction. The reactions with 2.0 and 2.6 equiv of **6** and LDA gave **7a** with 89.5% ee (63% yield) and 92.6% ee (27% yield), respectively (entries 2 and 3). (Note: **L6** is the enantiomer of **L5a**.) The results indicate that the use of excess amounts of **6** and LDA increases the enantioselectivity of the reaction. However, the observed increase in enantioselectivity is accompanied by a significant decrease in the yield of **7a**. Thus, the use of 1.2 equiv of **6** and LDA appears optimal.

Although it was already a remarkable improvement at this point that **7a** was obtained in 93% isolated yield and 86.2% ee as compared with Mori's original work,[7] we strongly felt that more improvement would be possible through systematic optimization of **L6**, which gives **7a** that has the correct absolute configuration for the total synthesis of (+)-γ-lycorane. Accordingly, we designed and synthesized a new

Table 2. Pd-Catalyzed Allylic Alkylation Reaction: Desymmetrization of **1** with **6**[a]



1 7a dr : 54/46 9

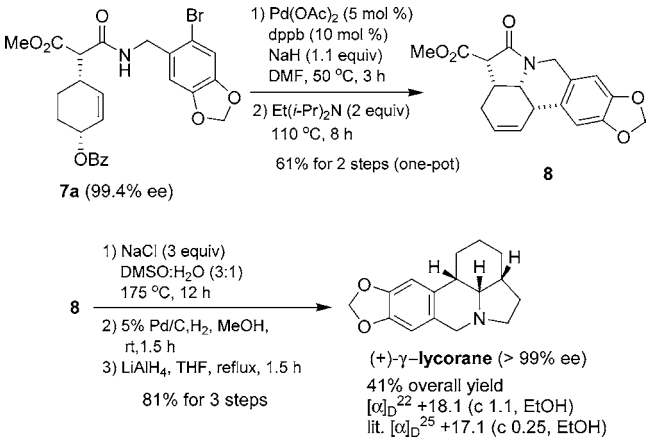
entry	ligand	yield[b] (%)	% ee[c]
1	**L5a**	93	86.2 (−)
2	**L5a**[d]	27	92.6 (−)
3	**L6**[e]	63	89.5 (+)
4	**L7**	conv <5%	nd[g]
5	**L8**	92	85.5 (+)
6	**L9**	85	83.0 (+)
7	**L10**[f]	76	**99.7** (+)
8	**L11**	conv 0%	nd[g]
9	**L12**	conv <5%	nd[g]
10	**L13**	conv <5%	nd[g]
11	**L14**[f]	83	**99.4** (+)

[a] Reactions were run with 100 mg (0.31 mmol) of **1**, $[Pd(allyl)Cl]_2$ (2 mol %), a ligand (8 mol %), **6** (1.2 equiv), and LDA (1.2 equiv) in THF at −60 °C for 15 h unless otherwised noted. [b] Isolated yield. [c] Estimated based on the enantiopurity of **9** determined by chiral HPLC analysis using a Daicel Chiralpak AD-RH column. [d] The reaction was run with 2.6 equiv of **6** and LDA and was completed in 20 min. [e] The reaction run with 2.0 equiv of **6** and LDA. [f] The reaction time was 8 h. [g] nd = not determined.

optimization library of phosphoramidite ligand **L6** by introducing various C_2-symmetric, pseudo-C_2-symmetric, and nonsymmetrical *N*,*N*-bis(1-arylethyl)amine moieties bearing different aryl groups, including those with an ortho substituent (ligands **L7**-**14**, Figure 1). 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 recently reported the markedly favorable effects of such substituents on the enantioselectivity as well as reaction rate in his Ir-catalyzed asymmetric allylic substitution reactions.[3e] Thus, we set out to examine the ortho substitution effect in our biphenol-based ligand−Pd-catalyst system. In addition, we designed nonsymmetrical *N*,*N*-bis-(1-arylethyl)amine moieties based on a combination of different aryl groups, i.e., 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 **6** using $[Pd(allyl)Cl]_2$ and 1.2 equiv of **6** and LDA in THF at −60 °C for 15 h. Results are summarized in Table 2. As Table 2 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) is worth mentioning (entries 4 and 5). The result for **L8** (85.5% ee) is similar to that for **L6** (entries 5 and 3), while the reaction with **L7** almost did not proceed under the same conditions and no change was observed even when the reaction was forced at room temperature. Use of even one 1-naphthyl group seems to kill the Pd-catalyst activity. Thus, the reaction using **L13** (R^3 =

Scheme 3. Completion of the Total Synthesis of (+)-γ-Lycorane from **7a**



1-Np, $R^{3'}$ = 2-MeO-Ph) virtually did not proceed (entry 10). To our surprise, ligands **L11** and **L12**, 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, while **L9** (R^3 = Ph, $R^{3'}$ = 2-tolyl) gave 83.0% ee (entry 6).

These results are unanticipated since the same amine moieties were reported to give excellent results in the Ir-catalyzed reactions with BINOL-based ligands.[3d,e] Thus, this reaction is found to be very sensitive to the bulkiness and arrangement of the aryl moiety at the coordination site.

A breakthrough in the enantioselectivity was achieved with ligands **L10** (R^3 = Ph, $R^{3'}$ = 2-MeO-Ph) and **L14** (R^3 = 2-Np, $R^{3'}$ = 2-MeO-Ph), bearing nonsymmetrical *N*,*N*-bis-(1-arylethyl)amine moieties wherein one of the aryl groups is a 2-MeO-phenyl. The reaction with **L10** and **L14** gave (+)-**7a** with 99.7% ee (76% yield) and 99.4% ee (83% yield), respectively (entries 7 and 11). Both reactions reached 100% conversion in 8 h. It appears that the 2-methoxyphenyl group in the nonsymmetrical *N*,*N*-bis(1-arylethyl)amine moiety exerts 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 **7a** from the reaction mixture is very easy, the reaction with **L14** 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 Scheme 3 illustrates, (+)-**7a** (99.4% ee) was converted to pentacyclic oxolycorane **8** in 61% yield through a one-pot, tandem allylic amination−intramolecular Heck reaction. Then, **8** was subjected to sequential demethoxycarbonylation, hydrogenation, and $LiAlH_4$ reduction to give the desired (+)-γ-lycorane (>99% ee) in 41% overall yield (six steps) from **1**.

In conclusion, highly efficient biphenol-based monodentate phosphoramidite ligands have been developed for Pd-catalyzed asymmetric allylic alkylation. The successful total synthesis of (+)-γ-lycorane demonstrates the advantage of the facile fine-tuning capability of our novel phosphoramidite ligands in developing extremely efficient ligands for a specific asymmetric transformation through rational modification of a lead ligand. Further studies on the expansion of our monodentate chiral phosphorus ligand library and their applications to various catalytic asymmetric transformations are actively underway.

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Supporting Information Available: Experimental procedures; characterization data for all new phosphoramidite ligands as well as (+)-γ-lycorane and the intermediates in its total synthesis. This material is available free of charge via the Internet at http://pubs.acs.org.

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