ORGANIC LETTERS

2003
Vol. 5, No. 18
3325−3327

Palladium-Catalyzed Enantiospecific Reaction of Propargylic Carbonates with Phenols: Cascade Chirality Transfer

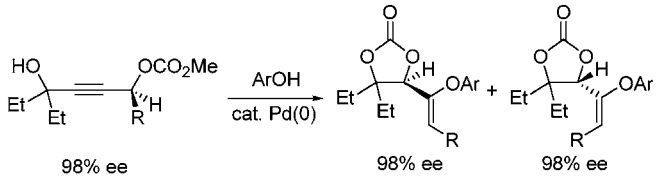
Masahiro Yoshida,* Mika Fujita, and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai, 980-8578, Japan

mihara@mail.pharm.tohoku.ac.jp

Received June 25, 2003

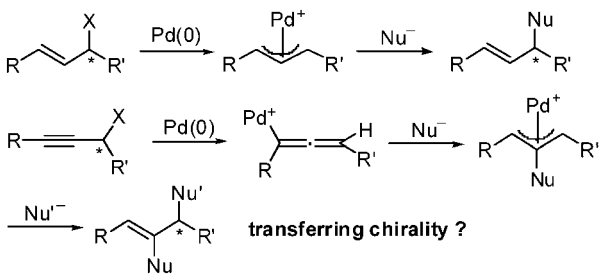
ABSTRACT



A cascade chirality transfer process has been achieved by the palladium-catalyzed reaction of substituted propargylic carbonates with phenols. The reaction proceeds in a highly enantiospecific manner to produce chiral cyclic carbonates, which supports the existence of the π-propargylpalladium intermediate in the reaction mechanism. The (*E*)- and (*Z*)-selectivity of the products can be controlled by choice of the phosphine ligand.

Palladium-catalyzed reactions of propargylic compounds with soft nucleophiles serve as a useful method for the construction of carbon−carbon and carbon−heteroatom bonds.[1] In these processes, allenylpalladium complexes are formed initially, and these complexes undergo secondary reactions with nucleophiles to form π-allylpalladium intermediates. Since the first report by Tsuji in 1985,[2] a large variety of reactions in this family have been developed and applied in the preparation of various organic substances.[1,3] However, to the best of our knowledge, studies examining stereochemical features of these processes have not been reported. Thus, in contrast to the well-known palladium-catalyzed allylation process, which proceeds via the formation of a π-allylpalladium complex followed by addition of a nucleophile with overall retention of configuration,[4] the stereochemical course of the palladium-catalyzed nucleophilic substitution reactions of asymmetric propargylic substrates is unknown (Scheme 1).[5]

Scheme 1



Recently studies in our laboratory have uncovered a novel palladium-catalyzed cascade reaction of propargylic carbon-

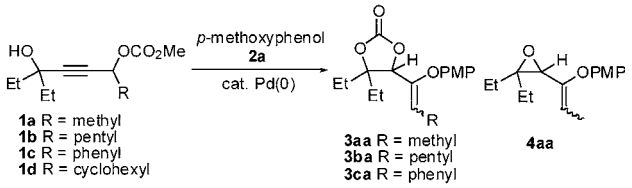
(1) For reviews on palladium-catalyzed reactions of propargylic compounds, see: (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Minami, I.; Yuhara, M.; Watanabe, H.; Tsuji, J. *J. Organomet. Chem.* **1987**, *334*, 225. (c) Tsuji, J.; Mandai. T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

(2) Tsuji, J.; Watanabe, H.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196.

(3) For recent examples of similar types of palladium-catalyzed reactions of propargylic carbonates with nucleophiles, see: (a) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Synlett* **1996**, 553. (b) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583. (c) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (d) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527. (e) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869. (f) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499. (g) Damez, C.; Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2003**, *44*, 557.

10.1021/ol0351753 CCC: $25.00
Published on Web 08/06/2003

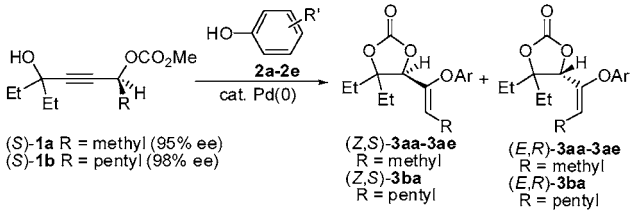
Table 1. Palladium-Catalyzed Reaction of Racemic Propargylic Carbonates **1a**−**d** with *p*-Methoxyphenol **2a**[a,b]



entry	substrate	ligand	product	yield (%)[c]	*Z*:*E*
1	**1a**	dppe	**3aa**[e]	66	10:1[g]
2	**1a**	dppp	**3aa**	47	1:3.3[g]
3	**1a**	dppb	**4aa**[e]	40	6.4:1[h]
4	**1a**	dppf	**4aa**	42	8:1[h]
5	**1a**	PPh_3[d]	**4aa**	20 (30)	*Z* only
6	**1b**	dppe	**3ba**[f]	81	3.7:1[g]
7	**1c**	dppe	**3ca**[f]	32 (47)	*Z* only
8	**1d**	dppe		tr	

[a] Reactions are carried out in the presence of 5 mol % $Pd_2(dba)_3$·$CHCl_3$ and 20 mol % ligand in dioxane at 50 °C for 10−24 h under CO_2 atmosphere. [b] PMP = *p*-methoxyphenyl. [c] The yields in parentheses are based on recovered starting material. [d] Using 40 mol % of PPh_3. [e] The stereochemistry of each product was determined by using the NOESY technique. See Supporting Information. [f] The stereochemistry of each product was tentatively assigned by comparison of its NMR spectra with (*Z*)- and (*E*)-**3aa**. [g] Ratios were determined by the isolation of each isomer. [h] Ratios were determined by ^1H NMR integration of methine proton on the epoxide ring.

Table 2. Palladium-Catalyzed Reaction of Chiral Propargylic Carbonates **1a,b** with Phenols **2a**−**e**[a]



entry	substrate	phenol	product	yield (%)	*Z*,*S*:*E*,*R*[d]	ee (%)[e,f] *Z*,*S*/*E*,*R*
1[b]	(*S*)-**1a**	**2a** R′ = 4-methoxy	**3aa**	66	10:1	95/95
2[c]	(*S*)-**1a**	**2a** R′ = 4-methoxy	**3aa**	47	1:3.3	95/95
3[b]	(*S*)-**1a**	**2b** R′ = 2-methoxy	**3ab**[g]	65	7:1	94/94
4[c]	(*S*)-**1a**	**2b** R′ = 2-methoxy	**3ab**	36	*E*,*R* only	92
5[b]	(*S*)-**1a**	**2c** R′ = 4-methyl	**3ac**[g]	72	5.5:1	95/95
6[c]	(*S*)-**1a**	**2c** R′ = 4-methyl	**3ac**	36	*E*,*R* only	94
7[b]	(*S*)-**1a**	**2d** R′ = 4-fluoro	**3ad**[h]	54	*Z*,*S* only	94
8[b]	(*S*)-**1a**	**2e** 1-naphthol	**3ae**[g]	51	2.9:1	93/93
9[b]	(*S*)-**1b**	**2a** R′ = 4-methoxy	**3ba**	81	3.7:1	98/98
10[c]	(*S*)-**1b**	**2a** R′ = 4-methoxy	**3ba**	41	*E*,*R* only	95

[a] All reactions are carried out in the presence of 5 mol % $Pd_2(dba)_3$·$CHCl_3$ and 20 mol % ligand in dioxane at 50 °C for 8−24 h under CO_2 atmosphere. [b] dppe was used as a ligand. [c] dppp was used as a ligand. [d] All isomers were isolated. [e] Enantiomeric excesses are determined by using chiral HPLC (CHIRALPAK OD-H or OJ-H). [f] Absolute configurations of (*Z*,*S*)- and (*E*,*R*)-**3aa** were each determined by using Kusumi's method, and other products were tentatively assigned on the basis of specific rotation. [g] The stereochemistry of the products were tentatively assigned by comparisons with the NMR spectra of (*Z*)- and (*E*)-**3aa**. [h] Stereochemistry was determined by using the NOESY technique.

ates with phenols, which involves a CO_2 elimination−fixation step and affords phenoxy-substituted cyclic carbonates.[6] In continuing investigations in this area, we have discovered that reactions of chiral substrates, which possess asymmetric propargylic centers, proceed in a highly enantiospecific manner to give chiral cyclic carbonates via an overall cascade chirality transfer process. Below we describe the preliminary result of this effort.

Our initial studies focused on reactions of racemic propargylic carbonates **1a**−**d**, which possess substituents at the propargylic position (Table 1). Reaction of the methyl-substituted substrate **1a** with *p*-methoxyphenol **2a** in the presence of 5 mol % $Pd_2(dba)_3$·$CHCl_3$ and 20 mol % dppe in dioxane at 50 °C under a CO_2 atmosphere for 12 h yields the cyclic carbonates (*Z*)- and (*E*)-**3aa** in a 10:1 ratio and 66% yield (entry 1). Interestingly, we found that the stereochemical course of this reaction is reversed (*Z*:*E* = 1:3.3 in entry 2) when dppp is used as the ligand. When dppb, dppf, and PPh_3 are employed as ligands, the reaction does not yield cyclic carbonates. Rather, the (*Z*)-epoxide **4aa** is generated selectively (entries 3−5). Reaction of the pentyl-substituted substrate **1b** in the presence of dppe produces (*Z*)- and (*E*)-**3ba** in 81% yield and a 3.7:1 ratio (entry 6). Substrate **1c**, which has a phenyl group at the propargylic position, reacts to afford **3ca** in low yield (32% and 47% yield based on recovered starting material, in entry 7). Finally, only a trace amount of products is generated by the reaction of **1d**, which has a bulky cyclohexyl group at the propargylic center (entry 8).

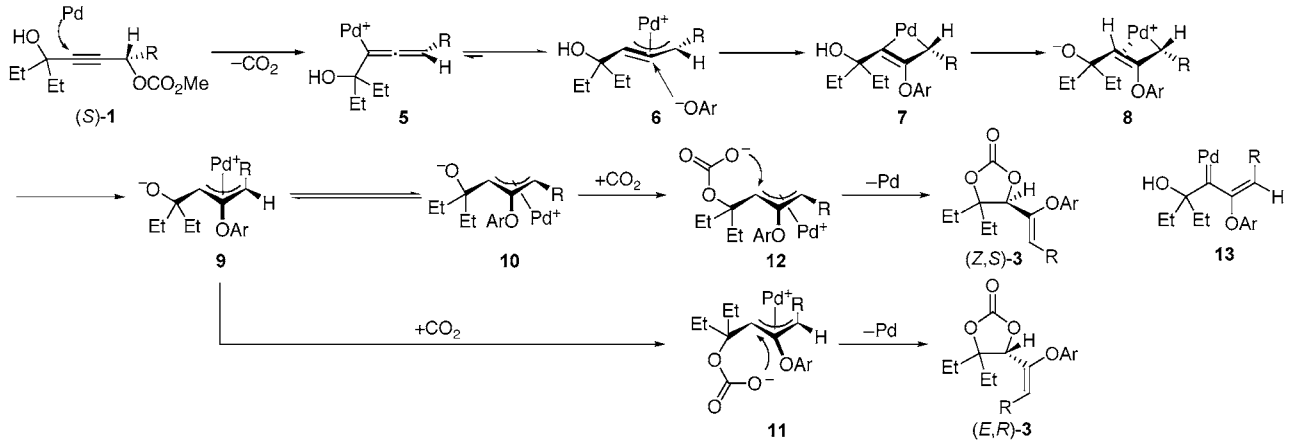
We next examined the reactions enantiomerically enriched, chiral propargylic carbonates (Table 2). When substrate (*S*)-**1a** (95% ee), prepared from (*S*)-3-butyn-2-ol, is subjected to reaction with *p*-methoxyphenol **2a** in the presence of 5 mol % $Pd_2(dba)_3$·$CHCl_3$ and 20 mol % dppe, chiral cyclic carbonates (*Z*)- and (*E*)-**3aa** are produced with 10:1 *Z*-selectivity (entry 1). The absolute configurations of (*Z*)- and (*E*)-**3aa** were determined to be *S* and *R*, respectively, by their conversion into and NMR analysis of their MTPA esters (see Supporting Information). It is noteworthy that the enantiomeric excess of both (*Z*,*S*)- and (*E*,*R*)-**3aa** is 95%. The results clearly show that *cascade reactions of chiral propargylic substrates occur with complete transferring chirality*. In addition, reaction of (*S*)-**1a** in the presence of dppp selectively affords (*E*,*R*)-**3aa** without any loss of enantiomeric purity (entry 2). Similar highly enantiospecific cascade reactions take place between **1a** and various phenols **2b**−**e** to afford the corresponding cyclic carbonates (*Z*,*S*)- and

(4) For reviews on stereochemical studies of palladium-catalyzed reactions of allylic compounds, see: (a) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (b) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257. (c) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (d) Heumann, A.; Réglier, M. *Tetrahedron* **1995**, *51*, 975. (e) Trost, B. M.; Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395.

(5) It is known that chiral allenes can be synthesized from the palladium-catalyzed reaction of chiral propargylic compounds via stereoselective S_N2' attack of palladium catalyst; see: (a) Elsevier: C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1983**, *48*, 1103. (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 367. (c) Dixneuf, P.; Guyot, T.; Ness, M. D.; Roberts, S. M. *Chem. Commun.* **1997**, 2083. (d) Konno, T.; Tanikawa, M.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **2000**, 1360.

(6) (a) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 616. (b) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874.

Scheme 2. Proposed Reaction Mechanism



(*E*,*R*)-**3ab**−**ae** (entries 3−8). Substrate (*S*)-**1b** (98% ee), having a pentyl propargylic substituent, is also converted stereoselectively and enantiospecifically to (*Z*,*S*)- and (*E*,*R*)-**3ba** (98% ee in entriy 9 and 95% ee in entry 10).

A plausible mechanism, which accounts for the highly enantiospecific nature of these processes, is shown in Scheme 2. In the first step of the reaction, regio- and stereoselective anti S_N2' attack of the palladium catalyst[5] on propargylic carbonate (*S*)-**1** takes place to yield the chiral allenylpalladium complex **5**. Next, transformation of complex **5** to π-propargylpalladium complex **6** (an equilibrium process),[7] is followed by selective addition of phenol to the central carbon of π-propargyl moiety to form the chiral palladacyclobutene **7**. Complex **7** is then converted to the allylpalladium complex **8** by intramolecular proton transfer without loss of the chirality. The complex **8** is delocalized to afford π-allylpalladium complexes **9** and **10**, and CO_2 fixation followed by cyclization from these complexes via **11** and **12** produces the cyclic carbonate (*E*,*R*)-**3** and (*Z*,*S*)-**3**, respectively. The cause of the phosphine ligand effect (dppe vs dppp) on stereochemistry is not clear, but it could be associated with an alteration of the $\pi-\sigma-\pi$ equilibrium[4] between π-allylpalladium complexes **9** and **10**.[8]

It has been postulated that palladium-catalyzed reactions of propargylic substrates with soft nucleophiles proceed via a pathway in which formation of a palladium−carbene intermediate is preceded by nucleophilic addition to the allenylpalladium complex.[1,2] On the basis of NMR studies, Ogoshi and Kurosawa have recently proposed an alternate mechanism for this process that involves the intermediacy of a π-propargylpalladium complex.[7c,d] Our finding that reactions of chiral propargylic substrates are highly enantiospecific offers strong support for the Ogoshi−Kurosawa mechanism. Accordingly, if reactions of the chiral propargylic carbonates (*S*)-**1** proceed via a route involving the intermediacy of palladium−carbene complexes **13**, complete loss of stereochemical integrity would be observed.

In conclusion, the effort described above has led to the discovery of a palladium-catalyzed cascade chirality transfer reaction occurring between chiral propargylic carbonates and phenols. The process yields cyclic carbonate products in a highly enantiospecific manner. Furthermore, the stereoselectivity of these reactions can be altered by the choice of the phosphine ligand. Continuing studies probing the scope, mechanism, and synthetic applications of this reaction are now in progress.

Acknowledgment. This study was supported in part by Grant-in-Aid for Encouragements for Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS) (for M.Y.) and Scientific Research on Priority Areas (A) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and characterization data for all products; data for NOESY correlations of (*Z*)- and (*E*)-**3aa**, **4aa**, and (*Z*)-**3ad**; procedure for determining the absolute configuration of (*Z*,*S*)- and (*E*,*R*)-**3ga**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0351753

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(8) Åkermark has reported changes in the syn/anti ratio of π-allylpalladium complexes by using various ligands: Sjögren, M.; Hansson, S.; Norrby, P.-O.; Åkermark, B. *Organometallics* **1992**, *11*, 3954.