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Pd^{II}-Catalyzed Cascade Reaction with 1,3-Chirality Transfer; Stereoselective Synthesis of Chiral Nonracemic 2,2′-THF−THF Ring Units

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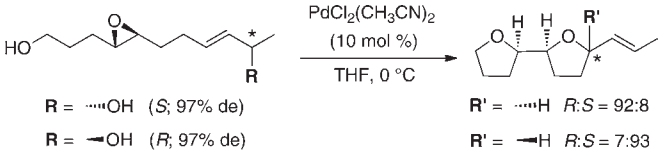
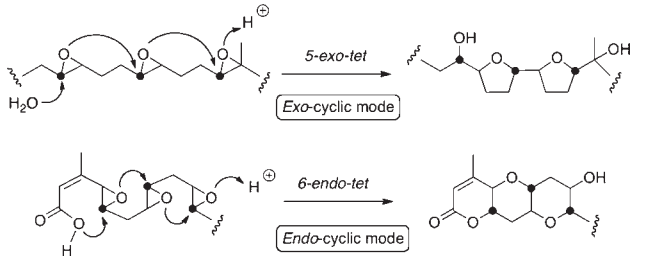
ABSTRACT



A Pd^{II}-catalyzed cascade reaction of chiral nonracemic allylic alcohols possessing an internal mono- or diepoxide and a terminal alcohol provided a contiguous THF−THF ring unit stereospecifically. The cyclization takes place in a 5-*exo-tet*-5-*exo-trig* fashion with high chirality transfer through a *syn*-S_N2' like process for the formation of the internal THF ring. Chiral bis- and tris-THF−THF ring units were effectively prepared from acyclic precursors by the Pd-catalyzed reaction.

An ionic ring-opening of a polyepoxide is well documented for the biosynthesis of polyoxocyclic natural products.[1] Two modes of cyclization in the cascade process result in two different types of polyoxocyclic products as illustrated in Scheme 1. A cascade reaction in *exo-tet* mode is proposed for the biosynthesis of contiguous THF rings in polyether antibiotics[2] as well as annonaceous acetogenins.[3] On the other hand, the *endo-tet* mode is proposed for that of the fused cyclic polyether natural products.[4] Regio- and stereoselective intramolecular ring opening of epoxides with a hydroxy group has been studied in both *5-exo-tet* and *6-endo-tet* modes, and the mode of cyclization depends on the substrate.[5]

Scheme 1. Biosynthetic Pathways Proposed for Polyoxocyclic Natural Products by Ionic Ring Opening of Polyepoxides



Although these cascade reactions were promoted by acid[6] as well as by base,[7] radical,[8] or enzymatic[9] initiations, very few transition metal catalyzed promotions have been reported.[10]

(1) (a) Garson, M. J. *Chem. Rev.* **1993**, *93*, 1699–1733. (b) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7182–7225. (c) Gallimore, A. R.; Spencer, J. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4406–4413.

(2) (a) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594–3600. (b) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vols. 1 and 2.

(3) (a) Coothankandawamy, V.; Liu, Y.; Mao, S.-C.; Morgan, J. B.; Mahdi, F.; Jekabsons, M. B.; Nagle, D. G.; Zou, Y.-D. *J. Nat. Prod.* **2010**, *73*, 956–961. (b) McLaughlin, J. L. *J. Nat. Prod.* **2008**, *71*, 1311–1321. (c) Bermejo, A.; Figadère, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303. (d) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540.

(4) (a) Nakanishi, K. *Toxicon* **1985**, *23*, 473–479. (b) Shimizu, Y. *Natural Toxins: Animal, Plant and Microbial*; Harris, J. B., Ed.; Clarendon: Oxford, 1986; p 123.

(5) (a) Vilotijevic., I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250–5281. (b) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic., I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175–3192. (c) Vilotijevic, I.; Jamison, T. F. *Mar. Drugs* **2010**, *8*, 763–809.

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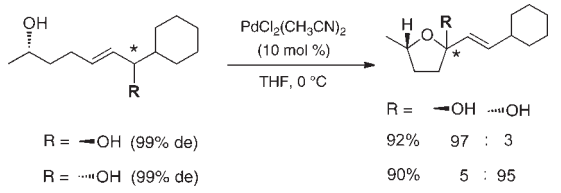
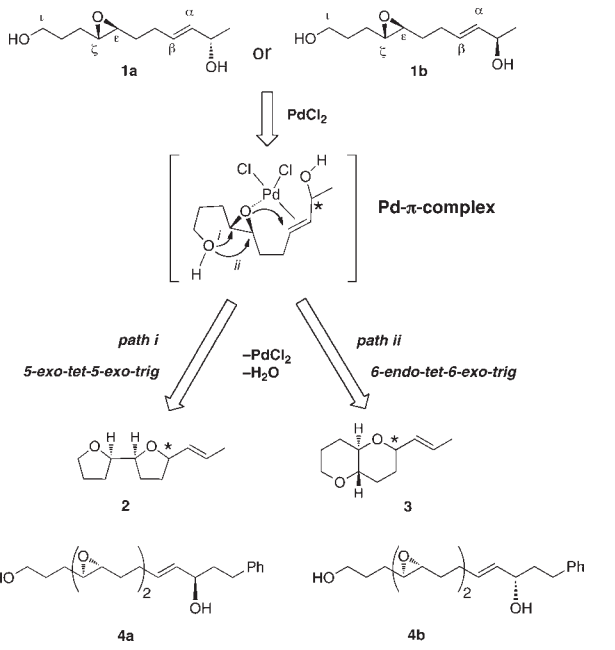
We have developed a Pd^{II}-catalyzed intramolecular oxypalladation reaction for the formation of 2-vinyl substituted oxoheterocycles.[11] For example, chirality on the secondary allylic alcohol was transferred by a $PdCl_2(CH_3CN)_2$ catalyst onto the newly formed THF ring stereospecifically, with retention of the configuration (Scheme 2).[12]

Scheme 2. Pd^{II}-Catalyzed THF Ring Formation[12]

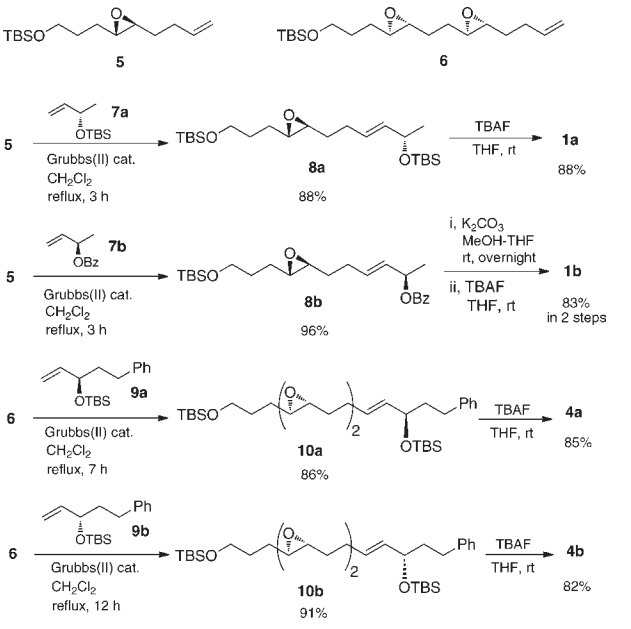


We were interested in cascade reactions in which the epoxide ring is opened by a Pd^{II}-catalyst, and we designed chiral allylic alcohol substrates **1a** and **1b** as precursors bearing an internal epoxide and a terminal hydroxy group at the appropriate positions. A cascade reaction would be expected by the initiation of a Pd^{II}-catalyst in the formation of a Pd^{II}-π-complex[11,12] coordinated with the chiral allylic alcohol, and a chirality transfer would occur (Scheme 3). If the Pd^{II}-catalyzed reaction of **1a** or **1b** proceeds in a *5-exo-tet-5-exo-trig* mode (path i), a contiguous THF−THF ring unit would form with generation of a new chiral center on the THF ring leading to product **2**. On the other hand, if the Pd^{II}-catalyst promotes the reaction in a 6-*endo-tet-6-exo-trig* mode (path ii), a fused THP ring product **3** would be produced. In this paper, we report a new Pd^{II}-catalyst triggered cascade reaction of monoepoxy allylic alcohols **1a** and **1b**, as well as diepoxy allylic alcohols **4a** and **4b**, that gives a contiguous chiral nonracemic 2,2′-THF−THF ring unit with high chirality transfer.

Scheme 3. Pd^{II}-Catalyst Triggered Cyclization of σ,ζ-Epoxy-ι-hydroxyallylic Alcohols



Scheme 4. Preparation of Precursors **1** and **4**



The syntheses of acyclic precursors, **1a**, **1b**, **4a**, and **4b**, are described in Scheme 4. First the chiral epoxides **5** and **6** were prepared with conventional methods, in which the chiral epoxide was introduced by the Sharpless asymmetric epoxidation[13] for **5** and Shi's epoxidation[14] for **6**, respectively. The cross-metathesis of **5** with chiral segments **7a**[15]

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(7) (a) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691–1694. (b) Hoye, T. R.; Jenkins, S. A. *J. Am. Chem. Soc.* **1987**, *109*, 6196–6198.

(8) Kumar, V. S.; Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 2489–2492.

(9) Shichijo, Y.; Migita, A.; Oguri, H.; Watanabe, M.; Tokiwano, T.; Watanabe, K.; Oikawa, H. *J. Am. Chem. Soc.* **2008**, *130*, 12230–12231.

(10) Recently, a Au−allene complex promoted intramolecular epoxide opening reaction was reported with medium stereoselectivity; see: Tarselli, M. A.; Zuccarello, J. L.; Lee, S. J.; Gagnè, M. R. *Org. Lett.* **2009**, *15*, 3490–3492.

(11) (a) Kawai, N.; Lagrange, J.-M.; Uenishi, J. *Eur. J. Org. Chem.* **2007**, 2808–2814. (b) Kawai, N.; Lagrange, J. M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530–4537. (c) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299–1303.

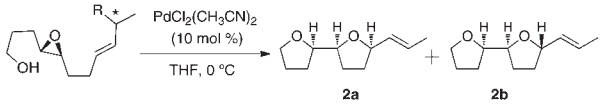
(12) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem.—Asian J.* **2008**, *3*, 473–484.

(13) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(97% ee) and **7b**[16] (97% ee) in the presence of Grubbs' catalyst gave **8a** in 88% yield and **8b** in 96% yield, respectively. Removal of the two TBS groups for **8a** with TBAF gave **1a** in 88% yield.[17] Compound **8b** gave **1b** in 85% yield in two steps by deprotection of silyl ether and benzoate.[17] Similarly, compounds **4a** and **4b** were obtained via **10a** and **10b** in 73% and 75% yield from **6**, respectively.

Pd^{II}-catalyzed cyclization was examined for diols **1a** and **1b** (Scheme 5). When diol **1a** was subjected to a Pd^{II}-catalyzed reaction with 10 mol % of $PdCl_2(CH_3CN)_2$ in THF at 0 °C for 10 min, the THF-2,5-*cis*-THF ring product **2a** was selectively obtained with a 92:8 ratio in 99% yield.[18] On the other hand, the reaction of **1b** required 40 min to reach completion to give THF-2,5-*trans*-THF ring product **2b** preferentially with a 93:7 ratio in 70% yield.[18]

Scheme 5. Pd^{II}-Catalyzed Cyclization of **1a** and **1b**



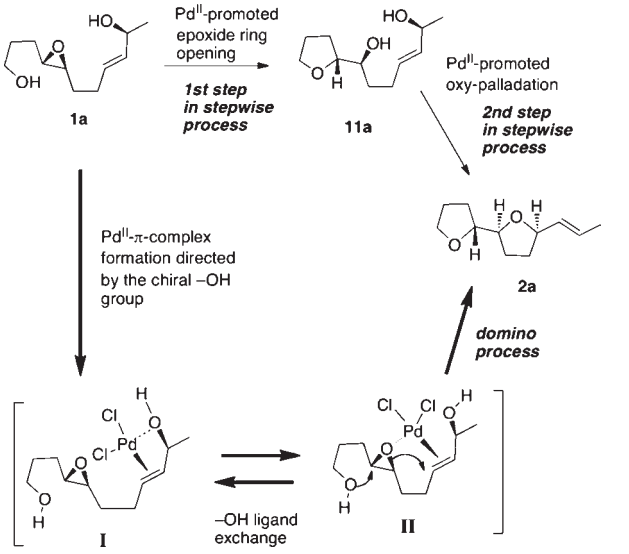
				2a		2b
1a	R = –OH (97% de)	10 min	99%	92	:	8
1b	R = ····OH (97% de)	40 min	70%	7	:	93

These results indicate that (i) the Pd^{II}-catalyst triggered epoxide ring-opening reaction proceeds in a 5-*exo*-*tet* mode rather than a 6-*endo*-*tet* mode to form two contiguous THF rings simultaneously and (ii) the chiral center of the allylic alcohol is transferred with retention of the configuration on the newly formed internal THF ring with a *syn*-S_N2' type fashion.

With respect to the reaction mechanism for the formation of **2a**, two possible pathways can be considered (Scheme 6). First, if the $PdCl_2$ catalyst serves as a Lewis acid to facilitate ring opening of the epoxide by the terminal alcohol, the successive Pd^{II}-catalyzed THF ring formation takes place in a stepwise fashion. In the second pathway, a Pd^{II}-catalyst triggered reaction *via* the epoxide-coordinated Pd^{II}-π-complex intermediate **II** is also possible.

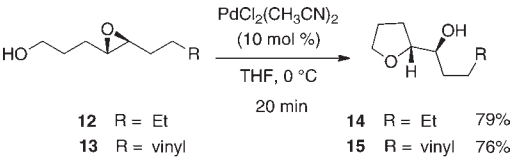
If the reaction takes place in stepwise manner, $PdCl_2$ itself activates the epoxide to open the ring. Although $PdCl_2$ is known as a weak Lewis acid,[19] the ring-opening

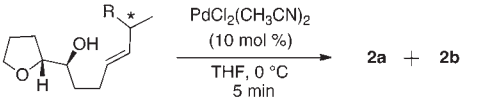
Scheme 6. Possible Reaction Pathways for the Formation of **2a**



reaction of internal epoxy alcohols **12** and **13** completed at 0 °C for 20 min to provide THF alcohols **14** and **15** (Scheme 7). On the other hand, both of the reactions of **11a** and **11b** which are anticipated as an intermediate in the stepwise process, under the same reaction conditions, completed within 5 min to give **2a** and **2b**, respectively. These results cannot explain a discrepancy in the diffent reaction times for **1a** and **1b** through the stepwise pathway.

Scheme 7





			2a	:	2b
11a	R = –OH (97% de)	76%	93	:	7
11b	R = ····OH (97% de)	86%	8	:	92

Therefore, we have concluded that the Pd^{II}-catalyzed cyclization of **1a** and **1b** would occur through the Pd^{II}-π-complex promoted domino cyclization pathway rather than the stepwise pathway, in which the Pd^{II}-π-complex formed by a hydroxy-directed coordination intermediate **I** initiates the cyclization. The different rates of reactions for **1a** and **1b** may be attributed to the stability of the precursor **II** for the cyclization (Scheme 6).

It was quite interesting in the case of diepoxide substrates. Although the Pd^{II}-catalyst triggered cyclization of **4a** was very slow at 0 °C, it occurred at rt and completed in

(14) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.

(15) Compound **7** was prepared from (*S*)-2-(*tert*-butyldimethylsilyl)-oxypropanal. Marshall, J. M.; Yanik, M. M.; Adams, N. D.; Ellis, K. C.; Chobanian, H. R. *Org. Synth.* **2005**, *81*, 157–170.

(16) Geurts, K.; Fletcher, S. F.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572–15573.

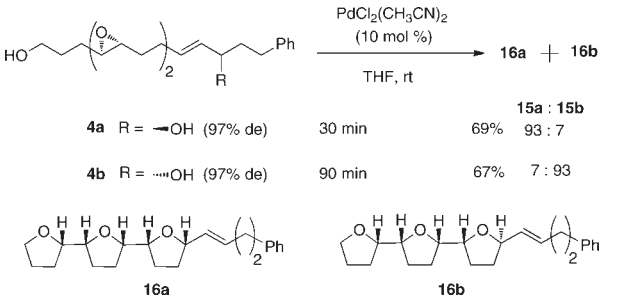
(17) NH-silica gel was used for the purification of **1a** and **1b** due to their acid sensitive property.

(18) All the diastereomeric ratios were determined by ^{1}H NMR (500 MHz).

(19) $PdCl_2$ is known to be a weak Lewis acid. Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem.—Eur. J.* **2000**, *6*, 3491–3494.

30 min to give a 2,2′-6′,2″-tris-THF ring product **16a** in 69% yield with a 93:7 diastereomeric ratio (Scheme 8). The reaction of **4b** was relatively slower than that of **4a** and gave **16b** in 67% yield with a 7:93 ratio. The reaction would proceed in a stepwise manner by the initial ring-opening step followed by the domino process. In fact, a monocyclized intermediate was observed in the initial stage of the reaction.[20]

Scheme 8



In summary, a $PdCl_2(CH_3CN)_2$ catalyzed cascade reaction of chiral nonracemic allylic alcohols possessing an internal epoxide and a terminal alcohol resulted in the stereospecific formation of chiral nonracemic 2,2′-THF-THF units with 1,3-chirality transfer. To our best knowledge, this is the first example of a Pd^{II}-catalyst that promotes the stereospecific ring opening of an internal epoxide with concomitant formation of a THF ring. The chirality transfer can be explained by the initial formation of a hydroxy-directed π-face recognition of the Pd^{II}-catalyst and the successive cyclization process through the intermediates **I** and **II**.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available. Synthesis and chracterization of all new compounds including the starting epoxides **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Further detail of the reaction mechanism is under investigation.