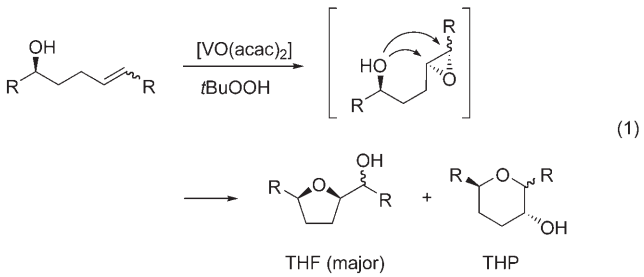
Asymmetric Synthesis

DOI: 10.1002/anie.200503852

Enantioselective Synthesis of Cyclic Ethers through a Vanadium-Catalyzed Resolution/ Oxidative Cyclization**

*Aurélien Blanc and F. Dean Toste**

Over the past 25 years, transition-metal-catalyzed oxidative cyclization of bishomoallylic alcohols has been successfully applied to the formation of substituted tetrahydrofurans (THFs), and both *trans*- and *cis*-substituted rings are now accessible depending on the olefin substitution and metal used.[1,2] In this area, catalysts based on vanadium(v) have proven to be the most useful in this transformation. Indeed, the reagent combination of catalytic vanadyl acetylacetonate and *tert*-butylhydroperoxide (TBHP) as the primary oxidant can be employed for the selective conversion of bishomoallylic alcohols into functionalized *cis*-THFs by catalytic olefin epoxidation followed by epoxide ring opening [Eq. (1)].[1,2]



(1)

[*] Dr. A. Blanc, Prof. Dr. F. D. Toste
Department of Chemistry
University of California
Berkeley, CA 94720 (USA)
Fax: (+1) 510-643-9480
E-mail: fdtoste@berkeley.edu

[**] We gratefully acknowledge the University of California (Berkeley), Merck Research Laboratories, Bristol-Myers Squibb, Amgen Inc., DuPont, GlaxoSmithKline, Eli Lilly & Co., Abbott, and Pfizer for financial support. A.B. thanks the Swiss National Science Foundation for a postdoctoral fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

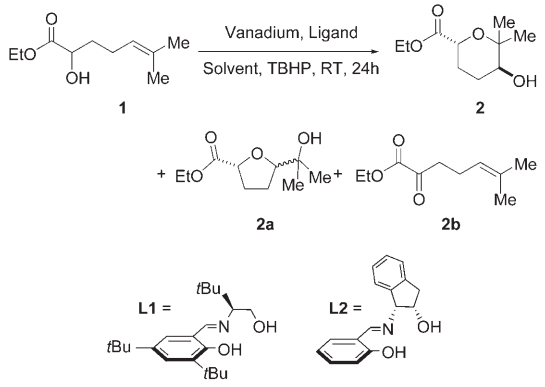
Recently, Hartung and co-workers[3] reported the oxidative cyclization of racemic bishomoallylic alcohols using vanadium(v)–oxo complexes with chiral, tridentate Schiff base ligands to induce high regio- and diastereoselectivities. In spite of the chiral ligand employed, the epoxidation/ring-opening reaction gave racemic 2,5-*cis*-THF rings as the major product. In accord with this report, our own attempts to introduce enantioselectivity in this reaction by resolution of bishomoallylic alcohols by catalytic epoxidation[4] resulted in very low stereoselectivity factors.[5] In sharp contrast, we recently described an efficient kinetic resolution of α-hydroxyesters catalyzed by a chiral vanadyl complex using molecular oxygen as the stoichiometric oxidant.[6] Notably, both allylic and homoallylic substrates showed good stereoselectivity in the resolution event and excellent chemoselectivity for alcohol oxidation over olefin epoxidation. The failure of the cyclization to provide enantioenriched cyclic ethers, prompted us consider an alternative one-pot strategy wherein the absolute stereochemistry is set using an asymmetric aerobic oxidation of unsaturated α-hydroxyesters followed by an epoxidation/cyclization reaction using the same vanadyl complex as a catalyst for both transformations.

The absence of vanadium-catalyzed olefin epoxidation under aerobic conditions led us to examine TBHP as an alternative oxidant for the epoxidation/cyclization reaction. Our preliminary results[7] showed that the best solvent for the asymmetric oxidative resolution of bishomoallylic alcohols was acetone (the best reaction rate and enantioselectivity was obtained for **1**, together with a stereoselectivity factor (*s*) of 35). Indeed, our initial attempts to obtain cyclic products from **1** in acetone, the solvent used for the kinetic resolution, resulted in chemoselective oxidation of the secondary alcohol even when TBHP was used as the stoichiometric oxidant (Table 1, entry 1). Fortunately, a pronounced solvent effect on the chemoselectivity of the oxidation reaction was observed. The vanadium-catalyzed oxidation of **1**, using $CHCl_3$ as the solvent and **L1** (Table 1, entry 2) or **L2** (Table 1, entry 4) as the ligand, cleanly afforded 2,5-*trans*-THP **2** (THP = tetrahydropyran; d.r. = > 95:5) with excellent diastereoselectivity accompanied by only minor amounts of THF **2a** (d.r. = 1:1) and α-ketoester **2b** (Table 1, entry 2).[8] In sharp contrast, classical conditions using $[VO(acac)_2]$/TBHP (acac = acetylacetone) gave poor selectivity for the formation of the THP and substantial amounts of alcohol oxidation (Table 1, entry 3). Based on these observations, the optimal procedure for the resolution/cyclization reaction simply requires a change of solvent and oxidant: acetone/O_2 used for the resolution is readily removed and replaced with $CHCl_3$/TBHP for oxidative cyclization.

Under these conditions ($[VO(OiPr)_3]$ (10 mol%), **L1** (11 mol%), O_2/acetone; then TBHP (0.55 equiv), $CHCl_3$), racemic unsaturated α-hydroxyester **1** was engaged in a tandem resolution/oxidative cyclization to give 2,5-*trans*-THP **2** in good yield (30%)[9] with excellent diastereo- and enantioselectivities (Scheme 1). The absolute stereochemistry of the chiral center bearing the ester was assigned the *R* configuration by analogy to the kinetic resolution of α-hydroxyesters.[6] We then examined the scope of different substrates with *E*- and *Z*-trisubstituted alkenes. As expected, compounds **3** and **5** gave 2,5-*trans*-substituted THPs **4** and **6** (in yields of 35 and 26%), respectively, with high diastereo- and enantioselectivities; furthermore, control of the C6 stereogenic center depended on the configuration of the olefin. Unsaturated α-hydroxyester **7**, with two double bonds, provided the possibility of carrying out a double cyclization. Unfortunately, the dioxacyclic compound was obtained as a mixture of two diastereoisomers (44% yield, d.r. = 1:1; $CHCl_3$, TBHP (2.2 equiv), 40 °C, 48 h), but tandem reaction conditions using 1.1 equivalents of TBHP gave **8** with high diastereoselectivity (d.r. = > 95:5) and in moderate yield (20%), as the double cyclization can not be completely prevented. While THP/THF ratios vary according to the substrate and remain on average at 4:1, in each case high diastereo- and enantioselectivities (d.r. = > 88:12, > 95% *ee*) were measured. The ketone resulting from the asymmetric oxidation was also recovered in good-to-moderate yield[7] and could be reused after reduction with sodium cyanoborohydride.

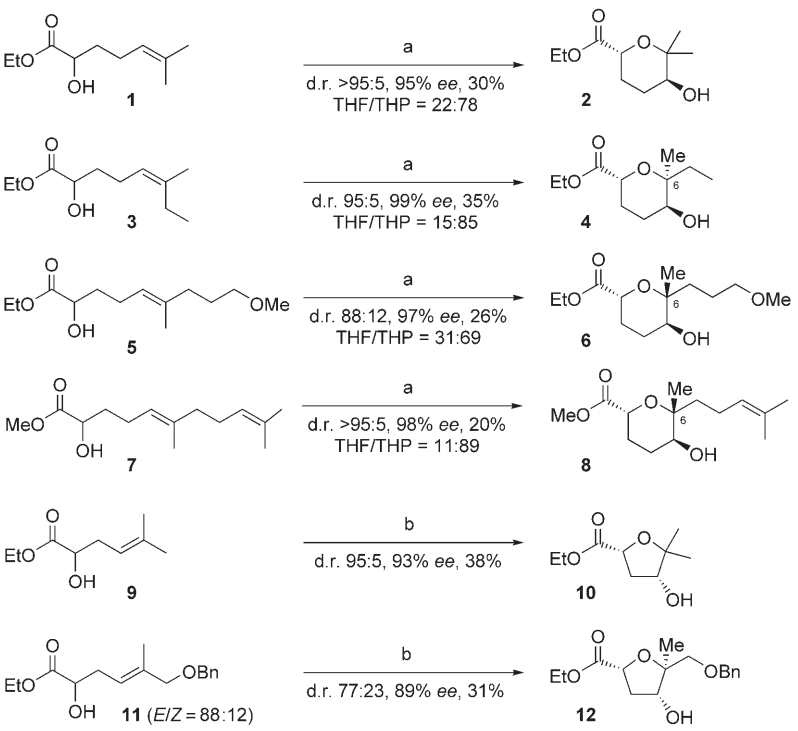
Enantiopure THF rings can also be synthesized as the exclusive regioisomer by using homoallylic alcohols in the tandem resolution/cyclization reaction. After resolution, alcohol **9** was efficiently converted into 2,4-*cis*-substituted THF product **10** (38% yield, d.r. = 95:5)

Table 1: Vanadium-catalyzed oxidative cyclization.[a]



Entry	Vanadium/ligand[b]	Solvent	Yield of **2** [%] (*cis*/*trans*)[c]	**2a** [%][c]	**2b** [%][c]
1	$[VO(OiPr)_3]$/**L1**	acetone	–	–	75
2	$[VO(OiPr)_3]$/**L1**	$CHCl_3$	78 (> 95:5)	22	trace
3	$[VO(acac)_2]$	CH_2Cl_2	36 (> 95:5)	18	46
4	$[VO(OiPr)_3]$/**L2**	$CHCl_3$	83 (> 95:5)	17	–

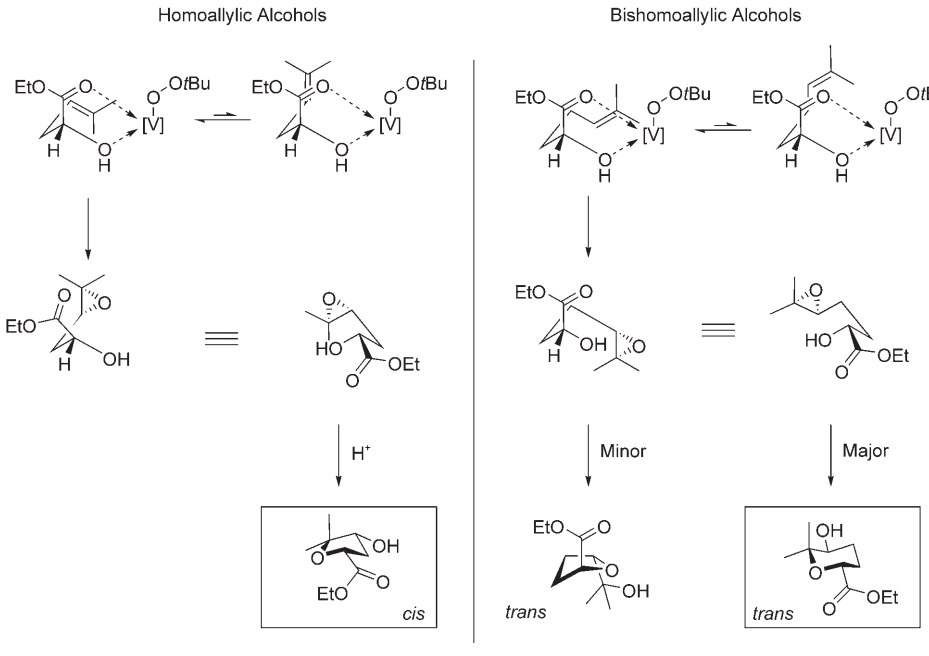
[a] No kinetic resolution took place under these conditions [b] Vanadyl complex (10 mol%) and TBHP (1.5 equiv) were used. [c] Ratio of products and the d.r. were determined by ^{1}H NMR spectroscopic analysis.



Scheme 1. Vanadium-catalyzed resolution/oxidative cyclization. Reagents and conditions: a) $[VO(OiPr)_3]$ (10 mol%), **L1** (11 mol%), O_2, acetone, 30°C, 30–48 h (≈50% conversion); then TBHP (0.55 equiv), $CHCl_3$, RT, 24–72 h; b) $[VO(OiPr)_3]$ (10 mol%), **L1** (11 mol%), O_2, acetone, 30°C, 30–48 h; TBHP (0.55 equiv), $CHCl_3$, RT, 3 h; then CSA (5 mol%), RT, 16 h.

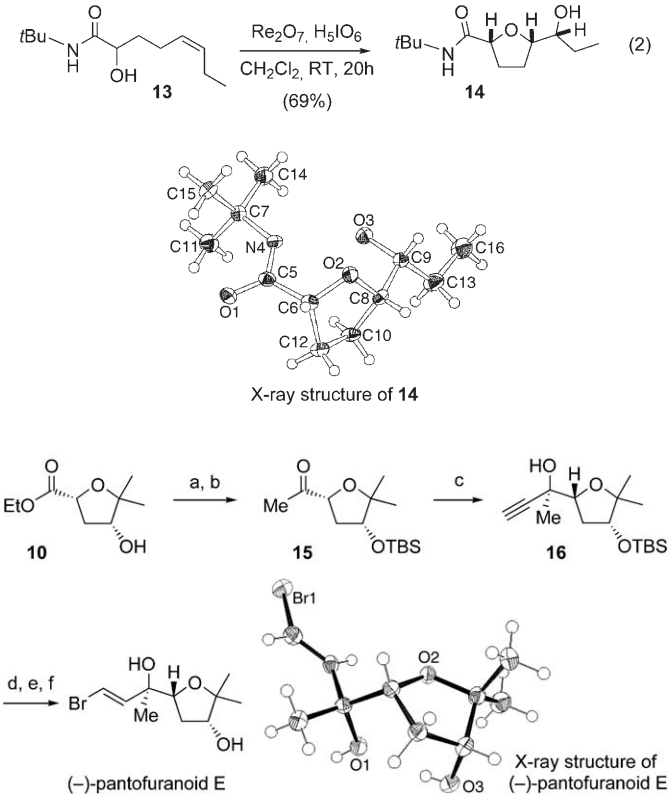
by epoxidation and subsequent addition of camphor sulfonic acid (CSA; 5 mol%) to complete the cyclization. Homoallylic alcohol **11** also furnished 2,4-*cis*-substituted THF ring **12** as the major product in good yield (31%) with high enantiomeric excess (89% *ee*) and only a slight decrease in the diastereoselectivity.

The formation of 2,5-*trans*-substituted THP rings from bishomoallylic alcohols and 2,4-*cis*-substituted THFs from homoallylic alcohols suggests a reverse in the diastereoselectivity during the epoxidation step. Indeed, the chairlike transition-state model proposed for the epoxidation of homoallylic alcohols rationalizes the *syn* diastereoselectivity through a transition state that requires that the sterically more demanding substituent (here the ethyl ester) occupies a pseudoequatorial position to minimize steric interactions;[10] however, in the case of α-hydroxyesters we observed the formation of a 2,4-*cis*-THF ring which requires the epoxidation to proceed with *anti* selectivity. On the basis of the epoxidation mechanism[11] and the fact that vanadium(v)–oxo complexes may form complexes with coordination numbers of up to seven,[12] we hypothesize that the reversed selectivity can be accounted for by considering a transition state in which coordination of the ester carbonyl group to the Lewis acidic vanadium center places the ester in a pseudoaxial position (Scheme 2). Our stereochemical model can also be applied to the oxidative cyclization of bishomoallylic alcohols and explains the formation of 2,5-*trans*-THPs as major products instead of THF rings.[3b] Finally, we also observed a reverse selectivity in the oxidative cyclization of bishomoallylic α-hydroxyamide using 50 mol% rhenium(VII) oxide [Eq. (2)], presumably due a similar chelation of the amide carbonyl group to the rhenium center.[13,14]



Scheme 2. Stereochemical model for the chelation-controlled vanadium-catalyzed epoxidation.

The enantioselective total synthesis of pantofuranoid E, isolated from *pantoneura plocamioides* (a red Antarctic alga),[15] highlights the application of the vanadium-catalyzed tandem sequence for the enantioselective construction of cyclic ethers (Scheme 3). The synthesis begins with 2,4-*cis*-THF **10**, available in 93% *ee* from our vanadium-catalyzed resolution/cyclization reaction. After protection of alcohol **10** with *tert*-butyldimethylsilyl (TBS; 95% yield), the ester group was directly converted into methyl ketone **15** by in situ formation of the Weinreb amide followed by addition of an excess of MeMgBr (76% yield).[16] Propargylic alcohol **16** was obtained in 60% yield (after desilylation) by addition of lithium trimethylsilylacetylide to **15** in the presence of anhydrous $CeCl_3$ (organocerium reagent), with d.r. = 4:1 in favor of the chelation-controlled product.[17] The



Scheme 3. Synthesis of (−)-pantofuranoid E. Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min (95 %); b) Me-(MeO)NH·HCl, MeMgBr (2 equiv); then MeMgBr excess, THF, −78 °C, 2 h (76 %); c) lithium trimethylsilylacetylide, $CeCl_3$, Et_2O/Et_3N (1:1), −78 °C, 4 h; then K_2CO_3, MeOH, RT, 1 h (60 %, d.r. = 4:1); d) nBu_3SnH, $[PdCl_2(PPh_3)_2]$, CH_2Cl_2, 0 °C→RT, 30 min (82 %); e) NBS, CH_2Cl_2, 0 °C, 1 h (87 %); f) TBAF, THF, RT, 1 h (94 %). Tf = triflate.

installation of vinyl bromide was achieved in two steps from **16**: first palladium-catalyzed hydrostannation[18] of the alkyne was carried out (82 % yield) followed by tin/bromide exchange with *N*-bromosuccinimide (NBS; 87 % yield). Deprotection of the TBS group with tetrabutylammonium fluoride (TBAF) gave (−)-pantofuranoid E in 94 % yield. Notably, this total synthesis and X-ray structural studies allowed the assignment of the absolute configuration of pantofuranoid E.

In conclusion, we have developed a highly diastereo- and enantioselective synthesis of 2,5-*trans*-THPs and 2,4-*cis*-THFs using sequential resolution/oxidative cyclization of racemic bis- and homoallylic α-hydroxyesters. Both steps in the reaction sequence are catalyzed by a vanadium(v)–oxo complex with a readily available tridentate Schiff base ligand. Additionally, the reversed diastereoselectivity observed in the formation of 2,5-*trans*-THPs and 2,4-*cis*-THFs is attributed to chelation of the ester carbonyl group to the Lewis acidic vanadium catalyst during the epoxidation event. This synthetic method provides an efficient asymmetric synthesis of cyclic ethers, as demonstrated by an expeditious enantioselective synthesis of (−)-pantofuranoid E.

Received: October 31, 2005
Published online: February 27, 2006

Keywords: kinetic resolution · natural products · oxidation · tetrahydrofurans · tetrahydropyrans

[1] J. Hartung, M. Greb, *J. Organomet. Chem.* **2002**, *661*, 67–84.
[2] M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407–2473.
[3] a) J. Hartung, P. Schmidt, *Synlett* **2000**, 367–370; b) J. Hartung, S. Drees, M. Greb, P. Schmidt, I. Svoboda, H. Fuess, A. Murso, D. Stalke, *Eur. J. Org. Chem.* **2003**, 2388–2408; c) J. Hartung, *Pure. Appl. Chem.* **2005**, *77*, 1559–1576.
[4] W. Zhang, A. Basak, Y. Kosugi, Y. Hoshino, H. Yamamoto, *Angew. Chem.* **2005**, *117*, 4363–4365; *Angew. Chem. Int. Ed.* **2005**, *44*, 4389–4391.
[5] The reaction of racemic bishomoallylic alcohol **1** was carried out under the conditions of Hartung ($[VO(OiPr)_3]$, $CHCl_3$, TBHP (1.1 equiv), RT, ligand **L1** (10 mol %)), and $s = 1.3$ was measured: $s = k_{rel(fast/slow)} = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$: "Kinetic Resolution": H. B. Kagan, J. C. Fiaud in *Topics in Stereochemistry*, *Vol. 18* (Eds.: E. L. Eliel, S. H. Wilen), Wiley, **1988**, pp. 249–330.
[6] A. T. Radosevich, C. Musich, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 1090–1091.
[7] See the Supporting Information.
[8] Only trisubstituted olefins gave promising results under these conditions; substrates containing disubstituted alkenes gave only minor amounts of cyclic products, and only alcohol oxidation was observed even using $CHCl_3$/TBHP.
[9] Reported yields were calculated for racemic alcohols before the resolution (i.e., highest theoretical yield = 50 %).
[10] E. D. Mihelich, K. Daniels, D. J. Eickhoff, *J. Am. Chem. Soc.* **1981**, *103*, 7690–7692.
[11] H. Mimoun, M. Mignard, P. Brechot, L. Saussine, *J. Am. Chem. Soc.* **1986**, *108*, 3711–3718.
[12] D. Rehder, *Coord. Chem. Rev.* **1999**, *182*, 297–322.
[13] Kennedy oxidative cyclizations generally provide *trans*-substituted THFs: a) S. Tang, R. M. Kennedy, *Tetrahedron Lett.* **1992**, *33*, 5303–5306; for exceptions, see: b) S. C. Sinha, A. Sinha, S. C. Sinha, E. Keinan, *J. Am. Chem. Soc.* **1997**, *119*, 12014–12015; c) Y. Morimoto, T. Iwai, *J. Am. Chem. Soc.* **1998**, *120*, 1633–1634.
[14] Reversal in selectivity has also been observed for the titanium-catalyzed epoxidation of homoallylic α-amino alcohols, see: A. Krasiński, J. Jurczak, *Tetrahedron: Asymmetry* **2002**, *13*, 2075–2078.
[15] M. Cueto, J. Darias, *Tetrahedron* **1996**, *52*, 5899–5906.
[16] J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 5461–5464.
[17] a) M. E. Jung, J. Pontillo, *J. Org. Chem.* **2002**, *67*, 6848–6851; b) E. M. Carreira, J. Du Bois, *Tetrahedron Lett.* **1995**, *36*, 1209–1212.
[18] B. M. Trost, Z. T. Ball, *Synthesis* **2005**, 853–887.

