Formation of Cyclic Ethers via the Palladium-Catalyzed Cycloaddition of Activated Olefins with Allylic Carbonates Having a Hydroxy Group at the Terminus of the Carbon Chain

Masaru Sekido, Kouichi Aoyagi, Hiroyuki Nakamura, Chizuko Kabuto, and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

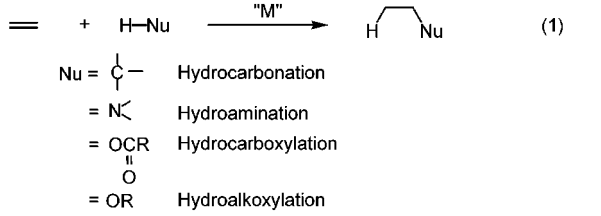
yoshi@yamamoto1.chem.tohoku.ac.jp

Received June 13, 2001

The reaction of the activated olefins **1** with the allylic carbonate **2**, having a hydroxy group at the terminus of the carbon chain, in the presence of catalytic amounts of Pd_2dba_3·$CHCl_3$ and dppe in THF at room temperature gave the corresponding cycloaddition products, tetrahydrofuran derivatives **5**, in good to very high yields. The diastereoselectivities (trans/cis ratios) of the products were in the range of ca. 60−70/40−30. The reaction of **1** with the hydroxy allylic carbonate **3** in the presence of catalytic amounts of Pd_2dba_3·$CHCl_3$ and (*o*-tolyl)$_3$P in THF at 50 °C afforded the corresponding cycloaddition products, tetrahydropyran derivatives **6**, in good to high yields. The trans/cis ratios of the products were in the range of ca. 0−40/99−80. The reaction of **1a** with the hydroxy allylic carbonate **4** needed higher reaction temperatures (∼100 °C) to give the cycloaddition product, the oxepane **7a**, in 31% yield with low diastereoselectivity. Next, catalytic asymmetric syntheses of tetrahydrofuran and -pyran derivatives were carried out. With the Trost ligand **15**, good to high ees were accomplished in the cycloaddition, although the diastereoselectivities were of low level. With the Hayashi ligand **16**, good to high ees were also achieved in the cycloaddition. The absolute stereochemistries of the major enantiomers of **5l**, **5m**, and **6d** were determined unambiguously by X-ray crystallographic analysis: *trans*-(2*R*,4*R*)-**5l**, *cis*-(2*S*,4*R*)-**5l**, 4*R*-**5m**, *trans*-(2*S*,4*S*)-**6d**, and *cis*-(2*R*,4*S*)-**6d** were major enantiomers. Based upon the absolute stereochemistries of the major enantiomers, the mechanism of catalytic asymmetric induction in the cycloaddition reaction is discussed.

Introduction

Transition-metal catalysts have changed dramatically the addition mode of pronucleophiles (H−Nu) to carbon−carbon multiple bonds (eq 1).[1] Hydrocarbonation of



carbon pronucleophiles to alkenes,[2] allenes,[3] alkynes,[4] enynes,[5] 1,3-dienes,[6] and methylenecyclopropanes[7] has been developed. Hydroamination of nitrogen pronucleophiles to allenes gives the corresponding hydroamination products.[8] Also, hydrocarboxylation[9] and hydroalkoxylation[10] have been developed. More recently, we found that the activated olefins **1** underwent alkoxyallylation with allylic carbonates in the presence of palladium(0) catalyst to give the corresponding 5-alkoxy-1-pentenes in good to high yields (three component alkoxyallylation, eq 2).[11] If

(1) For a review, (a) Radhakrishnan, U.; Yamamoto, Y. *Chem. Soc. Rev.* **1999**, *28*, 199. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.

(2) For direct addition of an aromatic C−H bond to a double bond, see: (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature (London)* **1993**, *366*, 529. (b) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475 and references therein. For Michael addition of pronucleophiles to activated olefins also proceeded in the presence of transition metal catalysts, (c) Naota, T.; Taki, H.; Mizuno, M.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1989**, *111*, 5954. (d) Paganelli, S.; Schionato, A.; Botteghi, C. *Tetrahedron Lett.* **1991**, *32*, 2807. (e) Sawamura, M.; Hamashita, H.; Ito, Y.; *J. Am. Chem. Soc.* **1992**, *114*, 8295.

(3) For unactivated allenes, (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Yamaguchi, M.; Omata, K.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 5689. (c) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 51 (d) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853. 56. For activated allenes, (e) Trost, B. M.; Kottirisch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816.

(4) (a) Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486. (b) Tsukada, N.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2477. (c) Jia, C.; Piao, D.; Oyamada, J.; Lu., W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. For propargylic compounds, (d) Kadota, I.; Shibuya, A.; Gyoung, Y.-S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262.

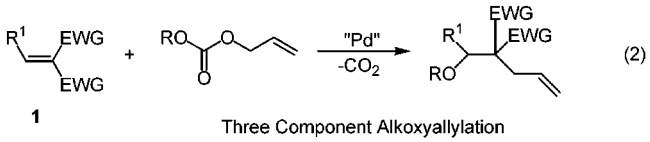
(5) Gevorgyan, V.; Kadowaki, C.; Salter, M. M.; Kadota, I.; Saito, S.; Yamamoto, Y. *Tetrahedron* **1997**, *53*, 9097.

(6) (a) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1183. (b) Andell, O. S.; Bäckvall, J.-E.; Moberg, C. *Acta Chem. Scand. Ser. B* **1986**, *40*, 184. (c) Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 770. (d) Mercier, C.; Miginani, G.; Aufrand, N.; Allmang, G. *Tetrahedron Lett.* **1991**, *32*, 1433. (e) Trost, B. M.; Zhi, L. *Tetrahedron Lett.* **1992**, *33*, 1831.

(7) (a) Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123. (b) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661.

(8) For a review, (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, 98, 675. For allenes, (b) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071. For enynes, (c) Radhakrishnan, U.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 1037. For propargyl compounds, (d) Kadota, I.; Shibuya, A.; Lutete, L.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570. For methylene-cyclopropanes, (e) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458.

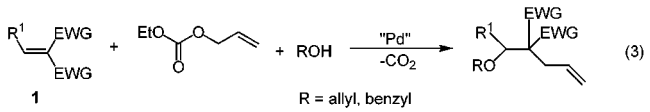
10.1021/jo0158332 CCC: $20.00
Published on Web 09/27/2001



(2)

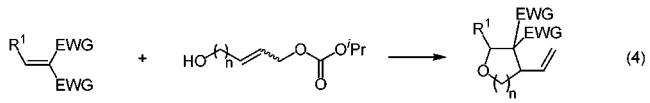
Three Component Alkoxyallylation

allyl ethyl carbonate was used in the presence of allyl or benzyl alcohol, an allyloxy or benzyloxy group, instead of an ethoxy group, was introduced at the β-position of **1** (eq 3).[11] Accordingly, the intermolecular three-component alkoxyallylation of activated olefins takes place not only with the internal alkoxy group of allyl carbonates but also with the external alkoxy group. It occurred to us that the intermolecular two-component alkoxyallylation may proceed by the use of the allylic carbonates **2**−**4** having a hydroxy group at the end of the carbon chain (eq 4).



(3)

External Three Component Alkoxyallylation



(4)

Two Component Alkoxyallylation

1a: R^1= Ph, E^1=E^2= CN
b: R^1= 4-MeC_6H_4, E^1=E^2= CN
c: R^1= 4-MeOC_6H_4, E^1=E^2= CN
d: R^1= 4-MeSC_6H_4, E^1=E^2= CN
e: R^1= 4-FC_6H_4, E^1=E^2= CN
f: R^1= 2-naphtyl, E^1=E^2= CN
g: R^1= *t*-Bu, E^1=E^2= CN
h: R^1= Ph, E^1= CN, E^2= CO_2Et
i: R^1= 4-MeOC_6H_4, E^1=E^2= -$CO_2C(CH_3)_2O_2C$-
j: R^1= Ph, E^1=E^2= -$CO_2C(CH_3)_2O_2C$-
k: R^1= 4-MeC_6H_4, E^1=E^2= -$CO_2C(CH_3)_2O_2C$-
l: R^1= 4-BrC_6H_4, E^1=E^2= CN
m: R^1= H, E^1=E^2= SO_2Ph

2: n=1
3: n=2
4: n=3

5: n=1
6: n=2
7: n=3

The two-component coupling may provide the cyclic ethers **5**−**7** through cycloaddition reactions,[12] whose structural framework is often found in natural products.[13] Although various methodologies for the synthesis of cyclic ethers have been developed,[14] there are few reports on the catalytic asymmetric synthesis of those substrates.[15] We wish to report that actually the two-component alkoxyallylation takes place readily in the presence of palladium catalyst to give the five- and six- membered cyclic ethers in good to high yields, and furthermore the catalytic asymmetric synthesis of such cyclic ethers has been accomplished with good to significantly high ees.

Table 1. Palladium(0)-Catalyzed Two-Component Alkoxyallylation of Activated Olefins 1 with Allylic Carbonates 2−4[a]

entry	olefin	allylic carbonate	ligand	product	yield (%)[b]	ratio (trans/*cis*)[c]
1	**1a**	**2**	dppe	**5a**	92	68/32
2	**1b**	**2**	dppe	**5b**	80	69/31 (84/16)[d]
3	**1c**	**2**	dppe	**5c**	72	65/35 (80/20)[d]
4	**1e**	**2**	dppe	**5e**	67	69/31
5	**1f**	**2**	dppe	**5f**	76	61/39
6	**1g**	**2**	dppe	**5g**	quant	73/27
7	**1h**	**2**	dppe	**5h**	80	60/40
8	**1i**	**2**	dppe	**5i**	77	58/42
9	**1a**	**3**	*o*-Tol_3P	**6a**	83	24/76
10	**1b**	**3**	*o*-Tol_3P	**6b**	68	38/62
11	**1c**	**3**	*o*-Tol_3P	**6c**	70	21/79
12	**1g**	**3**	*o*-Tol_3P	**6g**	92	25/75
13	**1h**	**3**	*o*-Tol_3P	**6h**	88	44/56
14	**1i**	**3**	*o*-Tol_3P	**6i**	90	-/>99
15	**1j**	**3**	*o*-Tol_3P	**6j**	62	-/>99
16	**1k**	**3**	*o*-Tol_3P	**6k**	65	-/>99
17	**1a**	**4**	PPh_3	**7a**	31	58/42[e]

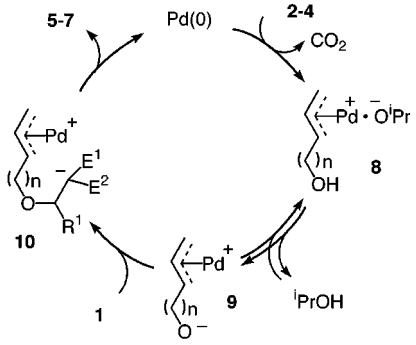
[a] **1a** (0.5 mmol), Pd_2dba_3·$CHCl_3$(0.025 mmol), dppe (0.1 mmol) and the mono-dentate ligands (0.2 mmol), THF (5 mL), **2**(0.6 mmol), **3** and **4** (0.75 mmol). [b] Isolated yields based on **1**. [c] The trans/cis ratio was determined by the isolation of each diastereoisomer. [d] The reaction was carried out in toluene, instead of THF. [e] The stereochemistry was not determined.

Results and Discussion

Two-Component Alkoxyallylation. Formation of Cyclic Ethers. We examined the palladium-catalyzed reaction of the various activated olefins **1** with the allylic carbonates **2**−**4** having a hydroxy group at the end of carbon chain. The results are summarized in eq 4 and Table 1. The reaction of benzylidenemalononitrile **1a** (1 equiv) with isopropyl 4-hydroxy-2-butenyl carbonate **2** (1.2 equiv) proceeded very smoothly in the presence of 5 mol % Pd_2dba_3·$CHCl_3$ (dba = dibenzylideneacetone)/20 mol % dppe (dppe = 1,2-bis(diphenylphosphinoethane)) catalyst in THF at room temperature to give 3,3-dicyano-2-phenyl-4-vinyltetrahydrofuran **5a** in 92% yield with a 68:32 mixture of trans and cis diastereomers (entry 1). The use of $Pd(PPh_3)_4$ without an additional ligand did not give **5a** at all. Among the catalysts examined, Pd_2dba_3·$CHCl_3$-dppe combination gave the best result. The use of dppm, dppp, and dppb as a ligand produced lower

(9) Al-Masum, M., Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242.
(10) For 1,3-dienes, (a) Smutny, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6793. (b) Yagi, H.; Tanaka, E.; Ishiwatari, H.; Hidai, M.; Uchida, Y. *Synthesis* **1977**, 334. (c) Coulson, D. R. *J. Org. Chem.* **1973**, *38*, 1483. For allenes, (d) Inoue, Y.; Ohtsuka, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3345. For methylenecyclopropanes, (e) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3365.
(11) Nakamura, H.; Sekido, M.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6838.
(12) For the palladium-catalyzed [3 + 2] cycloaddition via vinyloxides, see: (a) Larksap, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709. (b) Fujinami, T.; Suzuki, T.; Kamiya, M.; Fukuzawa, S.-I.; Sakai, S. *Chem. Lett.* **1985**, 199. (c) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. (d) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (e) Shim, J.-G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 3067. For the [3 + 2] cycloaddition of C-60 with a hydroxycarbonate, (f) Shen, C. K. F.; Chien, K.-M.; Liu, T.-Y.; Lin, T.-I.; Her, G.-R.; Luh, T.-Y. *Tetrahedron Lett.* **1995**, *36*, 5383. For the transformation of cyclic carbonates to cyclic carbamates, (g) Bando, T.; Haruyama, H.; Fukazawa, Y.; Shiro, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1994**, *59*, 1465. For sequential Michael addition−carbocyclizaton, (h) Marat, X.; Monteiro, N.; Balme, G. *Synlett.* **1997**, 845. For the reaction of TMM palladium complexes, (i) Trost, B. M.; King, A. S.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902. For the reaction of 1,3-butadiene with aldehydes, (j) Ohno, K.; Mitsuyasu, T.; Tsuji, J. *Tetrahedron Lett.* **1971**, *11*, 67.
(13) (a) Garson, M. J. *Chem. Rev.* **1993**, *93*, 1699. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.
(14) For recent reviews, see: (a) Alvarez, E.; Candenas, M.-L.; Perez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, *95*, 1953. (b) Burns, C. J. In *Contemporary Organic Synthesis*; Royal Society of Chemistry: Cambridge, 1994; p 189. (c) Roxburgh, C. J. *Tetrahedron* **1993**, *49*, 10749. (d) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631. (e) Elliott, M. C. In *Contemporary Organic Synthesis*; Royal Society of Chemistry: Cambridge, 1994; p 457, and references therein.
(15) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012. Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett.* **1998**, *39*, 97. Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403. Bednarski, M. O.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; vol. 2, p 682. Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789, and references therein.

Scheme 1



chemical yields, and the cycloaddition between **1a** and **2** did not proceed by the use of dppf and BINAP as a ligand or by the use of Pd_2dba_3·$CHCl_3$ alone. Palladium(II) catalysts, such as $Pd(OAc)_2$/dppe, $PdCl_2$/dppe, $Pd(NO_3)_2$/dppe, and $Pd(COD)_2Cl_2$/dppe, were totally ineffective. The various activated olefins **1b**−**f** having aryl substituents also underwent the cycloaddition to give the corresponding tetrahydrofurans **5b**−**f** in good yields (entries 2−5). The aliphatic activated olefin **1g**, derived from pivalaldehyde and malononitrile, gave **5g** in quantitative yield (entry 6).[16a] Not only the olefins derived from malononitrile (**1a**−**g**) but also those from ethyl cyanoacetate and Meldrum's acid (**1h** and **1i**) underwent the cycloaddition, giving **5h** and **5i** in 80% and 77% yields, respectively (entries 7 and 8). In all the above reactions, the diastereoselectivity was low. To improve the diastereoselectivity, we examined the effect of various metal salts, such as TBAX (TBA = tetrabutylammonium, X = F, Cl, Br, I, BF_4) and LiCl. Very interesting, the addition reaction was halted by the addition of such salts, suggesting that the ionic intermediates (**9** and **10**) should be free from salts (see Scheme 1, vide past).[16b] As shown in the parentheses of entries **2** and **3**, the diastereoselectivity increased by the use of toluene, instead of THF, as a solvent. Other solvents such as CH_3CN, 1,4-dioxane, DMA, CH_2Cl_2, and $CHCl_3$ gave lower chemical yields and lower diastereoselectivities. The stereochemistries of the diastereoisomers were determined by NOE experiments using 600 MHz ^{1}H NMR (Supporting Information), but unambiguous assignment was made by X-ray analysis of the products as mentioned later in the section of catalytic asymmetric synthesis (see also SI).

The cycloaddition of **1a** with isopropyl 5-hydroxy-2-pentenyl carbonate **3** also proceeded very smoothly in the presence of 5 mol % Pd_2dba_3·$CHCl_3$/40 mol % (*o*-tolyl)$_3$P catalyst at 50 °C to give **6a** in 83% yield with a 24:76 mixture of trans and cis diastereomers (entry 9). The use of the monodentate ligand gave better results in comparison with the use of dppe and other bidentate ligands. Here also, the use of $Pd(PPh_3)_4$ alone, Pd_2dba_3·$CHCl_3$ alone, or Pd(II) catalysts, did not give the cycloaddition products at all. Among the monodentate ligands examined, (*o*-tolyl)$_3$P gave the best result and the use of other ligands such as (*p*-tolyl)$_3$P, (furyl)$_3$P, (*p*-F-C_6H_4)$_3$P, (*p*-CF_3-C_6H_4)$_3$P, Ph_3P, and Bu_3P, afforded lower chemical yields. Various activated olefins **1b**−**h** underwent the cycloaddition reaction to give the corresponding tetrahydropyranes **6b**−**h** in good to high yields with 44−21:56−79 mixtures of trans and cis diastereomers (entries 10−13). Interestingly, the reactions of the Meldrum's acid derivatives **1i**, **1j**, and **1k** gave exclusively the cis isomers of **6i**, **6j**, and **6k**, respectively, in good to high yields (entries 14−16). Accordingly, the problem on lower diastereoselectivities in the six-membered cycloaddition can be solved by the use of the Meldrum's acid derivatives. The stereochemistries of the tetrahydropyrans were determined also by NOE experiments and by X-ray analysis (see SI). The cis-diastereomers were produced predominantly or exclusively in the six-membered ring formation, whereas the trans-diastereomers were afforded preferentially in the five-membered cycloaddition. The reason for this interesting contrast is explained in the mechanistic section. The cycloaddition of **1a** with **4** proceeded in the presence of 5 mol % Pd_2dba_3·$CHCl_3$/40 mol % PPh_3 catalyst at 100 °C, and the corresponding seven-membered cyclic ether **7a** was obtained in 31% yield (entry 17). The reaction did not proceed in the presence of 10 mol % $Pd(PPh_3)_4$ in THF at room temperature, but at 100 °C in a vial it gave **7a** in 13% yield. By the catalyst combination between Pd_2dba_3·$CHCl_3$ and bidentate ligands, the seven-membered ring product was not produced or at most was obtained in very low yields. The use of (Pd_2dba_3·$CHCl_3$/(*o*-tolyl)$_3$P did not produce **7a** and that of Pd_2dba_3·$CHCl_3$/Bu_3P gave **7a** in less than 10% yield. The reaction of **4** with **1f**, **1g**, or **1i** did not proceed even in the presence of Pd_2dba_3·$CHCl_3$/PPh_3 at 100 °C. Accordingly, this cycloaddition methodology is not of wide applicability to the synthesis of seven-membered cyclic ethers. It is known that the palladium-catalyzed reaction of vinylic oxides with activated olefins **1** gives the tetrahydrofuran derivatives, such as **5**, in high yields.[12e] However, this method cannot be extended to the six-membered ring formation reaction due to the structural factor of vinylic oxides. Accordingly, the present two-component alkoxyallylation is more widely applicable to constructing cyclic ethers than the previous method via vinylic epoxides.

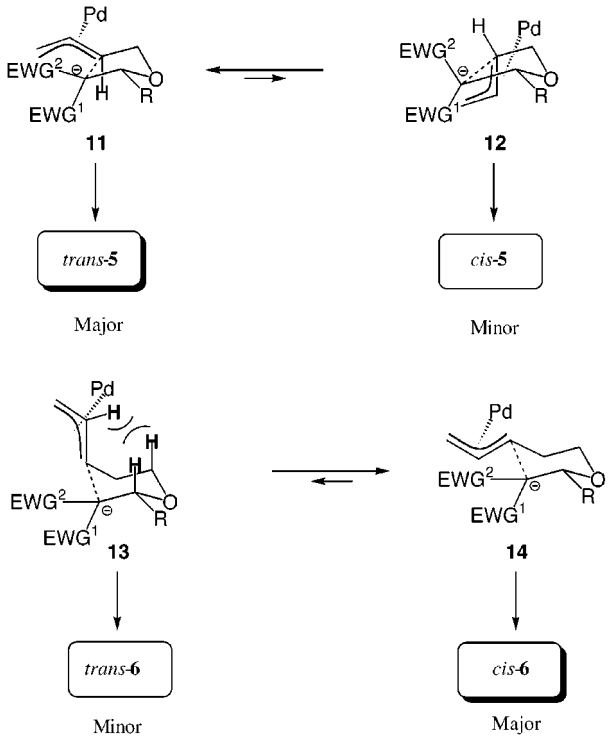
Mechanism. A plausible mechanism for the two component alkoxyallylation is shown in Scheme 1. The oxidative insertion of Pd(0) to the allylic carbonates **2**−**4** produces the π-allylpalladium complex **8**,[17] and then isopropyl alcohol would be removed through the in situ alkoxy exchange reaction to produce another π-allylpalladium complex **9**. This alkoxy exchange process is very similar to that observed in the external three-component alkoxyallylation (eq 3).[11] The Michael addition of the oxygen nucleophile of **9** to **1** would give the C−O bond forming product **10**, which would undergo the intramolecular attack of the nucleophilic carbon to the π-allylpalladium complex resulting in the formation of the cyclic ethers **5**−**7**.

In the five-membered cycloaddition, the bidentate ligand, dppe, gave the best result whereas the monodentate bulky ligand, (*o*-tolyl)$_3$P, produced the best result in

(16) (a) The reaction of the aliphatic activated olefins such as 1,1-dicyano-1-butene and 1,1-dicyano-1-propene, which have a proton at the allylic position, in the molecules, resulted in a complex mixture. (b) The starting material was recovered in the presence of such salts. Since, Pd(0) insertion to the carbonate takes place even in the presence of salts, it is thought that the dramatic salt effect seems to be operative on the processes after the formation of **8**.

(17) (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem*. **1985**, *50*, 1523. Also see the reviews; (b) Tsuji, J. In *Palladium Reagents and Catalysts*; John Wiley and Son: Chichester, 1995; p 61. (c) Codleski, S. A. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, 1991; vol. 4, p 585. (d) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; Mill Valley, 1987; p 417.

Scheme 2



the six-membered cycloaddition (Table 1). This interesting contrast may be ascribed to the difference of the bite angles of those ligands, but at the present stage it is difficult to give rational explanation on this observation. In the seven-membered cycloaddition, the stability of palladium catalysts at higher temperatures is presumably very important. The reaction was very slow at lower temperatures and at 100 °C most of the catalysts changed to palladium black upon prolonged reaction time. Comparison between the present and the previous cycloaddition,[12e] in which tetrahydrofuran derivatives were produced upon treatment of vinyl oxiranes with activated olefins in the presence of palladium catalyst, is interesting. In the previous case, several polar solvents and a wide range Pd(0) catalysts including $Pd(PPh_3)_4$ could be used, whereas applicable Pd(0) catalyst and solvent are very limited in the present cycloaddition. Perhaps, the oxiranes is much easier than that of allyl isopropyl carbonates because of the steric strain of oxirane ring, and thus Pd_2dba_3·$CHCl_3$, which has a labile ligand, would be a suitable catalyst in the present case.

Slight trans-preference in the five-membered cycloaddition and cis-preference in the six-membered cycloaddition can be explained in the following manner (Scheme 2). In the five-membered cyclic transition states due to the steric repulsion between $C(EWG)_2$ and the π-allyl group, **12** is destabilized in comparison with **11**. The transition state **11** leads to the trans isomer while **12** to the cis isomer. In the six-membered cyclic transition states **13** and **14**, **13** is destabilized compared to **14** due to the 1.3-diaxial interactions. The transition state **13** produces the trans isomer while **14** gives the cis isomer.

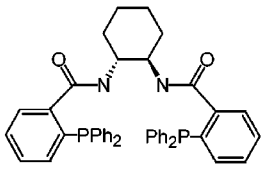
Catalytic Asymmetric Synthesis. Next, the asymmetric cycloadditions were examined with chiral phosphine ligands. At the beginning, we investigated the reaction of **1a** with **2** in the presence of Pd_2dba_3·$CHCl_3$ (2.5 mol %) and various chiral ligands (10 mol %) in THF at room temperature. With (*R*)-BINAP and (*R*)-Tolyl-BINAP, no reaction took place (see SI for the abbreviation of chiral ligands). With (+)-DIOP, (*R*,*S*)-BPPFOH **16**, and (*R*)-PROPHOS, **5a** was formed in low chemical yields (~30%) with low ees (~20%). With (*S*,*S*)-CHIRAPHOS, only trace amounts of **5a** were obtained. With **15** (Trost ligand),[18] **5a** was obtained in 78% combined yield; *trans*-**5a** was isolated in 38% yield with 38% ee and *cis*-**5a** in 40% yield with 41% ee. The ee values were determined by HPLC analysis using a chiral column (CHIRALCEL OD, IPA/hexane = 5/95). Since the Trost ligand gave the best result among the chiral ligands tested, we next investigated the solvent effect. In a nonpolar solvent such as CH_2Cl_2, the ee decreased dramatically; 0% ee for *trans*-**5a** and 38% ee for *cis*-**5a**. On the other hand, polar solvents such as CH_3CN, DMF, *N*,*N*-dimethylacetamide, and DMSO were effective and **5a** was obtained in moderate to high ees. Among them, the highest ees for both *trans*- and *cis*-**5a** were obtained in the reaction at room temperature in DMF; *trans*-**5a** was produced in 9% yield with 58% ee, whereas *cis*-**5a** was afforded in 10% yield with 87% ee. Very interestingly, the reaction in DMF at higher temperatures gave better chemical yields and ees. At 100 °C in 1 h, *trans*-**5a** was obtained in 36% yield with 77% ee and *cis*-**5a** was obtained in 33% yield with 84% ee (entry 1, Table 2).

Since the standard reaction conditions were settled, we carried out the catalytic asymmetric five-membered cycloadditions using various activated olefins **1b**−**l**. The cycloaddition of **1b**, **1c**, **1e**, **1f**, and **1l** with **2** in DMF at 100 °C proceeded smoothly to give the corresponding THF derivatives in good yields, although the diastereoselec-

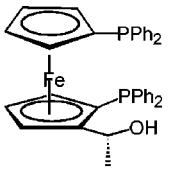
Table 2. Palladium(0)-Catalyzed Asymmetric Cycloadditions of Activated Olefins 1 with Allylic Carbonates 2 and 3 Using the Chiral Ligands 15 and 16[a]

entry	olefin	allylic carbonate	yield (%)[b]	ratio[c] (trans/cis)	ee (%)[d] trans	ee (%)[d] cis
1	**1a**	**2**	69	52/48	77	84
2	**1b**	**2**	76	57/43	66	75
3	**1c**	**2**	75	52/48	46	58
4	**1e**	**2**	57	50/50	78	81
5	**1f**	**2**	66	52/48	74	71
6	**1l**	**2**	56	55/45	55	60
7[e]	**1m**	**2**	42	-	87	
8	**1a**	**3**	54	41/59	82	55
9	**1b**	**3**	71	44/56	85	47
10	**1c**	**3**	52	85/15	92	72
11	**1d**	**3**	56	75/25	88	63
12	**1f**	**3**	55	44/56	80	58
13[e]	**1m**	**3**	29	-	62	

[a] **1a** (0.5 mmol), Pd_2dba_3·$CHCl_3$ (0.025 mmol), the chiral ligand **15** for entries 1−7 (or **16** for entries 8−13) (0.1 mmol), DMF (5 mL), **2** (0.5 mmol) or **3** (0.5 mmol), 100 °C, 1 h. [b] Isolated yields based on **1**. [c] The trans/cis ratio was determined by the isolation of each diastereoisomer. [d] The ee values were determined by chiral HPLC analysis (CHIRALCEL OD: entries 1−3, 5, CHIRALCEL AD: entry 4, CHIRALCEL AS: entries 6−10, IPA/Hexane = 5/95). [e] The reaction was carried out at room temperature.



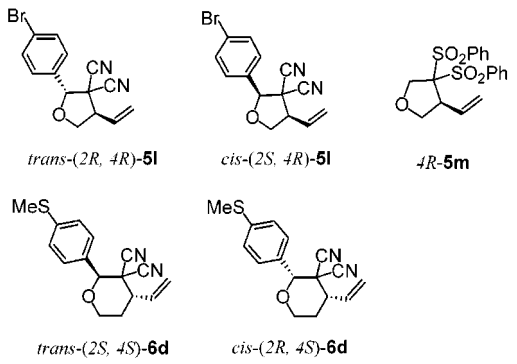
15



16
(*R*)-(*S*)-BPPFOH

(18) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

Scheme 3



tivities of the products were low (entries 2−6). The ees of both *trans*- and *cis*-**5a** were in general good to high. In entries 1−6, the activated olefins having aryl substituents were tested. The reaction of the aliphatic olefin **1g** under the same conditions as above gave the cycloadducts in 96% combined yields, but the ees of the *trans*-**5g** and *cis*-**5g** were only 20% and 16%, respectively. To know whether the cycloaddition proceeds with an unsubstituted activated olefin, we examined the reactions with 1,1-bis(diethoxycarbonyl)ethylene, 1,1-bis(cyano)ethylene, and 1,1-bis(phenylsulfonyl)ethylene **1m**. The reaction of the former two substrates with **2** under the catalytic asymmetric conditions or under the ordinary cycloaddition conditions in THF at room-temperature did not give the desired cycloadduct but resulted in the recovery of the activated olefins. However, the reaction of **1m** in DMF at room temperature produced **5m** in 42% yield with 87% ee (entry 7).

The catalytic asymmetric six-membered cycloaddition between **1a** and **3** was examined using various chiral ligands. With (*R*)-BINAP and (*R*)-Tolyl-BINAP, here again no reaction took place. The chemical yields of **6a** were around 30% with (*R*)-PROPHOS and (*R*,*S*)-BPPFA. The use of the Trost ligand **15** resulted in low ee. The use of (*R*,*S*)-BPPFOH **16**[19] (the Hayashi ligand) enhanced the ee of *trans*-**6a**; the reaction of **1a** (1 equiv) with **3** (3 equiv) in the presence of Pd_2dba_3·$CHCl_3$ (2.5 mol %) and (*R*,*S*)-BPPOH (10 mol %) in THF at 100 °C in a vial for 1 h gave *trans*-**6a** in 32% yield with 86% ee and *cis*-**6a** in 29% yield with 33% ee. When 5 mol % of the palladium catalyst and 20 mol % of the ligand were used, *trans*- and *cis*-**6a** were obtained in 22% yield with 82% ee and in 32% yield with 55% ee, respectively (entry 8, Table 2). Accordingly, we applied these latter conditions for the other activated olefins (**1b, 1c, 1d**, and **1f**). In general, the ees of *trans*-**6** were good to high, whereas those of *cis*-**6** were in the range of 50−70% (entries 9−12). Here again, the Michael acceptor **1m** reacted at room temperature to give **6m** having no substituent at the α-position of tetrahydropyran ring, although the chemical yield was low (entry 13).

Mechanistic Consideration of Asymmetric Induction. The absolute stereochemistries of the major enantiomers of *trans*- and *cis*-**5l**, *trans*- and *cis*-**6d**, and **5m** were determined by X-ray crystallographic analysis (Scheme 3) (SI). The absolute stereochemistries of other enantiomers in Table 2 were not determined unambiguously. It should be noted that in the five-membered cycloaddition the absolute configuration at the C-4 position of the major enantiomers of both *trans*- and *cis*-**5l** is R, whereas that at the C-2 position is *R* for trans and *S* for *cis*-**5l**. Trost and Toste provide a model for understanding asymmetric allylic alkylations catalyzed by palladium with the use of the Trost ligand **15**.[20] Since the trans/cis diastereoselectivity of **5** is generally low, the Michael addition of the oxygen nucleophile of π-allylpalladium complex to **1**, proceeds with low face-selectivity. The model **17** proposed by Trost and Toste can explain nicely the chiral induction at the C-4 position of **5l**.[21] Among possible transition state geometries of the π-allylpalladium complexes **10** having the Trost ligand, **18** leading to *trans*-(2*R*,4*R*)-**5l** is more stable than **19** leading to *trans*-(2*S*,4*S*)-**5l**, due to the steric reason.[20] Accordingly, the major enantiomer of trans-**5l** has (2*R*,4*R*) absolute configuration. Similar discussion can be made for *cis*-(2*S*,4*R*)-**5l**. It is interesting observation that the stereoselection at the Michael addition (from **9** to **10** in Scheme 1) is low and is not influenced significantly by the presence of the chiral ligand **15** (see trans/cis ratios of Table 1 and Table 2), and that good to high chiral induction is realized in the C−C bond formation (from **10** to **5** in Scheme 1). The latter observation is confirmed further by the reaction of **1m** in which the trans/cis diastereoselection is not associated; *R* configuration at the C-4 position of **5m** was produced in 87% ee.

In the six-membered cycloaddition, the Trost ligand **15** was not suitable but BPPFOH **16** gave significantly high ees although here again the trans/cis diastereoselection was low except for entry 10 in Table 2. It should be noted that the absolute stereochemistries of the major enantiomers of **6** are opposite to those of **5**: the major enantiomers of *trans*- and *cis*-**6d** have (2*S*,4*S*) and (2*R*,4*S*) configuration, respectively, whereas those of *trans*- and *cis*-**5l** have (2*R*,4*R*) and (2*S*,4*R*) configuration, respectively. In the alkoxy-π-allylpalladium intermediate **9** (Scheme 1), when (*R*,*S*)-BPPFOH **16** is used as a ligand, **20** is more stable than **21** due to a hydrogen bonding between OH of **16** and the alkoxy anion of the π-allyl complex (Scheme 5).[22] Here, it is assumed that the π-allylpalladium complexes take s-trans configuration. In **20**, the alkoxy anion is forced to be away from the hydroxy group. The Michael addition to **1d** as shown in **20** followed by the backside attack of the nucleophilic carbon $^{-}C(CN)_2$ to the π-allyl plane produces *trans*-(2*S*,4*S*)-**6d**. On the other hand, in the less stable **21**, *trans*-(2*R*,4*R*)-**6d** is produced, which is a minor enantiomer. The use of (*R*,*S*)-BPPFA, instead of **16**, resulted in low chemical yield and low ee, supporting the importance of hydrogen bonding shown in **20** since BPPFA has $N(CH_3)_2$ group instead of OH at the side chain of ferrocene ring and thus a hydrogen bonding is not feasible. One may ask a question why the Trost ligand **15** is suitable to the five-membered cycloaddition and the Hayashi ligand (BPPFOH) **16** to the six-membered addition mode, and the reverse does not work well. In the transition state-geometries including the Trost ligand (Scheme 4), if one carbon is elongated between the nucleophilic carbon and C-3 of the π-allyl complex,

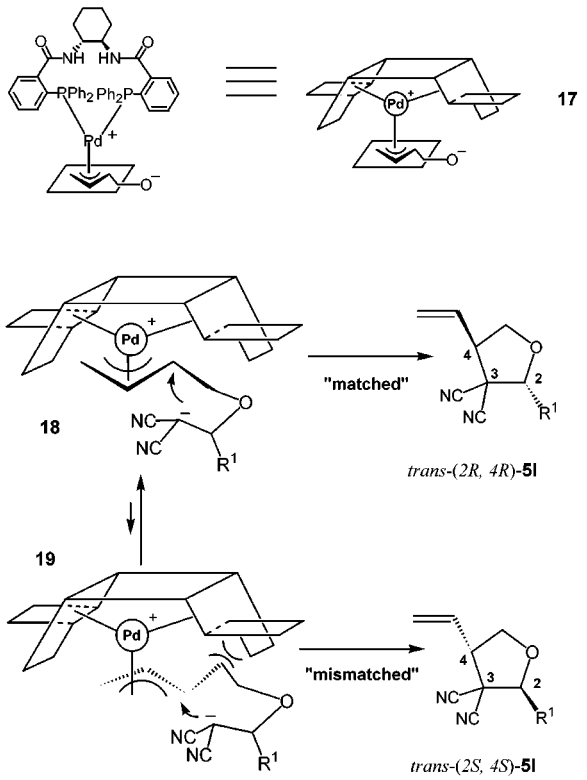
(19) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 1138.

(20) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1999**, *121*, 4545. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395.

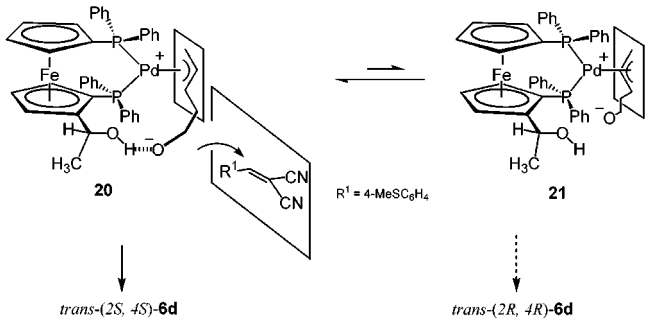
(21) (a) Trost, B. M.; Weber, L.; Strege, P. E.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc*. **1978**, *100*, 3416. (b) Trost, B. M. *Acc. Chem. Res*. **1980**, *13*, 385.

(22) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett*. **1986**, *27*, 191.

Scheme 4



Scheme 5



perhaps the C−C bond formation through **19′** (in which one carbon is elongated in comparison to **19**) would become more feasible due to the increase of flexibility of carbon chain, leading to low ee of **6a**. In the transition state-geometries including BPPFOH (Scheme 5), if one carbon is short, a hydrogen bonding between OH and O^- (as proposed in **20**) would become difficult, producing **5a** with low ee.

Conclusion

The two-component alkoxyallylation between **1** and the hydroxy allylic carbonates **2** and **3** proceeds very smoothly to produce the corresponding tetrahydrofuran **5** and tetrahydropyran derivatives **6** in good to high yields. The reaction between **1a** and **4** gives the seven membered cyclic ether **7a** in low yield. Significantly high to good ees are accomplished in the reactions between **1** and **2** and between **1** and **3**, although the diastereoselectivities are low. Nowadays, a number of excellent catalytic asymmetric syntheses have been developed, but most of them are applicable to create one chiral center: only few reliable catalytic asymmetric procedures are available for producing two chiral centers at once. The five- and six-membered cycloadditions reported here are also not exceptional and do not provide two chiral centers with satisfactory ees, although one chiral center is produced with significantly high to good ees. In this sense, the Sharpless epoxidation is superb since it creates two chiral centers at once with very high ees.

Experimental Section

General Procedure for the Five-Membered Cycloaddition of Activated Olefins. To a solution of activated olefin **1** (0.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol), and dppe (0.025 mmol) in THF (5 mL) was added the allylic carbonate **2** (0.6 mmol) at room temperature under Ar, and the mixture was stirred for 3 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1). The structures of the resulting tetrahydrofurans, **5a**, **5c**, **5f**−**i**, were determined unambiguously by comparison with the reported data.[12e]

General Procedure for the Six-Membered Cycloaddition of Activated Olefins. To a solution of activated olefin **1** (0.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol), and *o*-Tol_3P (0.10 mmol) in THF (5 mL) was added the allylic carbonate **3** (0.75 mmol) at room temperature under Ar, and the mixture was stirred for 6 h at 50 °C. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1).

Procedure for the Seven-Membered Cycloaddition of 1a with 4. To a solution of benzylidene malononitrile **1a** (0.5 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.025 mmol), and PPh_3 (0.2 mmol) in THF (5 mL) was added **4** (0.75 mmol) at room temperature under Ar, and the mixture was stirred in vial tube for 6 h at 100 °C. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1).

General Procedure for Asymmetric Five-Membered Cycloaddition of Activated Olefins. To a solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol) and the chiral ligand **15** (0.05 mmol) in DMF (2.5 mL) was added allylic carbonate **2** (0.25 mmol) at room temperature under Ar. DMF solution of the activated olefin **1** (0.25 mmol) was added subsequently, and the mixture was stirred for 3 h at 100 °C. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1). The ee was determined by the chiral HPLC analysis.

General Procedure for Asymmetric Six-Membered Cycloaddition of Activated Olefins. To a solution of activated olefin **1** (0.25 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.0125 mmol), and (*R*,*S*)-BPPFOH **16** (0.05 mmol) in THF (2.5 mL) was added allylic carbonate **3** (0.75 mmol) at room temperature under Ar, and the mixture was stirred in vial tube for 3 h at 100 °C. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1). The ee was determined by the chiral HPLC analysis.

Supporting Information Available: Details for the preparation and spectroscopic date for compounds **3**−**6** (PDF). This material is available free charge via the Internet at http://pubs.acs.org.

JO0158332