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Stereoselective Construction of Substituted Chromans by Palladium-Catalyzed Cyclization of Propargylic Carbonates with 2-(2-Hydroxyphenyl)acetates

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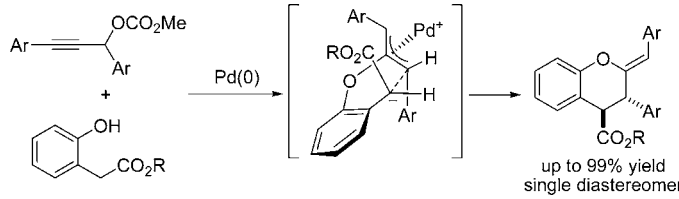
ABSTRACT



Highly substituted chromans have been constructed in a highly stereoselective manner by a palladium-catalyzed reaction of propargylic carbonates with 2-(2-hydroxyphenyl)acetates. Enantioselective reactions also successfully proceeded to give the optically active chromans with high enantioselectivity.

Transition-metal-catalyzed reactions of propargylic compounds have received considerable attention and have been extensively studied as a result of their versatile and specific reactivity.[1] The palladium-catalyzed reaction of propargylic compounds with soft nucleophiles is one of the most successful chemical processes developed to date.[2−5] For example, a substrate having two nucleophilic moieties within the molecule reacted with propargylic carbonate via palladium catalysis to generate the π-allylpalladium intermediate, which further reacted with the other nucleophilic part intramolecularly to afford the cyclized product (Scheme 1). In our studies on the palladium-catalyzed reaction of propargylic compounds with soft nucleophiles,[4e,5] we focused on the nucleophilic activity of 2-(2-hydroxyphenyl)acetates. By introducing a nucleophilic oxygen and a carbon moiety within the substrate, we thought that substituted chromans, common structures in many pharmaceutical and agricultural compounds,[6] could be constructed in one step. Herein, we describe the palladium-catalyzed reaction of propargylic carbonates **1** with 2-(2-hydroxyphenyl)-acetates **2**, in which functionalized chromans **3** have been constructed in a highly stereoselective manner (Scheme 2).

(1) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1995; p 453.

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

(3) For recent examples of palladium-catalyzed reactions of propargylic compounds with nucleophiles, see: (a) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2001**, *42*, 4869. (b) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 1499. (c) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749. (d) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 8068. (e) Tsubakiyama, M.; Sato, Y.; Mori, M. *Heterocycles* **2004**, *64*, 27. (f) Ambrogio, I.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2006**, *8*, 2083. (g) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777. (h) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 1538. (i) Bi, H.-P.; Liu, X.-Y.; Gou, F.-R.; Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 3527. (j) Bi, H.-P.; Liu, X.-Y.; Gou, F.-R.; Guo, L.-N.; Duan, X.-H.; Shu, X.-Z.; Liang, Y.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7068. (k) Ohno, H.; Okanao, A.; Kosaka, S.; Tsukamoto, K.; Ohata, M.; Ishihara, K.; Maeda, H.; Tanaka, T.; Fujii, N. *Org. Lett.* **2008**, *10*, 1171. (l) Bi, H.-P.; Guo, L.-N.; Gou, F.-R.; Duan, X.-H.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2008**, *73*, 4713.

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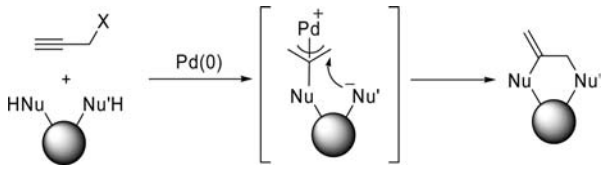
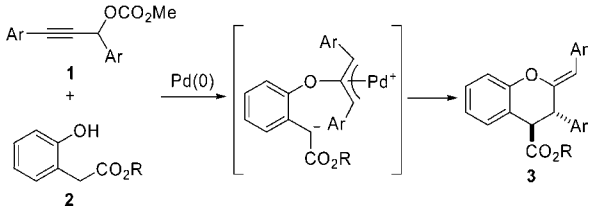
Scheme 1. Reactivity of Propargylic Compounds with Soft Nucleophiles



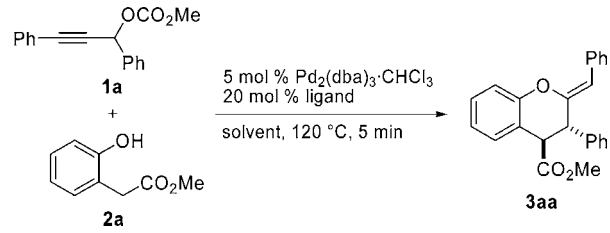
Scheme 2. Palladium-Catalyzed Reaction of Propargylic Carbonates **1** with 2-(2-Hydroxyphenyl)acetates **2**



The initial reactions were attempted using 1,3-diphenylprop-2-ynyl methyl carbonate (**1a**) and methyl 2-(2-hydroxyphenyl)acetate (**2a**). When **1a** and **2a** were subjected to the reaction in the presence of 5 mol % $Pd_2(dba)_3$·$CHCl_3$ and 20 mol % 1,1′-bis(diphenylphosphino)-ferrocene (DPPF) in dioxane at 120 °C for 5 min, the substituted chroman **3aa** containing the *trans* stereochemistry with the (*Z*)-alkenyl moiety was obtained in 18% yield as a single stereoisomer (Table 1, entry 1). After experimenting with various solvents and ligands (entries 2−6), we found that the yield of **3aa** was dramatically improved to 99% when the reaction was carried out in DMSO (entry 3). The structure of the resulting product **3aa** was confirmed by an X-ray crystallographic analysis of the carboxylic acid **4**, which was prepared by hydrolysis of **3aa** (Scheme 3).

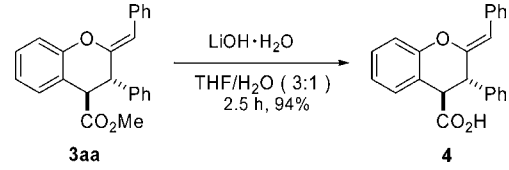
Having identified a useful set of reaction conditions, we next carried out a study of the substrate scope (Table 2). Benzyl 2-(2-hydroxyphenyl)acetate (**2b**) successfully reacted with **1a** to produce the chroman **3ab** in 99% yield (entry 1). When the reaction of substrates **2c** and **2d** having a methoxy group at the 2- and 4-positions on the benzene ring was carried out, the corresponding products **3ac** and **3ad** were

Table 1. Effect of Solvent and Ligand in the Reaction of **1a** with **2a**



entry	solvent	ligand	yield of **3aa** (%)
1	dioxane	DPPF	18
2	DMF	DPPF	78
3	DMSO	DPPF	99
4	DMSO	DPPB	81
5	DMSO	DPPPentane	86
6	DMSO	Tol-BINAP	44

Scheme 3. Hydrolysis of **3aa**



obtained in 80% and 88% yields, respectively (entries 2 and 3). The naphthyl-substituted substrate **2e** also reacted with **1a** to deliver the product **3ae** in 51% yield (entry 4). The reaction of di-4-fluorophenyl-substituted propargylic carbonate **1b** with **2b** uneventfully proceeded to afford the chroman **3bb** in 66% yield (entry 5). Similarly, the propargylic acetate **1c**,[7] containing two 4-methoxyphenyl groups, was converted to the corresponding product **3cb** in 95% yield (entry 6). Since in all cases the resulting products **3aa**−**3ae** and **3bb**−**3cb** had been obtained as a single stereoisomer, it was determined that the reaction had proceeded in a highly stereoselective manner.

Next we evaluated the reactivity of the propargylic carbonate **1d**, which has no substituent at the terminal alkynyl position (Scheme 4). Thus the reaction of **1d** with **2a** proceeded to give the desired chroman **3da** in 26% yield, along with the isomerized product **5** in 26% yield (Scheme 4).[8]

A plausible mechanism, which may account for the highly stereoselective nature of this process, is shown in Scheme 5. On reacting with the palladium catalyst, the propargylic carbonate **1** undergoes decarboxylation to give the π-prop-

(4) (a) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (b) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527. (c) Damez, C.; Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2003**, *44*, 557. (d) Duan, X.-H.; Liu, X.-Y.; Guo, L.-N.; Liao, M.-C.; Liu, W.-M.; Liang, Y.-M. *J. Org. Chem.* **2005**, *70*, 6980. (e) Yoshida, M.; Higuchi, M.; Shishido, K. *Tetrahedron Lett.* **2008**, *49*, 1678.

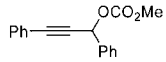
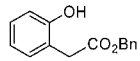
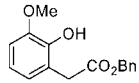
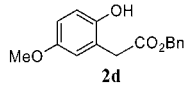
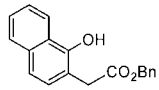
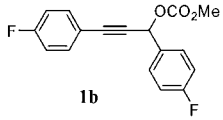
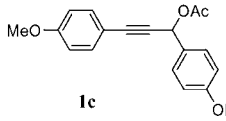
(5) (a) Yoshida, M.; Nemoto, H.; Ihara, M. *Tetrahedron Lett.* **1999**, *40*, 8583. (b) Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616. (c) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874. (d) Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325. (e) Yoshida, M.; Komatsuzaki, Y.; Nemoto, H.; Ihara, M. *Org. Biomol. Chem.* **2004**, 3099. (f) Yoshida, M.; Ihara, M. *Chem.—Eur. J.* **2004**, 2886. (g) Yoshida, M.; Morishita, Y.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 3669. (h) Yoshida, M.; Murao, T.; Sugimoto, K.; Ihara, M. *Synlett* **2006**, 1923.

(6) (a) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963. (b) Ellis, G. P.; Lockhart, I. M. *Chromans and Tocopherols*; Wiley: New York, 1977. (c) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, *3*, 465.

(7) When the corresponding propargylic carbonate was examined, the reaction resulted in the decomposition of the substrate, presumably because of the instability of the carbonate moiety caused by the electron-donating effect of the methoxy groups.

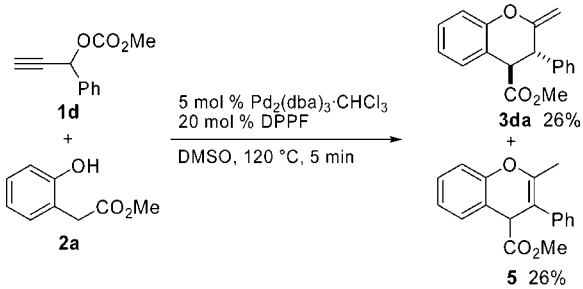
(8) We also attempted other non-symmetrical substrates such as aryl- and alkyl-substituted substrates at the terminal alkynyl and propargylic position, but complex mixtures including regio- and stereoisomers were produced in each cases.

Table 2. Reactions Using Various Substrates **1a−c** and **2b−d**

entry	propargylic ester **1**	phenol **2**	product	yield (%)
1	 **1a**	 **2b**	**3ab**	99
2	**1a**	 **2c**	**3ac**	80
3	**1a**	 **2d**	**3ad**	88
4	**1a**	 **2e**	**3ae**	51
5	 **1b**	**2b**	**3bb**	66
6[a]	 **1c**	**2b**	**3cb**	95

[a] The reaction was carried out in the presence of 2 equiv of K_3PO_4.

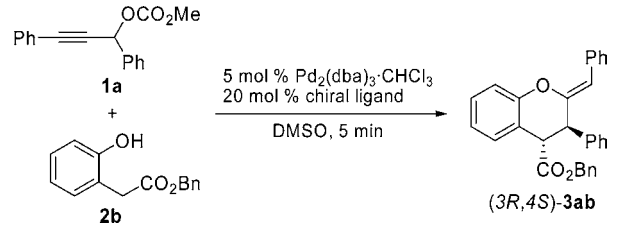
Scheme 4. Reaction of **1d** with **2a**



argylpalladium complex **6**,[9] which further reacts with the 2-(2-hydroxyphenyl)acetate **2** to lead to the *anti*-π-allylpalladium intermediate **8**. Complex **8** is then subjected to the intramolecular attack of the enolate to produce the chroman **3**, which contains the *trans* stereochemistry and the (*Z*)-alkenyl moiety. The observed high diastereoselectivity is likely the result of steric factors that influence the relative energies of the competing transition states **TS A** and **TS B**. It was expected that the transition state **TS A**, leading to the product **3**, would have lower energy because of the absence of steric repulsion between the ester and aryl groups that is present in **TS B**, which would furnish the diastereomer **3′**.[10]

We next turned our attention to the application of this process to an enantioselective reaction. Although numbers of asymmetric reactions of allylic compounds with nucleophiles are known, examples of palladium-catalyzed asymmetric reactions using propargylic compounds with nucleophiles are limited.[4b,c,5c] In the reaction we designed, an asymmetric center is formed via the achiral π-allylpalladium intermediate **8**, and it is anticipated that the absolute configuration of the newly formed stereogenic center could be controlled by chiral palladium catalysts. To achieve this enantioselective process, we first examined the reactions of **1a** with **2b** under various conditions (Table 3). When the reaction was carried out in the presence of 5 mol % $Pd_2(dba)_3$•$CHCl_3$, 20 mol % (*S*)-BINAP in DMSO at 120 °C, the optically active chroman (3*R*,4*S*)-**3ab** formed in 62% yield with 71% ee (entry 1).[11]

Table 3. Enantioselective Cyclization of **1a** with **2b**



entry	ligand	temp (°C)	yield (%)	ee (%)[a]
1	(*S*)-BINAP	120	62	71
2	(*S*)-Tol-BINAP	120	59	68
3	(*S*)-H_8-BINAP	120	78	70
4	(*S*)-DM-BINAP	120	53	52
5	(*S*)-SEGPHOS	120	51	91
6	(*S*)-SEGPHOS	80	55	90
7[b]	(*S*)-SEGPHOS	60	59	96

[a] Enantiomeric excess was determined by HPLC using a chiral column. [b] The reaction was carried out for 3 h.

After several attempts using various chiral phosphine ligands (entries 2−5), we discovered that when (*S*)-SEGPHOS was used, the enantiomeric excess increased to 91% (entry 5). Better results were obtained under low reaction temperature (entries 6 and 7), and (3*R*,4*S*)-**3ab** was produced in 96% ee by carrying out the reaction at 60 °C for 3 h (entry 7).

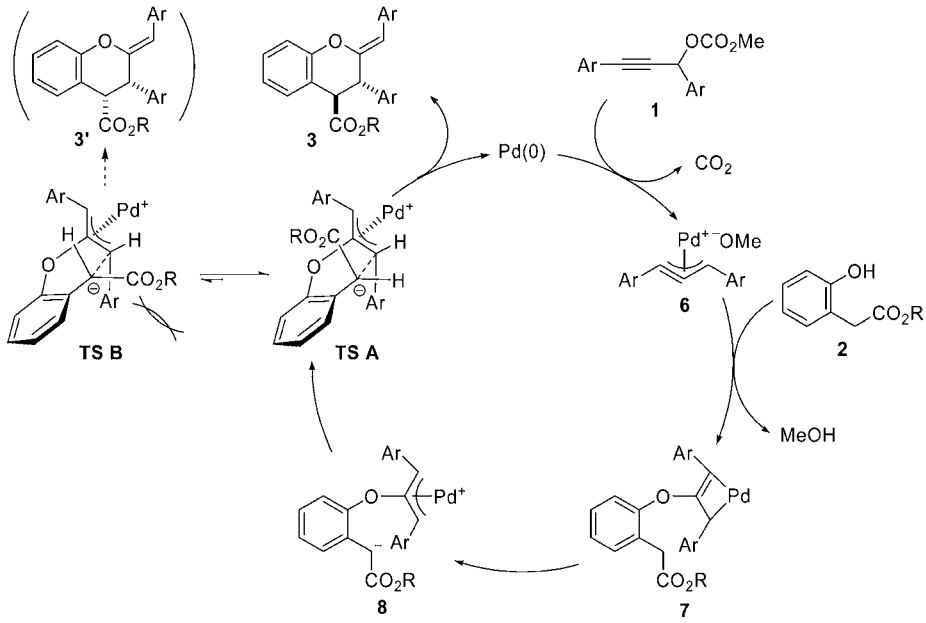
In conclusion, the effort described above has led to the development of the palladium-catalyzed reaction of propar-

(9) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938.

(10) As another hypothesis, the initially produced *cis*-product **3′** was epimerized to the thermodynamically preferred *trans* product **3.**

(11) The absolute configuration was determined to be 3*R*,4*S* by Kusumi's PGME method: Nagai, Y.; Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853. See Supporting Information.

Scheme 5. Proposed Reaction Mechanism



gylic carbonates with 2-(2-hydroxyphenyl)acetates. The process produces substituted chromans having the *trans* stereochemistry with the (*Z*)-alkenyl moiety in a highly stereoselective manner. Enantioselective reactions successfully proceeded in the presence of SEGPHOS to give the optically active chromans with high enantioselectivity. Biologically active compounds having similar chroman structures have been reported,[6] and our methodology would provide a new and significant protocol for the synthesis of these compounds.

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Supporting Information Available: Experimental procedures and compound characterization data, including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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