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HIGHLY REGIOSELECTIVE PALLADIUM-MEDIATED SUBSTITUTION OF ALLYLIC AND DIENYLIC CYCLIC CARBONATES

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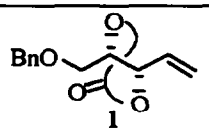
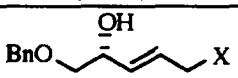
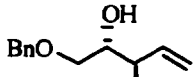
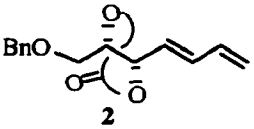
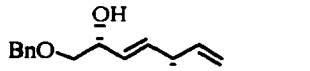
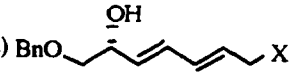
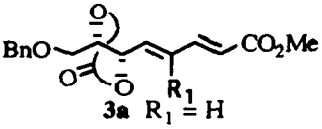
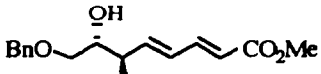
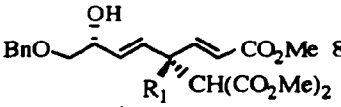
Abstract: Reaction of chiral allylic and dienylic cyclic carbonates with various nucleophiles in the presence of $(PPh_3)_4Pd$ as a catalyst afforded α-, γ-, or ε-substituted products with high regio-, (*E*)-stereo-, and diastereoselectivity depending on nucleophiles.

Reaction of allylic compounds with various nucleophiles catalyzed by palladium complexes *via* π-allylpalladium complexes has been well established as an important synthetic method for C-C, C-N, C-O, and C-S bond formations in inter- and intramolecular reactions.[1] Acyclic allylic carbonates were found to be valuable substrates for palladium-catalyzed nucleophilic substitution by Tsuji.[2] Recently, we have reported[3a] neutral alkylation of soft carbon nucleophiles with chiral allylic cyclic carbonates catalyzed by $(PPh_3)_4Pd$.[3b] We have explored palladium-catalyzed nucleophilic substitution of allylic and dienylic cyclic carbonates with carbon, oxygen, and sulfur nucleophiles, which resulted in high regio- and diastereoselective substitution depending on nucleophiles.

The results of the reactions of allylic and dienylic cyclic carbonates with nucleophiles are summarized in Table 1. The optically active cyclic carbonate **1**[4] reacted with PhOH in the presence of Et_3N and sodium benzenesulfinate in refluxing THF for 1 h in the presence of $(PPh_3)_4Pd$ (5 mol%) to give the (*E*)-allylic alcohols **4a** and **4b**, respectively, as a sole product (entries 1 and 2).[5] However, sodium thiophenoxide attacked 'proximal' to oxygen atom with inversion to afford the *threo*-β-hydroxy sulfide **5**[6] (entry 3) contrasting the regioselectivity associated with palladium-catalyzed *S*-alkylation of acyclic carbonates.[7] Presumably, in this particular system the substitution was proceeded by internal attack of thiophenoxide to carbon *via* π-allylpalladium complex with net inversion.[8] In our control experiment, only deprotected diol and the starting material **1** were isolated from the reaction of **1** with NaSPh (2 equiv) in THF at reflux for 1 h without Pd(0)-catalyst. Thus, the possible non-palladium substitution reaction was eliminated. It is also notable that the problem of catalytic poisoning with thiophenoxide was avoided in this system.[9] For the (*E*)-dienylic cyclic carbonate **2**[10], dimethyl malonate under neutral conditions in the presence of $(PPh_3)_4Pd$ afforded γ-alkylated product **6**[6] as a major product with high diastereoselectivity (~ 98%) along with a minor ε-alkylated compound in the ratio of 6 : 1 (entry 4). This is in contrast to the ε-alkylation with dienylic acetate and sodium malonate reported by Bäckvall[11,12] and Trost.[13] Pd(0)-catalyzed substitution reaction of (*E*)-dienylic cyclic carbonate **2** with PhOH in the presence of Et_3N and $NaSO_2Ph$ provided complete regioselective introduction of these nucleophiles to ε-position to afford the (*E*, *E*)-dienylic alcohols **7a** and **7b** (entries 5 and 6). The (*E*, *E*)-dienylic ester **3a** with sodium thiophenoxide yielded **8**[6] (entry 7). Finally, reaction of **3b** with dimethyl malonate afforded the adduct **9**[6], which was introduced a quaternary center at γ-position with high diastereoselectivity (~ 92%) (entry 8). The typical

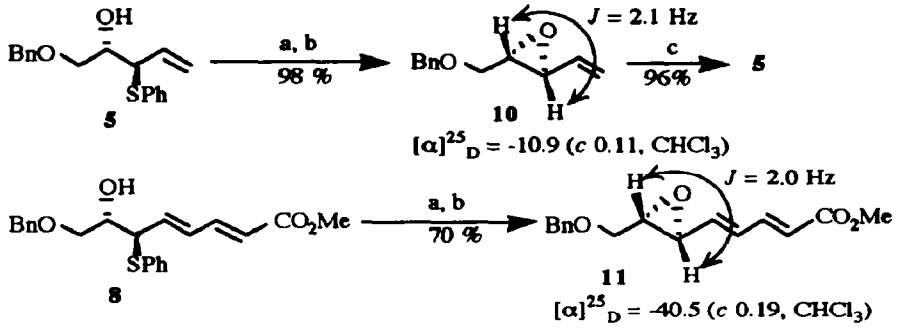
procedure is as follows. To a stirred solution of the allylic cyclic carbonate **1** (258 mg, 1.10 mmol) in dry THF (4 mL) under nitrogen atmosphere was added sodium benzenesulfinate (388 mg, 2.20 mmol) and $(PPh_3)_4Pd$ (63 mg, 5 mol%). After stirring for 10 min at reflux, the reaction mixture was cooled and THF was evaporated. The crude product was purified by SiO_2 column chromatography (EtOAc/hexanes 1 : 1, R_f = 0.19) to afford **4b** (290 mg, 80%).

Table 1. Regioselective Palladium-Mediated Substitution of Allylic and Dienylic Cyclic Carbonates.

Entry	Substrate	Nucleophile[a]	Product	Yield(%)[b]	$[\alpha]_D^{25}$ in $CHCl_3$
1	 **1**	$PhOH/Et_3N$(2)	 **4a** X = OPh	79	-1.72 (*c* 0.64)
2	**1**	$NaSO_2Ph$(2)	**4b** X = SO_2Ph	80	+2.03 (*c* 0.74)
3	**1**	NaSPh(2)	 **5**[c] SPh	74	-4.71 (*c* 1.50)
4	 **2**	$CH_2(CO_2Me)_2$(1)	 **6** γ- : ε- = 6 : 1	85	
5	**2**	$PhOH(2)/Et_3N$(2)	 **7a** X = OPh	83	+1.74 (*c* 0.35)
6	**2**	$NaSO_2Ph$(2)	**7b** X = SO_2Ph	72	+9.52 (*c* 0.21)
7	 **3a** R_1 = H	NaSPh(2)	 **8** SPh	77	-10.27 (*c* 0.19)
8	**3b** R_1 = Me	$CH_2(CO_2Me)_2$(1)	 **9**[d] R_1 = Me	89	-2.60 (*c* 0.73)

[a]With $(PPh_3)_4Pd$ (5 mol%), THF, reflux, 1 h. The molar equivalents are given in parentheses. [b]The yields are isolated yields. [c]The diastereoselection has been found to be nearly perfect (>99%) judged by ^1H NMR spectrum and GC-MS analysis of the acetate of **5**. The GLC analysis was performed using Hewlett Packard 5880 GC system (column: Hewlett Packard SE-54, 0.2 mm x 16 mm, oven temp.: 150→300 °C, carrier gas: N_2, 1.0 mL /min, injection temperature: 280 °C). The retention time of the acetate of **5** was 7.95 min. [d]The diastereoselectivity of **9** was determined ~92 % by ^1H NMR analysis with $Eu(hfc)_3$ and capillary GLC analysis of the acetate of **9**.

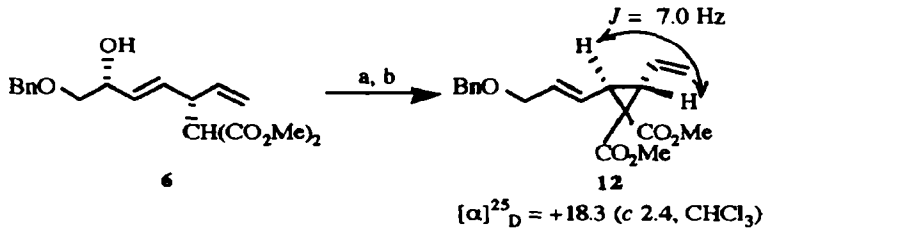
To establish the relative stereochemistry of the newly introduced C-S bonds in **5** and **8**, the β-hydroxy sulfides **5** and **8** were converted[14] to the corresponding vinyl *trans*-epoxides **10**[6] and **11**[6], respectively, by treating with trimethyloxonium tetrafluoroborate followed by 10% aquous NaOH. The *trans*-epoxides were inferred from ^1H NMR (200 MHz) coupling constants of the two vicinal protons of the epoxides.[15] Alternatively, the epoxide **10** was returned to the *threo* compound **5** by the reaction[16] with PhSH (Scheme 1).



Reagents: (a) Me_3OBF_4 (1 equiv), CH_2Cl_2, rt, 2 h (b) 10% NaOH (aq.), rt, 30 min (c) PhSH, Et_3N, MeOH, rt, 1 h.

Scheme 1.

On the other hand, to deduce the relative stereochemistry of C-C bond in **6**, the compound **6** was converted to the carbonate followed by cyclopropanation[17] to afford **12**[6] of which structure was confirmed from the coupling constant (J = 7.0 Hz, *trans* coupling) of ^{1}H NMR (200 MHz) (Scheme 2).



Reagents: (a) EtOCOCl, DMAP, pyridine, rt, 1 h (97%) (b) $Pd_2(dba)_3CHCl_3$, dppe, THF, rt, 6 h (61%).

Scheme 2

In summary, using allylic and dienylic cyclic carbonates as substrates, Pd(0)-catalyzed reaction with nucleophiles afforded α-, γ-, or ε- substituted products with high regio- and diastereoselectivity.

Acknowledgment. Generous financial support by KOSEF-OCRC is gratefully acknowledged. We thank to the referee for helpful comments.

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6. The spectral data of all the compounds described are in agreement with assigned structure. Selected spectral and physical data are as follows. **5**: TLC; SiO_2, EtOAc / hexanes 1 : 3 R_f = 0.48. ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (bs, 1H, OH), 3.58 (d, 2H, *J* = 4.8 Hz), 3.78 (dd, 1H, *J* = 9.2, 5.2 Hz), 3.90 (m,1H), 4.56 (s, 2H), 5.04 (dd, 1H, *J* = 17.0, 1.1 Hz), 5.12 (dd, 1H, *J* = 10.1, 1.1 Hz), 5.87 (ddd, 1H, *J* = 17.0, 10.0, 9.2 Hz), 7.31 (m, 8H), 7.43 (m, 2H). IR(neat) 3450, 1640, 1583, 1495 cm^{-1}. **6**: TLC; SiO_2, EtOAc / hexanes 1 : 2 R_f = 0.31. ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (bs, 1H), 3.35 (m, 1H), 3.50 (m, 3H), 3.69 (s, 3H), 3.70 (s, 3H), 4.30 (m, 1H), 4.55 (s, 2H), 5.10 (m, 1H), 5.60 (m, 2H), 5.80 (m, 2H), 7.35 (s, 5H). **8**: TLC; SiO_2, EtOAc / hexanes 1 : 2 R_f = 0.41. ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (d, 1H, *J* = 4.3 Hz, OH), 3.60 (d, 2H, *J* = 5.3 Hz), 3.73 (s, 3H), 3.85 (dd, 2H, *J* = 9.1, 5.2 Hz), 4.05 (m, 1H), 4.55 (s, 2H), 5.74 (d, 1H, *J* = 15.4 Hz), 5.95 (d, 1H, *J* = 15.2, 10.7 Hz), 6.15 (dd, 1H, *J* = 15.2, 9.1 Hz), 7.18 (dd, 1H, *J* = 15.4, 9.1 Hz), 7.35 (s, 5H). **9**: TLC; SiO_2, EtOAc / hexanes 1 : 1 R_f = 0.43. ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 3H), 2.50 (bs, 1H, OH), 3.35 (dd, 1H, *J* = 9.3, 6.7 Hz), 3.45 (dd, 1H, *J* = 9.3, 3.4 Hz), 3.50 (s, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 3.75 (s, 3H), 4.30 (m, 1H), 4.60 (s, 2H), 5.50 (dd, 1H, *J* = 16.2, 7.0 Hz), 5.80 (dd, 1H, *J* = 16.2, 1.0 Hz), 6.00 (d, 1H, *J* = 16.0 Hz), 6.80 (d, 1H, *J* = 16.0 Hz), 7.35 (s, 5H). IR(neat) 3600, 1735, 1705 cm^{-1}. **10**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.10 (ddd, 1H, *J* = 5.3, 3.2, 2.1 Hz), 3.28 (dd, 1H, *J* = 7.2, 2.1 Hz), 3.53 (dd, 1H, *J* = 11.5, 5.3 Hz), 3.76 (dd, 1H, *J* = 11.5, 3.2 Hz), 4.59 (s, 2H), 5.30 (dd, 1H, *J* = 9.5, 2.1 Hz), 5.49 (dd, 1H, *J* = 17.2, 2.1 Hz), 5.58 (ddd, 1H, *J* = 17.2, 9.5, 7.2 Hz), 7.35 (s, 5H). 11: ^1H NMR (200 MHz, $CDCl_3$) δ 3.16 (ddd, 1H, *J* = 5.1, 3.1, 2.0 Hz), 3.38 (dd, *J* = 7.6, 2.0 Hz), 3.58 (dd, 1H, *J* = 11.5, 5.1 Hz), 3.75 (s, 3H), 3.76 (m, 1H), 4.59 (s, 2H), 5.81 (dd, 1H, *J* = 15.3, 7.6 Hz), 5.93 (d, 1H, *J* = 15.3 Hz), 6.50 (dd, 1H, *J* = 15.3, 11.0 Hz), 7.25 (d, 1H, *J*= 15.3 Hz), 7.35 (s, 5H) **12**: TLC; SiO_2 EtOAc / hexanes 1 :2 R_f = 0.63. ^1H NMR (200 MHz, $CDCl_3$) δ 2.72 (dd, 1H, *J* = 8.1, 7.0 Hz), 2.76 (dd, 1H, *J* = 8.1, 7.0 Hz), 3.74 (s, 3H), 3.75 (s, 3H), 3.98 (dd, 2H, *J* = 7.8, 1.6 Hz), 4.48 (s, 2H), 5.16 (m, 1H), 5.21 ~ 5.50 (m, 3H), 5.90 (dt, 1H, *J* = 15.6, 6.1 Hz), 7.34 (s, 5H). (±)-**14**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.38 (dd, 1H, *J* = 6.1, 4.4 Hz), 3.50 (dd, 1H, *J* = 6.9, 4.4 Hz), 3.58 (dd, 1H, *J* = 11.2, 6.1 Hz), 3.71 (dd, 1H, *J* = 11.2, 4.4 Hz), 4.60 (s, 2H), 5.37 (dd, 1H, *J* = 10.2, 2.2 Hz), 5.51 (dd, 1H, *J* = 17.2, 2.2 Hz), 5.70 (ddd, 1H, *J* = 17.2, 10.2, 6.9 Hz), 7.35 (s, 5H). (±)-**15**: ^1H NMR (200 MHz, $CDCl_3$) δ 3.55 (dd, 1H, *J* = 9.7, 6.0 Hz), 3.68 (dd, 1H, *J* = 9.7, 3.3 Hz), 3.77 (dd, 1H, *J* = 8.8, 7.3 Hz), 3.87 (m, 1H), 4.50 (s, 2H), 5.01 (dd, 1H, *J* = 17.1, 1.5 Hz), 5.03 (dd, 1H, *J* = 10.5, 1.5 Hz), 5.75 (ddd, 1H, *J* = 17.1, 10.1, 8.8 Hz), 7.40 (m, 10H).
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10. The compound **2** was prepared from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (a) $Ph_3PCHCHO$, benzene, reflux, 1 h (92%) (b) *n*-BuLi, $Ph_3P^+CH_3Br^-$, THF, -10 °C→ rt, 12 h (67%) (c) 10% HCl, THF, rt, 12 h (87%) (d) $CO(Im)_2$, CH_2Cl_2, rt, 10 min (74%). For the preparation of 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose, See, Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 256.
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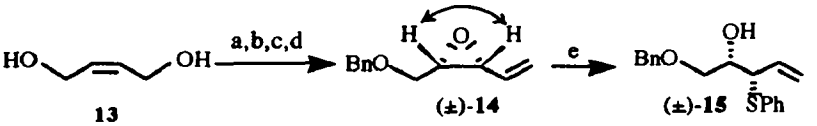
15. In order to confirm the stereochemistry of C-S bonds in **5** and **10**, the other stereoisomers **14**[6] and **15**[6] were synthesized from readily available *cis*-diol **13** by the following reaction sequence. By comparing ^1H NMR (200 MHz) spectra of **5** and **10** with (±)-**15** and (±)-**14**, the structure of **5** was unambiguously assigned.



13 (±)-**14** (±)-**15**

Reagents: (a) NaH, $PhCH_2Br$, DMF, -20 °C, 5 h (72%). (b) MCPBA, CH_2Cl_2, 0 °C→ rt, 12 h (86%). (c) PDC, CH_2Cl_2, 4 A molecular sieves, rt, 4 h (85%). (d) $Ph_3P^+CH_3Br^-$, $KN(SiMe_3)_2$, PhH, 0 °C→rt, 1 h (47%). (e) PhSH, Et_3N, MeOH, rt, 1 h (93%).
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