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Stereochemistry of Intermolecular Oxypalladation: Pd^{II}-Catalyzed 1,3-Chirality Transfer Reaction of Chiral Allylic Alcohol with Methanol

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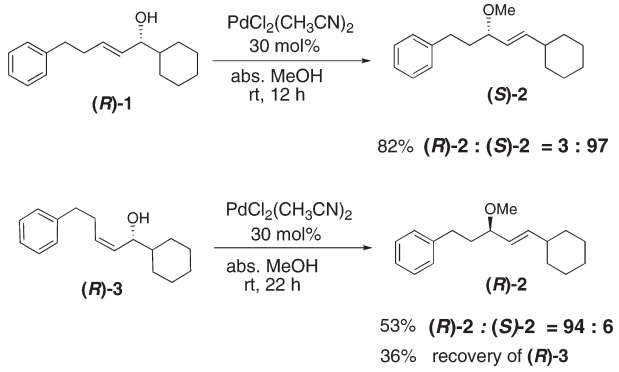

The intermolecular oxypalladation of chiral nonracemic allylic alcohols **(*S*)-1**, **(*R*)-1**, and **(*R*)-3** in methanol gave chiral nonracemic methyl allyl ethers **(*S*)-2** and/or **(*R*)-2** with excellent selectivity. The reaction induced the 1,3-chirality transfer to give *syn*-S_N2' product exclusively through *syn* oxypalladation. On the other hand, the *anti*-S_N2' product was produced in 20−33% in THF, toluene, and CH_2Cl_2 and predominantly in CH_3CN. The π-olefin−Pd complexes **I** and **II** are proposed as important intermediates to explain the *syn*- and *anti*-oxypalladation pathways. The byproduct **9** was formed through the second *syn*-oxypalladation from the methyl allyl ether **2**, though the rate of this second reaction was far slower than that of allylic alcohol.

Introduction

Pd^{II}-catalyzed reactions are used as versatile and valuable tools in synthetic organic chemistry.[1] Oxypalladation reactions including the Wacker oxidation have been in use and a topic of interest for decades (Scheme 1).[2] The reaction gives enol (ketone; R = H, enol ether; R = alkyl) or alkyl allyl ether.[3] The catalytic process of the reaction involves oxypalladation to alkenyl bond by Pd^{II} and oxy nucleophiles such as water, alcohol, or carboxylic acid and β-hydride elimination from the resulting σ-alkyl Pd complex. However, there has been a controversy regarding *syn* or *anti* stereochemistries of oxypalladtion reaction at the addition step.[2b]

Bäckvall and co-workers reported that oxypalladation is an *anti* process in the presence of a high chloride ion concentration.[4] Stille and Kurosawa reported that methoxypalladation is also an *anti* process.[5,6] Henry and co-workers

(1) (a) Tsuji, J. *Palladium reagents and catalysts: Innovation in Organic synthesis*; John Wiley & Sons: Chichester, 1995. (b) Hegedus, L. S. In *Organometallics in Synthesis*; Schlosser, M., Eds.; John Wiley & Sons: Chichester, 2002; pp 1123−1217. (c) *Handbook of Organopalladium Chemistry for Organic synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (e) Tietze, L. F.; IIa, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516.

(2) (a) Hosokawa, T., Murahashi, S.-I. In *Handbook of Organopalladium Chemistry for Organic synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; pp 2141−2192. (b) Henry, P. M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; pp 2119−2139. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. (d) Muzart, J. *Tetrahedron* **2005**, *61*, 5955–6008.

(3) (a) Hosokawa, Y.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49–54. (b) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318–2323.

(4) (a) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264–265. (b) Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411–2416. (c) Bäckvall, J. E. *Tetrahedron Lett.* **1977**, *5*, 467–468.

(5) (a) Stille, J. K.; James, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 674–676. (b) James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1806–1809. (c) Stille, J. K.; Divakaruni, R. J. *J. Am. Chem. Soc.* **1978**, *100*, 1303–1304.

(6) Majima, T.; Kurosawa, H. *J. Chem. Soc., Chem. Commun.* **1977**, 610–611.

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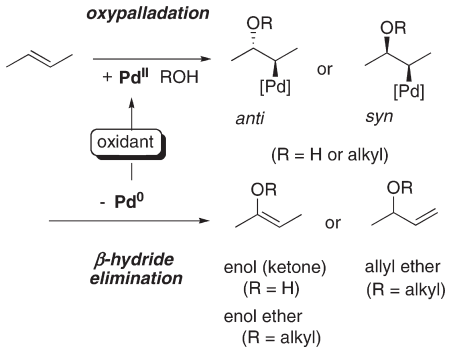
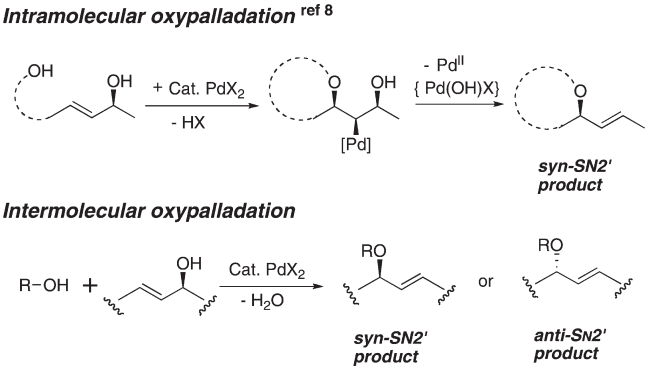
SCHEME 1. Oxypalladation Reaction of Alkene with Oxynucleophile



proposed that oxypalladation process depends on the reaction conditions and oxypalladation is *syn* at low chloride ion concentrations, while the process is *anti* at high chloride ion concentrations.[7] Recently, Pd-catalyzed carboetherification was reported to proceed through syn addition by Wolf et al.[8] In the case of intramolecular oxypalladation reactions, Hayashi and co-workers, and Stoltz and co-workers performed the deuterium labeling experiment to establish *syn* stereochemistry.[9] However, most of these studies were carried out in the presence of oxidants such as quinone, $CuCl_2$, or oxygen, which were essential for the oxidation of Pd^0 to Pd^{II} in the catalytic cycle. Recently, we investigated the Pd^{II}-catalyzed intramolecular oxypalladation reactions of chiral nonracemic allylic alcohols and demonstrated that the reaction is highly stereospecific through the *syn* oxypalladation pathway to give various oxaheterocycles.[10] The most interesting part of our study was to use acyclic chiral allylic alcohol with the $PdCl_2(CH_3CN)_2$ catalyst in organic solvents without reoxidant.

After investigating intramolecular oxypalladation,[10] we turned our attention to intermolecular oxypalladation. If we carefully selected an appropriate chiral nonracemic allylic alcohol and an alcoholic nucleophile for the intermolecular reaction, we would be able to deduce the reaction mechanism by analyzing the stereochemistry of products produced through the 1,3-chirality transfer process, as shown in Scheme 2. Herein, we report an intermolecular Pd^{II}-catalyzed oxypalladation with methanol as a nucleophile in organic solvents under mild reaction conditions and propose the mechanism with clear stereochemical evidence.

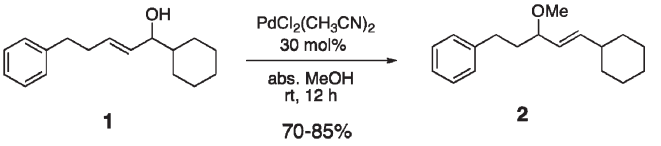
SCHEME 2. 1,3-Chirality Transfer in Intra- and Intermolecular Oxypalladation Reactions



Results and Discussion

We have chosen (*R*)- and (*S*)-1-cyclohexyl-5-phenylpent-2-en-1-ol, **(*S*)-1**, **(*R*)-1**, and **(*R*)-3** as substrates for the reaction. In fact, the preliminary reaction of racemic **1** with 30 mol % of $PdCl_2(CH_3CN)_2$ in absolute methanol afforded 1-cyclohexyl-3-methoxy-5-phenylpent-2-ene **2** in 70−85% yield, as shown in Scheme 3.

SCHEME 3. Intermolecular Oxypalladation of Compound 1



If (*R*)-1-cyclohexyl-3-methoxy-5-phenylpent-2-ene **(*R*)-2** is obtained from **(*S*)-1**, then the *syn*-S_N2' process proceeds by *syn* oxypalladation. If **(*R*)-2** is obtained from **(*R*)-1**, then the *anti*-S_N2' process proceeds by *anti* oxypalladation (Figure 1). The mechanistic pathway will be further confirmed using **(*R*)-3** as a substrate.

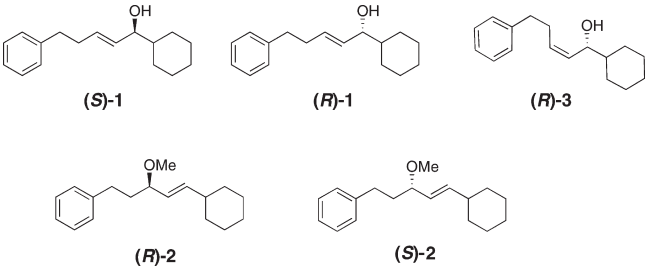


FIGURE 1. Structures of precursors **(*S*)-1**, **(*R*)-1**, and **(*R*)-3** and expected products **(*R*)-2** and **(*S*)-2**.

Synthesis of Precursors of the Reaction. The synthesis of precursors **(*S*)-1**, **(*R*)-1**, and **(*R*)-3** are shown in Scheme 4. The chiral centers of the secondary allylic alcohols **(*S*)-1** and **(*R*)-1** are constructed by Carreira's asymmetric alkynylation.[11] The addition of 4-phenyl-1-butyne to cyclohexanecarboxaldehyde in the presence of $Zn(OTf)_2$ and triethylamine with chiral ligand (−)-*N*-methylephedrine gave **(*S*)-4** in 89% yield with 97% ee, while the same reaction using (+)-*N*-methylephedrine gave **(*R*)-4** in 98% yield with 98% ee.

(7) (a) Henry, P. M.; Lee, H. B. *Can. J. Chem.* **1976**, *54*, 1726–1738. (b) Zaw, K.; Henry, P. M. *J. Org. Chem.* **1990**, *55*, 1842–1847. (c) Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498–3503. (d) Zaw, K.; Henry, P. M. *Organometallics* **1992**, *11*, 2008–2015. (e) Francis, J. W.; Henry, P. M. *Organometallics* **1992**, *11*, 2832–2836. (f) Francis, J. W.; Henry, P. M *J. Mol. Catal. A: Chem.* **1996**, *112*, 317–326. (g) Hamed, O.; Henry, P. M. *Organometallics* **1997**, *16*, 4903–4909. (h) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082–7083. (i) Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745–7750.

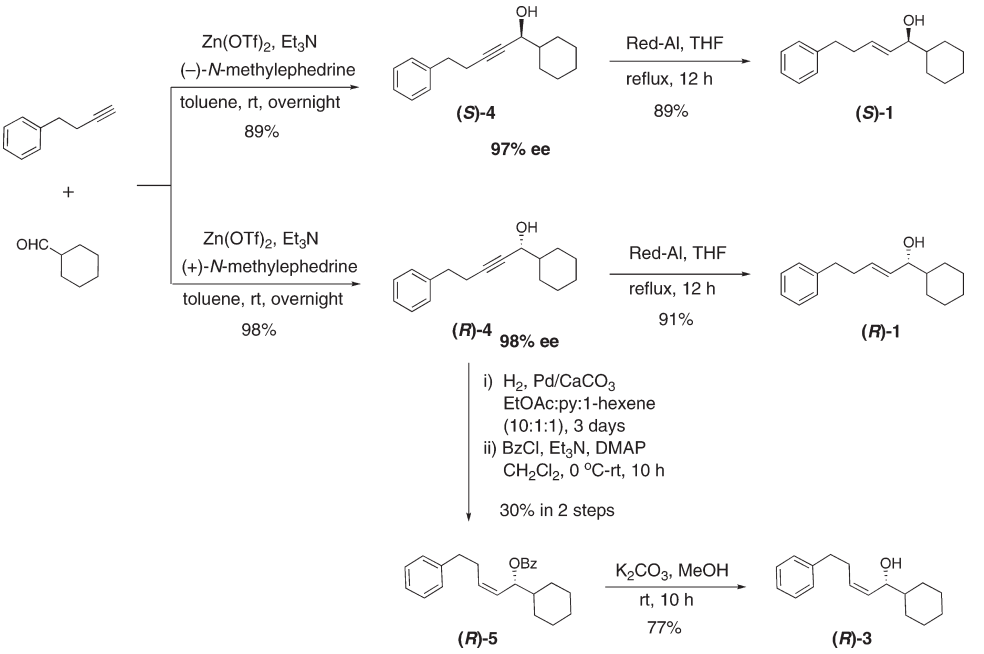
(8) (a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621. (b) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476. (c) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901.

(9) (a) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788.

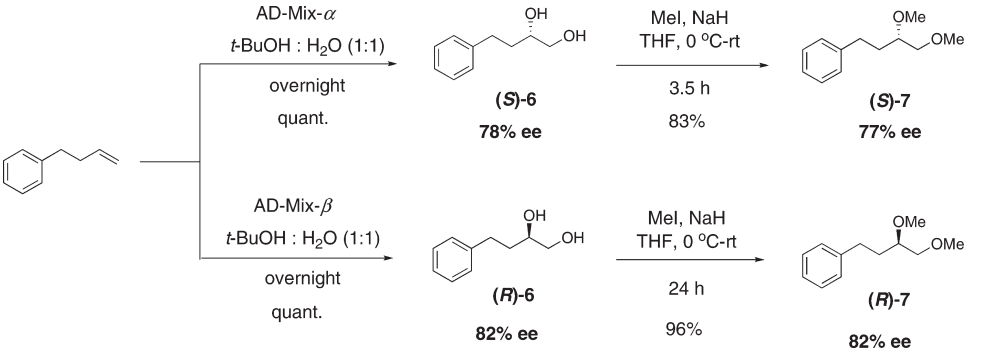
(10) (a) Kawai, N.; Lagrange, J. -M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530–4537. (b) Kawai, N.; Lagrange, J. -M.; Uenishi, J. *Eur. J. Org. Chem.* **2007**, 2808–2814. (c) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299–1303. (d) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. Asian J.* **2008**, *3*, 473–483. (e) Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2009**, *74*, 244–253.

(11) For the asymmetric addition, see: Frantz, D. E.; Fässler, R.; Carreira, E. M *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807.

SCHEME 4. Asymmetric Synthesis of Precursors (*S*)-1, (*R*)-1, and (*R*)-3



SCHEME 5. Preparation of Authentic Materials (*S*)-7 and (*R*)-7



The partial reduction of the triple bond of **(*S*)-4** and **(*R*)-4** was performed with Red-Al in refluxing THF to afford *trans*-alkenes **(*S*)-1** in 89% and **(*R*)-1** in 91% yield, respectively.[12] The preparation of (*Z*)-allylic alcohol **(*R*)-3** was performed in three steps from **(*R*)-4**. *Cis* hydrogenation of **(*R*)-4** in the presence of Lindlar's catalyst under a hydrogen atmosphere was slow and gave an inseparable mixture of **(*R*)-3** and **(*R*)-4** after 3 days. Therefore, after benzoylation of the mixture and separation of the corresponding benzoates, allyl benzoate **(*R*)-5** was isolated in 30% yield along with a benzoate of **(*R*)-4** in 52% yield in two steps. Finally, saponification of **(*R*)-5** gave pure **(*R*)-3** in 77% yield.

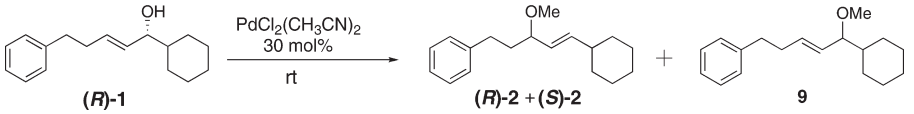
Determination of Absolute Configurations. The absolute stereochemistry of **(*R*)-2** and **(*S*)-2** could be determined after converting them to 1,2-dimethoxy-4-phenylbutane **(*S*)-7** and **(*R*)-7** and comparing them with the authentic optically pure (*R*)- and (*S*)-compounds **(*S*)-7** and **(*R*)-7**. The authentic samples would be prepared in two steps from 4-phenyl-1-butene, as shown in Scheme 5. The Sharpless asymmetric dihydroxylation of 4-phenylbutene with AD-mix-α gave **(*S*)-6** with 78% ee in quantitative yield.[13] *O*-Methylation of **(*S*)-6** with iodomethane and NaH gave **(*S*)-7** in 83% yield. Similarly, its enantiomer **(*R*)-7** was obtained with 82% ee in two steps using AD-mix-*β* instead of AD-mix-α in the first step. These enantiomers were separable in chiral HPLC.

Intermolecular Chirality Transfer Reaction. First, **(*R*)-1** (98% ee) was treated with $PdCl_2(CH_3CN_2)$ (30 mol %) in absolute methanol at room temperature for 12 h to give **2** in 82% yield. Chiral HPLC analysis revealed an enantiomeric ratio of a 3:97. It was then converted to **7** using the following two-step reaction sequence: (i) ozonolysis and reduction of the resulting ozonide with $NaBH_4$; (ii) *O*-methylation of its sodium salt with iodomethane (Scheme 6). This conversion gave 1,2-dimethoxy-4-phenylbutane **7** in 97% yield, of which the stereochemistry of the major enantiomer was identified to be **(*S*)-7** by chiral HPLC analysis in comparison with the authentic materials prepared in Scheme 5. The reaction of **(*S*)-1** (97% ee) under the same reaction conditions gave **(*R*)-2**

(12) Compound **(*S*)-1** has been reported; see: Ji, J. -X.; Qiu, L. -Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589–1590.

(13) (a) Wang, Z. -M.; Zang, X. -L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267–2270. (b) Wang, F. -D.; Yue, J. -M. *Eur. J. Org. Chem.* **2005**, 2575–2579.

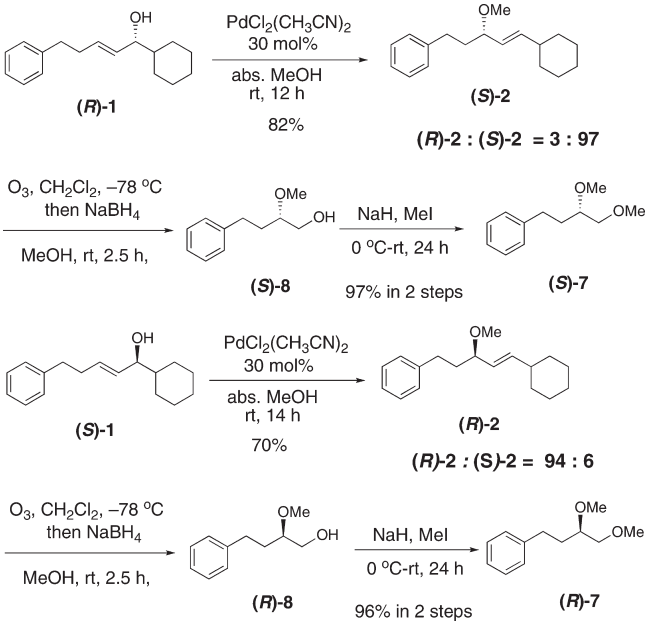
TABLE 1. Pd^{II}-Catalyzed Intermolecular Oxypalladation Reaction in Different Solvents



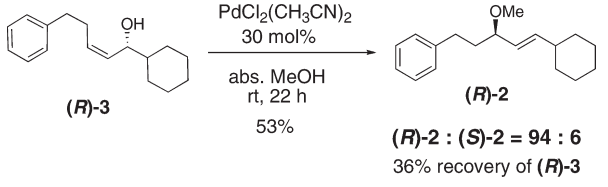
entry	solvent MeOH (equiv)	time	**2**, yield [a](%)	ratio[b] **(R)-2/(S)-2**	**9**, yield (%)
1	MeOH	12 h	82	3:97	3
2	THF MeOH (10 equiv)	26 h	65	33:67	12
3	MeOH LiCl (3 M soln.)	4 days[c]	58	50:50	28
4[b]	CH_3CN MeOH (10 equiv)	2 days[c]	40	66:34	12
5	Toluene MeOH (10 equiv)	22 h	84	19:81	13
6	CH_2Cl_2 MeOH (10 equiv)	45 min	63	31:69	15
7[d]	DMF MeOH (10 equiv)	3 days[d]			

[a] Combined yields of **(R)-2** and **(S)-2**. [b]The ratios were determined by chiral HPLC analysis. [c] The reaction was not complete. [d]No reaction occurred.

SCHEME 6. Intermolecular Oxypalladation Reaction of (*R*)-1 and (*S*)-1



SCHEME 7. Intermolecular Oxypalladation Reaction of (*R*)-3

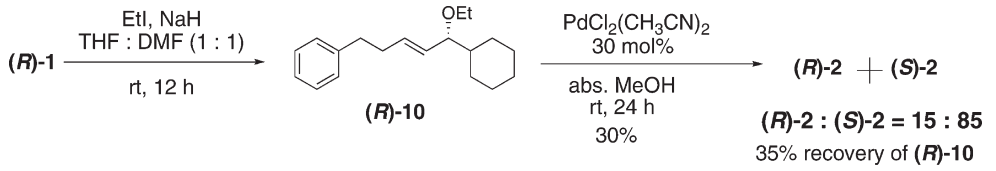


in 70% yield with excellent selectivity in a 94:6 ratio. The stereochemistry of the major enantiomer was confirmed to be ***R*** using the same analysis as above. Therefore, **(*S*)-2** was obtained as a *syn*-S_N2' product from **(*R*)-1**, and **(*R*)-2** was obtained as a *syn*-S_N2' product from **(*S*)-1**.

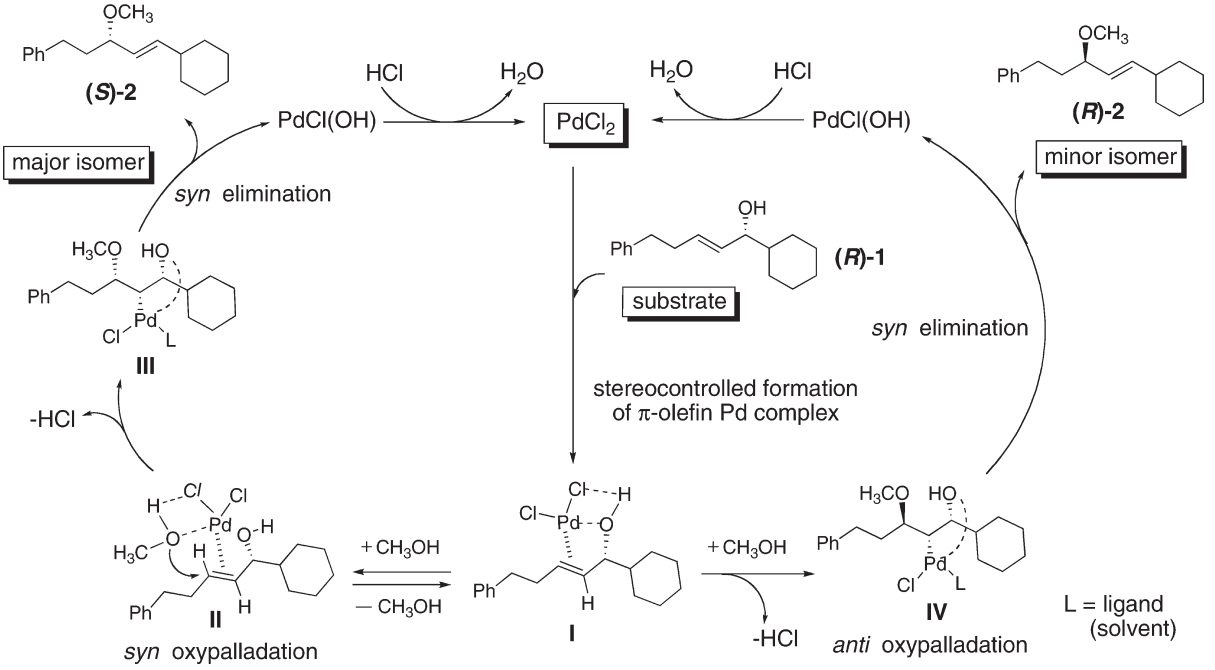
Similar to the reactions of **(*R*)-1** and **(*S*)-1**, an oxypalladation reaction of (*Z*)-allyl alcohol **(*R*)-3** (98% ee) was carried out with $PdCl_2(CH_3CN)_2$ (30 mol %) in absolute methanol at room temperature. The reaction was slower than that of the (*E*)-allyl alcohols and took 22 h to give **(*R*)-2** in 53% yield with excellent selectivity (94:6 ratio), along with the recovery of **(*R*)-3** in 36% yield (Scheme 7). It is interesting to note that the oxypalladation reactions of **(*R*)-1** and **(*R*)-3**, having a configurationally different alkenyl unit, produced different enantiomers **(*S*)-2** and **(*R*)-2** with excellent selectivity. Use of both the (*E*)- and/or (*Z*)-allyl alcohols does not alter the mode of the oxypalladation reaction, that is, *syn*-S_N2' reaction takes place totally through a highly selective 1,3-chirality transfer process. It is interesting that Henry et al. reported that the reactions of both (*Z,R*)- and (*E,R*)-allylic alcohols with water in the presence of K_2PdCl_4 under a 0.1 M of chloride ion concentration afforded the same (*R*)-enantiomer, and the ee values of each of the starting allylic alcohols (66% and 65%) decreased to 28% and 42% in the products, respectively.[7i] In comparison with their results, the chirality transfer reactions in our study gave *syn*-S_N2' reaction product through the same mode of oxypalladation. This stereochemical behavior was similar to that of the intramolecular oxypalladation reactions.[9,10]

Solvent Effect and Stereoselectivity. Next, the reaction of **(*R*)-1** and methanol was carried out in various solvents with $PdCl_2(CH_3CN)_2$ (30 mol %) at room temperature, and the results are summarized in Table 1. The result from Scheme 6 is listed in entry 1 for comparison. The reaction in THF gave **(*S*)-2** as a major isomer in 65% yield with retention of the configuration the same as in methanol. The selectivity [**(*R*)-2**:**(*S*)-2** = 33:67] was lower than that (3:97) in methanol, indicating that two modes of oxypalladation occurred simultaneously (entry 2). Careful analysis of the product revealed the formation of methyl ether **9** in 12% yield. Addition of an excess of LiCl in methanol (3 M solution) deaccelerated the reaction rate and gave racemic products (entry 3). No high chloride concentration effect was observed. The result was more interesting when the reaction was carried out in CH_3CN (entry 4). The reaction rate was slow and gave **(*R*)-2** as a major isomer in a 66:34 ratio, which was a completely opposite stereochemical outcome to others. This result suggests that the chirality transfer in CH_3CN and other solvents altered the mode of methoxypalladation. The reaction in toluene gave the product in a satisfactory yield with good selectivity (entry 5). Surprisingly, the reaction in CH_2Cl_2 was faster than that in methanol (entry 6 vs entry 1) and was completed in 45 min with moderate chemical yield in a 31:69 ratio, which was similar to that in THF. No reaction occurred in DMF even after 3 days (entry 7).

SCHEME 8. Intermolecular Oxypalladation Reaction of Ethyl Allyl Ether (*R*)-10



SCHEME 9. Proposed Reaction Mechanism for Intermolecular Oxypalladation Reaction



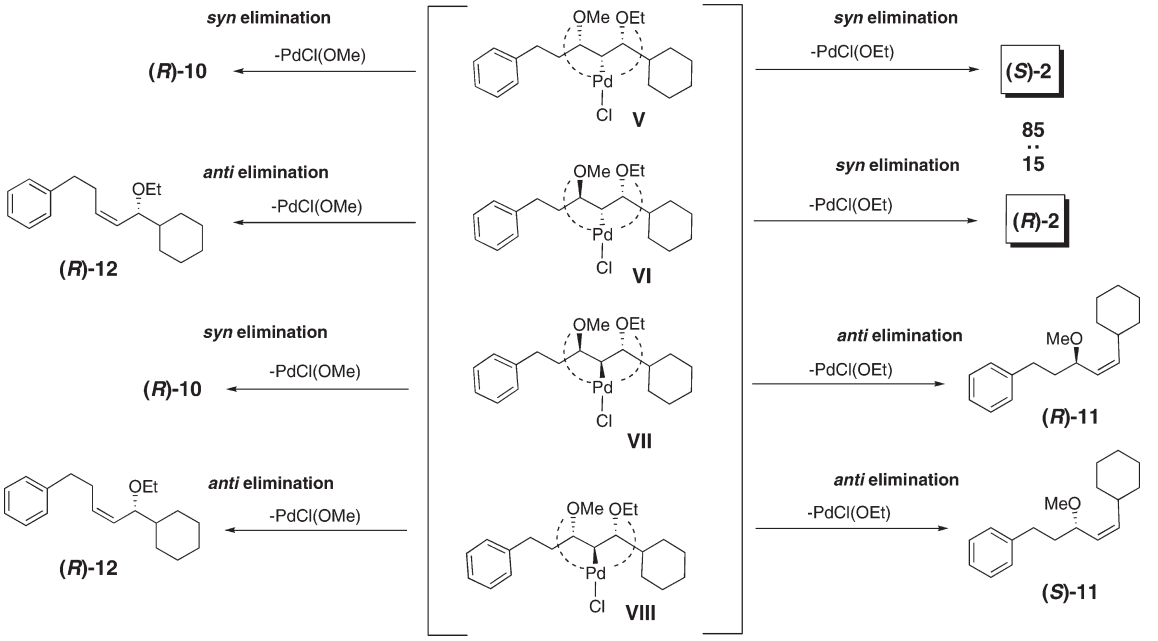
Compound **9** was isolated in a 3% to 28% yield in all reactions. The longer the reaction time, the more byproduct **9** was produced, suggesting that **9** might be formed from **2**. One may consider the possibility that π-allyl Pd intermediate would be generated from **1**. However, it is not rational because the Pd^{II} catalyst could not be regenerated from Pd^0 in the absence of an oxidant in the catalytic cycle. Despite many attempts, the enantiomers of **9** would not be separate on chiral HPLC. In order to confirm its mechanistic pathway as well as its stereochemistry, we prepared substrate **(*R*)-10** by ethylation of **(*R*)-1** and subjected it to the reaction as shown in Scheme 8. When optically pure **(*R*)-10** (98% ee) was treated with $PdCl_2(CH_3CN)_2$ (30 mol %) in absolute methanol at room temperature for 24 h, a mixture of **(*S*)-2** and **(*R*)-2** resulted in 30% yield with a 85:15 ratio along with 35% recovery of the starting material. Therefore, alkyl allyl ether is not a good substrate for the oxypalldation reaction, but the reaction surely occurs stereoselectively with 1,3-chirality transfer. This result indicates that the rate of second oxypalladation of methyl allyl ether **2** is much slower than that of allyl alcohol in the reaction of **1** in methanol. This reaction mechanism is discussed in the next section.

Proposed Reaction Mechanism. Based on the above results, we propose the reaction mechanism of Pd^{II}-catalyzed intermolecular oxypalladation reaction, depicted in Scheme 9. First, $PdCl_2$ coordinates to form π-olefin Pd complex **I** *syn* selectively on alkene with respect to the chiral allylic alcohol. Ligand exchange with a methanol occurs to generate another π-complex **II**, which exists in equilibrium with **I**. Then, a *syn* attack of the coordinated methanol in the intermediate **II** gives σ-alkyl Pd intermediate **III** through *syn* oxypalladation.[14] Finally, *syn* elimination of PdCl(OH) gives the major *syn*-S_N2' product **(*S*)-2**. The minor *anti*-S_N2' product **(*R*)-2** is formed by the *anti* oxypalladation with methanol from **I**. Thus, a methanol attacks externally from the back side of π-olefin Pd complex of **I** to form σ-alkyl Pd intermediate **IV** through *anti* oxypalladation, which undergoes *syn* elimination of PdCl(OH) to afford **(*R*)-2**. $PdCl_2$ can be regenerated by the reaction of PdCl(OH) with HCl in its catalytic cycle. These results suggest that the selectivity depends on the formation of π-olefin Pd intermediates **I** or **II**, and solvents may play an important role in this process. When the π-olefin Pd complex **I** is solvated well with a polar solvent like CH_3CN, the nucleophilic attack of methanol takes place from the backside of π-olefin Pd complex **I** and results in *anti* oxypalladation to give **IV**.[15] In methanol, as in THF, toluene, or CH_2Cl_2, the intermediate **II** can generate favorably in an equilibrium between **I** and **II**. *Syn* attack of a methanol to **II** occurs to give **III**. Our experimental results strongly support the hypothesis that the intermolecular oxypalladation reaction proceeds through *syn* oxypalladation.

(14) A migratory attack of coordinated oxy nucleophile on the Pd complex to olefin was supported by the calculation study; see: Nelson, D. J.; Li, R.; Brammer, C. *J. Am. Chem. Soc.* **2001**, *123*, 1564–1568.

(15) *Anti* oxypalladation product in CH_3CN was also reported in ref 5c. The result can be explained similarly.

SCHEME 10. Mechanistic Consideration of Intermolecular Oxypalladation Reaction of Ethyl Allyl Ether (*R*)-10



As described, we assumed the formation of **9** from **2** in the reaction of **1** based on the evidence that the reaction of allyl ethyl ether **(*R*)-10** with methanol gave **(*S*)-2** predominantly. The plausible intermediates in the mechanism for the formation of **(*S*)-2** and **(*R*)-2** in a 85:15 ratio were described in Scheme 10. As shown in the parentheses, there are four possible intermediates, **V**−**VIII**, depending on the combination of *syn* and/or *anti* coordination/oxypalladation processes. *Syn* elimination of PdCl(OEt) from the intermediate **V** takes place to give major isomer **(*S*)-2**, while *syn* elimination of PdCl(OMe) from **V** reverts back to **(*R*)-10**. *Syn* elimination of PdCl(OEt) from *anti* oxypalladation intermediate **VI** proceeds because of the formation of some **(*R*)-2** in the experimental result. Since no (*Z*)-allyl ethers such as **11** and **12** were produced, *anti* elimination did not occur in the intermediates **VI** to **VIII**.

These results clearly indicated that the formation of **(*S*)-2** occurred from **(*R*)-10** through *syn* oxypalladation and *syn* elimination with excellent selectivity. Therefore, the formation of methyl allyl ether **9** can be explained similarly as a second order product from **2** under the reaction conditions. However, it is less stereospecific than allylic alcohol substrates.

Conclusions

In summary, we have demonstrated that oxypalladation of the chiral nonracemic allylic substrate with $PdCl_2(CH_3CN)_2$ catalyst in methanol gives *syn*-S_N2' product stereospecifically with 1,3-chirality transfer. The reaction can be explained by *syn* coordination of the Pd^{II} catalyst on alkene directed by the chiral allylic alcohol, followed by *syn* oxypalladation and *syn* elimination in methanol. A considerable amount of *anti*-S_N2' product can be obtained using solvents such as THF, toluene, and CH_2Cl_2. When CH_3CN was used as a solvent, *anti*-S_N2' product was formed as a major isomer in a 2:1 ratio. We proposed that the equilibrium between π-olefin Pd intermediates **I** and **II** determines the pathway of the *syn* or *anti* attack of methanol. The results indicate that *syn* or *anti* stereochemistry in the intermolecular oxypalladation process is anticipated not to be simple. However, at least in methanol, *syn* oxypalladation occurs with high 1,3-chirality transfer. Similarly, using **(*R*)-10** as a substrate, we have demonstrated that allyl ether **9** could be formed from allyl ether **2** through *syn* oxypalladation and *syn* elimination. In this study, we successfully answered questions regarding the mechanisms inherent in intermolecular oxypalladation and provided clear evidence to support our conclusions.

Experimental Section

General Conditions for Pd^{II}-Catalyzed Reaction in Methanol. To a solution of **1**, **3**, or **10** (0.1 mmol) in absolute methanol (2.5 mL) was added $PdCl_2(CH_3CN)_2$ (7.8 mg, 30 mol %) at room temperature. After being stirred for 12−24 h, the reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The solvent was evaporated, and the residue was purified by column chromatography on silica gel eluted with 3% EtOAc in hexane to give **2**. The chemical yield and reaction time are indicated below.

The reaction of **(*R*)-1** (98% ee) gave (*E*,3*S*)-1-cyclohexyl-3-methoxy-5-phenylpentene [**(*S*)-2**] in 82% yield with 93% ee: reaction time 12 h; colorless oil; R_f = 0.33 (3% EtOAc in hexane); $[\alpha]^{21}_D$ −15.9 (*c* 0.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.14 (m, 5H), 5.53 (dd, *J* = 15.5, 6.6 Hz, 1H), 5.25 (ddd, *J* = 15.5, 8.1, 1.2 Hz, 1H), 3.43 (q, *J* = 6.6 Hz, 1H), 3.24 (s, 3H), 2.65 (td, *J* = 6.9, 1.4 Hz, 2H), 2.03−1.85 (m, 2H), 1.79−1.61 (m, 6H), 1.34−1.02 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2 (ph), 140.6 (C-1), 128.5 (ph),128.3 (ph), 127.4 (C-2), 125.7 (ph), 81.8 (C-3), 55.6 (OMe), 40.4 (C-4), 37.2 (C-5), 33.0 (c-hexyl), 31.7 (c-hexyl), 26.1 (c-hexyl), 26.0 (c-hexyl); IR (film, cm^{-1}) 3025, 2923, 2851, 1603, 1495, 1449, 1349, 1102, 971, 891, 745, 699; MS (EI) *m*/*z* 258 (M^+), 226, 175, 162, 153; HRMS calcd for $C_{18}H_{26}O$ (M^+) 258.1984, found *m*/*z* 258.1980. Enantiomeric excess value was determined by chiral HPLC [column: Daicel Chiralcel ODH, UV detection at 254 nm, solvent: 2-propanol/hexane (1/99), flow rate 0.5 mL min^{-1}, retention time: **(*S*)-2** t_R = 8.3 min and **(*R*)-2** t_R = 27.2 min].

The reaction of **(*S*)-1** (97% ee) gave (*E*,3*R*)-1-cyclohexyl-3-methoxy-5-phenylpentene [**(*R*)-2**] in 70% yield with 88% ee: reaction time 14 h; $[\alpha]^{21}_{D}$ +16.3 (*c* 0.57, $CHCl_3$). Other physical and spectroscopic data are the same as described for **(*R*)-2**.

The reaction of **(*R*)-3** (98% ee) gave **(*R*)-2** in 53% yield with 89% ee along with a recovery of the starting material in 36% yield: reaction time 22 h.

The reaction of **(*R*)-10** (98% ee) gave **(*S*)-2** in 30% yield with 69% ee along with a recovery of the starting material in 35% yield: reaction time 24 h.

General Conditions for Pd^{II}-Catalyzed Reaction in Other Organic Solvents. To a solution of **(*R*)-1** (0.1 mmol) and methanol (40 μL, 1 mmol) in each dry solvent (1.5 mL) (THF, CH_3CN, toluene, CH_2Cl_2, or DMF) was added $[PdCl_2(CH_3CN)_2]$ (7.8 mg, 30 mol %) at room temperature. The mixture was stirred for appropriate time listed in Table 1, diluted with EtOAc, and filtered through Celite pad. The solvent was evaporated and the residue was purified by column chromatography on silica gel eluted with 3% EtOAc in hexane to give **2**. All the products including the side product **9** were separable by HPLC (normal-phase silica gel column). Their chemical yields are listed in Table 1. (*E*)-(5-Cyclohexyl-5-methoxypent-3-enyl)benzene (**9**): colorless oil; R_f = 0.33 (3% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.24 (m, 2H), 7.18−7.14 (m, 3H), 5.55 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.26 (ddt, *J* = 15.4, 6.9, 1.2 Hz, 1H), 3.17 (s, 3H), 3.15 (dd, *J* = 7.3, 6.7 Hz, 1H), 1.83−1.78 (m, 1H), 1.72−1.52 (m, 4H), 1.43−1.30 (m, 1H), 1.25−1.04 (m, 3H), 0.94−0.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (ph), 133.6 (C-4), 129.8 (C-3), 128.4 (ph), 128.2 (ph), 125.7 (ph), 87.2 (C-5), 56.0 (OMe), 42.4 (C-2), 35.7 (C-1), 34.0 (c-hexyl), 29.2 (c-hexyl), 28.7 (c-hexyl), 26.6 (c-hexyl), 26.14 (c-hexyl), 26.1 (c-hexyl); IR (film, cm^{-1}) 2922, 2850, 2352, 1450, 1096, 962; MS (EI) *m*/*z* 258 (M^+), 175, 153, 143; HRMS calcd for $C_{18}H_{26}O$ (M^+) 258.1984, found *m*/*z* 258.1991.

Preparation of the Standard Compounds (*R*)-7 and (*S*)-7.[16] To a stirred solution of AD-mix-β (1.4 g) in a 1:1 mixture of *t*-BuOH/H_2O (10 mL) was added 4-phenyl-1-butene (132 mg) at 0 °C, and the mixture was stirred overnight at the same temperature. Then, Na_2SO_3 (1.5 g) was added to the mixture, and the stirring was continued at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and water and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue on silica gel column chromatography eluted with 15% EtOAc in hexane afforded **(*R*)-6**[13b] in quantitative yield. (*R*)-4-Phenylbutane-1,2-diol: colorless oil; R_f = 0.27 (80% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.16 (m, 5H), 3.72−3.64 (m, 2H), 3.47 (dd, *J* = 7.5, 7.8 Hz, 1H), 2.86−2.64 (m, 2H), 2.33 (bs, 1H), 2.12 (bs, 1H), 1.84−1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6 (ph), 128.43 (ph), 128.37 (ph), 125.9 (ph), 71.4 (C-2), 66.7 (C-1), 34.6 (C-3), 31.7 (C-4). The ee value of **(*R*)-6** was determined to be 82% ee by chiral HPLC analysis [column: Daicel Chiralcel ODH, 254 nm, solvent: 2-propanol/hexane (20: 80) flow rate: 1 mL min^{-1}, **(*R*)-6**: 7.2 min and **(*S*)-6**: 9.4 min]. To a solution of **(*R*)-6** (50 mg, 0.3 mmol) in THF (1.7 mL) was added NaH (36 mg, 0.9 mmol) at 0 °C. After the reaction mixture was stirred for 10 min at the same temperature, MeI (0.25 mL, 1.8 mmol) was added. The reaction mixture was stirred at room temperature for 3.5 h and then quenched with satd NH_4Cl (5 mL), extracted with EtOAc (10 mL × 3), washed with water, and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue on silica gel column chromatography eluted with 15% EtOAc in hexane afforded **(*R*)-7** (56.3 mg) in 96% yield. (*R*)-1,2-Dimethoxy-4-phenylbutane: colorless oil; $[\alpha]^{25}_{D}$ −4.73 (*c* 1.14, $CHCl_3$); R_f = 0.38 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.14 (m, 5H), 3.42 (s, 3H), 3.36 (s, 3H), 3.43−3.29 (m, 3H), 2.78−2.60 (m, 2H), 1.89−1.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (ph), 128.37 (ph), 128.3 (ph), 125.7 (ph), 79.1 (C-2), 74.4 (C-1), 59.1 (OMe), 57.3 (OMe), 33.0 (C-3), 31.5 (C-4); IR (film, cm^{-1}) 3026, 2926, 1603, 1496, 1455, 1358, 1193, 1128, 965, 746, 700; MS (CI) *m*/*z* 195 (M^++1); HRMS calcd for $C_{12}H_{19}O_2$ (M^++1) 195.1385, found *m*/*z* 195.1381. The ee value was determined to be 82% ee by chiral HPLC analysis [column: Daicel Chiralcel ODH, 254 nm, solvent: 2-propanol/hexane (10:90), flow rate: 0.5 mL min^{-1}, **(*R*)-7**: 14.6 min and **(*S*)-7**: 8.9 min]. The synthesis of **(*S*)-6** was prepared quantitatively in similar manner as described for preparation of **(*R*)-6** using AD-mix-α instead of AD-mix-β. The ee value was identified to be 78%. Compound **(*S*)-7** was prepared from **(*S*)-6** in 83% yield with 77% ee by the same manner as described for preparation of **(*R*)-7**.

Transformation of 2 to 7. Through a solution of **2** (20 mg, 0.077 mmol) in CH_2Cl_2 (2 mL) was bubbled a dilute stream of O_3 in O_2 at −78 °C for 2−3 min until a blue color persisted in the solution. An excess of ozone was removed by bubbling N_2 gas. $NaBH_4$ (11.7 mg, 0.309 mmol) was added, and the reaction mixture was warmed to room temperature during 1 h. MeOH (0.5 mL) was added, and the mixture was stirred for an additional 30 min. After the addition of satd NH_4Cl (5 mL), the mixture was extracted with CH_2Cl_2 (5 mL × 3) and dried over $MgSO_4$. Evaporation of solvent and purification of the residue on silica gel column chromatography eluted with 60% EtOAc in hexane afforded **8** (13.8 mg) in quantitative yield. Physical and spectroscopic data of **(*S*)-8**, which was derived from **(*S*)-2**. (*R*)-2-Methoxy-4-phenylbutanol: colorless oil; $[\alpha]^{20}_{D}$ +20.1 (*c* 0.85, $CHCl_3$); R_f = 0.1 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 3.70 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.53 (dd, *J* = 11.7, 5.8 Hz, 1H), 3.40 (s, 3H), 3.31−3.23 (m, 1H), 2.67 (td, *J* = 7.3, 1.2 Hz, 2H), 2.15 (br s, 1H), 1.97−1.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8 (ph), 128.4 (ph), 128.3 (ph), 125.8 (ph), 80.6 C-2), 63.6 (C-1), 57.0 (OMe), 32.1 (C-3), 31.4 (C-4). IR (film, cm^{-1}) 3433 2930 1601 1455 1115 692; MS (EI) *m*/*z* 180 (M^+), 149, 148, 130, 117; HRMS calcd for $C_{11}H_{16}O_2$ (M^+) 180.1150, found *m*/*z* 180.1156. To a solution of **8** (10 mg, 5.5 μmol) in THF (1 mL) at 0 °C was added NaH (5.2 mg, 0.22 mmol), and the mixture was stirred for 10 min at the same temperature. MeI (83 μL, 0.55 mmol) was then added, and the mixture was stirred for 24 h at room temperature. The mixture was quenched with satd NH_4Cl (5 mL) and extracted with EtOAc (10 mL × 3). The combined extract was dried over $MgSO_4$ and condensed. The residual oil was purified by column chromatography on silica gel eluted with 15% EtOAc in hexane to give **7** (10.5 mg) in 98% yield. The ee value was determined by chiral HPLC analysis under the same conditions described above.

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Supporting Information Available: Synthetic procedures and physical and characterization data for compounds **(*R*)-1**, **(*S*)-1**, **(*R*)-3**, **(*R*)-4**, **(*S*)-4**, **(*R*)-5**, and **(*R*)-10**, copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **2**, **3**, **5**−**10**, and chiral HPLC charts of racemic and optically active compounds for 1, **2**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) For racemic **7**, see: Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. 1* **1976**, 811–817.