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Preliminary communication

Asymmetric cyclization of 2-alkenylphenols. A comparative study on the use of palladium(II) and titanium(IV) complexes

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Abstract

The oxidative cyclization of 2-(3-pentenyl)phenol catalyzed by $[(\eta^3\text{-pinene})PdOAc]_2$ gives optically active (+)-2-vinylchroman (25% e.e.), while (−)-2-(1-hydroxyethyl)chroman (56% e.e.) is formed as a single diastereomer upon treatment with t-BuOOH in the presence of $Ti(O^iPr)_4$ and L-(+)-diethyl tartrate. 2-(2-Butenyl)phenol also undergoes the Ti-promoted asymmetric cyclization to give (2*S*,1′*R*)-(−)-2-(1-hydroxyethyl)-2,3-dihydrobenzofuran (29% e.e.).

The palladium(II)-catalyzed asymmetric cyclization of 2-(2-butenyl)phenols has been shown to be potentially useful for the synthesis of optically active 2,3-dihydrobenzofurans [1]. Furthermore, the information on the asymmetric induction serves as a useful probe in elucidating the nature of Pd^{II} species in the oxidations of alkenes [2,3]. Our interest in this type of reactions led us to studies on the usefulness of d^0 early transition metals such as Ti and Mo in the asymmetric cyclizations of 2-alkenylphenols. Described herein is a comparative study on the use of Pd^{II} and Ti^{IV} complexes as mediators in the reaction.

The cyclization of 2-(3-pentenyl)phenol (**1a**; R = H) by $[(\eta^3\text{-pinene})PdOAc]_2$ (**2**) in the presence of $Cu(OAc)_2$ and O_2 (1 atm) in MeOH gave optically active 2-vinylchroman (**3a**) in 25% e.e. as a single product (Table 1, entry 1). Introduction of methyl group on the pentenyl C(3) carbon lowered the rate of cyclization as well as the enantioselectivity (3% e.e., entry 2). The O_2 uptake for the oxidation of **1a** (R = H) was faster by a factor of 3 than that of **1b** (R = Me).

When the phenols **1** were treated with t-butylhydroperoxide (TBHP) in the presence of $Ti(O^iPr)_4$ and (+)-diethyltartrate (DET) in CH_2Cl_2, optically active 2-(1-hydroxyethyl)chroman (**4**) was obtained as a single diastereomer (Table 1). In this case, the presence of an alkyl substituent on the olefin increases the rate of reaction (entries 3 and 4), and 56% enantioselectivity was attained with **1b** (R = Me). Although the carbon–carbon double bond of **1b** is separated from the OH by four carbons, the realization of such a high % e.e. is remarkable [4].

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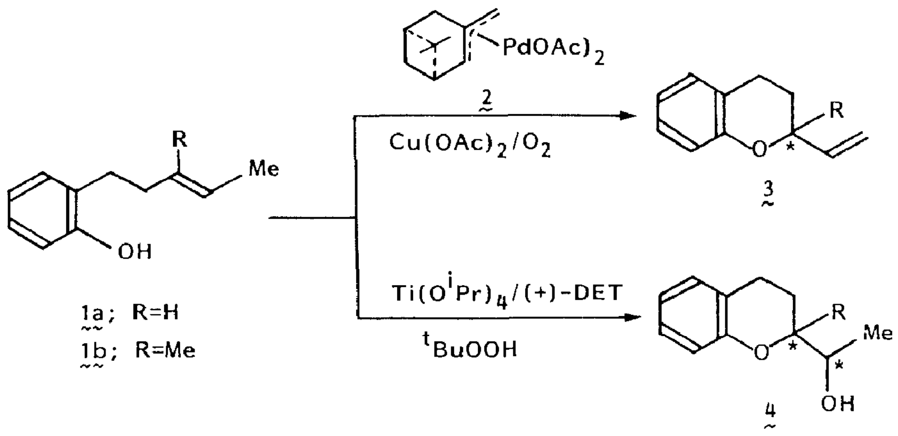


The asymmetric cyclization of 2-(2-butenyl)phenol (**5**) by $[(\eta^3\text{-pinene})\text{PdOAc}]_2$ (**2**) catalyst with TBHP in MeOH gives (*S*)-(+)-2-vinyl-2,3-dihydrobenzofuran (**6**) in 17% e.e. along with **7** (**6**/**7** = 83/17) [3]. When TBHP was replaced by $Cu(OAc)_2$ and O_2 as the oxidant, the same result was obtained with respect to the product composition and enantioselectivity, suggesting that the function of t-BuOOH is virtually the same as that of $Cu(OAc)_2$ and O_2.

The Ti^{IV}-mediated asymmetric cyclization of **5** under the aforementioned conditions gave a 22% yield of (−)-2-(1-hydroxyethyl)-2,3-dihydrobenzofuran (**8**) in 29% e.e. (Table 1, entry 5). However, no reaction took place with 2-(2-propenyl)phenol. This again indicates that the presence of an alkyl substituent on the olefin facilitates the reaction.

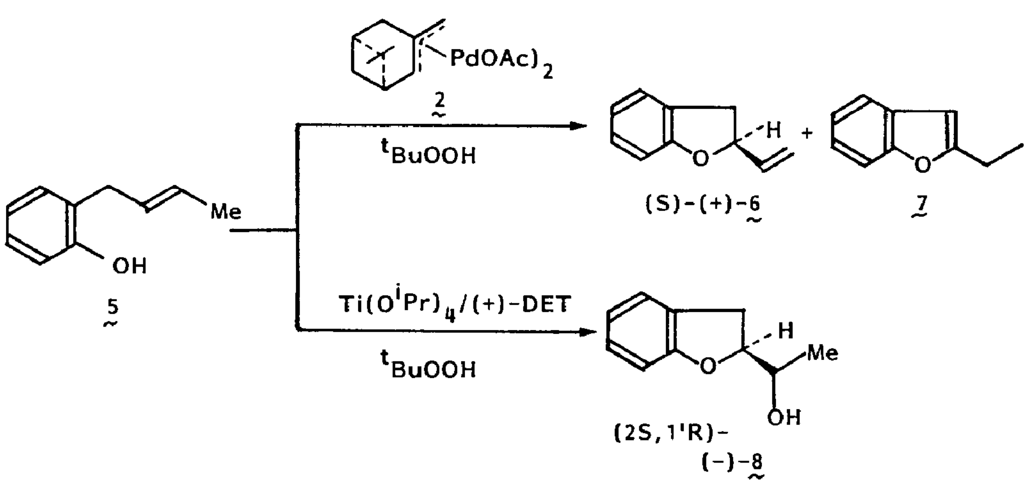
The absolute configuration of the newly created chiral C(2) carbon in **8** is assigned as (*S*), since the oxidation with MnO_2 gave (*S*)-(−)-2-acetyl-2,3-dihydro-

Table 1

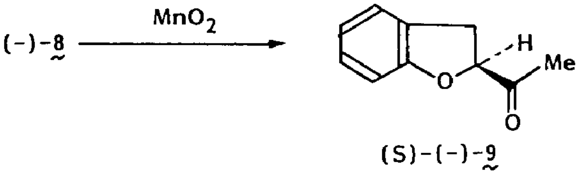
Asymmetric cyclization of **1** and **5** using Pd^{II} [a] or Ti^{IV} [b] complexes

Entry	Substrate	Metal	Product	Yield [c] (%)	$[\alpha]_D$ deg(*c*, CCl_4)	% e.e.
1	**1a**	Pd	**3a**	64 [d]	+16.0 (0.36)	25 [e]
2	**1b**	Pd	**3b**	78	−4.30 (0.48)	3 [f]
3	**1a**	Ti	**4a**	<10	–	– [g]
4	**1b**	Ti	**4b**	49	−3.71 (0.73) [h]	56 [i]
5	**5**	Ti	**8**	22	−7.42 (1.12)	29 [i]

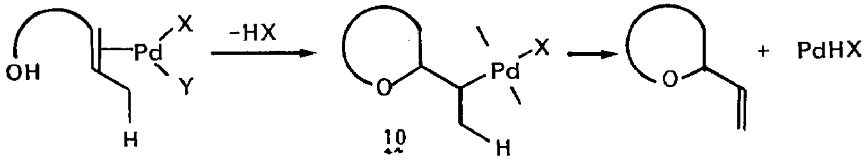
[a] The reaction was performed by using phenol **1** (1 mmol), complex **2** (0.1 mmol), and $Cu(OAc)_2$ (0.1 mmol) in MeOH (1 ml) at 35 °C under O_2 (1 atm) for 7–9 h. [b] The reaction was performed by using phenol **1** (3.0 mmol), L-(+)-DET (3.5 mmol), $Ti(O^iPr)_4$ (3.0 mmol), and TBHP (6.0 mmol) in CH_2Cl_2 at 0 °C for 48 h [4]. [c] Isolated yield by preparative TLC (SiO_2). [d] A lower yield of **3a**, compared to that of **3b**, may be due to losses during the isolation. [e] The % e.e. was determined by ^1H NMR with $Eu(tfc)_3$ (tfc = tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorate]) through 2-methoxycarbonylchroman derived from **3a** by its MnO_4 oxidation followed by esterification with CH_2N_2. [f] The % e.e. was determined by ^1H NMR through MTPA ester of 2-hydroxymethyl-2-methylchroman derived from **3b** by ozonolysis followed by $NaBH_4$ reduction. [g] Not determined. [h] Measured in $CHCl_3$. [i] The % e.e. was determined by ^1H NMR upon addition of $Eu(tfc)_3$.



benzofuran (9) of known configuration [3]. The reduction of 9 with $NaBH_4$ gave the two diastereomers of **8** which have J(H(2)–H(1′)) values of 3.4 and 6.6 Hz in ^1H NMR, corresponding to the *erythro* and *threo* isomers, respectively [5]. Comparison of the J value allows us to assign (−)-**8** (3.4 Hz) to the *erythro* isomer of (2*S*,1′*R*) configuration. The product (−)-**4a** having J 3.7 Hz must have the same configuration. The cyclization seems to involve the epoxidation of olefin and subsequent ring opening with the phenoxy group in an S_N2 and the configuration of the product agrees with the process.



Oxidative cyclization of 2-alkenylphenols with TBHP is induced by titanium(IV) as well as palladium(II). Obviously, the Ti-promoted reaction involves a metal alkylperoxide species (TiOOBu^t), and the oxygen bonded to the metal is electrophilically transferred to the olefin to give the epoxide [6]. The alkyl substituent on the olefin thus increases the rate of reaction. On the other hand, no palladium alkylperoxide (PdOOBu^t) [7] seems to participate in the oxidative cyclization. The reaction proceeds by coordination of the olefin to Pd^{II} followed by intramolecular oxypalladation to give the intermediate **10**. The steric effect of alkyl group on the olefin hinders the coordination to Pd^{II}, and the reactivity and enantioselectivity become less. The PdHX species formed by β-elimination from **10** is oxidized by TBHP, generating a catalytically active species, such as Pd(OH)X [3]. The behaviour of TBHP is completely different from that in the Ti system.



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