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Stereoselective cyclization using palladium(II) catalyst via hemiacetal intermediates

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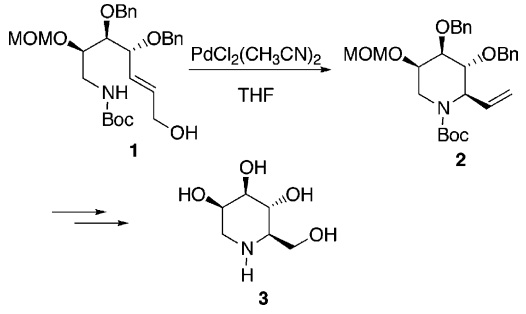
Abstract—A stereoselective palladium-catalyzed cyclization of 3-phenyl-7-hydroxy-5-heptenal was developed. The reaction was carried out to give 2,4,6-trisubstituted tetrahydropyran with highly controlled 4,6-*cis* stereochemistry.

Substituted tetrahydropyran moieties occur widely in natural products such as sugars, polyketides, and polycyclic ethers. Continuous interest has been sustained to develop methods for the synthesis of tetrahydropyran derivatives.[1]

We have reported the usefulness of a new synthetic method in the synthesis of biologically active natural products, inter alia alkaloid[2] and aza sugar.[3] We have recently developed a stereoselective construction of polysubstituted piperidine via palladium-catalyzed intramolecular N-alkylation of urethane (Scheme 1).[3]

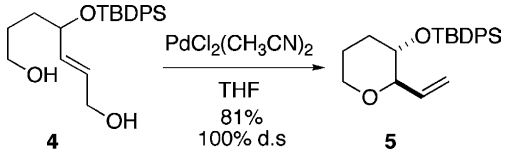
The palladium(II)-catalyzed cyclization proceeds smoothly. The piperidine is produced by the palladium(II)-catalyzed reaction with allylic alcohol. Allylic alcohols are rather unreactive substrates for π-allylpalladium complex formation under usual conditions.[4] Recently, we also developed a stereoselective construction of cyclic ether via Pd(II)-catalyzed intramolecular O-alkylation of alcohol (Scheme 2).[5] These methods provide a powerful tool in construction of five- and six-membered heterocyclic ring systems.



Scheme 1.

In connection with these stereocontrolled cyclization, the new cyclization of some allyl alcohols **6** including an aldehyde moiety might yield corresponding cyclic acetals **8** via hemiacetal **7** (Scheme 3).[6] The question is whether the unstable hemiacetal reacts as a nucleophile, because nucleophilic addition of a hemiacetal is rather exceptional.[7,8] Now, we report here an efficient and highly stereoselective construction of 2,4,6-trisubstituted tetrahydropyran derivatives via Pd(II)-catalyzed intramolecular cyclization of 7-hydroxy-3-phenyl-5-pentenal **15**.

The synthesis was started by Johnson–Claisen rearrangement of cinnamyl alcohol and trimethyl orthoacetate, which afforded the methyl ester **10** in 70% yield. Reduction ($LiAlH_4$) of **10** followed by silylation (TBSCl,



Scheme 2.

Keywords: Palladium catalyst; Hemiacetal; Tetrahydropyran; Cyclization.

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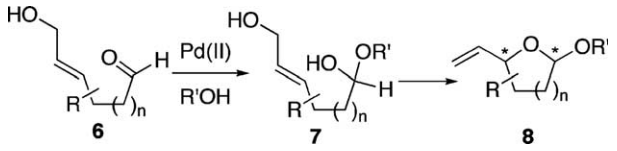


Scheme 3.

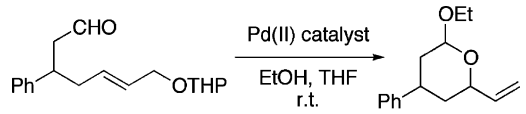
imidazole) afforded the TBS-ether **11** (55%). Then, hydroboration and oxidation to the alcohol **12** from **11** was performed using a borane dimethyl sulfide complex (63%). Oxidation of **12** by Swern oxidation followed by Emmons–Horner reaction (triethyl phosphonoacetate, NaH) afforded the (*E*)-α,β-unsaturated ester **13** in 88% yield. A reaction sequence of reduction of the ester **13** with DIBAL-H, protection of the resulting alcohol with DHP, and deprotection of the TBS group (TBAF) furnished the alcohol **14**. Oxidation of the alcohol **14** (Dess–Martin periodinane) finished the synthesis of the aldehyde **15**.[9] Additionally, acidic treatment of **15** gave the alcohol **16** (Scheme 4).

The cyclization of the aldehyde **15** was examined under various conditions (Table 1). A variety of Pd(II) catalysts were initially screened, and each of the palladium dihalide complexes afforded product within 16–40 h (entries 1–3). Of these salts, the palladium dichloride benzonitrile complex was the most effective. On the contrary, palladium acetate, allylpalladium chloride dimmer, and cationic complexes were not effective (entries 4–6).

We then examined the scope of the reaction with a variety of alcohols (Table 2). In general, 5 mol% of $PdCl_2(PhCN)_2$ and 2.2 equiv of alcohol as a nucleophile at room temperature in THF were used.[10] This cyclization reaction tolerated primary, secondary, and tertiary alcohols, and it smoothly prepared the corresponding 2,4,6-trisubstituted tetrahydropyran ring skeleton from the tested aldehydes in moderate yield (56–70%) based on the starting aldehyde. From the data in Table 2, it can be seen that the reaction of aldehyde and less steric hindered alcohols requires a shorter reaction time, and gives higher yields of products.

The relative configuration of C2, C4, and C6 in the four diastereoisomers **18** and **19** was determined on the basis of the ^1H –^1H *J*-coupling values.

Table 1. Heterocyclization reaction with the aldehyde **15** using Pd(II) catalyst



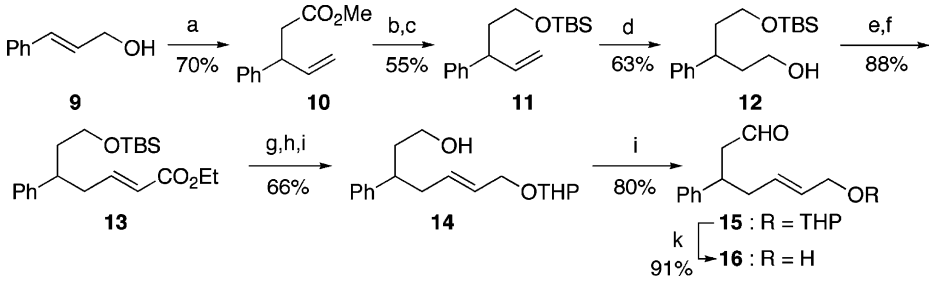
15 **17a**

Entry	Catalyst	Time (h)	Yield (%)
1	$PdCl_2(CH_3CN)_2$	16	29
2	$PdCl_2(PhCN)_2$	16	70
3	$PdBr_2(PhCN)_2$	40	56
4	$Pd(OAc)_2$	24	0
5	$(CH_2{=}CHCH_2PdCl)_2$	24	0
6	[Pd(cod)(acac)]BF_4	24	0

The cyclization of the aldehyde **15** may, in principle, lead to four possible diastereomers. The HPLC analysis of the cyclized products revealed the formation of two diastereomers exclusively. The reactions were, in general, quite diastereoselective (C4–C6 *cis* selective), most particularly in the use of hindered alcohols, where the C4–C6 *trans* isomers were not detectable by NMR spectroscopy (Table 2, entry 1 vs entries 2–4). The major products were 2β isomers and the stereoselectivity (2β:2α) was almost 3:1–2:1. Remarkably, the C4–C6 relative ratios of tetrahydropyrans were found to be dramatically influenced by variation of the alcohols, although the C2–C4 relative ratios of tetrahydropyrans were almost invariant in a variety of alcohols.

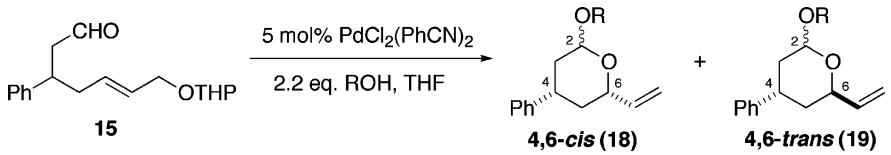
The next cyclization experiments were conducted on the alcohol **16** (Table 3). The reaction rates of the alcohol **16** are faster than that of the THP ether **15** but produce lower yields of the desired products due to the facile dimerization of the alcohol **16** (Table 2 vs Table 3).

The mechanism for cyclization of the aldehyde **15** is shown in Scheme 5. First, the substrate **15** was converted into the alcohol **16** under these conditions. Alcohol (ROH) was then added to the aldehyde **16**, and the reaction generated a hemiacetal intermediate. The olefin and hydroxy groups of the allylic alcohol may be coordinated to the palladium prior to cyclization. For the arrangement of the palladium complex, there are four conformations (**A**–**D**) that allow the alcohol of the hemiacetal to attack the olefin.



Scheme 4. Reagents and conditions: (a) $CH_3C(OMe)_3$, *p*-TsOH, xylene; (b) $LiAlH_4$, THF; (c) TBSCl, imidazole, DMF; (d) BH_3/SMe_2, THF then H_2O_2, NaOH; (e) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N; (f) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (g) DIBAL-H, THF; (h) DHP, *p*-TsOH, CH_2Cl_2; (i) TBAF, THF; (j) Dess–Martin periodinane, CH_2Cl_2; (k) 3 N HCl, THF.

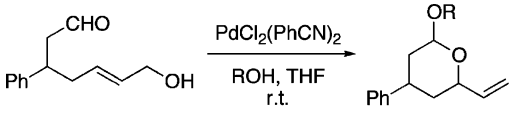
Table 2. Heterocyclization reaction with the aldehyde **15** using $PdCl_2(PhCN)_2$



Entry	R	Time (h)	Yield (%)	Diastereomeric ratio (%)[a]		Diastereomeric ratio (%)[a]	
				4,6-*cis*	4,6-*trans*	2(α)	2(β)
1	Et	16	70	85	15	29[b]	71[b]
2	*i*-Pr	16	59	100	0	23	77
3	Cyclohexyl	16	63	100	0	25	75
4	*t*-Bu	24	56	100	0	29	71

[a] Diastereomeric ratio was determined on HPLC.
[b] Ratio of the 4,6-*cis* isomers.

Table 3. Heterocyclization reaction with the aldehyde **16** using $PdCl_2(PhCN)_2$

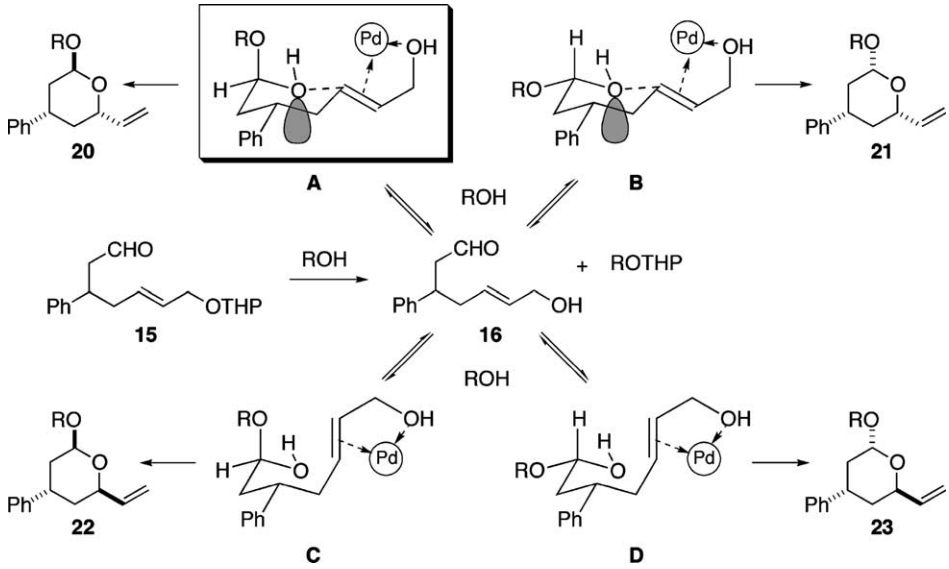


Entry	R	Time (h)	Yield (%)
1	Et	2	72
2	*i*-Pr	8	41
3	*t*-Bu	10	41

Initially, examination of the four chairlike transition-state conformations reveals why the 4,6-*cis* product invariably predominates. Conformations **A** and **B**, with the equatorial allylic alcohol, lead to the 4,6-*cis* products, whereas the less likely conformations **C** and **D**, with the axial allylic alcohol, lead to the 4,6-*trans* products. Conformations **C** and **D** are destabilized by a 1,3-diaxal interaction. The stereochemistry of the cyclized reaction is rationalized by the model **A**, which was stereoelectronically favorable much more than **B** (anomeric effect). The hemiacetal reacts intramolecularly with palladium-coordinated olefin shown in **A** to result in the observed major 2β-isomer **20**.

In addition, we prepared an allyl methyl carbonate from the allylic alcohol **16** with methyl chloroformate. Treatment of the carbonate with ethanol and $Pd(PPh_3)_4$ or $PdCl_2(PhCN)_2$ did not yield the cyclized product. Based on these observations, the cyclization reaction does not proceed via π-allylpalladium complex.

In summary, we have found that 3-phenyl-7-hydroxy-5-heptenal undergoes facile palladium(II)-catalyzed intramolecular cyclization via a hemiacetal intermediate to provide 2,4,6-trisubstituted tetrahydropyran stereoselectively. Application of the method to natural product synthesis is currently in progress in our laboratory.



Scheme 5.

Acknowledgements

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10. Representative procedure for the synthesis of 2-alkoxy-4-phenyl-6-vinyltetrahydropyran: To a solution of $PdCl_2(PhCN)_2$ (4 mg, 0.01 mmol) in THF (4.4 mL) was added abs ethanol (0.03 mL, 0.47 mmol) and a solution of aldehyde **15** (62 mg, 0.21 mmol) in THF (2 mL) at room temperature under an argon atmosphere. The mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with diethyl ether, and the solution was filtered through a Florisil pad. The pad was washed with diethyl ether. The combined organic layer was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent with hexane/ethyl acetate = 97 : 3) to afford 35 mg (70%) of **17a** as a colorless oil.
(2*S**,4*S**,6*S**)-2-ethoxy-4-phenyl-6-vinyltetrahydropyran: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.28 (m, 2H), 7.25–7.23 (m, 1H), 7.22–7.18 (m, 2H), 5.89 (ddd, J = 5.9, 10.8, 17.1 Hz, 1H), 5.28 (dd, J = 0.9, 17.3 Hz, 1H), 5.13 (dd, J = 0.7, 10.5 Hz, 1H), 5.04 (d, J = 2.9 Hz, 1H), 4.39 (dd, J = 5.3, 11.2 Hz, 1H), 3.80 (dq, J = 9.5, 7.1 Hz, 1H), 3.53 (dq, J = 9.5, 7.1 Hz, 1H), 3.24 (tt, J = 3.8, 12.5 Hz, 1H), 1.95–1.97 (m, 2H), 1.81 (ddd, J = 3.4, 12.9, 12.9 Hz, 1H), 1.57 (dt, J = 12.4, 12.4 Hz, 1H,), 1.26 (t, J = 7.1 Hz, 3H).
(2*R**,4*S**,6*S**)-2-ethoxy-4-phenyl-6-vinyltetrahydropyran: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.28 (m, 2H), 7.25–7.23 (m, 1H), 7.22–7.18 (m, 2H), 5.93 (ddd, J = 5.3, 10.6, 17.3 Hz, 1H), 5.31 (ddd, J = 1.5, 1.5, 17.3 Hz, 1H), 5.13 (ddd, J = 1.5, 1.5, 10.7 Hz, 1H), 4.63 (dd, J = 2.0, 9.4 Hz, 1H), 4.07–4.05 (m, 1H), 4.03 (dq, J = 9.5, 7.1 Hz, 1H), 3.60 (dq, J = 9.5, 7.1 Hz, 1H), 2.89 (tt, J = 3.8, 12.5 Hz, 1H), 2.04 (dddd, J = 1.9, 1.9, 3.9, 12.9 Hz, 1H), 1.85 (dddd, J = 1.9, 1.9, 3.9, 12.9 Hz, 1H), 1.67 (dt, J = 9.6, 12.8 Hz, 1H), 1.54 (dt, J = 12.5, 12.9 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H).
(2*S**,4*S**,6*R**)-2-ethoxy-4-phenyl-6-vinyltetrahydropyran: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.28 (m, 2H), 7.25–7.23 (m, 1H), 7.22–7.18 (m, 2H), 6.29 (ddd, J = 7.1, 10.4, 17.4 Hz, 1H), 5.23 (dd, J = 1.7, 17.3 Hz, 1H), 5.12 (dd, J = 1.7, 10.2 Hz, 1H), 4.88 (dd, J = 3.7, 7.3 Hz, 1H), 4.35–4.28 (m, 1H), 3.88 (dq, J = 9.8, 7.1 Hz, 1H), 3.47 (dq, J = 9.2, 7.1 Hz, 1H), 3.37 (tt, J = 4.6, 9.2 Hz, 1H), 2.11–1.88 (m, 4H), 1.22 (t, J = 7.1 Hz, 3H).
(2*R**,4*S**,6*R**)-2-ethoxy-4-phenyl-6-vinyltetrahydropyran: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32–7.28 (m, 2H), 7.25–7.23 (m, 1H), 7.22–7.18 (m, 2H), 6.03 (ddd, J = 4.2, 10.9, 17.7 Hz, 1H), 5.32 (dd, J = 1.7, 17.8 Hz, 1H), 5.24 (dd, J = 1.7, 10.9 Hz, 1H), 4.90 (dd, J = 3.2, 8.9 Hz, 1H), 4.70 (m, 1H), 3.95 (dq, J = 9.6, 7.1 Hz, 1H), 3.56 (dq, J = 9.6, 7.1 Hz, 1H), 2.97 (tt, J = 3.7, 12.6 Hz, 1H), 2.04 (dt, J = 3.1, 12.7 Hz, 1H), 1.94–1.91 (m, 2H), 1.74 (ddd, J = 8.7, 12.4, 12.4 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H).
^{13}C NMR (400 MHz, $CDCl_3$) δ: 145.43, 138.88, 128.47, 126.79, 126.30, 114.90, 97.17, 69.46, 62.49, 38.80, 38.05, 35.45, 15.19; IR (neat) 3063, 3028, 2930, 1647, 1454, 1375, 1335, 1125, 1060, 700, 519 cm^{-1} ; MS (EI) : m/z 232(28, M^+), 187 (15), 186 (38); Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found : C, 77.51; H, 8.93.