

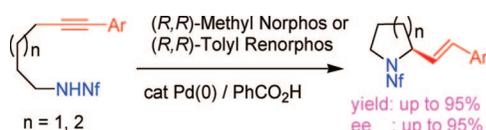
# Catalytic Asymmetric Intramolecular Hydroamination of Alkynes in the Presence of a Catalyst System Consisting of Pd(0)-Methyl Norphos (or Tolyl Renorphos)-Benzoic Acid

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Enantiomerically pure methyl Norphos (**A**), tolyl Norphos (**B**), CF<sub>3</sub> Norphos (**C**), methyl Renorphos (**D**), and tolyl Renorphos (**E**) were synthesized and used as chiral bisphosphine ligands for the catalyst system, Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>/PhCOOH, in an intramolecular hydroamination of aminoalkynes **15**. Among the Norphos series, methyl Norphos (**A**) was the best ligand for the hydroamination, and the corresponding five- and six-membered nitrogen heterocycles **16** were obtained in high yields with high enantioselectivities. Among the Renorphos series, tolyl Renorphos (**E**) gave the best result; both methyl Norphos (**A**) and tolyl Renorphos (**E**) afforded high yields and high enantioselectivities. NMR investigation using Me-Norphos revealed that this ligand was oxidized gradually in the presence of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in C<sub>6</sub>D<sub>6</sub> even under the conditions using Ar atmosphere to give Me-Norphos oxide, which prevented the intramolecular hydroamination. On the other hand, Me-Norphos was rather stable in C<sub>6</sub>D<sub>6</sub> in the absence of the palladium catalyst under Ar atmosphere and was not converted to its oxide even after 3 days. The gradual oxidation of ligands (**A** and **E**) in the presence of the Pd catalyst is perhaps a reason why 20 mol % of **A** or **E** was needed to obtain high yields and high ee's of **16**.

## Introduction

The catalytic addition of the N–H bond of amines to alkenes or alkynes (hydroamination) to give nitrogen-containing molecules is of immense interest to both academic research and industrial products since most amines are made today in multistep syntheses.<sup>1</sup> It has been shown that hydroamination can be catalyzed by d- and f-block transition metals,<sup>2</sup> by alkali metals,<sup>3</sup> and, very recently, by calcium.<sup>4</sup> Early transition metals (group 4 and especially the lanthanides) are highly efficient catalysts for the hydroamination reaction of various compounds containing C–C multiple bonds.<sup>2</sup> In the lanthanide chemistry, amido and alkyl metallocene complexes have proven to be active

catalysts for the hydroamination/cyclization of primary amino olefins, allenes, and alkynes.<sup>5</sup> Besides the well-established metallocenes, today a number of noncyclopentadienyl lanthanide complexes, which are based on amido and alkoxide ligands, are known to be efficient in hydroamination/cyclization catalysis.<sup>6,7</sup> Although catalytic hydroamination has been well-established, only few reports are available on the enantioselective version of this process.<sup>8</sup> Among these, rare earth metal catalysts have been proven to be competent catalysts for enantioselective hydroamination reactions. However, the catalysts based on chiral cyclopentadienyl ligands

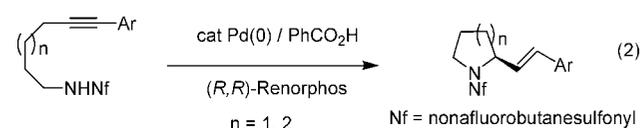
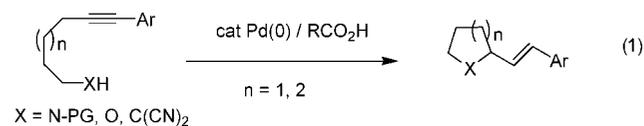
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were prone to undergo facile epimerization, hampering wide use of those catalysts.<sup>9</sup> Recently, new chiral rare earth metal catalysts based on noncyclopentadienyl ligands such as chiral bis(oxazolines),<sup>10</sup> bis(phenolates),<sup>11</sup> bis(naphtholates),<sup>12</sup> and bis(naphtholamides)<sup>13,14</sup> were developed. However, the enantioselectivities of the hydroamination through those newly developed ligands have not been improved markedly compared to those through the previously known lanthanocene ligands. Furthermore, these rare earth metal catalysts are highly moisture-sensitive and also show a very limited tolerance to polar functional groups when compared to late transition metal catalysts. Hence, development of a new catalytic asymmetric hydroamination using robust late transition metals, which can be handled more easily, is highly desired.

Previously, we reported an entirely new method for the addition of carbon pronucleophiles<sup>15</sup> to alkynes in the presence of a Pd(0)/carboxylic acid combined catalyst, and it was extended to the addition of nitrogen<sup>16</sup> and oxygen<sup>17</sup> nucleophiles to alkynes (eq 1). These results encouraged us to develop a catalytic asymmetric hydroamination method.<sup>18</sup> Accordingly, we developed a catalytic asymmetric intramolecular hydroami-

nation of aminoalkynes using Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and PhCOOH catalytic system in the presence of (*R,R*)-Renorphos as a chiral ligand, which produced five- and six-membered nitrogen heterocycles in good yields with good to high ee's (eq 2). The use of the ordinary conditions A, 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, 10 mol % of PhCOOH, and 25 mol % of (*R,R*)-Renorphos, gave good to fair enantioselectivities. To obtain higher enantioselectivities (81–91% ee), we had to use the conditions B, 20 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, 40 mol % of PhCOOH, and 100 mol % of (*R,R*)-Renorphos.<sup>18</sup>



The use of a stoichiometric amount of the expensive chiral ligand for obtaining a better yield and enantioselectivity was a drawback for this reaction. During this investigation, we examined various commercially available bisphosphine ligands<sup>19</sup> and realized that only Renorphos was effective. In the hydroamination of aminoalkynes using Norphos ligand, the product was obtained in a very low yield, but with a better enantioselectivity, compared to Renorphos. From these results, it is clear that a small change in the norbornane framework of the bisphosphine ligands gave a drastic change both in the rate of reaction and in the enantioselectivity of the hydroamination of aminoalkynes. Therefore, we prepared various Norphos and Renorphos derivatives (Figure 1) and investigated the effectiveness and usefulness of these ligands in the catalytic asymmetric intramolecular hydroamination of aminoalkynes.

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(18) For a preliminary communication, see: Lutete, M. L.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, 126, 1622–1623. The key observations in the previous communication are following. A NH-Nf group is much less common than NH-Tf or NH-Ts, but NH-Nf gave better ee's and chemical yields than the other protective groups. The reaction without a protective group, that is, the reaction using -NH<sub>2</sub> itself, gave lower ee's. The hydroamination of **15a** did not proceed at all in the absence of PhCOOH, and the starting material was recovered. A reviewer asked what would happen in the presence of 10 mol % of a base under the standard conditions (Table 2, entry 5). The reaction of **15a** in the presence of Cs<sub>2</sub>CO<sub>3</sub> or tricyclohexylamine gave lower ee's and lower yields. The reaction in the presence of tricyclohexylphosphine gave **16a** with 87% ee and 93% yield.

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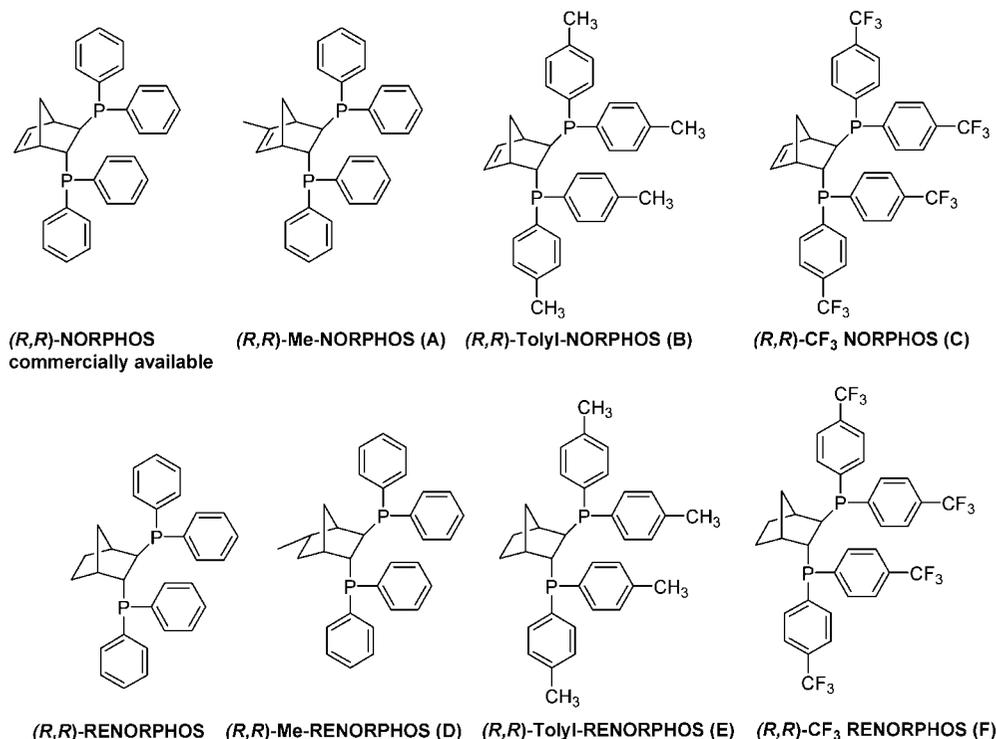


FIGURE 1. Norphos and Renorphos derivatives.

## Results and Discussion

**Synthesis of Bisphosphine Ligands.** In 1979, Brunner et al. reported the synthesis of chiral Norphos ligand, which gave excellent results in Rh-catalyzed asymmetric hydrogenation of (*Z*)- $\alpha$ -(*N*-acetamido)cinnamic acid.<sup>20</sup> Later, Brunner reported the Rh-catalyzed asymmetric hydrogenation of (*Z*)- $\alpha$ -(*N*-acetamido)cinnamic acid and itaconic acid using Me-Norphos (A) as a ligand,<sup>21</sup> and the hydrogenated products were obtained with 92 and 60% ee.<sup>21</sup> Since then, Me-Norphos ligand (A) was never applied as a bisphosphine ligand for asymmetric catalysts. Chiral Norphos, Renorphos, and their derivatives were used by Brunner's group themselves<sup>22</sup> and by other researchers,<sup>23</sup> but mostly unsatisfactory results were obtained,<sup>23</sup> except for Rh-catalyzed hydrogenation,<sup>20–22</sup> Co-catalyzed Diels–Alder reaction,<sup>24</sup> and hydrogenation of  $\alpha$ -keto acids.<sup>25</sup> It seems that this type of bisphosphine ligands derived from norbornene framework have been underestimated in spite of Brunner's success a long time ago;<sup>20</sup> instead, nowadays other C-2 symmetric bisphosphine ligands have been used frequently, and successful results have been obtained with those ligands. As mentioned above, in our hydroamination of aminoalkynes, only Renorphos gave satisfactory to allowable results, and all the other com-

mercially available C-2 symmetric bisphosphine ligands together with monodentate ligands gave unsatisfactory results. Therefore, efforts were undertaken to prepare Norphos and Renorphos derivatives by slightly modifying the original procedure,<sup>21</sup> in order to find a better phosphine ligand. Treatment of chlorodiphenylphosphine **1** with Li wire in THF at room temperature followed by addition of *trans*-1,2-dichloroethylene gave *trans*-1,2-ethenediylbis(diphenylphosphine) **2**, which upon air oxidation using 30% H<sub>2</sub>O<sub>2</sub> led to formation of the corresponding oxide **3**. The Diels–Alder reaction of **3** with an excess amount of methylcyclopentadiene in an autoclave reactor at 170 °C gave the racemic 5-methyl Norphos oxide **4** in 80% yield (Scheme 1). All the spectral data of **4** were identical with the reported data.<sup>21</sup> Then, according to the literature procedure,<sup>21</sup> we carried out the resolution of **4** using dibenzoyl-L-(–)-tartaric acid monohydrate as a chiral resolving agent. In the literature procedure, the authors mentioned that, after three successive operations, the *R,R*-enantiomer of **4** could be obtained in a pure form (100% ee) with  $[\alpha]^{20}_D = -64$  (*c* 1, CHCl<sub>3</sub>).

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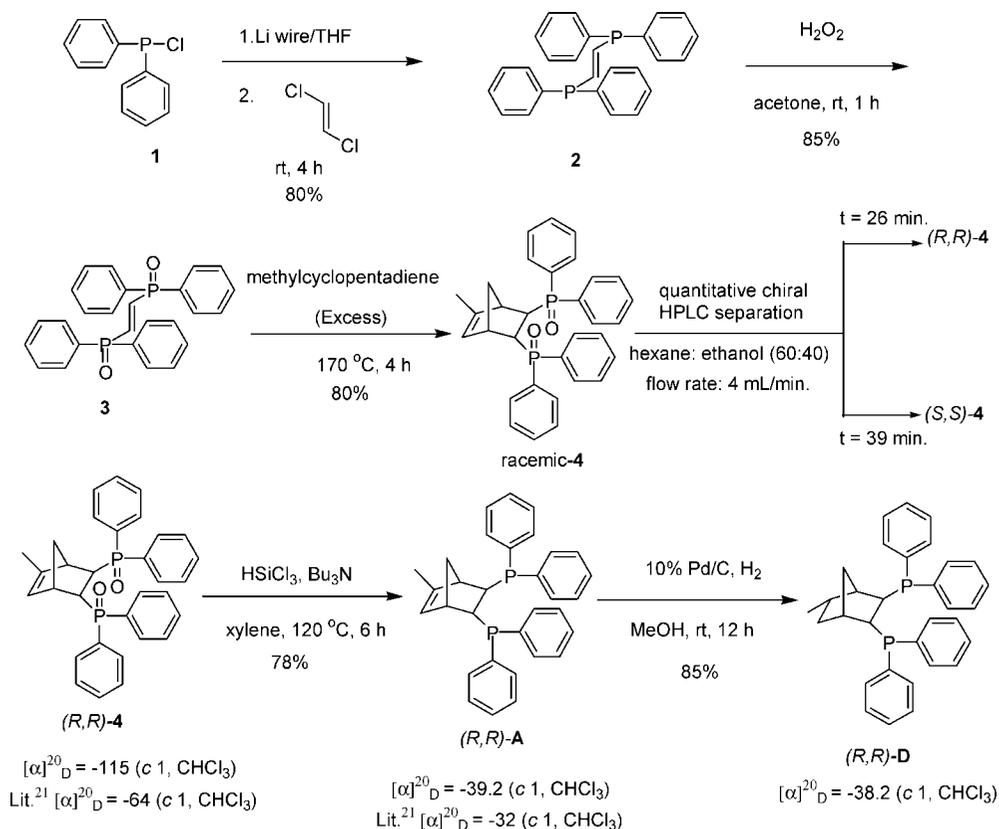
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## SCHEME 1. Synthesis of Methyl Norphos Ligand (A)



However, we obtained an  $[\alpha]_D^{20}$  value higher than the reported one after three successive operations. We doubted that an enantiomer (*R,R*)-**4** having  $[\alpha]_D^{20} = -64$  (c 1,  $\text{CHCl}_3$ ) would not be 100% pure. To obtain a really 100% pure (*R,R*)-**4**, we carried out the separation of racemic methyl Norphos oxide **4** into pure enantiomers using quantitative chiral HPLC with hexane/ethanol (60:40) as a mobile phase, and the flow rate was 4 mL/min. Then, the  $[\alpha]_D^{20}$  value of each enantiomer was recorded to be  $-115$ . Accordingly, it is now clear that (*R,R*)-**4**, which Brunner et al. thought to be enantiomerically pure, was not pure, but perhaps contaminated with enantiomer or byproduct. Then, we carried out the reduction of chiral methyl Norphos oxide using trichlorosilane and tributylamine in xylene at 120 °C, giving (*R,R*)-methyl Norphos **A** in 78% yield;  $[\alpha]_D^{20} = -39.2$  (c 1,  $\text{CHCl}_3$ ). The previously reported data for **A** were  $[\alpha]_D^{20} = -32$  (c 1,  $\text{CHCl}_3$ ).<sup>21</sup> The difference between the  $[\alpha]_D^{20}$  value of our (*R,R*)-**4** and that of Brunner's (*R,R*)-**4**,  $-115$  versus  $-64$ , was far greater than the difference between the  $[\alpha]_D^{20}$  value of our (*R,R*)-**A** and that of Brunner's (*R,R*)-**A**,  $-39.2$  versus  $-32$ . Although there is no strict relation between the difference of the  $[\alpha]_D^{20}$  values of the enantiomers and their enantiopurities, we guess that Brunner's (*R,R*)-**4** was contaminated with significant amounts of byproduct rather than with its enantiomer. Hydrogenation of (*R,R*)-**A** using 10% Pd/C with hydrogen balloon gave the corresponding (*R,R*)-methyl Renorphos **D** in 85% yield;  $[\alpha]_D^{20} = -38.2$  (c 1,  $\text{CHCl}_3$ ). The stereochemistry of a methyl group was determined unambiguously by NOE experiments (see Supporting Information).

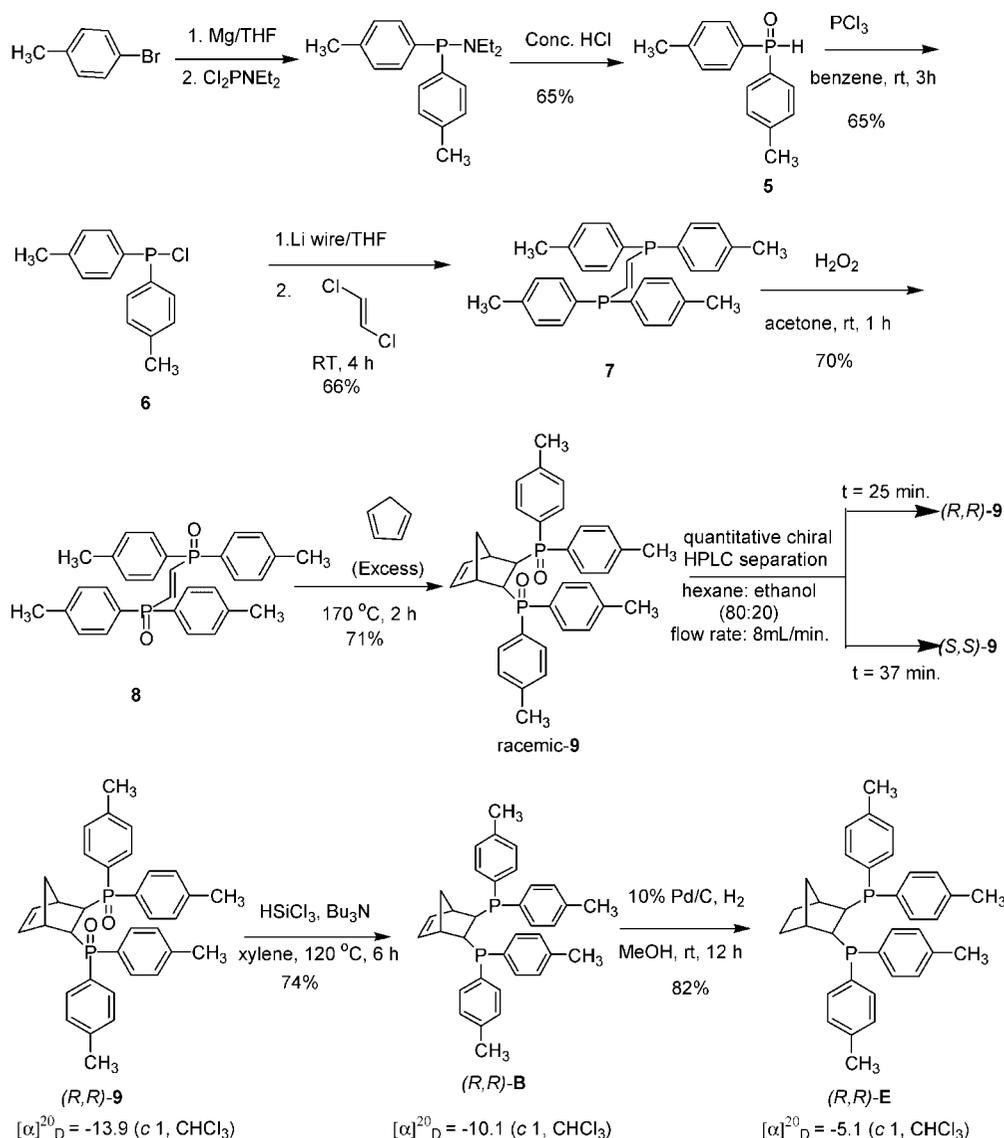
In a similar way, we carried out the synthesis of tolyl Norphos (Scheme 2) and  $\text{CF}_3$  Norphos ligands (Scheme 3). In the preparation of these new phosphine ligands, initially bisphos-

phine oxides **5**<sup>26</sup> and **10**<sup>26</sup> were prepared through the reaction of the corresponding para-substituted arylmagnesium bromides with  $\text{Cl}_2\text{PNEt}_2$ . In the case of tolyl Norphos ligand, the chloro derivative **6** was prepared from **5** using  $\text{PCl}_3$  in benzene. Then the reaction of this chloro compound **6** with lithium wire followed by addition of *trans*-1,2-dichloroethylene gave the *trans*-1,2-alkenylbis(ditolylphosphine) **7**, which upon air oxidation with 30%  $\text{H}_2\text{O}_2$  gave the corresponding oxide **8**. In the case of  $\text{CF}_3$  Norphos ligand, we tried to prepare the corresponding  $\text{CF}_3$ -based alkenylphosphine oxide **13** in a similar way. However, we were unable to obtain **13** through a procedure similar to that mentioned in Scheme 2. The reason was not yet clear. The bisphosphine oxide **10** was reduced to the bisphosphine **11** using DIBAL-H in THF at  $-78$  °C for 3 h according to a reported procedure,<sup>26</sup> and the cross-coupling between this bisphosphine and *trans*-1,2-dichloroethylene in the presence of Ni catalyst in DMF gave **12** in 52% yield, which upon air oxidation with  $\text{H}_2\text{O}_2$  gave the Diels–Alder precursor **13** in 90% yield.

Racemic tolyl Norphos oxide **9** and  $\text{CF}_3$  Norphos oxide **14** were prepared by the Diels–Alder reaction of **8** and **13**, respectively, with excess amounts of cyclopentadiene in an autoclave reactor. The separation of these racemic Norphos oxides into pure enantiomers was carried out using quantitative chiral HPLC in a manner similar to that mentioned in Scheme 1. In the case of tolyl Norphos oxide **9**, hexane/ethanol (80:20) as a mobile phase with 8 mL/min flow rate was used. Similarly, in the case of  $\text{CF}_3$  Norphos oxide **14**, hexane/ethanol (50:50) as a mobile phase with 4 mL/min flow rate was used. Then,

(26) Busacca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 4277–4280.

## SCHEME 2. Synthesis of Tolyl Norphos Ligand



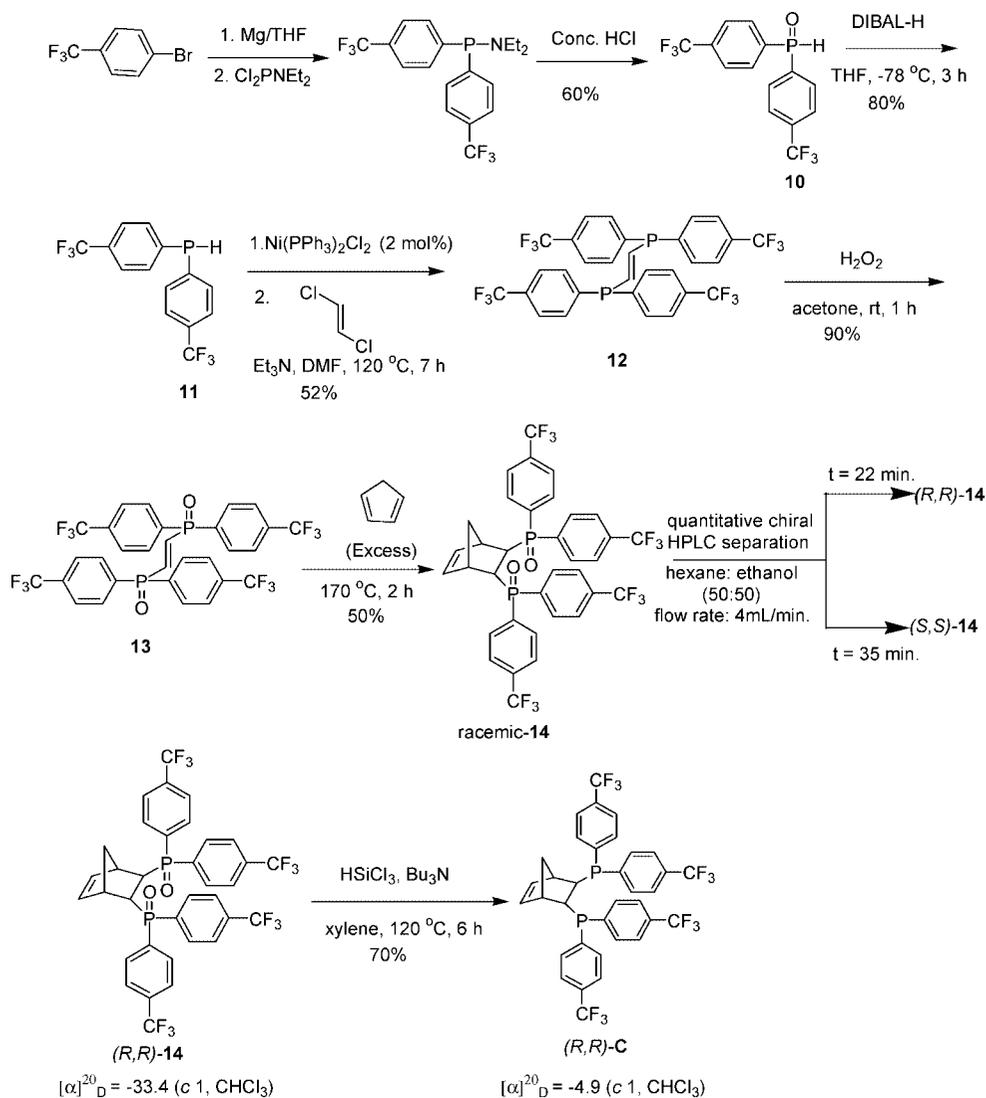
these pure Norphos oxides (*R,R*-**9**) and (*R,R*-**14**) were reduced to the corresponding Norphos derivatives (*R,R*-**B**) and (*R,R*-**C**) using  $\text{HSiCl}_3$  and tributylamine in xylene.

Newly synthesized tolyl Norphos (**B**), tolyl Renorphos (**E**), and  $\text{CF}_3$  Norphos (**C**) were prone to be oxidized very gradually by air, leading to the corresponding oxides (vide infra, the NMR study section). More or less, this trend was observed also for the known Norphos, Renorphos, Me-Norphos (**A**), and Me-Renorphos (**D**). Especially, **C** was rather easily oxidized among Norphos and Renorphos series. Furthermore, as mentioned later, the outcome on the enantioselectivity in the hydroamination of **15a** in the presence of  $\text{CF}_3$  Norphos (**C**) was the worst among the ligands tested (Table 1). Accordingly, we did not synthesize  $\text{CF}_3$  Renorphos (**F**) since we could not expect that a better result would be obtained using **F**.

**Intramolecular Hydroamination of Aminoalkynes Using Norphos and Renorphos Series.** To know the effectiveness of newly synthesized ligands in the hydroamination of alkynes, the reaction of substrate **15a** under the previous optimized conditions<sup>18</sup> was carried out for comparison, and the results are summarized in Table 1.

Comparison of these results indicates that Me-Norphos (**A**) is the best one among the ligands tested for the hydroamination, and the corresponding product **16a** was obtained in a high yield with a high enantioselectivity (95% yield, 95% ee). It should be noted that tolyl Renorphos (**E**) gave an excellent result comparable to **A**. Then we monitored the reaction progress of the hydroamination of **15a** using 25 mol % of **A**, 5 mol % of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ , and 10 mol % of  $\text{PhCOOH}$  in benzene at 100 °C. Also, we measured the ee of **16a** at the same point as the reaction progress was monitored. The results are shown in Figure 2. It is clear that the product yield increased smoothly as reaction time increased up to 48 h, and beyond this, the yield of the product did not increase at all. The enantioselectivity of the product was always the same throughout the reaction (95% ee). We also examined the chloroform-free Pd(0) catalysts, such as  $\text{Pd}_2(\text{dba})_3$ ,  $\text{Pd}(\text{dba})_2$ , and  $\text{Pd}(\text{PPh}_3)_4$ , under the conditions similar as above; **16a** was obtained in high chemical yields as well, but enantioselectivities were very low.

We also studied the effect of the amount of methyl Norphos **A**, Pd catalyst, and  $\text{PhCOOH}$  on the product yield and enantioselectivity, and the results are shown in Table 2.

SCHEME 3. Synthesis of CF<sub>3</sub> Norphos LigandTABLE 1. Intramolecular Hydroamination of **15a** using (*R,R*)-Norphos and (*R,R*)-Renorphos Derivatives

| ligand                      | yield (%) <sup>a</sup> | ee (%) <sup>b</sup> |
|-----------------------------|------------------------|---------------------|
| Norphos <sup>18</sup>       | 5                      | 92                  |
| methyl Norphos (A)          | 95                     | 95                  |
| yolyl Norphos (B)           | 15                     | 68                  |
| CF <sub>3</sub> Norphos (C) | 75                     | 36                  |
| Renorphos <sup>18</sup>     | 65                     | 83                  |
| methyl Renorphos (D)        | 90                     | 60                  |
| tolyl Renorphos (E)         | 98                     | 92                  |

<sup>a</sup> Yields are of isolated products. <sup>b</sup> All the ee's were confirmed by chiral HPLC.

When we used 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, 20 or 25 mol % of methyl Norphos, and 10 mol % of PhCOOH in benzene, the product was obtained in high yields with high ee's (Table 2, entries 4 and 5). However, when the reaction was carried out with 2.5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, 10 mol % of methyl Norphos, and 5 mol % of PhCOOH in benzene, the product was obtained in high yield but the enantioselectivity was very

TABLE 2. Effect of the Amount of the Methyl Norphos A, Pd, and PhCO<sub>2</sub>H on Yields and Enantiomeric Excess in the Intramolecular Asymmetric Hydroamination of Aminoalkyne **15a**<sup>a</sup>

| entry | Pd <sub>2</sub> (dba) <sub>3</sub> ·CHCl <sub>3</sub> (mol %) | A (mol %) | PhCO <sub>2</sub> H (mol %) | yield of <b>16a</b> (%) <sup>b</sup> | ee of <b>16a</b> (%) <sup>c</sup> |
|-------|---|-----------|-----------------------------|--------------------------------------|-----------------------------------|
| 1     | 2.5   | 10        | 5                           | 95                                   | 11                                |
| 2     | 3   | 15        | 6                           | 85                                   | 10                                |
| 3     | 5   | 15        | 10                          | 95                                   | 7                                 |
| 4     | 5   | 25        | 10                          | 95                                   | 95                                |
| 5     | 5   | 20        | 10                          | 93                                   | 92                                |

<sup>a</sup> All the reactions were carried out in benzene solvent at 100 °C for 48 h. <sup>b</sup> Yields are of isolated products. <sup>c</sup> All the ee's were confirmed by chiral HPLC.

low (Table 2, entry 1). The reaction without palladium catalyst, that is, the reaction in the presence of Me-Norphos and PhCOOH in benzene at 100 °C, did not proceed at all, and the starting material **15a** was recovered. Nowadays, the use of benzene as a solvent is not desirable, and therefore, we examined the reaction in toluene. The reaction of **15a** in toluene under the standard conditions (entry 5) at 100 °C gave **16a** in similar yield and ee as that in benzene. From these results, it is clear that at least 20 mol % of the ligand and 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> are required to obtain a high yield and high enantioselectivity; in this case, the ratio of Pd and P is 1:4,

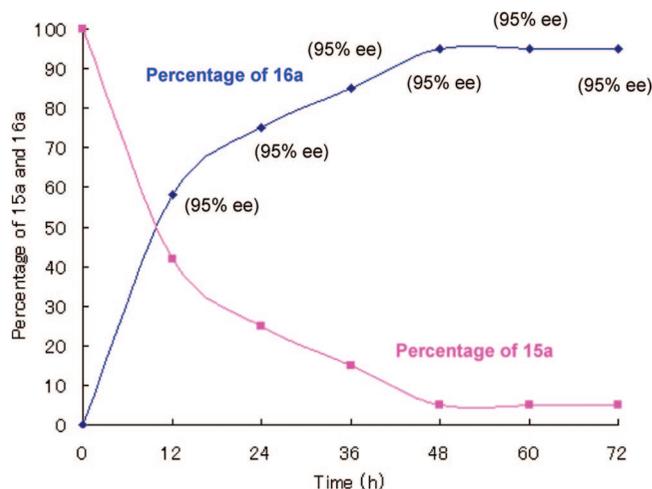


FIGURE 2. Reaction profile of **15a** using **A** as a ligand.

corresponding a palladium complex coordinated by four phosphine atoms. Such a fully coordinated complex is inactive as a catalyst. As mentioned later, gradual oxidation of the ligand might make a hemilabile ligand. We also examined the concentration effect of substrate on the enantioselectivity and chemical yield. A higher concentration (1 mol) of substrate decreased the ee and chemical yield, and the present diluted condition (0.08 mol) gave the best result (entries 4 and 5). The substrate concentration was kept at 0.08 mol at the early stage of the reaction, and then **15a** was added portion-wise along the reaction progress, but this attempt gave a lower ee. The effect of an electron-donating group (EDG) and electron-withdrawing group (EWG) at the *para*-position of benzoic acid upon the chemical yield and enantioselectivity was examined. The reaction of **15a** using *p*-MeO- or *p*-NO<sub>2</sub>-substituted benzoic acid, instead of benzoic acid, under the standard conditions (entry 5) afforded similarly high chemical yield (~95%), but the ee in the former case was 2% and that in the latter case was 30%. The reason for this dramatic change of enantioselectivity is not clear. Since the optimized conditions on the reaction time and on the catalyst composition were obtained, we carried out the hydroamination of various aminoalkynes, and the results are summarized in Table 3.

In the case of a catalyst system, Pd(0)/**A**/PhCO<sub>2</sub>H, the five-membered nitrogen heterocycles **16a–e** were obtained from the aminoalkynes **15a–e** in high yields with high to good enantioselectivities (entries 1–5). It is clear that the ligand is effective for hydroamination of the aromatic alkynes (entries 1–5 and 7–8) compared to the aliphatic alkyne **15f** (entry 6) as for the completion of reaction. The reaction of the aliphatic alkyne needs long reaction time (5 days) as observed previously in the case of the reaction using Renorphos,<sup>18</sup> and also the product is obtained as a 1:1 mixture of *cis*- and *trans*-isomers. The substrates **15c** and **15d** having electron-donating and -withdrawing groups gave the corresponding products **16c** and **16d** in good yields and with high enantioselectivities. The cyclization of **15g** having one carbon longer on the tether afforded the six-membered piperidine **16g** in 92% yield and 79% ee (entry 7). The reaction of **15h** with a benzene ring linker on the tether gave the tetrahydroisoquinoline derivative **16h** in a high yield and with an excellent ee (entry 8). The reaction using tolyl Renorphos **E** was carried out similarly. Again, very high to good chemical yield and enantioselectivities were obtained for the aminoalkynes bearing phenyl groups at the alkyne terminus

(entries 1–4). In the case of naphthyl derivative, rather low ee was obtained. The six-membered nitrogen heterocycles were obtained in high chemical yields with high enantioselectivities (entries 7 and 8). We tested the present optimized conditions to the intramolecular hydroamination of aniline derivatives,<sup>16f</sup> but the ee's of the products were not improved so much.

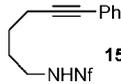
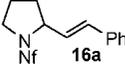
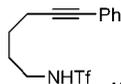
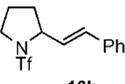
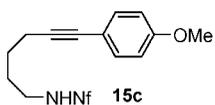
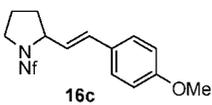
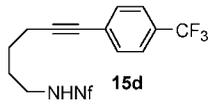
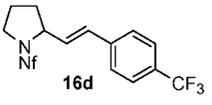
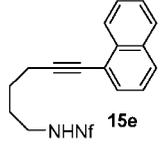
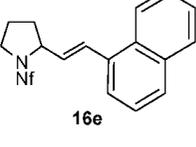
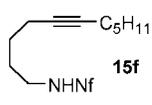
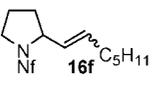
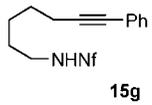
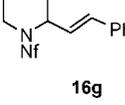
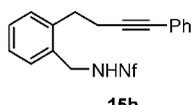
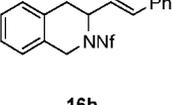
**NMR Studies of the Hydroamination of Alkynes.** In the Table 2, when the amount of **A** decreased from 20–25 to 10–15 mol % (entries 4 and 5 vs entries 1–3), dramatic decrease of ee's of **16a** was observed. In order to help clarify this remarkable change, mechanistic investigation using NMR was carried out. We examined the reaction of **15a** using 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, 10 mol % of PhCOOH, and 25 mol % of methyl Norphos oxide **4** in benzene at 100 °C. Even after 3 days, no cyclization product **16a** was formed at all, and the starting material **15a** was recovered. This clearly shows that intramolecular hydroamination does not proceed in the presence of methyl Norphos oxide **4** as a ligand. Methyl Norphos **A** was air sensitive and very slowly converted to its oxide if it was exposed to air for many days. Similar observation was made also for the other Norphos and Renorphos series. It was necessary to store **A** under Ar and to be used under the conditions of inert atmosphere. Hence we carried out all the reactions under Ar atmosphere. As mentioned above, methyl Norphos **A** was very effective in the cyclization of **15a**, and the product **16a** was obtained in an excellent yield with very high enantioselectivity (Scheme 4). After completing the reaction, we were unable to recover **A**. Accordingly, we assumed that the ligand **A** was oxidized after the completion of reaction or during the reaction progress, and it was converted to the corresponding stable oxide.

We carried out NMR experiments using Me-Norphos because we have carried out the hydroamination of alkynes **15**, and the corresponding products **16** were obtained in very high ee using 20 mol % of Me-Norphos (Table 3). Initially, an NMR sample of Me-Norphos was prepared under Ar atmosphere, and its <sup>1</sup>H and <sup>31</sup>P NMR spectra in C<sub>6</sub>D<sub>6</sub> were recorded (Figures 3 and 4). After 3 days, again its <sup>1</sup>H and <sup>31</sup>P NMR were recorded, and it was confirmed that there was no change in the spectra (Figure 3a and 4a). This clearly indicates that Me-Norphos is not oxidized even after 3 days under this condition.

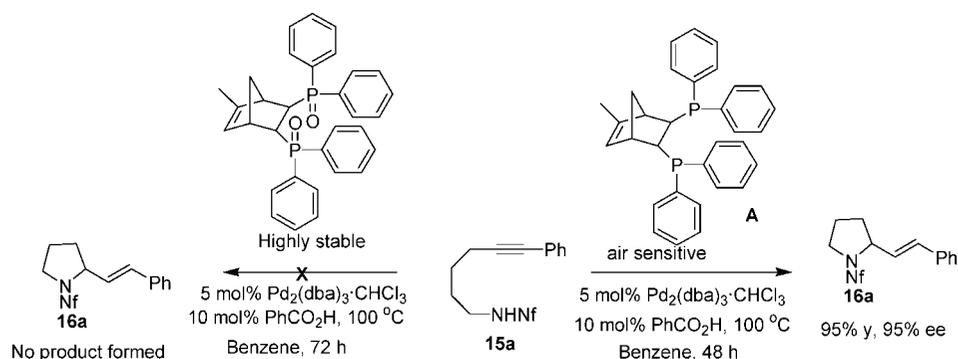
Next, a 4:1 mixture of Me-Norphos and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in C<sub>6</sub>D<sub>6</sub> was prepared under Ar atmosphere, and immediately, its <sup>1</sup>H NMR spectra were recorded (Figure 3c). We have also taken the spectra of dba in C<sub>6</sub>D<sub>6</sub> alone. In this, the olefinic peaks appeared in the aromatic region. <sup>1</sup>H NMR spectra of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in C<sub>6</sub>D<sub>6</sub> are shown in Figure 3b. An ethyl signal appeared in the spectra of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, which was obtained commercially.<sup>27</sup> We repeatedly measured the <sup>1</sup>H NMR spectra of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> obtained through different sources, but always an ethyl signal appeared. Perhaps, an unidentified impurity is contaminated in commercially available Pd<sub>2</sub>(dba)<sub>3</sub>·

(27) We used other Pd(0) reagents, such as Pd<sub>2</sub>(dba)<sub>3</sub>, Pd(dba)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Pd(OAc)<sub>2</sub>/excess diphosphine, instead of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>. The reaction of **15a** proceeded smoothly, and the product **16a** was obtained in high chemical yields, but the enantioselectivities in these cases were significantly lower than the reaction with Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>. We also took NMR spectra of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, purchased from several different sources. However, all of those samples exhibited small peaks, resembling Et of ethyl ether, around 1 and 3 ppm region, as observed in Figure 3! We could identify this Et is due to ethyl ether. Furthermore, we found that the reaction of **15a** with a catalyst system, 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub> plus 1 equiv CHCl<sub>3</sub>, under the conditions similar as those of entry 4, Table 2, gave **16a** in 94% ee and 95% yield. This result clearly indicates that the presence of CHCl<sub>3</sub> is essential to obtain high enantioselectivity. The effect of ethyl ether contaminated in commercially available Pd<sub>2</sub>(dba)<sub>3</sub>CHCl<sub>3</sub> upon enantioselectivity is not so important.

**TABLE 3.** Intramolecular Asymmetric Hydroamination of Aminoalkynes Using Pd(0)/Methyl Norphos A/PhCO<sub>2</sub>H or Pd(0)/Tolyl Renorphos E/PhCO<sub>2</sub>H<sup>a</sup>

| entry | substrate   | product   | Pd(0)/A/PhCO <sub>2</sub> H |                     | Pd(0)/E/PhCO <sub>2</sub> H |                     |
|-------|---|---|-----------------------------|---------------------|-----------------------------|---------------------|
|       |   |   | yield (%) <sup>b</sup>      | ee (%) <sup>c</sup> | yield (%) <sup>b</sup>      | ee (%) <sup>c</sup> |
| 1     |    |    | 93                          | 92                  | 95                          | 90                  |
| 2     |    |    | 90                          | 88                  | 92                          | 85                  |
| 3     |    |    | 90                          | 80                  | 93                          | 88                  |
| 4     |    |    | 87                          | 85                  | 90                          | 90                  |
| 5     |    |    | 87                          | 90                  | 85                          | 48                  |
| 6     |   |   | 75                          | d                   | 70                          | d                   |
| 7     |  |  | 92                          | 79                  | 88                          | 86                  |
| 8     |  |  | 90                          | 95                  | 93                          | 92                  |

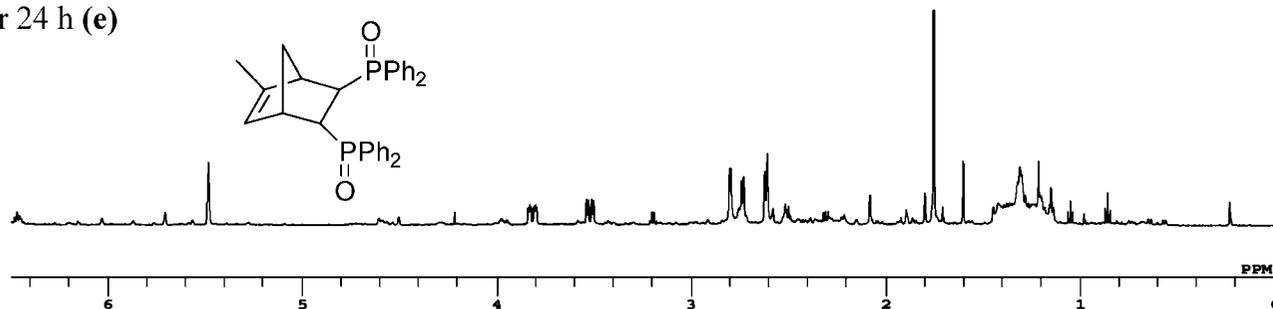
<sup>a</sup> All the reactions were carried out using aminoalkyne (0.125 mmol), 5 mol % of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, 10 mol % of PhCOOH, and 20 mol % of methyl Norphos in benzene (1.5 mL) at 100 °C for 48 and 72 h in the case of tolyl Renorphos ligand (20 mol %). <sup>b</sup> Yields are of isolated products. <sup>c</sup> All the ee's were confirmed by chiral HPLC. <sup>d</sup> No satisfactory separation of enantiomers could be obtained.<sup>18</sup>

**SCHEME 4.** Hydroamination in the Presence of A or in the Presence of Its Oxide

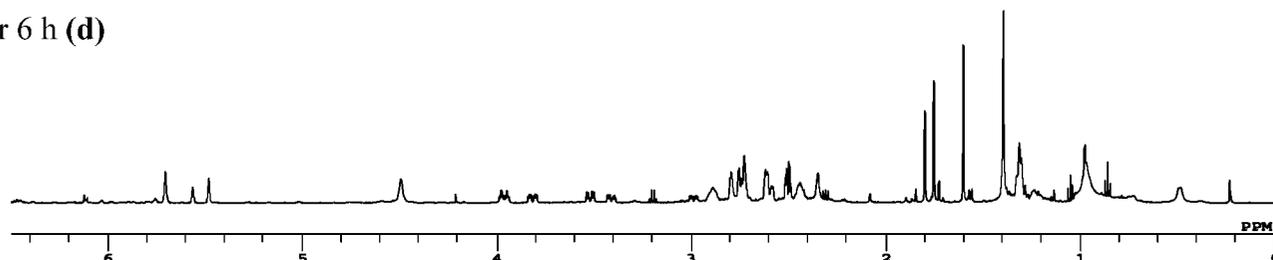
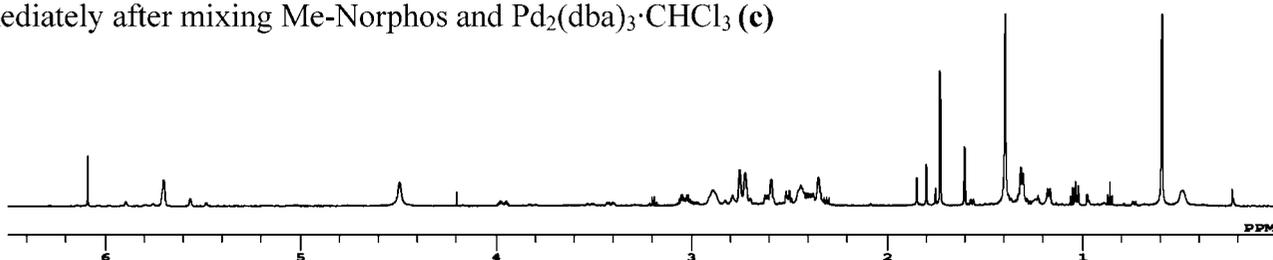
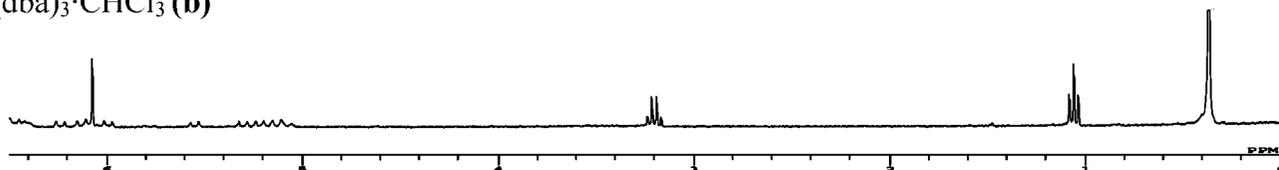
CHCl<sub>3</sub>, but as mentioned later, this ethyl signal works as an internal standard in the NMR experiments and the impurity due

to this ethyl signal does not exert any significant influence on the reaction progress. Comparison of the spectra of Figure 3c

After 24 h (e)



After 6 h (d)

Immediately after mixing Me-Norphos and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (c)Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (b)

Me-Norphos (a)

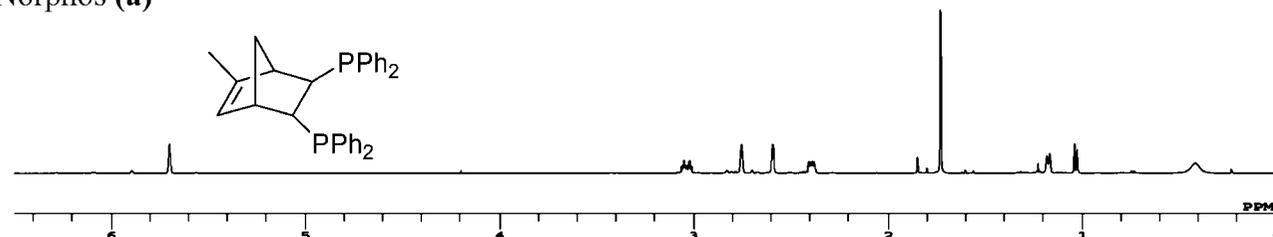


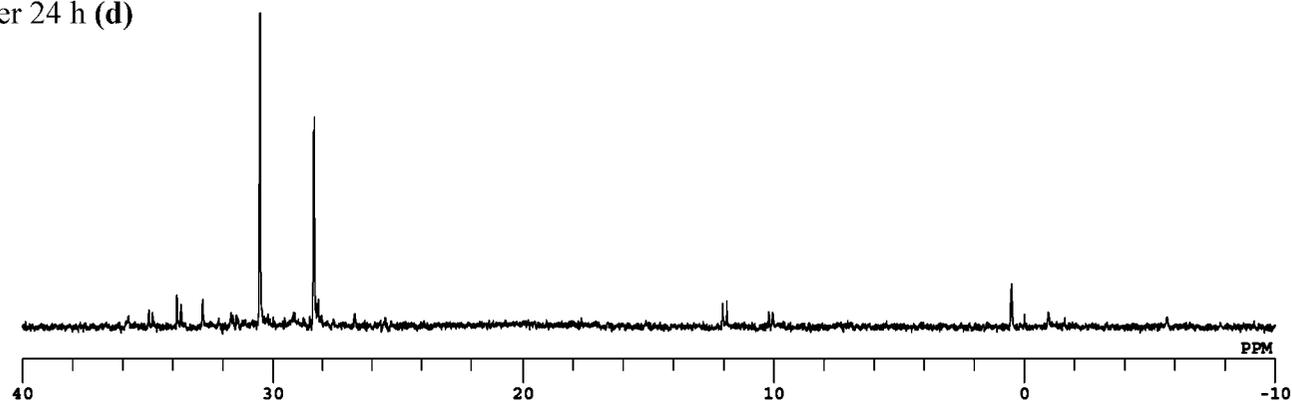
FIGURE 3. <sup>1</sup>H NMR spectra of Me-Norphos and its oxide in C<sub>6</sub>D<sub>6</sub>. The spectra of the aromatic region were omitted.

with those of Figure 3a,b clearly indicates that new spectra appear immediately after mixing Me-Norphos and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>. The new spectra consist of the peaks of Me-Norphos, Me-Norphos oxide, unidentified peaks, and the ethyl signal. We expanded this spectra in order to see the olefinic peaks of dba, but those peaks could not be found; perhaps they were shifted to some other region by coordination of palladium to Me-Norphos. It was thought that unidentified peaks correspond to Me-Norphos monoxides (a mixture of *exo*- and *endo*-monoxides) and/or palladium–phosphine complexes. After 6 h, the spectra 3c changed gradually, as shown in Figure 3d. After 24 h, completely different spectra were obtained (Figure 3e), which

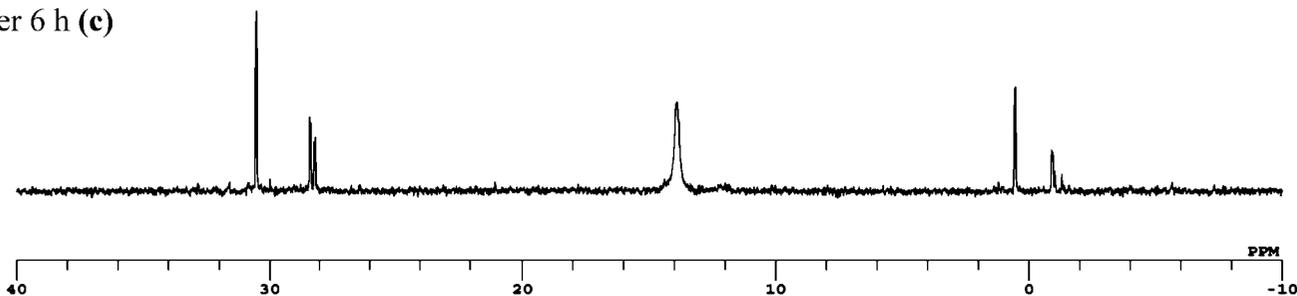
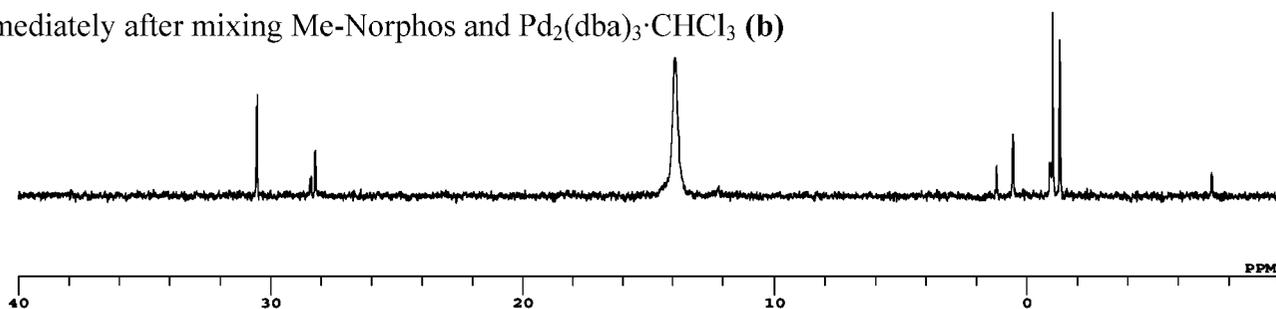
matched the spectra of Me-Norphos oxide. It should be noted that an internal standard, ethyl signal, remains unchanged. More detailed spectral changes depending on time are shown in the Supporting Information.

Accordingly, it is now clear that, in presence of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, Me-Norphos was converted to Me-Norphos oxide even under the conditions using Ar atmosphere. Oxygen dissolved in C<sub>6</sub>D<sub>6</sub> for the NMR experiments was not removed, but we handled C<sub>6</sub>D<sub>6</sub>, Me-Norphos, Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, and NMR tube under Ar atmosphere. Therefore, it was thought that oxygen dissolved in the solvent worked as an oxidant in the presence of palladium catalyst.<sup>28</sup> Formation of the phosphine oxide

After 24 h (d)



After 6 h (c)

Immediately after mixing Me-Norphos and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (b)

Me-Norphos (a)

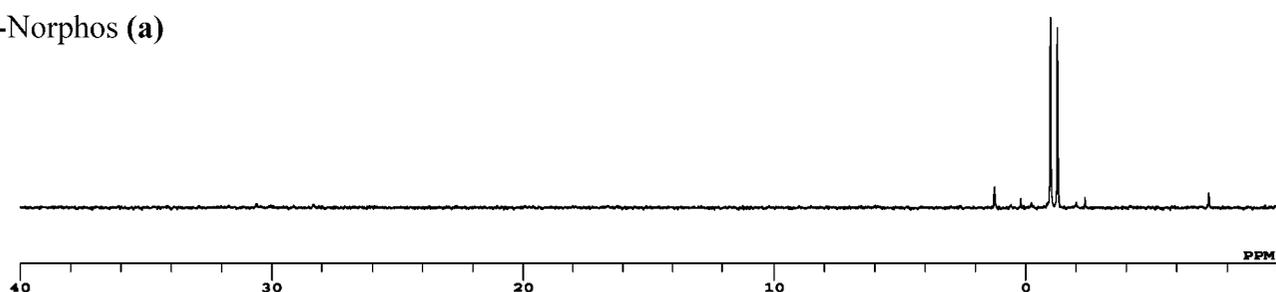


FIGURE 4. <sup>31</sup>P NMR spectra of Me-Norphos and its oxide in C<sub>6</sub>D<sub>6</sub>.

prevents the hydroamination of alkyne (Scheme 4). To overcome this problem, we weighed all the materials under a glovebox and used C<sub>6</sub>D<sub>6</sub> bubbled by passing Ar and carried out the NMR experiments. However, the same results were obtained. If we use a vacuum line to completely deoxygenate C<sub>6</sub>D<sub>6</sub>, oxidation of Me-Norphos must be prevented. We were unable to minimize or halt completely oxidation of Me-Norphos in the presence of

Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>. It should be noted that oxidation of Me-Norphos to Me-Norphos oxide is facilitated remarkably by the palladium catalyst; as mentioned above, Me-Norphos is not oxidized *in the absence of palladium catalyst* even after 3 days. From the NMR experiments, it is now clear why initially the rate of reaction using **A** as a ligand is very fast; there is no formation of methyl Norphos oxide at an early stage of the reaction (Figure 2). As time goes on, the rate of reaction becomes slow due to the gradual conversion of methyl Norphos **A** to its oxide **4** form. After 12 h, the product was obtained in 58% yield, after 24 h 70% yield, and after 2 days 95% yield (Figure 2).<sup>29</sup> As shown in Table 2, 20 mol % of **A** was required to obtain high ee and high yield of **16a**, and use of a less amount

(28) The use of a vacuum line and vacuum technique, as physical chemists often use it to make a completely degassed solvent, must give a really oxygen-free C<sub>6</sub>D<sub>6</sub>. We did (or do) not have such equipment. We are not able to completely remove solvated oxygen merely by bubbling a solvent with Ar. Similar oxidation of DuPhos has been observed by Charette and co-workers: Charette, A. B.; Cote, A.; Desrosiers, J.-N.; Bonnaventure, I.; Lindsay, V. N. G.; Lauzon, C.; Tannous, J.; Boezio, A. A. *Pure Appl. Chem.* **2008**, *80*, 881–890. They reported that DuPhos monoxide produces high enantioselectivities.

of **A** was not suitable because of gradual oxidation of **A** to methyl Norphos monoxides and the methyl Norphos oxide. More remarkable change with the use of less amounts of **A** was the enantioselectivities (Table 2, entries 1–3 vs 4–5). Perhaps, only **A** could produce high ee and methyl Norphos monoxides formed before conversion to **A** (dioxide) would produce very low ee, although the hydroamination proceeded in the presence of the monoxides. In the previous communication,<sup>18</sup> a stoichiometric amount (100 mol %) of Renorphos was needed to obtain high ee and high yield of the hydroamination products. A reason for this is also now clear; oxidation of Renorphos in the presence of palladium catalyst would compete with the intramolecular hydroamination process. In Table 1 and in the previous communication,<sup>18</sup> we reported that the use of Norphos gave a high ee (92% ee) but the yield was very low (5%). We observed that the rate of reaction is very slow with Norphos ligand compared to other Norphos and Renorphos derivatives (Table 1), and from the NMR experiments, it was clear that oxidation of Norphos to Norphos oxide occurring in the presence of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> in C<sub>6</sub>D<sub>6</sub> was quick when compared to the rate of the hydroamination reaction (more details about the NMR experiments using Norphos ligand are shown in the Supporting Information). Accordingly, the hydroamination using Norphos would be halted by conversion of the ligand to its oxide. Now all of these previous observations are understandable.

Since the difference between the <sup>1</sup>H NMR spectra of the intermediate stages (Figure 3c,d) is not necessarily clear, <sup>31</sup>P NMR spectra were measured. Two singlet peaks of Me-Norphos appeared at –1.247 and –0.970 ppm (Figure 4a). Immediately after mixing Me-Norphos and Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>, Me-Norphos and a small amount of Me-Norphos oxide were observed together with unidentified signals, perhaps due to intermediates of palladium–methyl Norphos complex or due to Me-Norphos monoxides (Figure 4b). After 6 h, the signals of Me-Norphos oxide and of unidentified intermediates increased, whereas those of Me-Norphos decreased (Figure 4c). After 24 h, two doublet signals of Me-Norphos oxide appeared at 28.367 and 30.522 ppm (Figure 4d).

## Conclusion

We have developed a convenient method for the synthesis of chiral Norphos derivatives and used diphosphine ligands for the hydroamination of alkynes with a Pd catalyst. Among Norphos derivatives, methyl Norphos **A** was found to be the best ligand for the hydroamination of alkynes, and the corresponding five- and six-membered nitrogen heterocyclic compounds were obtained in high yields with high enantioselectivities. Tollyl Renorphos **E** gave also excellent results. NMR experiments revealed that these Norphos and Renorphos ligands underwent slow oxidation in the presence of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> catalyst in C<sub>6</sub>D<sub>6</sub> even under Ar atmosphere.

## Experimental Section

**Synthesis of Tollyl Norphos (B) and Tollyl Renorphos (E).**  
**Synthesis of Bis(4-methylphenyl)phosphineoxide 5:** A 1.0 M solution of 4-methylphenylmagnesium bromide was prepared by slow addition of 4-methylbromobenzene (12.3 mL, 100 mmol) in 30 mL of THF to a slurry of 2.6 g (110 mmol) of Mg turnings in 60 mL of dry THF. After stirring this mixture at rt for 2 h, this solution was added slowly to a solution of 8.3 g (50 mmol) of (Et<sub>2</sub>N)PCl<sub>2</sub> in 50 mL of THF at 0 °C. The resulting mixture was further stirred at rt overnight. This reaction mixture was cooled to

0 °C, and concentrated aqueous hydrogen chloride (8.0 mL, 100 mmol) was added slowly, and the resulting mixture was stirred at rt for 4 h. The reaction was quenched by adding water (100 mL). Ethyl acetate (200 mL) was added, and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate (50 mL) two times. The combined organic layers were washed with brine (20 mL) and dried over magnesium sulfate. After evaporation of the solvents under vacuum, the residue was purified by column chromatography on silica gel (hexane/EtOAc = 1:1) to give the product **5** (14.1 g, 65% yield) as a white solid. All the spectral data were identical with the reported data.<sup>26</sup>

**Synthesis of Bis(4-methylphenyl)chlorophosphine 6:** To a stirred solution of PCl<sub>3</sub> (6.00 g, 45 mmol) in benzene (20 mL) was added dropwise bis(4-methylphenyl)phosphine oxide **5** (10.0 g, 46 mmol) in 25 mL of toluene at 0–10 °C. The reaction mixture was stirred for 30 min at 0–10 °C. Distillation of the solvent under vacuum gave the crude product, which was further purified by high vacuum distillation: bp 145–150 °C/mmHg. Pure **6** (7.0 g) was obtained in 65% yield as a yellowish liquid. All the spectral data were identical with the reported data.

**Synthesis of trans-1,2-Ethenediylbis[di(4-methylphenyl)phosphineoxide] 8:** To a stirred solution of Li wire (0.5 g, 72 mmol) in THF (100 mL) was added bis(4-methylphenyl)chlorophosphine **6** (6.0 g, 24 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 4 h and then refluxed for 1 h. The organic layer was transferred to another reaction flask via a cannula to remove an excess amount of unreacted Li wire and cooled to 0 °C. To this cooled solution was added *trans*-1,2-dichloroethylene (1.9 g, 12 mmol), and the reaction mixture was allowed to stir at room temperature for 3 h. Removal of the solvent under vacuum, addition of water, filtration of solid, followed by washing with water, methanol, and acetone gave *trans*-1,2-ethenediylbis[di(4-methylphenyl)phosphine] **7** (7.2 g, 66% yield). This compound was dissolved in acetone (500 mL) and treated with aqueous hydrogen peroxide (3.5 mL). The reaction mixture was stirred at room temperature for 1 h. Removal of the solvent under vacuum, addition of water, filtration of solid, followed by washing with water, methanol, and acetone gave *trans*-1,2-ethenediylbis[di(4-methylphenyl)phosphineoxide] **8**, which was purified by column chromatography on silica gel using CHCl<sub>3</sub>/MeOH (95:5) as an eluent, giving the product **8** as a white solid (5.1 g, 70% yield from **7**): mp 315–316 °C; IR (neat) 3017, 2987, 1600, 1184, 1166, 709 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.31 (s, 12H), 7.18 (m, 8H), 7.49 (m, 8H), 7.61 (d, *J* = 24 Hz, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 21.9, 128.5 (4 lines), 129.8 (m), 131.6 (m), 141.6 (5 lines), 143.1; HRMS (ESI) calcd for C<sub>30</sub>H<sub>30</sub>O<sub>2</sub>P<sub>2</sub>Na [M + Na] *m/z* 507.1619, found 507.1613.

**Synthesis of Tollyl Norphos Oxide 9:** *trans*-1,2-Ethenediylbis[di(4-methylphenyl)phosphineoxide] **8** (2.4 g, 5 mmol) and freshly cracked cyclopentadiene (9 mL, 100 mmol) were heated in a sealed metal reactor at 170 °C for 4 h. Then the reactor was cooled to rt. The product was taken out of the reactor by dissolving in dichloromethane. The solvent was evaporated under vacuum to obtain the crude product, which was further purified by silica gel column chromatography using CHCl<sub>3</sub>/EtOAc (1:1) as an eluent, giving tollyl Norphos oxide **9** as a white solid (1.9 g, 71% yield): mp 158–160 °C; IR (neat) 3027, 2980, 1603, 1501, 1394, 1171, 1107, 767 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.23 (m, 1H), 2.14 (s, 3H), 2.17 (br s, 1H), 2.22 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 2.89 (br s, 1H), 3.16 (dd, *J* = 4.5, 15.6 Hz, 1H), 3.68 (dm, *J* = 15 Hz, 1H), 5.83 (dd, *J* = 2.7, 5.1 Hz, 1H), 6.29 (dd, *J* = 2.7, 5.7 Hz, 1H), 6.77 (d, *J* = 6 Hz, 2H), 6.85 (d, *J* = 6.3 Hz, 2H), 7.21 (t, *J*

(29) A reviewer pointed out that the following observations seemed to be contradictory; the diphosphine has been oxidized after 24 h as shown in Figures 3 and 4, while the catalytic cycle is still active after 36 h, as shown in Figure 2. We think that the former case consists of a two-component system (phosphine and palladium), whereas the latter case consists of a three-component system (phosphine, palladium, and substrate), and this difference may lead to seemingly contradictory observations.

= 8.1 Hz, 4 H), 7.36 (dd,  $J = 8.1, 10.5$  Hz, 2H), 7.47 (dd,  $J = 7.8, 10.8$  Hz, 2H), 7.58 (dd,  $J = 8.1, 10.5$  Hz, 2H), 7.67 (dd,  $J = 8.1, 10.5$  Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  21.3 (2C), 21.4 (2C), 38.4 (d,  $J_{\text{CP}} = 74.6$  Hz), 39.5 (d,  $J_{\text{CP}} = 66.6$  Hz), 47.0 (d,  $J_{\text{CP}} = 14.1$  Hz), 48.0 (d,  $J_{\text{CP}} = 10.5$  Hz), 129.1 (8 lines for 2C), 130.6 (9 lines for 2C), 137.9 (7 lines); HRMS (ESI) calcd for  $\text{C}_{35}\text{H}_{36}\text{O}_2\text{P}_2\text{Na}$  [M + Na]  $m/z$  573.2088, found 573.2083.

**Resolution of Tollyl Norphos Oxide 9:** Racemic tolyl Norphos oxide **9** was separated using quantitative chiral HPLC CHIRALPAK IA. The racemic compound **9** (50 mg) dissolved in 5 mL of ethanol was injected in the column using hexane/EtOH (80:20) as an eluent. The flow rate was 8 mL/min. First, the enantiomer (*R,R*)-**9** was collected at 25 min, and then the enantiomer (*S,S*)-**9** was collected at 37 min. This procedure was repeated several times, and each enantiomer was collected in separate conical flasks. Evaporation of the solvents gave the pure enantiomers as a white solid. For (*R,R*)-**9**:  $[\alpha]_{\text{D}}^{20} = -13.9$  ( $c$  1,  $\text{CHCl}_3$ ); mp 253–255 °C. For (*S,S*)-**9**:  $[\alpha]_{\text{D}}^{20} = +14.0$  ( $c$  1,  $\text{CHCl}_3$ ); mp 253–255 °C.

**Synthesis of (*R,R*)-Tollyl Norphos (B):** To a stirred solution of tolyl Norphos oxide (*R,R*)-**9** (1.0 g, 2 mmol) in xylene (25 mL) were added tributylamine (1 mL, 10 mmol) and trichlorosilane (2.38 mL, 10 mmol). The reaction mixture was heated to 120 °C for 6 h in an autoclave excluding air and moisture. The solvent and excess of reagents were evaporated. The residue was dissolved in benzene. After cooling to 0 °C, 25 mol % of NaOH (10 mL) was added slowly. The water phase was washed with benzene (25 mL). The combined benzene solution was evaporated under vacuum to obtain the crude product, which was purified by column chromatography on silica gel (hexane/EtOAc = 10:1) to obtain (*R,R*)-tolyl Norphos (**B**) as a white solid (0.77 g, 74% yield):  $[\alpha]_{\text{D}}^{20} = -10.1$  ( $c$  1,  $\text{CHCl}_3$ ); mp 129–130 °C; IR (neat) 3065, 2917, 1597, 1495, 1020, 800, 751  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  1.25 (d,  $J = 9.9$  Hz, 1H), 1.38 (d,  $J = 9.9$  Hz, 1H), 1.89 (m, 2H), 1.97 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.06 (s, 3H), 2.62 (dd,  $J = 5.3, 11.1$  Hz, 1H), 2.90 (br s, 1H), 3.16 (dm,  $J = 17$  Hz, 1H), 6.25 (br s, 2H), 6.75 (d,  $J = 7.5$  Hz, 2H), 6.80 (d,  $J = 7.9$  Hz, 2H), 6.92 (d,  $J = 8.4$  Hz, 2H), 6.96 (d,  $J = 7.5$  Hz, 2H), 7.32 (dd,  $J = 6.6, 7.5$  Hz, 2H), 7.65 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  21.1, 21.2 (2C), 21.2, 40.9 (dd,  $J = 16, 23$  Hz), 42.8 (dd,  $J = 11, 22$  Hz), 47.3 (multiple lines, 2C), 47.7 (dd,  $J = 4, 12$  Hz), 129.0 (d,  $J_{\text{CP}} = 6$  Hz, 2C), 129.3 (d,  $J_{\text{CP}} = 4$  Hz), 129.4 (d,  $J_{\text{CP}} = 4$  Hz), 133.1 (d,  $J_{\text{CP}} = 17$  Hz), 134.2 (dd,  $J_{\text{CP}} = 2, 21$  Hz), 134.3 (d,  $J_{\text{CP}} = 20$  Hz), 135.0 (d,  $J_{\text{CP}} = 20$  Hz), 135.1 (m), 136.6 (dd,  $J_{\text{CP}} = 1, 28$  Hz), 136.7 (dd,  $J_{\text{CP}} = 2, 24$

Hz), 137.5, 138.1, 138.4, 138.9 (4 lines for 2C); HRMS (ESI) calcd for  $\text{C}_{35}\text{H}_{37}\text{P}_2$  [M + H]  $m/z$  519.2370, found 519.2365.

**Synthesis of (*R,R*)-Tollyl Renorphos:** To a solution of (*R,R*)-tolyl Norphos **B** (0.52 g, 1 mmol) in methanol (20 mL) was added 5% Pd/C (0.187, 10 mol %). Reaction mixture was stirred at rt for 12 h under hydrogen atmosphere (hydrogen balloon). Reaction mixture was filtered through Celite to remove the Pd/C and washed with methanol. Evaporation of the solvent under vacuum yielded (*R,R*)-tolyl Renorphos **E** as a white solid (0.42 g, 82% yield):  $[\alpha]_{\text{D}}^{20} = -5.1$  ( $c$  1,  $\text{CHCl}_3$ ); mp 123–125 °C; IR (neat) 3068, 2947, 1599, 1885, 1495, 1081, 793  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  0.63 (d,  $J = 11$  Hz, 1H), 0.74 (d,  $J = 11$  Hz, 1H), 0.95 (m, 1H), 1.29 (m, 2H), 1.67 (s, 3H), 1.73 (s, 3H), 1.75 (s, 3H), 2.03 (s, 1H), 2.21 (m, 2H), 2.82 (m, 1H), 6.54 (dd,  $J = 8, 12$  Hz, 4H), 6.65 (dd,  $J = 8, 12$  Hz, 4H), 7.00 (m, 2H), 7.00 (m, 2H), 7.00 (t,  $J = 7$  Hz, 2H), 7.39 (m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  21.2, 25.7 (d,  $J = 23.4$  Hz), 32.2, 32.7, 41.4 (dd,  $J = 3, 11$  Hz), 41.8 (d,  $J = 3$  Hz), 44.1 (dd,  $J = 20, 22$  Hz), 44.3 (dd,  $J = 8, 12$  Hz), 129.3 (ddd,  $J = 7.5, 12.3$  Hz), 132.8 (d,  $J = 17$  Hz), 134.0 (d,  $J = 20$  Hz), 135.2 (m), 136.0 (d,  $J = 11$  Hz), 137.1, 138.6 (3 lines); HRMS (ESI) calcd for  $\text{C}_{35}\text{H}_{39}\text{P}_2$  [M + H]  $m/z$  521.2527, found 521.2522.

**General Procedure for Asymmetric Intramolecular Hydroamination of Alkynes.** To  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (5 mol %), PhCOOH (10 mol %), and (*R,R*)-methyl Norphos or (*R,R*)-tolyl Renorphos derivatives (20 mol %) was added the substrate **15** (0.125 mmol) in 1.5 mL of benzene under Ar atmosphere in a screw capped vial. After heating at 100 °C for 48 h, the reaction mixture was filtered through a short silica gel column using diethyl ether as an eluent. After evaporation of the solvents, the residue was purified by silica gel column chromatography to afford the corresponding cyclization product **16**. All the products were identified by IR, NMR, Mass, and elemental analysis data, and those data were compared with the reported data if they were known.<sup>18,19</sup> All the ee's were confirmed by chiral HPLC using CHIRALCELL OD.

**Supporting Information Available:** Complete experimental procedures for the synthesis of methyl Norphos, methyl Renorphos, and  $\text{CF}_3$  Norphos ligands, characterization,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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