Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1299–1303

Pd^{II}-Catalyzed stereospecific formation of tetrahydro- and 3,6-dihydro[2*H*]pyran rings: 1,3-chirality transfer by intramolecular oxypalladation reaction

Jun'ichi Uenishi,* Masashi Ohmi and Atsushi Ueda

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan

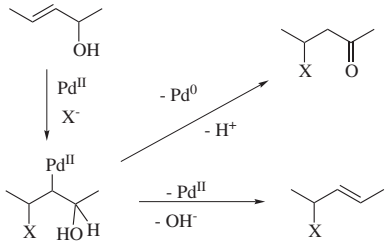
Received 10 January 2005; accepted 4 February 2005

Abstract—The stereospecific synthesis of 2,6-disubstituted tetrahydropyran and 3,6-dihydro[2*H*]pyran is described. The Pd^{II}-catalyzed cyclization of the hydroxy nucleophile to the allylic alcohol takes place efficiently under mild conditions, with the stereogenic center on the secondary allylic alcohol transfers to a newly generated stereogenic center on pyran ring via a *syn*-S_N2' type process.

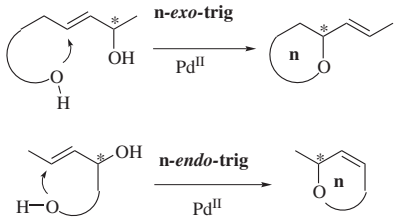
1. Introduction

Tetrahydro- and 3,6-dihydro[2*H*]pyran rings bearing substituents at the 2- and/or 6-positions are often observed in many biologically important natural products, such as phorboxazole,[1a] zampanolide,[1b] lasonolide,[1c] ratjadone,[1d] leucascandrolide,[1e] swinholides,[1f] misakinolides,[1g] sorangicin A,[1h] scytophycins,[1i,j] laulimalide[1k] and so on. The *cis* or *trans* configuration of the 2,6-substituents on the rings can influence both the three dimensional molecular configuration and biological activity of these natural products. Therefore, the stereocontrolled synthesis of 2,6-disubstituted tetrahydro- and 3,6-dihydro[2*H*]pyrans is an important task for synthetic organic chemistry. Although a number of methods for hydropyran synthesis have been reported,[2a–k] an efficient and highly stereocontrolled method for rings construction is still in need.

Nucleophilic attack of heteroatoms to Pd π-complexes is well known in Pd-catalyzed reactions.[3] When the reaction occurs to an allyl alcohol, as shown in Scheme 1, an S_N2'-type replacement takes place to give an α-heteroatom-substituted alkene by addition of Pd^{II} and X^- to alkene and elimination of hydroxide anion and Pd^{II}, while it also gives the β-heteroatom-substituted ketone by the Wacker type process. If the former reaction can occur intramolecularly with the hydroxy nucleophile in an *exo*- or *endo*-trigonal fashion, an oxygen heterocycle would be formed, as shown in Scheme 2.[4,5]



Scheme 1.

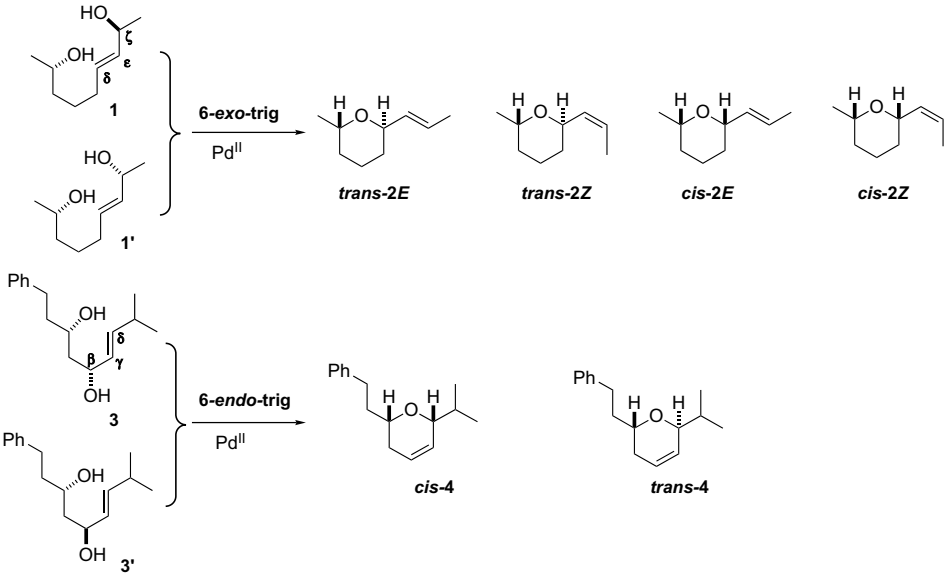


Scheme 2.

In addition, if a stereogenic center of a secondary alcohol is designed properly, a stereospecific intramolecular oxypalladation and elimination can take place to give stereodefined tetrahydro- and 3,6-dihydro[2*H*]pyran rings by a 1,3-chirality transfer process. Therefore, we chose substrates **1** and **1′** for the synthesis of tetrahydropyran **2** via 6-*exo*-trig cyclization and **3** and **3′** for that of

* Corresponding author. E-mail: juenishi@mb.kyoto-phu.ac.jp

0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2005.02.006



Scheme 3.

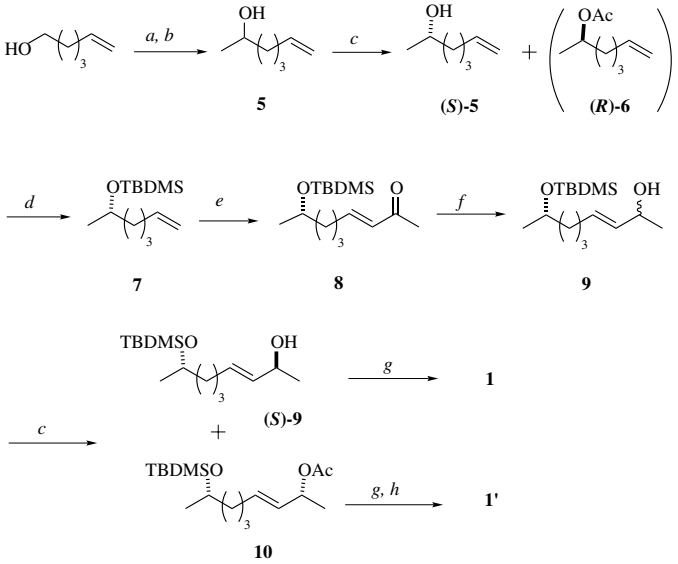
3,6-dihydro[2*H*]pyran **4** via 6-*endo*-trig cyclization. The expected products for these reactions are *cis*- and *trans*-**2** and **4**, as shown in Scheme 3.

Herein we report a novel stereospecific ring construction for tetrahydro- and 3,6-dihydro[2*H*]pyrans by the $PdCl_2(MeCN)_2$ catalyzed cyclization of ζ-hydroxy-δ,ε-unsaturated and β-hydroxy-γ,δ-unsaturated alcohols.

2. Results and discussion

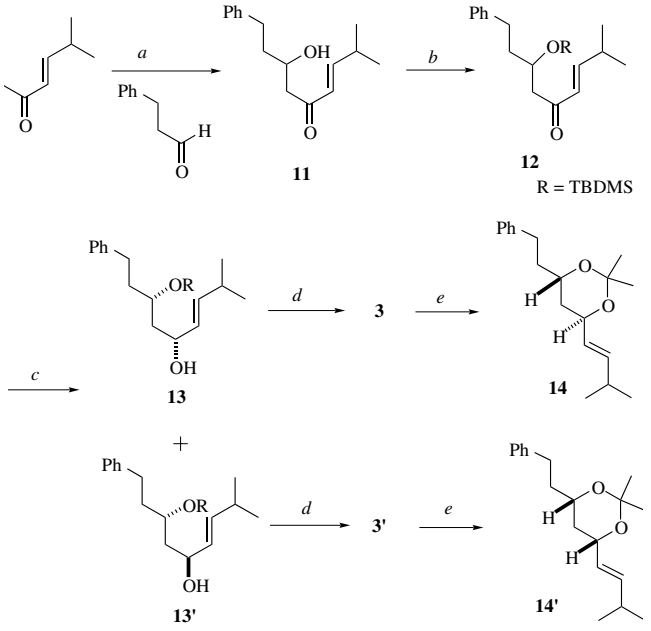
2.1. Synthesis of the starting materials

The synthesis of **1** and **1′** is described in Scheme 4. Since the separation of remote diastereomeric diols is anticipated to be difficult, an enantioselective synthesis has been undertaken. Racemic 6-hepten-2-ol **5** was prepared from 5-hexen-1-ol by Swern oxidation and Grignard addition of the resultant aldehyde with MeMgI. The racemic alcohols were subjected to lipase catalyzed kinetic acetylation by *Candida antarctica* lipase (*Ca*l) with vinyl acetate.[6] An (*S*)-alcohol (*S*)-**5** was recovered in 45% yield with >98% ee along with (*R*)-acetate (*R*)-**6** in 49% yield with >98% ee. Silylation of (*S*)-**5** with TBDMSCl gave **7** in 78% yield. Ozonolysis and Wittig reaction with triphenylphospholideneacetone gave (*S*)-8-TBDMSoxy-3-nonen-2-one **8** in 79% yield in two steps. Reduction of the carbonyl group with $NaBH_4$ in the presence of $CeCl_3$ heptahydrate gave diastereomeric alcohols in a 1:1 ratio in 91% yield, which was acetylated again with vinyl acetate in the presence of lipase *Ca*l to



Scheme 4. Reagents and conditions: (a) Swern oxidation (80%); (b) MeMgI, Et_2O, 0 °C–rt (75%); (c) *Ca*l, vinyl acetate, MS 4 Å, $^iPrO_2$, rt [(*S*)-**5**: 45%, (*R*)-**6**: 49%]; (d) TBDMSCl, imidazole, DMF, rt (78%); (e) ozonolysis then $Ph_3P{=}CHCOMe$, CH_2Cl_2, −78 °C to rt (79%); (f) $NaBH_3$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C–rt (91%); (g) TBAF, THF, rt (95–98%); (h) K_2CO_3, MeOH, rt (88%).

give the (*R*)-acetate **10** in 45% yield and the (*S*)-alcohol (*S*)-**9** in 48% yield. After desilylation of (*S*)-**9**, diol **1** was obtained in 95% yield. On the other hand, treatment of **10** with TBAF followed by methanolysis with K_2CO_3 in methanol gave **1′** in 86% yield (Scheme 5).

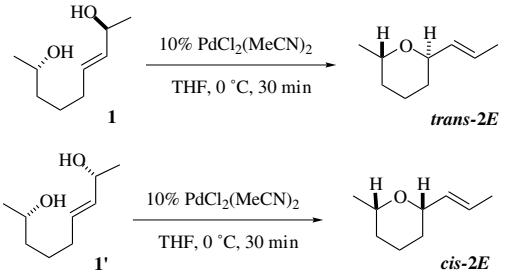


Scheme 5. Reagents and conditions: (a) LDA, THF, −78 °C (79%); (b) TBDMSCl, imidazole, DMF, rt (82%); (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C–rt (**13**: 48%, **13′**: 45%); (d) TBAF, THF, rt (**3**: quant., **3′**: quant.); (e) 2,2-dimethoxypropane, CSA, rt (**14**: 86%, **14′**: 86%).

The synthesis of **3** and **3′** was performed in four steps. The lithium salt of 5-methyl-3-hexen-2-one, generated with LDA in THF, was quenched with 3-phenylpropanal to give 7-hydroxy-2-methyl-9-phenyl-3-nonen-5-one **11** in 79% yield. Silylation of the secondary alcohol gave silyl ether **12** in 82% yield, whose reduction with $NaBH_4$ in the presence of $CeCl_3$ heptahydrate gave a mixture of **13** and **13′**. These were separable by flash column chromatography on silica gel affording the less polar isomer **13** in 48% yield and polar isomer **13′** in 45% yield. Deprotection of silyl ether **13** and **13′** with TBAF gave **3** and **3′**, respectively, in quantitative yields. The relative structures were determined by NOE experiments with ^1H NMR after the formation of acetonides **14** and **14′**. Thus, the polar isomer was identified to be a *syn* diol when the carbon chain was described in extended structure and while the less polar was an *anti* diol.

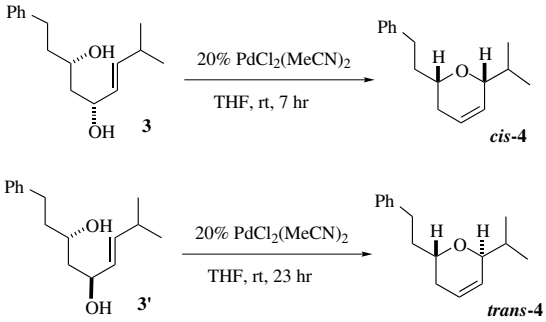
2.2. Pd-Catalyzed 6-*exo*-trigonal and 6-*endo*-trigonal cyclizations

When diol **1** was treated with 10% mol of $PdCl_2(MeCN)_2$ in THF at 0 °C, *trans*-(*E*)-tetrahydropyran *trans*-**2***E* was obtained as a single stereoisomer in 71% yield.[7] Meanwhile, that of **1′** under the same conditions gave *cis*-(*E*)-tetrahydropyran *cis*-**2***E*[8] as a single isomer in 78% yield. The structures of the products were identified by NOE experiments with ^1H NMR. Both reactions proceeded very smoothly to completion within 30 min under the mild reaction conditions employed, in nearly quantitative yield.[9] The results indicate that the 1,3-chirality transfer of the starting allylic alcohol to the tetrahydropyran ring is perfectly controlled, in which a *syn*-S_N2' type cyclization takes place stereospecifically by Pd^{II}-promoted 6-*exo*-trig cyclization. This stereochemical outcome is more interesting in comparison with the case of the nitrogen nucleophile in the piperidine synthesis (Scheme 6).[10]



Scheme 6.

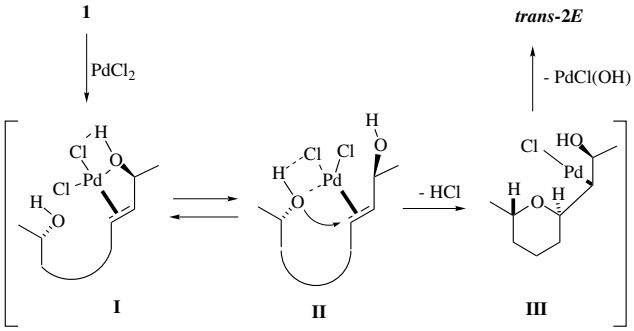
On the other hand, when diol **3** was subjected to the above conditions at rt, *cis*-**4** was obtained as a single diastereoisomer in 68% yield after 7 h.[11] The reaction of **3′** with $PdCl_2(MeCN)_2$ under the same reaction conditions was completed in 23 h to give *trans*-**4** in 60% yield.[11] Both reactions afford a *syn*-S_N2' type product, the same as that in the above 6-*exo*-trig cyclizations. Although 6-*endo*-trig cyclization is allowed in Baldwin's rule,[12] the reaction rate for the 6-*endo*-type cyclization is slower than that in the *exo*-type (Scheme 7).



Scheme 7.

In the case of the 6-*exo*-trig cyclization of **1**, we considered its mechanism as shown in Scheme 8. If the chiral secondary allylic alcohol controls the initial formation of the Pd-complex **I** with the β-face of the olefinic plane, it is in equilibrium with complex **II** by a ligand exchange. A *syn*-attack of the hydroxy nucleophile to the carbon of **II** occurs from the same side of the Pd-complex in a 6-*exo*-trig fashion to give the σ-Pd complex **III**. Subsequently, *syn*-elimination of PdCl(OH) afforded *trans*-pyran *trans*-**2***E* with an (*E*)-olefinic substituent.[13,14]

On the other hand, as in the case of the 6-*endo*-trig cyclization of **3** or **3′**, the mechanism cannot be fully



Scheme 8.

elucidated at this point.[15] Further studies are currently in progress.

3. Conclusion

2,6-Disubstituted tetrahydro- and 3,6-dihydro[2*H*]-pyrans were synthesized stereospecifically by intramolecular Pd^{II}-catalyzed cyclization of allylic alcohol with a hydroxy nucleophile under mild conditions. This result should be useful not only for the synthesis of these hydrated pyran rings, but also to give further mechanistic insights into the intramolecular oxypalladation reaction.

Acknowledgements

This research was supported (in part) by the 21st COE Program from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References

1. (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126–8131; (b) Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535–5538; (c) Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. J. *J. Am. Chem. Soc.* **1994**, *116*, 6015–6016; (d) Schummer, D.; Gerth, K.; Reichenbach, H.; Hofle, G. *Liebigs Ann.* **1995**, 685–688; (e) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51–60; (f) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511–514; (g) Tanaka, J.; Higa, T.; Kobayashi, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2967–2970; (h) Jansen, R.; Wray, V.; Irschik, H.; Reichenbach, H.; Hofle, G. *Tetrahedron Lett.* **1985**, *26*, 6031–6034; (i) Moore, R. E.; Patterson, G. M. L.; Mynderse, J. S.; Barchi, J., Jr. *Pure Appl. Chem.* **1986**, *58*, 263–271; (j) Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300–5306; (k) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159–162.
2. (a) Recent syntheses of pyran ring Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11027–11028; (b) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665–2668; (c) Hansen, E. C.; Lee, D. *Tetrahedron Lett.* **2004**, *45*, 7151–7155; (d) Joo, J. M.; Kwak, H. S.; Park, J. H.; Song, H. Y.; Lee, E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1905–1908; (e) Hayakawa, H.; Iida, K.; Miyazawa, M.; Miyashita, M. *Chem. Lett.* **1999**, 601–602; (f) Hartung, J.; Drees, S.; Greb, M.; Schmidt, P.; Svoboda, I.; Fuess, H.; Murso, A.; Stalke, D. *Eur. J. Org. Chem.* **2003**, 2388–2408; (g) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102–11113; (h) Fettes, A.; Carreira, E. M. *J. Org. Chem.* **2003**, *68*, 9274–9283; (i) Aubele, D. L.; Lee, C. A.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 4521–4523; (j) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3579–3582; (k) Chakraborty, T. K.; Reddy, V. R.; Reddy, T. J. *Tetrahedron* **2003**, *59*, 8613–8622.
3. Henry, P. The Wacker Oxidation and Related Asymmetric Syntheses. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley and Sons: New York, 2002; Vol. 2, pp 2119–2139.
4. Hosokawa, T.; Murahashi, S. Intramolecular Oxypalladation In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley and Sons: New York, 2002; Vol. 2, pp 2169–2192.
5. No 6-*endo*-trigonal type intramolecular oxypalladation for chiral allylic alcohol substrate with hydroxy nucleophile has been reported so far. 6-*exo*-Trigonal cyclization to allylic alcohol without a stereogenic center has been reported very recently by Miyazawa, M.; Hirose, Y.; Narantsetseg, M.; Yokoyama, H.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **2004**, *45*, 2883–2886.
6. (a) Faber, K. *Biotransformations in Organic Chemistry*; Springer: Berlin, 1992; (b) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695–707; (c) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114–120; (d) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071–1140.
7. Typical experiment. A mixture of diol **1** or **1′** (1 mmol) and $PdCl_2(MeCN)_2$ (0.1 mmol) in THF (10 mL) was stirred at 0 °C for 30 min. The mixture was diluted and carefully purified by silica gel column chromatography (10% ether in pentane) to give *trans*- or *cis*-**2***E*. *trans*-**2***E*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (3H, d, J = 6.4 Hz), 1.19–1.32 (2H, m), 1.59–1.68 (4H, m), 1.71 (3H, dd, J = 6.1 and 1.3 Hz), 3.91 (1H, dqd, J = 7.5, 6.4, and 2.8 Hz), 4.25–4.29 (1H, m), 5.62–5.66 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 18.6, 20.4, 29.6, 32.1, 67.0, 71.9, 127.2, 131.4. *cis*-**2***E*; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (3H, d, J = 6.2 Hz), 1.25–1.35 (2H, m), 1.46–1.60 (3H, m), 1.68 (3H, ddd, J = 6.4, 1.5, and 0.7 Hz), 1.78–1.85 (1H, m), 3.48 (1H, dqd, J = 11.0, 6.2, and 1.6 Hz), 3.77 (1H, br dd, J = 11.3 and 6.6 Hz), 5.51 (1H, ddq, J = 15.4, 6.6, and 1.5 Hz), 5.69 (1H, dqd, J = 15.4, 6.4, and 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 22.2, 23.5, 31.4, 33.0, 73.7, 78.3, 126.7, 132.7.
8. The synthesis of racemic *cis*-**2***E* has been reported, see Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925–4928.
9. The quantitative conversion was observed in an NMR tube experiment. Since products **2** are volatile liquid, some technical loss occurs during the work-up and purification process in the above scale of the reaction.
10. The reaction with a nitrogen nucleophile for piperidine synthesis has been reported, in which an opposite stereochemical result was described, see Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21–22.
11. Their stereochemistries were determined by NOE experiments with their ^{1}H NMR.
12. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
13. Alternatively, a chloride intermediate generated by the addition of Pd^{II} and a chloride anion can be considered,[3] this idea could be eliminated because of the low concen-

tration of chloride ion under these reaction conditions and poor S_N2 reactivity of the oxygen nucleophile to secondary alkyl chlorine in the absence of base.

14. The recent intramolecular *syn*-oxypalladation in 5-*exo*-trigonal type cyclization reaction via phenoxy(π-alkenyl)palladium(II) species, see Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037.
15. Although the 5-*endo*-trig cyclization is disfavored according to the Baldwin's rule (Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736–739); An example for the synthesis of the dihydrofuran was reported, in which a *syn*-S_N2' type product was obtained. See Saito, S.; Hara, T.; Takahashi, N.; Hirai, M.; Moriwake, T. *Synlett* **1992**, 237–238.