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Palladium(II)-Catalyzed Diastereoselective Acetalization of Hydroxyalkenes

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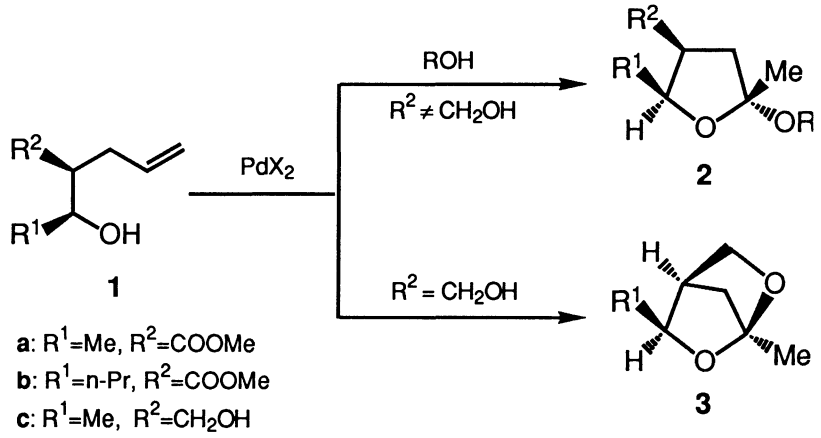
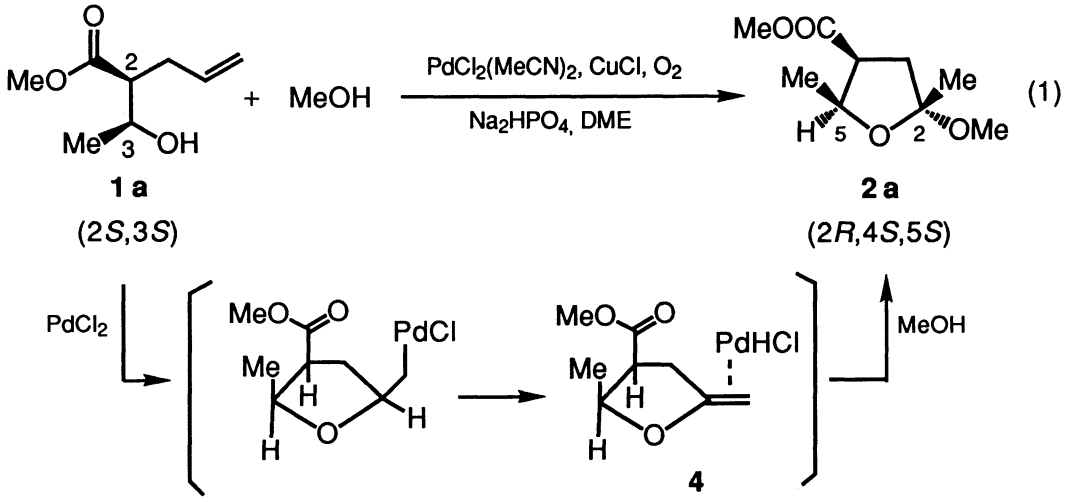
Pd(II)-Catalyzed cyclization of methyl (2*S*,3*S*)-2-allyl-3-hydoxybutyrate with methanol gives (2*R*,4*S*,5*S*)-2,5-dimethyl-2-methoxy-4-methoxycarbonyltetrahydrofuran in 88% de. The cyclization of (2*R*,3*S*)-2-allyl-1,3-butanediol gives homochiral bicyclic acetal **3** (R^1=Me).

Palladium(II)-catalyzed intramolecular cyclization of dihydroxyalkenes is a versatile entry to bicyclic acetals.[1] The shortest syntheses of both natural and unnatural frontalin use this method.[2] Hydroxyalkenes of type **1** lead to either monocyclic acetals **2** or bicyclic acetals **3** depending on whether external or internal OH attack is involved in the cyclization (Scheme 1). Control of stereoselectivity can be induced by chiral centers present in hydroxyalkenes **1**. Increasing interest in this type of cyclizations[3,4] prompts us to report the first Pd(II)-catalyzed diastereoselective acetalization of hydroxyalkenes.



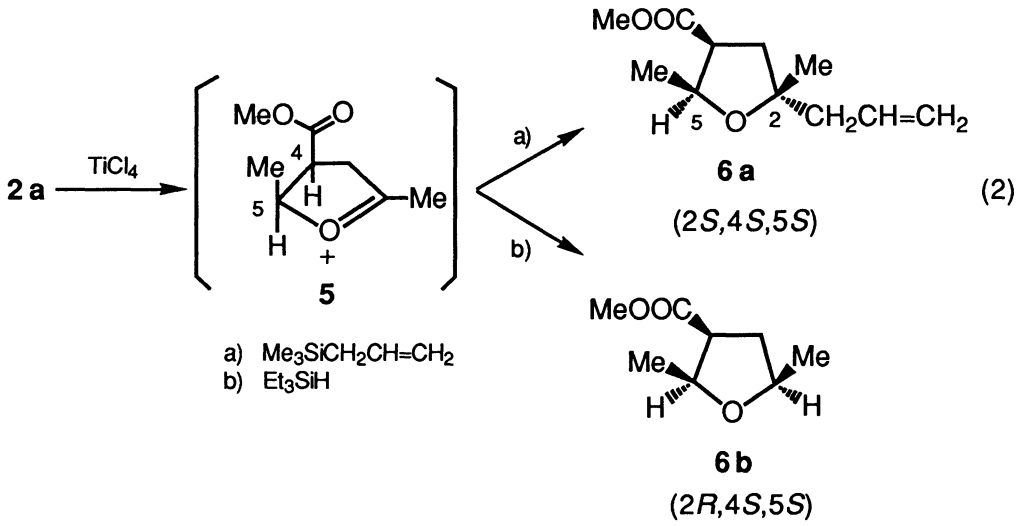
Scheme 1.

Enantiomerically pure hydroxyalkenes **1**[5] were chosen as substrate in this study, since the resulting acetals should be useful building blocks of optically active highly substituted oxygen heterocycles.[6] Cyclization of (2*S*,3*S*)-**1a** with methanol (3 equiv.) in the presence of $PdCl_2(MeCN)_2$ and CuCl catalyst under O_2 [7] gives tetrahydrofuran **2a** in 71% isolated yield (Eq. 1), where the 2-methoxy substituent is introduced in 88% de (94 : 6). The major isomer of **2a**[8] can be assigned as the (2*R*,4*S*,5*S*)-configuration by NOEDS experiments, since irradiation at the C-5 proton clearly enhances the C-2 methoxy, whereas no enhancement was observed with the C-2 methyl group. Monohydroxyalkene **1b** (R^1=n-Pr; Scheme 1) also gives the corresponding acetal **2b** in 81%



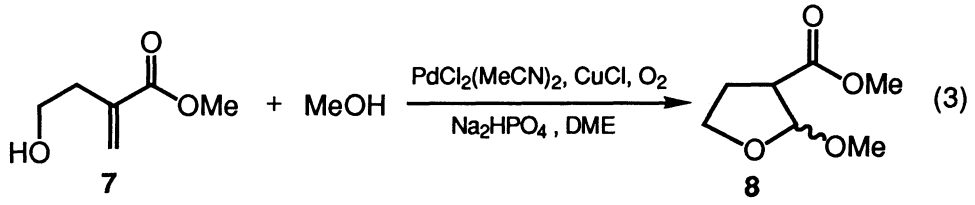
de (80%yield). The cyclization-alkoxylation of **1a** proceeds via intramolecular oxypalladation followed by Pd-H elimination to give *exo*-methylene tetrahydrofuran **4**. The nucleophilic attack of methanol onto **4** gives the product **2a.**

The C-2 methoxy group of **2a** is readily replaced by a nucleophile in the presence of Lewis acids (Eq. 2). Trimethylallylsilane reacts with **2a** in the presence of $TiCl_4$ (-78 °C, CH_2Cl_2) to give 2-allyl substituted tetrahydrofuran **6a**[9] (85% yield) in >99% de, the configuration of which is assigned as (2*S*,4*S*,5*S*), again by NOEDS. The use of Et_3SiH as nucleophile affords (2*R*,4*S*,5*S*)-**6b** in 92% de (67% yield).



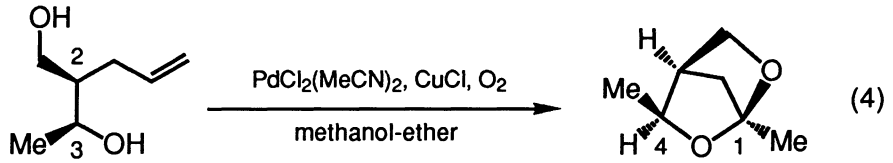
The observed stereoselectivities (>99-92% de) in Eq. 2 exceed the diastereomeric purity of the starting **2a** (88% de). This suggests that the highly strained oxonium ion **5** formed during the reaction[3d] undergoes nucleophilic attack from the site opposite to the C-4 and C-5 substituents more easily, when compared to *exo*-methylene intermediate **4**. The substitution reaction of this type has attracted recent interest for the synthesis of C-furanosides.[10]

The sterically encumbered 1,1-disubstituted olefin **7** gives a 52% yield of acetal **8** in 40% de (Eq. 3). Thus, the cyclization-alkoxylation of monohydroxy alkenes appears to be a general process.



7 8 (3)

Pd(II)-Catalyzed cyclization of (2*R*,3*S*)-dihydroxyalkene **1c** gives a 63% yield of (1*S*,3*S*,4*R*)-2,6-dioxabicyclo[2.2.1]heptane **3**[11] {$[\alpha]_D^{25}$ -13.1 (*c* 0.55, $CHCl_3$)} (Eq. 4). To promote the cyclization smoothly, 3 equiv. of methanol is required as additive, but external alkoxylation of methanol does not occur in this case.



1c (2*R*,3*S*) **3** (1*S*,3*S*,4*R*) (4)

References

1) N. T. Byrom, R. Grigg, B. Kongkathip, G. Reimer, and A. R. Wade, *J. Chem. Soc., Perkin Trans. 1,* **1984,** 1643 (1984); B. Kongkathip, R. Sookkho, and N. Kongkathip, *Chem. Lett.*, **1985**, 1849; P. C. B. Page, C. M. Rayner, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, **1988**, 356.
2) T. Hosokawa, Y. Makabe, T. Shinohara and S.-I. Murahashi, *Chem. Lett.*, **1985,** 1529.
3) a) M. F. Semmelhack and N. Zhang, *J. Org. Chem.*, **54**, 4483 (1989); b) M. McCormick, R. Monahan III, J. Soria, D. Goldsmith, and D. Liotta, *ibid.*, **54**, 4485 (1989); c) S. Igarashi, Y. Haruta, M. Ozawa, Y. Nishide, H. Kinoshita, and K. Inomata, *Chem. Lett.*, **1989**, 737; d) C. P. Holmes and P. A. Bartlett, *J. Org. Chem.*, **54**, 98 (1989);
4) T. Hosokawa and S.-I. Murahashi, *Acc. Chem. Res.*, **23**, 49 (1990).
5) The homochiral **1a** can be prepared as follows. Alkylation of enantiomerically pure methyl (S)-3-hydroxybutyrate with allyl bromide {G. Fráter, U. Müller, and W. Günther, *Tetrahedron*, **40**, 1269 (1984)} gave a 96:4 mixture of (2*S*,3*S*)- and (2*R*,3*S*)-2-allyl-3-hydroxybutyrate in 72% yield. The mixture was converted into the corresponding dibenzylammonium salt upon treatment with dibenzylamine after hydrolysis. Recrystallization from methanol followed by acidification and esterfication (CH_2N_2) gave diastereomerically and enantiomerically pure (2S,3S)-**1a** {$[\alpha]_D^{24}$ +5.9 (*c* 1.19, $CHCl_3$)}. (2*R*,3*S*)-dihydroxyalkene **1c** {$[\alpha]_D^{25}$ +4.2 (*c* 0.92, $CHCl_3$)} was obtained by $LiAlH_4$ reduction of the above ester.

6) For example, see: Y. G. Kim and J. K. Cha, *Tetrahedron Lett.*, **29**, 2011 (1988); D. Hoppe, T. Kramer, C. F. Erdbrugger, and E. Egert, *ibid.*, **30**, 1233 (1989).

7) The reaction was performed by using 10 mol% of $PdCl_2(MeCN)_2$ with CuCl (20 mol%) and Na_2HPO_4 (15 mol%) in dimethoxyethane (DME) under O_2 (1 atm) at 50 °C for 1 h. The base of Na_2HPO_4 was required in order to trap HCl generated in situ; otherwise, a complex mixture of products was formed.

8) (2*R*,4*S*,5*S*)-**2a**; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.17 (d, J=6.7 Hz, 3H, C_5-CH_3), 1.49 (s, 3H, C_2-CH_3), 2.14 (dd, J=13.1 and 8.5 Hz, 1H, C_3-H), 2.43 (dd, J=13.1 and 8.0 Hz, 1H, C_3-H), 3.21 (s, 3H, C_2 -OCH_3), 3.31 (ddd, J=8.5, 8.3, and 8.0 Hz, 1H, C_4-H), 3.69 (s, 3H, $COOCH_3$), 4.39 (dq, J=8.3 and 6.7 Hz, 1H, C_5-H); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 16.9, 20.7, 41.2, 47.1, 48.4, 51.5, 74.7, 107.0, and 173.4.

9) (2*S*,4*S*,5*S*)-**6a**; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.15 (d, J=6.4 Hz, 3H, C_5-CH_3), 1.36 (s, 3H, C_2-CH_3), 2.02 (dd, J=13.4 and 8.4 Hz, 1H, C_3-H), 2.13 (dd, J=13.4 and 8.4 Hz, 1H, C_3-H), 2.21 (d, J=7.4 Hz, 1H, C_2-CH), 2.24 (d, J=7.4 Hz, C_2-CH), 3.22 (ddd, J=8 4, 8.4, and 7.9 Hz, 1H, C_4-H), 3.69 (s, 3H, $COOCH_3$), 4.38(dq, J=7.9 and 6.4 Hz, 1H, C_5-H), 5.03-5.13 (m, 2H, $C=CH_2$), 5.81 (ddt, J=16.3, 10.9, and 7.4 Hz, 1 H, $C\underline{H}=CH_2$); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 18.0, 27.1, 38.5, 45.3, 48.5, 51.6, 74.9, 82.6, 117.9, 134.4, and 173.2; HRMS calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1290.

10) O. R. Martin, S. P. Rao, K. G. Kurz, and H. A. El-Shenawy, *J. Am. Chem. Soc.*, **110**, 8698 (1988), and references cited therein.

11) The reaction was performed by using 5 mol% of $PdCl_2(MeCN)_2$ with CuCl (5 mol%) in methanol (3 equiv.) and ether under O_2 (1 atm) at 30 °C for 1 h to give (1*S*,3*S*,4*R*)-**3**; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.35 (d, J=6.4 Hz, 3H, C_3-CH_3), 1.53 (s, 3H, C_1-CH_3), 1.89 (dd, J=9.3 and 1.8 Hz, 1H, C_7-H), 1.94 (m, 1H, C_7-H), 2.45 (ddddd, J=2.3, 2.3, 1.8, 1.8, and 0.6 Hz, 1 H, C_4-H), 3.76 (ddd, J=7.6, 2.3, and 2.1 Hz, 1H, C_5-H), 4.11 (dd, J=7.6 and 0.6 Hz, 1H, C_5-H), 4.25 (qdd, J=6.4, 2.3, and 2.1 Hz, 1 H, C_3-H); HRMS calcd for $C_7H_{12}O_2$ 128.0837, found 128.0930.

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