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Palladium-Catalyzed Intramolecular Asymmetric Hydroamination, Hydroalkoxylation, and Hydrocarbonation of Alkynes

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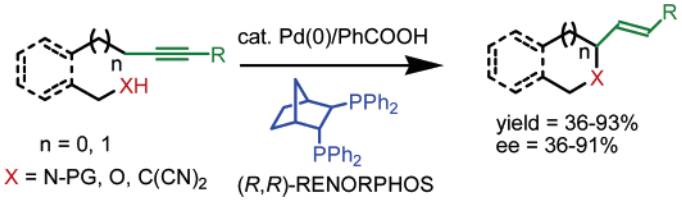

A conceptually novel approach for asymmetric intramolecular hydroamination, hydroalkoxylation and hydrocarbonation of alkynes using chiral palladium catalysts are described. The reactions of the aminoalkynes **5**, alkynols **7**, and alkynylmethines **9** in the presence of $Pd_2(dba)_3$·$CHCl_3$/PhCOOH/renorphos **4** in benzene (or benzene−hexane) at 100 °C gave the corresponding cyclization products (nitrogen heterocycles **6**, oxygen heterocycles **8**, and carbocycles **10**) in good yields with good enantioselectivities. The origins of enantioselectivities in the hydroamination reaction are discussed based on DFT computations.

Introduction

The metal-catalyzed addition of nucleophiles to activated C−C bonds such as alkenes,[1] allenes,[2] and 1,3-dienes[3] is one of the most important processes in organic synthesis. The addition of carbon, amine, and alcohol nucleophiles across an activated C−C bond is referred as hydrocarbonation,[4] hydroamination,[5] and hydroalkoxylation,[6] respectively (Scheme 1, eqs 1−3). In contrast to substitution reactions (eq 4),[7] these processes are very important from the synthetic point of view because, in principle, the addition reactions can be performed

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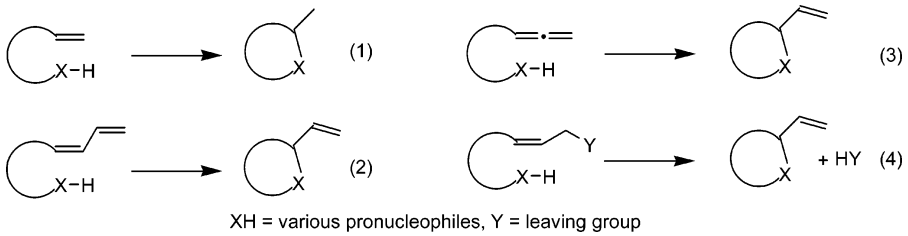
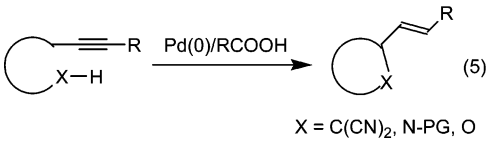
SCHEME 1. Cyclization via Addition of Pronucleophiles to Activated C−C Bonds



with 100% atom efficiency,[8] without any waste formation. Although tremendous amounts of the related work have been carried out in the field of hydrocarbonation and hydroamination reactions, very few reports are known for hydroalkoxylation reactions partly due to the diminished nucleophilicity and the weaker Lewis base character of oxygen nucleophiles compared to those of amines. Although some progress has been made in this area, reports on asymmetric versions of these processes are scarce.[9] Therefore, the development of enantioselective methods for the formation of C−C and C−X bonds by these processes is highly desired.

Recently, we reported a new approach for the addition of carbon[10] nucleophiles to alkynes in the presence of a Pd(0)/carboxylic acid[11] combined catalyst.[12] Later we extended our work to the addition of nitrogen[13] and oxygen[14] nucleophiles to alkynes (eq 5). Since the product is obtained via formal



substitution at the propargylic position with X^- and subsequent addition of H−H to alkyne, no waste elements are produced. Moreover, the presence of a base, which is required in the case of Tsuji−Trost allylation (eq 4), was not needed in these reactions. Particularly interesting is the intramolecular asymmetric version of these reactions, which would lead to the synthesis of a variety of chiral building blocks (eq 5).

After a detailed literature survey we found that the only successful examples toward this goal involved the hydroamination/cyclization of aminoalkenes and aminodienes using lanthanide complexes to form chiral piperidines.[15] Although good enantioselectivities (ee up to 89%) were achieved, the susceptibility of these complexes to moisture and oxygen constituted a serious drawback. The intermolecular enantioselective hydroamination of olefins catalyzed by late transition metals has also been reported.[16] However, to the best of our knowledge, there have been no reports on intramolecular asymmetric hydroalkoxylation[17] and hydrocarbonation. We realized that the scope and synthetic utility of our newly discovered process (eq 5) would be enhanced dramatically if a chiral ligand which allows the reaction to be carried out in an enantioselective manner could be found. Since then we initiated our search for a proper chiral ligands. Finally, we found that a chiral palladium catalyst, derived from $Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*,*R*)-renorphos, is highly effective for catalyzing asymmetric intramolecular hydroamination.[18]

In this paper we report that (i) the intramolecular catalytic asymmetric hydroamination, hydroalkoxylation, and hydrocar-

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(12) This process is similar to the hydroacylation process for the allylation of acetic acid with alkynes which gives allylic acetates. See: Trost, B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335−1336.

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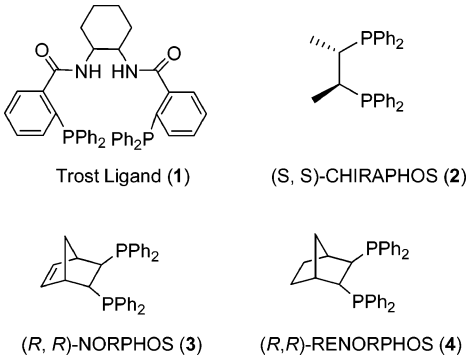
(18) For a preliminary communication, see: Lutete, M. L.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1622−1623.

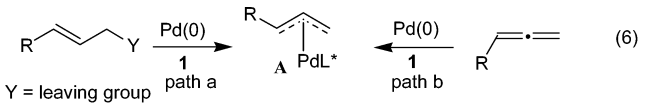
SCHEME 2. Structure of Some Ligands



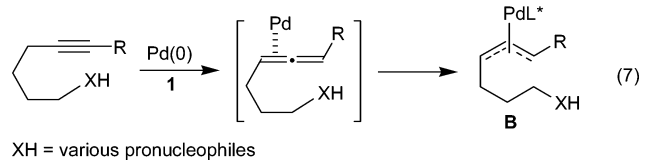
bonation of alkynes using chiral palladium catalyst [prepared in situ by mixing $Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*,*R*)-renorphos][19] give the corresponding heterocycles and carbocycles in good yields and with good enantioselectivities and (ii) DFT computational studies help to clarify the origin of the enantioselectivities of the present catalytic asymmetric cyclization.

Results and Discussion

Asymmetric Hydroamination of Alkynes. The Trost ligand **1**[7] (Scheme 2) emerges as the ligand of choice for the highly enantioselective allylic alkylation of various nucleophiles with allylic substrates through intermediacy of the π-allyl−Pd complex **A** (eq 6, path a). Pioneering work from the same group



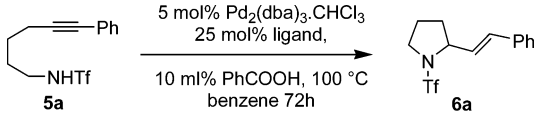
(6)



(7)

also revealed the asymmetric allylation of carbon nucleophiles with allenes,[2h] wherein allenes form the chiral π-allyl−Pd complex **A** (eq 6, path b). As we proposed the intermediacy of allenes in our reaction, we envisioned that, in the presence of the ligand **1**, chiral π-allyl−Pd complex **B** would be generated and the enantiopure products would be obtained after subsequent reaction with the tethered nucleophiles (eq 7). Accordingly, the aminoalkyne **5a** was treated with $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), **1** (25 mol %), and benzoic acid (10 mol %) in benzene at 100 °C for 72 h. Disappointingly, the reaction was very sluggish, and the product **6a** was isolated in 51% yield with 12% ee (Table 1, entry 1). Although we investigated various palladium sources in the presence of **1** and changed stoichiometries of the palladium sources and the ligand, the enantioselectivity could not be improved. Then we screened a variety of chiral nonracemic phosphine ligands (monophosphines, bisphosphines, and mixed P, N ligands) using the aminoalkyne **5a** as a model substrate.[20] The results of selected ligand screening are summarized in Table 1. When we employed (*R*,*R*)-chiraphos **2** as a

TABLE 1. Selected Ligand Screening[a]



entry	ligand	yield[b]	ee
1	Trost ligand (**1**)	51	12
2	(*R*,*R*)-chiraphos (**2**)	92	25
3	(*R*,*R*)-norphos (**3**)	5	98
4	(*R*,*R*)-renorphos (**4**)	54	81
5	(*R*,*R*)-renorphos (**4**)	65	82[c]

[a] The reactions of alkyne **5a** (0.125 mmol) in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (5 mol %), ligands (25 mol %), and benzoic acid (10 mol %) were carried out at 100 °C in benzene for 72 h. [b] Isolated yields. [c] An amount of 30 mol % of (*R*,*R*)-renorphos was used.

ligand the product **6a** was obtained in 92% yield with 25% ee (entry 2). Although the ee was not satisfactory, this result led us to examine diphosphine ligands because the bite angle of ligands often changes the nature of palladium catalysts and dramatically increases the reactivity. The use of (*R*,*R*)-norphos **3** gave **6a** with 98% ee; however, the yield was only 5% (entry 3). Encouraged by this result we next tried (*R*,*R*)-renorphos **4**, and to our pleasure **6a** was obtained in 65% yield with 82% ee.

We next examined the effect of various protecting groups; instead of −Tf, (65%, 82% ee), benzyl (95%, 8% ee), acetyl (0%), Boc (0%), and tosyl (25%, 47% ee) were used, but unsatisfactory results were obtained. We were pleased to find that nonafluorobutanesulfonyl (−Nf) as an amine protecting group gave the best result. The reactions were examined under two conditions that differ about the relative stoichiometries of $Pd_2(dba)_3{\cdot}CHCl_3$, PhCOOH, and the ligand **4**: condition A, 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 10 mol % of PhCOOH, and 25 mol % of (*R*,*R*)-renorphos **4** in benzene at 100 °C for 72 h; condition B, 20 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 40 mol % of PhCOOH, and 100 mol % of (*R*,*R*)-renorphos **4** in benzene/hexane (2:1) at 80 °C for 72 h. Various nitrogen heterocycles **6b**−**g** were synthesized from aminoalkynes **5b**−**g** under those conditions, and the results are summarized in Table 2.

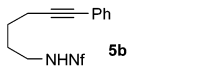
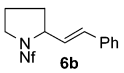
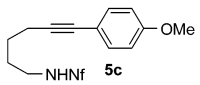
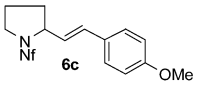
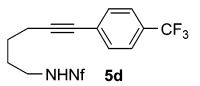
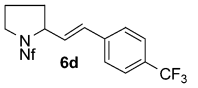
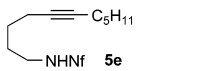
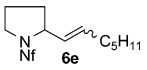
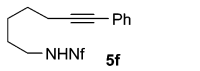
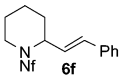
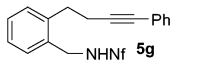
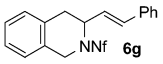
Asymmetric Hydroalkoxylation of Alkynes. Next, we envisioned that, in the presence of the chiral palladium catalyst, oxygen nucleophiles (alkynols) must undergo catalytic asymmetric intramolecular hydroalkoxylation in a similar manner, allowing the synthesis of optically active cyclic ethers[21] which are known to be structural elements of many naturally occurring compounds. Thus, the alkynol **7a** was treated with the palladium catalyst under condition A, which gave the corresponding cyclic ether **8a** in 20% yield with 79% ee. Although the ee was not bad, the yield was very low. After detailed investigation on various chiral ligands, we found that renorphos **4** gave the best result again, and the combination of $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol %), PhCOOH (20 mol %), and (*R*,*R*)-renorphos **4** (60 mol %) (condition C) gave better results than conditions A and B. As shown in Table 3, the optimized conditions were applied to a

(19) The formation of the chiral rhodium complex Rh(I)−renorphos is known; see ref 32. However the formation of the Pd−renorphos complex has not been known in the literature.

(20) See the Supporting Information for details.

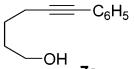
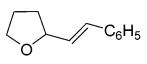
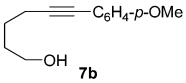
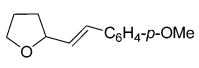
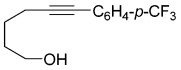
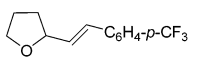
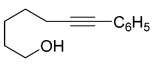
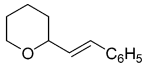
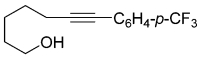
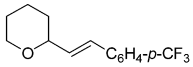
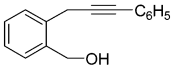
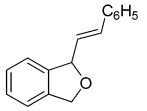
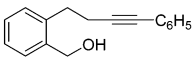
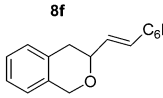
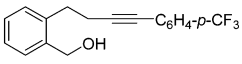
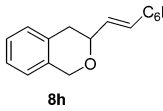
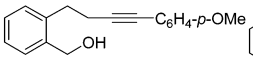
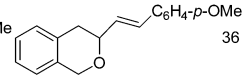
(21) There are innumerable reports on the synthesis and importance of optically active cyclic ethers. For instance, see: (a) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057−1059. (b) Ghosh, A. K.; Xu, C.-X.; Kulkarni, S. S.; Wink, D. *Org. Lett.* **2005**, *7*, 7−10. (c) Boto, A.; Hernandez, D.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **2003**, *68*, 5310−5319. (d) Tanaka, K.; Pescitelli, G.; Bari, L. D.; Xiao, T. L.; Nakanishi, K.; Armstrong, D. W.; Berova, N. *Org. Biomol. Chem.* **2004**, *2*, 48−58. (e) Ghorai, S.; Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron* **2005**, *61*, 2999−3012.

TABLE 2. Catalytic Intramolecular Asymmetric Hydroamination of Alkynes

entry	substrate (**5**)	product (**6**)	cond.[a]	yield[b] (%)	ee[c] (%)
1	 **5b**	 **6b**	A	68	83
			B	93	91
2	 **5c**	 **6c**	A	90	47
			B	90	81
3	 **5d**	 **6d**	A	52	77
			B	85	88
4	 **5e**	 **6e**	B	82	-[d]
5	 **5f**	 **6f**	A	63	77
			B	92	90
6	 **5g**	 **6g**	A	70	72
			B	90	87

[a] Condition A: 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 10 mol % of PhCOOH, and 25 mol % of (*R*,*R*)-renorphos **4** in benzene at 100 °C for 72 h. Condition B: 20 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 40 mol % of PhCOOH, and 100 mol % of (*R*,*R*)-renorphos **4** in benzene/hexane (2:1) at 80 °C for 72 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC. [d] The ee was not determined.

TABLE 3. Catalytic Intramolecular Asymmetric Hydroalkoxylation of Alkynes[a]

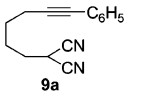
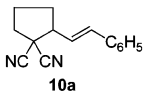
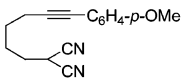
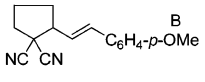
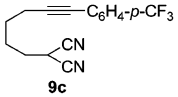
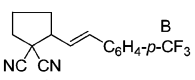
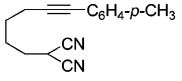
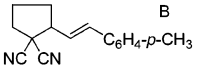
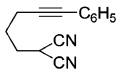
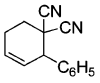
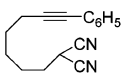
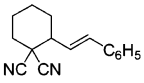
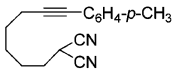
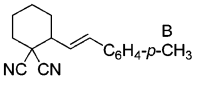
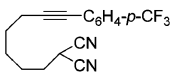
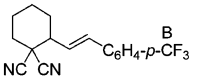
entry	substrate (**7**)	product (**8**)	yield (%)[b]	ee (%)[c]
1	 **7a**	 **8a**	52	80
2	 **7b**	 **8b**	48	40
3	 **7c**	 **8c**	60	82
4	 **7d**	 **8d**	61	78
5	 **7e**	 **8e**	67	74
6	 **7f**	 **8f**	92	88
7	 **7g**	 **8g**	57	86
8	 **7h**	 **8h**	55	86
9	 **7i**	 **8i**	36	42

[a] Condition C: 10 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % of PhCOOH, and 60 mol % of (*R*,*R*)-renorphos in benzene (0.5 M) at 100 °C for 72 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC.

wide range of substrates. Hydroalkoxylation of **7a** under the best conditions that we found gave the desired product **8a** in 52% yield with 80% ee (entry 1). The alkynol **7b** having the −OMe group at the para position gave **8b** in 48% yield; however, the enantioselectivity was low (entry 2). The alkynol **7c** having the $-CF_3$ group at the para position gave **8c** in 60% yield with 82% ee. Six-membered cyclic ethers **8d** and **8e** were obtained, in good yields and with good enantioselectivities, from the corresponding alkynols **7d** and **7e** (entries 4 and 5). The hydroalkoxylation reaction of the substrates wherein alkynes were tethered with alcohols through the aromatic ring was found to be a good substrate for this reaction. Thus, when **7f** was employed as a substrate, the reaction proceeded smoothly to produce **8f** in 92% yield with 88% ee (entry 6). The alkynol **7g** produced the isochromane **8g** in a high enantioselectivity (86% ee) with 57% yield (entry 7). Introduction of the $-CF_3$ group at the para position of the aryl group substituted at the terminus of the alkyne resulted in slight decrease of yield, but the enantioselectivity remained unaffected (entry 8). As shown in entry 9, substrate **7i** gave the corresponding heterocycle **8i** in a lower yield and with lower enantioselectivity. It becomes clear that this hydroalkoxylation reaction is very sensitive to the electronic effect of substituents at the aromatic ring attached at the terminus of the alkynes. Electron-donating substituents attached at the para position of the aromatic group gave lower yields and ee's.

Asymmetric Hydrocarbonation of Alkynes. We envisioned that, in the case of hydrocarbonation, the mode of reaction might be different from that of the hydroamination and hydroalkoxylation since carbon analogues are generally regarded as much softer nucleophiles in comparison with amines and alcohols. Accordingly, we tried several nonracemic chiral ligands that were tested for the hydroamination reaction. However, all of them gave unsatisfactory results except (*R*,*R*)-renorphos **4**. Thus, the catalytic system, Pd−renorphos, was extended to the asymmetric hydrocarbonation of alkynes tethered with active methines. Similar to the hydroamination, two conditions were examined; conditions A and B. Condition C gave results more or less similar to those using condition A. The results are summarized in Table 4. Under condition A, the substrate **9a** underwent cyclization to give the carbocycle **10a** in 70% yield with 65% ee. However, when **9a** was treated under condition B, a dramatic increment in yield and enantioselectivity was observed giving **10a** in 80% yield with 90% ee (entry 1). The substrates **9b**, **9c**, and **9d** bearing −OMe, $-CF_3$, and $-CH_3$ at the para position of the aromatic ring at the terminus of the alkyne gave the corresponding chiral carbocycles **10b**, **10c**, and **10d**, respectively, in good to high yields with good to high enantioselectivities (entries 2−4). Interestingly, the cyclization of **9e** smoothly proceeded to give the product **10e** in a high yield; however, determination of the ee proved difficult (entry

TABLE 4. Catalytic Intramolecular Asymmetric Hydrocarbonation of Alkynes

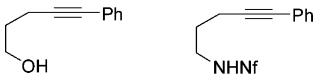
entry	substrate (**9**)	product (**10**)	cond[a]	yield (%)[b]	ee (%)[c]
1	 **9a**	 **10a**	A B	70 80	65 90
2	 **9b**	 **10b**	B	73	71[d]
3	 **9c**	 **10c**	B	81	68
4	 **9d**	 **10d**	B	81	88[d]
5	 **9e**	 **10e**	B	85	.[e]
6	 **9f**	 **10f**	A B	60 82	42 72
7	 **9g**	 **10g**	B	75	76[d]
8	 **9h**	 **10h**	B	85	61

[a] Condition A: 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 10 mol % of $PhCO_2H$, 25 mol % of (*R*,*R*)-renorphos **4** in benzene, 100 °C, 72 h. Condition B: 20 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, 40 mol % of $PhCO_2H$, 100 mol % of (*R*,*R*)-renorphos **4** in benzene, 100 °C, 72 h. [b] Isolated yield. [c] The ee was determined by chiral HPLC. [d] (*S*,*S*)-renorphos was used. [e] Determination of ee proved difficult.

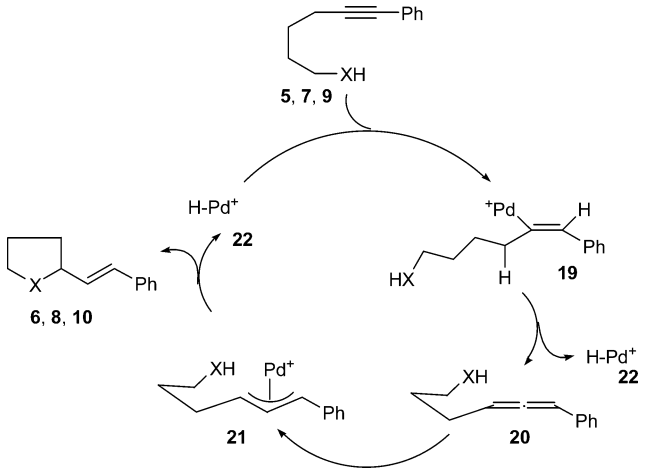
5).[22] Thus, the mode of the intramolecular cyclization strongly depends on the ring size of the products. This result is in contrast to the hydroamination and hydroalkoxylation results wherein the reactions of the corresponding aminoalkynes and alkynols did not give the desired products; the starting materials were recovered.[23] As stated in the entries 6−8, this method is also suitable for synthesizing six-membered carbocycles in good yields and with good enantioselectivities. It should be noted that the hydroamination, hydroalkoxylation, and hydrocarbonation reactions described herein are applicable to the cyclization forming five- and six-membered rings; however, it has turned

(22) Efforts to determine the ee of **10e** were undertaken using GC with different chiral columns. However, no satisfactory separation of enantiomers could be obtained.

(23) We tested the reactivity of the following substrates. Unlike the hydrocarbonation, these substrates proved inert under conditions A and B.

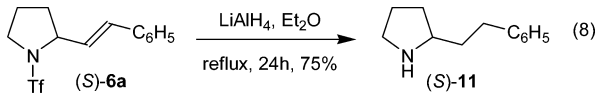


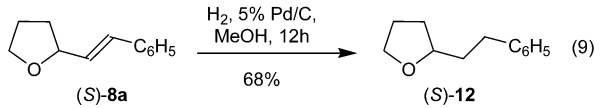
SCHEME 3. Plausible Mechanism for the Intramolecular Cyclizations



out that those reactions were not applicable to the cyclization forming larger ring sizes.[24] It is also notable that only renorphos is applicable to the catalytic asymmetric hydroamination, hydroalkoxylation, and hydrocarbonation, and the other well-known ligands are not useful.

Determination of Absolute Configurations. The absolute configuration of hydroamination product **6a** (82% ee) was determined by transforming it to the known compound **11** (eq 8). The literature[25] attributes the *R*-configuration to (+)-2-





phenethylpyrrolidine, although no value of ee is stated. Because the optical rotation of **11** was $[\alpha]^{22}_D = -8.7$ (*c* 0.75, $CHCl_3$), it was confirmed that the absolute configuration of **6a** is *S*. In a similar way, the absolute configuration of the hydroalkoxylation product **8a** (80% ee) was determined by transforming it to the known compound **12** (eq 9). It is known in the literature that (+)-2-phenethyltetrahydrofuran $[\alpha]^{23}_D = +4.2$ (*c* 1.06, $CHCl_3$) has *S*-configuration.[26] Since the optical rotation of **12** was $[\alpha]^{25}_D = +2.8$ (*c* 1.0, $CHCl_3$), it was unequivocally confirmed that the absolute configuration of **8a** is *S*. However, in the case of asymmetric hydrocarbonation, it proved difficult to assign the absolute configuration of the products.

Computational Studies. In our previous communication we proposed the catalytic cycle of hydroamination (Scheme 3).[18]

(24) We also tried the reaction of alkynes, bearing various electron-withdrawing groups (SO_2Ph and COOEt, instead of CN) at the end of the tethered carbon chain; however, the desired products were not obtained at all; instead, the corresponding dienes were obtained. For the formation of 1,3-dienes from π-allyl−Pd species, see: (a) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *117*, 55956−5957. (b) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301−2303.

(25) Armstrong, D. W.; Li, W.; Stacup, A. M.; Secor, H. V.; Izac, R. R.; Seeman, J. I. *Anal. Chim. Acta* **1990**, *234*, 365−380.

(26) Aquino, M.; Cardani, S.; Fronza, G.; Fuganti, C.; Fernandez, R. P.; Tagliani, A. *Tetrahedron* **1991**, *47*, 7887−7896.

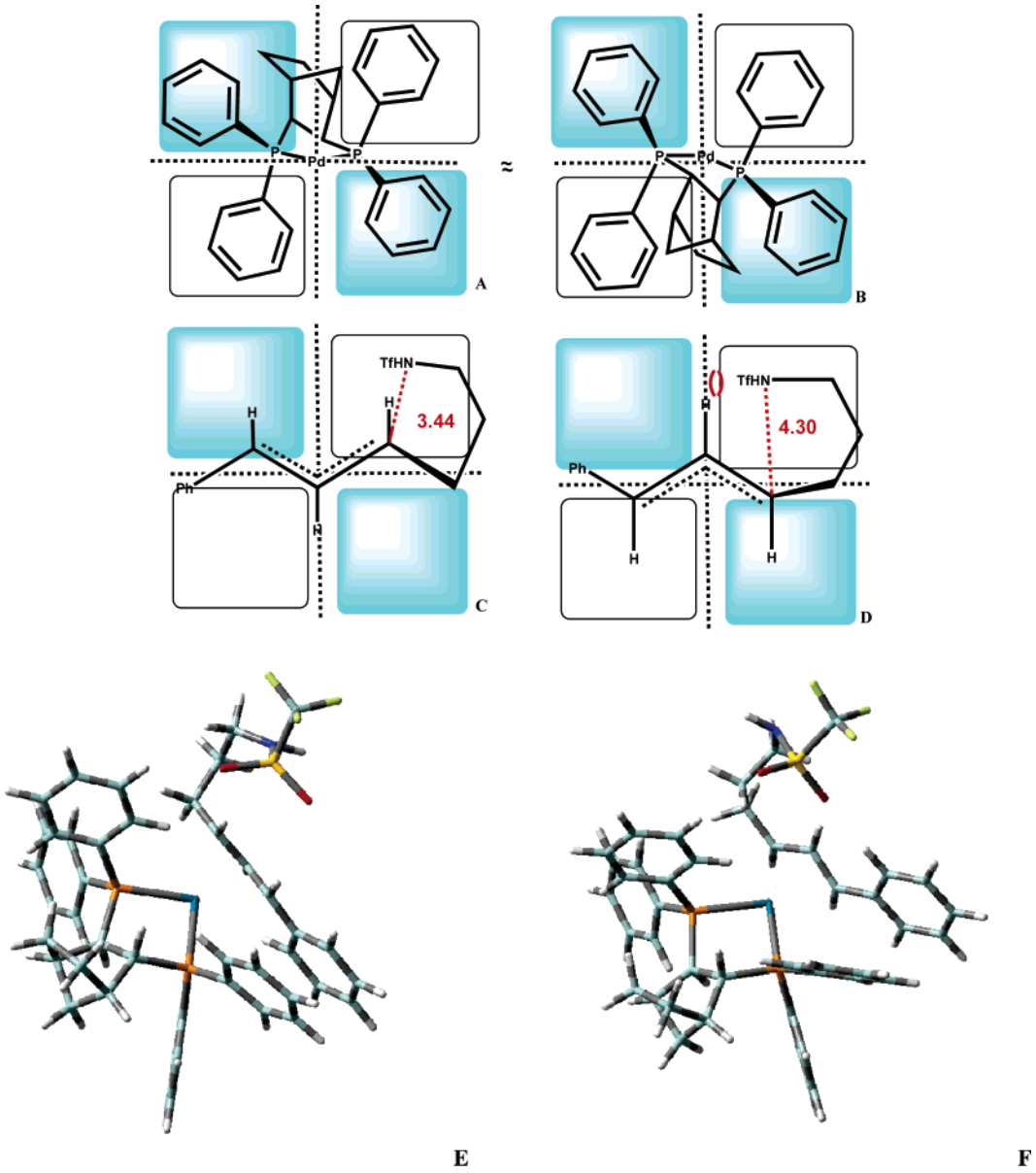


FIGURE 1. Origin of enantioselectivity in Pd-catalyzed intramolecular hydroamination. Parts A and B represent **4** as a C_2-symmetric ligand; equatorial phenyls of the diphosphine constitute hindered quadrants shown with filled blue squares; axial phenyls provide relatively smaller hindrance, and the corresponding quadrants are marked with hollow squares. Parts C and D represent the arrangement of the aminoalkyl chain in the precursors of *S*- (C) and *R*- (D) enantiomers in which the Pd complex is not shown for clarity, and the quadrants are marked in the same fashion as above. Parts E and F represent optimized structures (B3LYP/SDD) of the corresponding π-allyl complexes: carbons are sea-green, hydrogens are gray, P is orange, Pd is marine blue, N is blue, S is yellow, O is red, and F is green. Hindrance between the aminoalkyl chain and the central C−H group of the π-allyl moiety is shown with red brackets.

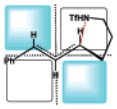
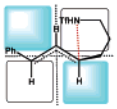
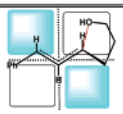
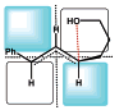
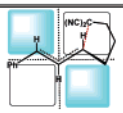
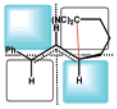
Hydropalladation of the alkynes **5**, **7**, and **9** with the hydridopalladium species **22** generated from Pd(0) and benzoic acid produces the vinylpalladium species **19**, which, via β-elimination, gives substituted phenyl allene **20**.[27] Subsequent hydropalladation of the allene **20** with **22** gives the π-allyl−Pd species **21**. Intramolecular nucleophilic attack of the tethered nucleophiles to the π-allyl carbon gives the products **6**, **8**, and **10** along with the hydridopalladium species **22**.

To get insight into the possible origins of enantioselectivity in the Pd-catalyzed cyclizations, we have carried out DFT computations[28] of the selected intermediates of the proposed catalytic cycle. First, we have considered the possibility of stereoselection on the last cyclization step, suggesting that under the reaction conditions different diastereomeric π-allyl−Pd species might interconvert reversibly, and the stereoselectivity appears as a result of selective cyclization of one diastereomer. Regarding **4** as a ligand creating a C_2-symmetric environment

(27) Palladium-catalyzed isomerization of alkynes to allenes, see: (a) Sheng, H.; Lin, S.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 4893−4894. (b) Lu, X.; Ji, J.; Ma, D.; Shen, W. *J. Org. Chem.* **1991**, *56*, 5774−5778. (c) See refs 24a and 24b.

(28) The theoretical data on the Pd-catalyzed enantioselective reactions is rather limited, see: (a) Tang, D.; Luo, X.; Shen, W.; Li, M. *J. Mol. Struct.: THEOCHEM* **2005**, *716*, 79−87. Before the recent DFT study of asymmetric allylic alkylation only the mechanism of the epimerization of π-allyl−Pd intermediates was studied, see: (b) Sakaki, S.; Nishikawa, M.; Ohyoshi, A.; *J. Am. Chem. Soc*. **1980**, *102*, 4062−4069. (c) Braunstein, P.; Naud, F. *Organometallics* **2001**, *20*, 2966−2981. (d) Solin, N.; Szabo, K. J. *Organometallics* **2001**, *20*, 5464−5471.

TABLE 5. Relative Energies (B3LYP/SDD) and Selected Interatomic Distances for the π-Allyl Intermediates in the Catalytic Cycles of Intramolecular Hydroamination, Hydroalkoxylation, and Hydrocarbonation

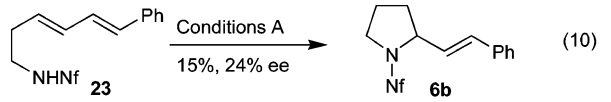
Reaction	Intermediate	Resulting enantiomer	Relative energy, kcal/mol	Distance between bond-making atoms, Å
Hydroamination		*S*	0.8	3.27
Hydroamination		*R*	1.4	4.30
Hydroalkoxylation		*S*	0.0	2.96
Hydroalkoxylation		*R*	0.7	3.51
Hydrocarbonation		*S*	0.0	3.78
Hydrocarbonation		*R*	0.9	4.26

around the metal complex (Figure 1, parts A and B) one can build two isomers of the *syn*,*syn*-π-allyl−Pd complexes **21** (Figure 1, parts C and D) with Pd bound to either face of the π-allyl moiety. The most characteristic structural feature of the optimized geometries of the π-allyl intermediates (Figure 1, parts E and F) is that the definite conformation of the aminoalkyl chain is invariably acquired in the optimization process demonstrating the existence of a specific attraction between the nitrogen atom and the Pd−π-allyl moiety. Furthermore, in both optimized π-allyl complexes the folded aminoalkyl chain resides in the less-hindered quadrant made by the axial phenyl of the chiral ligand (Figure 1, parts C and D). Attempts to locate the structures with the folded chain in a hindered quadrant invariably led to the conformational reorganization during the optimization resulting in essentially the same structures with the folded aminoalkyl chain in the less-hindered quadrant.

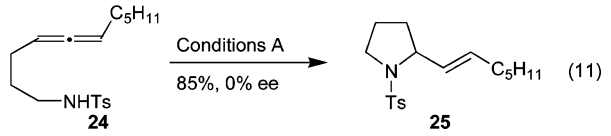
The relative energies of the diastereomers are very close (see Table 5); therefore, the stereoselection cannot take place on the stage of formation of these complexes. However, in the cyclization step the nitrogen atom must approach the carbon atom of the π-allyl moiety. And the structures of the π-allyl complexes suggest that this approach can be stereoselective, because to accommodate the aminoalkylchain in the less-hindered quadrant, the π-allyl moiety must take a certain orientation. As a result, in the precursor of the *S*-product (Figure 1C) the aminoalkyl chain does not meet any hindrance, and the nitrogen atom spontaneously approaches the bond-forming carbon at 3.44 Å. On the other hand, in the precursor of the *R*-product (Figure 1D) the hindrance provided by the central proton of the π-allyl moiety does not allow the C−N distance to be made shorter than 4.30 Å. Since it is evident that the same stereoregulating factors must be operative during the formation of the cyclization transition state, we concluded that the predominant formation of the *S*-product might be thus sufficiently accounted. Similar results have been obtained for the corresponding π-allyl intermediates of the hydroalkoxylation and hydrocarbonation catalytic cycles: the stereodetermining features for all π-allyl intermediates are listed in Table 5. From examination of Table 5 one can see that the general trend is uniformly reproduced for the π-allyl intermediates from different reactions: the folding of the functionalized alkyl chain is observed; it takes place in the less-hindered quadrant, and as a result, the formation of the *R*-product must overcome the inevitable steric hindrance of the C−H part of the π-allyl moiety.

If the stereoregulating step is the final cyclization, then how the π-allyl intermediates are generated must not be important. It is well-known that the Pd-catalyzed hydroamination of dienes and allenes takes place through the formation of π-allyl intermediates.[3,2m] We thought therefore that the intramolecular hydroamination of dienes and allenes yielding the same π-allyl intermediates might be also enantioselective. Accordingly, the aminodiene **23** and aminoallene **24** were prepared and tried in the reaction. When **23** was submitted to condition A, the

cyclized product **6b** was obtained in only 15% yield and with24% ee (eq 10). Under the same conditions, **24** gave **25** in



(10)



(11)

85% yield after 12 h (eq 11);[29] however, no asymmetric induction was observed at all. Moreover, the same result has been obtained when only one enantiomer of **24** has been used in the reaction (both enantiomers were tried).[30] These results suggest that the chiral discrimination does not take place at the stage of π-allyl−Pd complex **21**.

Since the use of a chiral allene does not result in the formation of the chiral product, we concluded that in the course of the enantioselective reaction the formation of the allene intermediate **20** is not only stereoselective but proceeds without dissociation of the substrate that might keep a definite coordination mode throughout the whole transformation. We argued that the attractive interaction between the aminoalkyl chain and the metal atom found in the π-allyl intermediates might serve as a stereodiscriminating factor even in the case of nonchiral intermediates.

To check this idea, we looked more closely at the initial acetylene association step. The rodlike symmetry of the triple bond does not imply the possibility of a prochiral coordination. However, if the aminoalkyl chain is folded in a way similar to that in the optimized geometries of the π-allyl complexes (Figure 1), then the substrate becomes prochiral, and the stereodiscrimination on the alkyne association step becomes theoretically possible (Figure 2). We have looked for the conformational minima of the alkyne complexes with alternatively coordinated substrates (Figure 2, parts E and F). If we suggest that the initial coordination of alkyne determines the stereochemistry of the product, then the complex preceding the *S*-product (Figure 2E) is 1.7 kcal/mol more stable than the complex ultimately yielding the *R*-product (Figure 2F). Moreover, and more important for the reactivity is the almost ideal coplanar orientation of the Pd−H and C≡C bonds acquired in the coordinated substrate of the complex ultimately yielding the *S*-product (the deviation from the parallel orientation is less than 9°, Figure 2C). In the case of alternative coordination of acetylene the unfavorable interaction between the folded aminoalkyl chain and the hindered quadrant of the chiral Pd complex forces the triple bond to rotate far away from the coplanar orientation with the Pd−H bond (the deviation from the parallel orientation is over 50°, Figure 2D). In the same fashion, the additional interaction between the aminoalkyl chain and palladium may favor a certain conformation of the nonchiral vinylpalladium intermediate **19** formed after addition of the hydride to the acetylene complex, thus provoking the formation of the chiral allene complex in a fixed coordination state. The latter must rearrange into the π-allyl complex without dissociation of allene, since free allene as a substrate fail to provide stereoselective reaction. At present we are unable to provide a detailed analysis of the stereodiscriminating formation of the coordinated chiral allene. However, we believe that the participation of the aminoalkyl chain in the stereoselective process of the reactions described here is well established in the present study. This fact gives stimulating ideas for the further development of the enantioselective catalytic transformations.

Conclusions

In conclusion, we developed a catalytic enantioselective intramolecular asymmetric hydroamination, hydroalkoxylation, and hydrocarbonation of alkynes using the chiral palladium catalyst derived from $Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*,*R*)-renorphos. Various optically active heterocycles and carbocycles could be prepared using simple and readily available starting materials. To our knowledge, it represents the first example of transition metal catalyzed asymmetric intramolecular addition of oxygen and carbon nucleophiles to an activated C−C bond. The reaction has some limitations, for example, high catalyst loading, high temperature, and longer reaction time. The chemical and optical yields are also not excellent in some cases. Nevertheless, the reaction presented herein is promising because these studies disclose a versatile mechanistic platform for the development of novel carbon−carbon and carbon−heteroatom bond-forming processes through the intermediacy of the chiral π-allyl−Pd complex.

The computational studies suggest that the important stereoregulating factor in the intramolecular hydroamination[31] is being created by the particular conformational folding of the aminoalkyl chain directed by the attractive interaction between the positively charged π-allyl moiety and the nucleophilic amino group. Once this folding is established, the substrate becomes prochiral, and the enantioselection is regulated via normal stereochemical preferences of the C_2-symmetric diphosphine complexes. These findings can be useful for understanding the important difference between intra- and intermolecular enantioselective hydroaminations, clarifying the reasons for the latter being more difficult.

Experimental Section

1. General Procedures for Asymmetric Intramolecular Hydroamination, Hydroalkoxylation, and Hydrocarbonation Reactions. 1.1. Condition A. To $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), PhCOOH (10 mol %), and (*R*,*R*)-renorphos[32] (25 mol %) was added a substrate (0.125 mmol) in 1.5 mL of benzene under Ar atmosphere in a screw-capped vial. After heating at 100 °C for 72 h, the reaction mixture was filtered through a short silica gel column using diethyl ether as an eluent. After evaporation of the solvent, the residue was purified by silica gel column chromatography to afford the corresponding cyclization product.

(29) The −Ts protecting group was used because the determination of the ee of the product from the corresponding Nf-protected compound proved difficult.

(30) The method for the preparation of racemic **24** is known, see ref 2k. The chiral allene **24** was prepared from (*S*)-(−)-1-octyn-3-ol following the same procedure {$[\alpha]^{25}_D = -60$ (*c* 1.0, $CHCl_3$), 94% ee}. For the preparation of chiral allene from chiral propynyl methanesufonates, see: Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726−3730.

(31) For selected examples on the computational studies, see: (a) Motta, A.; Lanza, G.; Fragala, I. L.; Marks, T. J. *Organometallics* **2004**, *23*, 4097−4104. (b) Tobisch, S. *J. Am. Chem. Soc.* **2005**, *127*, 11979−11988. (c) Tobisch, S. *Chem. Eur. J.* **2005**, *11*, 6372−6385. (d) Straub, B. F.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4632−4635.

(32) Kyba, E. P.; Davis, R. E.; Juri, P. N.; Shirley, K. R. *Inorg. Chem.* **1981**, *20*, 3616−3623.

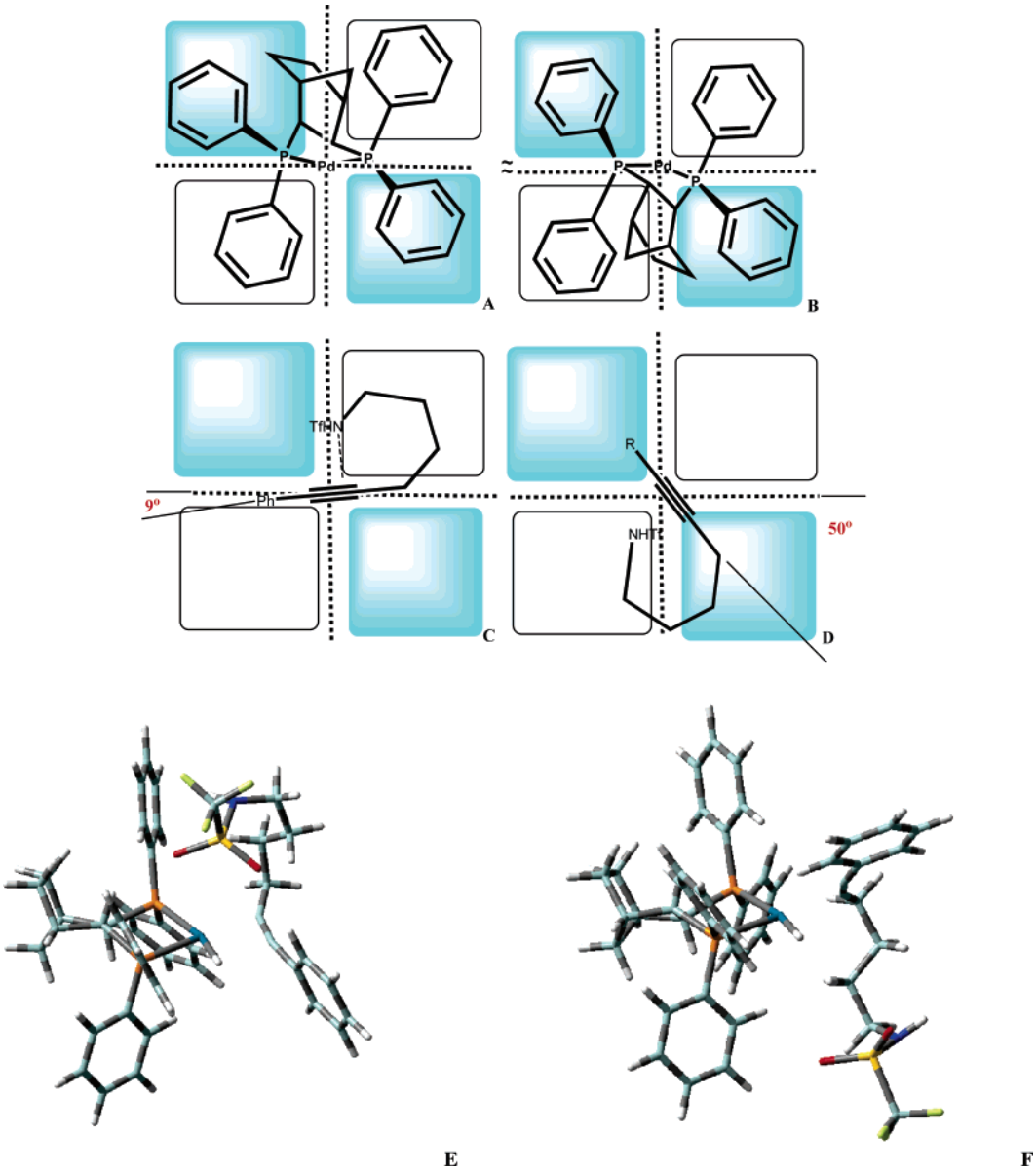


FIGURE 2. Possibility of enantioselection on the acetylene association step. Parts A and B represent **4** as a C_2-symmetric ligand; equatorial phenyls of the diphosphine constitute hindered quadrants shown with filled blue squares; axial phenyls provide relatively smaller hindrance, and the corresponding quadrants are marked with hollow squares. Part C and D demonstrate that if the aminoalkyl substituent acquires a definite conformation, the molecule becomes prochiral; the Pd complex is not shown for clarity, and the quadrants are marked in the same fashion as above. Parts E and F represent optimized structures (B3LYP/SDD) of the corresponding acetylenic complexes: carbons are sea-green, hydrogens are gray, P is orange, Pd is marine blue, N is blue, S is yellow, O is red, and F is green.

1.2. Condition B. To $Pd_2(dba)_3 \cdot CHCl_3$ (20 mol %), PhCOOH (40 mol %), and (*R*,*R*)-renorphos (100 mol %) was added a substrate (0.125 mmol) in 1.5 mL of benzene/hexane (2:1) under Ar atmosphere in a screw-capped vial. After heating at 80 °C for 72 h, the reaction mixture was filtered through a short silica gel column using diethyl ether as an eluent. After evaporation of the solvent, the residue was purified by silica gel column chromatography to afford the corresponding cyclization product.

1.3. Condition C. To $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol %), PhCOOH (20 mol %), and (*R*,*R*)-renorphos (60 mol %) was added a substrate (0.125 mmol) in benzene (0.5 M) under Ar atmosphere in a screw-capped vial. After heating at 100 °C for 72 h, the reaction mixture was filtered through a short silica gel column using diethyl ether as an eluent. After evaporation of the solvent, the residue was purified by silica gel column chromatography to afford the corresponding cyclization product.

2. Computational Details. Geometries of all stationary points were optimized using analytical energy gradients of self-consistent-field[33] and density functional theory (DFT).[34] The latter utilized Becke's three-parameter exchange-correlation functional[35] including the nonlocal gradient corrections described by Lee−Yang−Parr (LYP),[36] as implemented in the Gaussian 03 program package.[37] All geometry optimizations were performed using the SDD basis

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(34) (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989. (b) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *Chem. Phys. Lett.* **1996**, *52*, 211.

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set.[38] This approach is widely used for the recent computational studies of transition metal complexes and was shown to yield results conforming with experimental data in the works of our group[39] and those of others.[40]

Acknowledgment. N.T.P. thanks the Japan Society for the Promotion of Science (JSPS) for a postdoctoral research fellowship. The computational results in this research were obtained using supercomputing resources at Information Synergy Center, Tohoku University.

Supporting Information Available: Experimental details for the preparation of starting materials, characterization data, ^{1}H NMR spectra of newly synthesized compounds, Cartesian coordinates of the optimized structures, complete ref 37. This material is available free of charge via the Internet at http://pubs.acs.org.

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