reaction time (typically 20 h) would ideally be shorter, and aromatic and conjugated aldehydes tend to require even longer reaction times (Table 3), the four conditions for an ideal reagent outlined above have otherwise been met fully. In this context it is especially noteworthy, and bears repeating, that reagent **3** is a readily prepared stable solid that may be briefly handled in air with no apparent decomposition, and may be stored in a freezer under N_2 or Ar for long periods of time (> 1 month). Investigations into the mechanistic basis for the sluggish reactivity of some aromatic and conjugated aldehydes and a method to overcome this limitation have been initiated.

Experimental Section

Preparation of reagent (*R,R*)-**3**: To a cooled (0 °C) solution of allyltrichlorosilane (2.05 mL, 14.1 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.24 mL, 28.4 mmol) in dichloromethane (50 mL) was added (*R,R*)-*N,N′*-bis-(4-bromobenzyl)cyclohexane-1,2-diamine (5.37 g, 11.9 mmol) in dichloromethane (20 mL) over 50 min. After 2 h, the mixture was warmed to room temperature, and was stirred for 13 h. The reaction mixture was concentrated. After diethyl ether (60 mL) was added, the mixture was stirred for 1 h and filtered through a pad of celite, and the residue was washed with diethyl ether (2 × 10 mL). The filtrate was concentrated. Benzene (10 mL) was added, and the solution was concentrated. This procedure was repeated to give the product as an oil (5.37 g, 88 %). Upon standing (under Ar) in a freezer, the oil solidified to a white solid that may be stored in a freezer (under Ar) and used as needed. ^{1}H NMR (300 MHz, C_6D_6): $\delta = 7.43$ (d, $J = 8.4$ Hz, 2H; Ar-H), 7.42 (d, $J = 8.4$ Hz, 2H; Ar-H), 7.18 (d, $J = 8.5$ Hz, 2H; Ar-H), 7.17 (d, $J = 8.5$ Hz, 2H; Ar-H), 5.72 (m, 1H; C*H*=CH_2), 5.00–4.92 (m, 2H; CH=CH_2), 3.98 (d, $J = 16.2$ Hz, 1H; one of NCH_2Ar), 3.95 (d, $J = 15.1$ Hz, 1H; one of NCH_2Ar), 3.65 (d, $J = 15.1$ Hz, 1H; one of NCH_2Ar), 3.64 (d, $J = 16.2$ Hz, 1H; one of NCH_2Ar), 2.63–2.75 (m, 2H; two of C*H*N), 1.42–1.79 (m, 6H; four of Cy and SiCH_2CH=CH_2), 0.83–1.05 ppm (m, 4H; four of Cy); ^{13}C NMR (75 MHz, C_6D_6): $\delta = 141.7$, 140.7, 131.7, 131.4, 130.3, 129.5, 128.7, 121.2, 120.9, 116.6, 66.8, 65.8, 48.3, 47.5, 31.1, 30.7, 25.1, 25.0 ppm; ^{29}Si NMR (60 MHz, C_6D_6): $\delta = -4.4$ ppm.

General procedure for the reaction of (*R,R*)-**3** with aldehydes: To a cooled (−10 °C) solution of (*R,R*)-**3** in CH_2Cl_2 (0.2 M) was added the aldehyde (1.0 equiv). The reaction mixture was transferred to a freezer (−10 °C) and maintained at that temperature for 20 h. To this cooled solution was added 1N HCl and EtOAc, and the mixture was vigorously stirred at room temperature for 15 min. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were diluted with hexane, dried ($MgSO_4$), filtered, and concentrated. The homoallylic alcohol products may be purified further by chromatography on silica gel. All yields listed in Tables 1–3 are for chromatographed, analytically pure material.

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[1] a) S. E. Denmark, N. G. Almstead in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, chap. 10; b) S. R. Chemler, W. R. Roush in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, chap. 11; c) T. Herold, R. W. Hoffmann, *Angew. Chem.* **1978**, *90*, 822; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 768; d) H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1983**, *105*, 2092; e) P. K. Jadhav, K. S. Bhat, P. T. Perumal, H. C. Brown, *J. Org. Chem.* **1986**, *51*, 432; f) U. S. Racherla, H. C. Brown, *J. Org. Chem.* **1991**, *56*, 401; g) W. R. Roush, A. E. Walts, L. K. Hoong, *J. Am. Chem. Soc.* **1985**, *107*, 8186; h) W. R. Roush, W. L. Banfi, *J. Am. Chem. Soc.* **1988**, *110*, 3979; i) M. T. Reetz, T. Zierke, *Chem. Ind.* **1988**, 663; j) R. P. Short, S. Masamune, *J. Am. Chem. Soc.* **1989**, *111*, 1892; k) E. J. Corey, C.-M. Yu, S. S. Kim, *J. Am. Chem. Soc.* **1989**, *111*, 5495; l) J. W. Faller, D. L. Linebarrier, *J. Am. Chem. Soc.* **1989**, *111*, 1937; m) A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, Rothe-P. Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, *114*, 2321.

[2] For a recent review of enantioselective Lewis acid catalyzed allylmetal additions, see: a) A. Yanagisawa in *Comprehensive Asymmetric Catalysis, Vol. II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, chap. 27. Enantioselective Lewis base catalysis: b) S. E. Denmark, D. M. Coe, N. E. Pratt, B. D. Griedel, *J. Org. Chem.* **1994**, *59*, 6161; c) S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 12021; d) S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 9488; e) K. Iseki, Y. Kuroki, M. Takahashi, Y. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 5149; f) K. Iseki, Y. Kuroki, M. Takahashi, S. Kishimoto, Y. Kobayashi, *Tetrahedron* **1997**, *53*, 3513; g) K. Iseki, S. Mizuno, Y. Kuroki, Y. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 2767; h) K. Iseki, S. Mizuno, Y. Kuroki, Y. Kobayashi, *Tetrahedron* **1999**, *55*, 977; i) M. Nakajima, M. Saito, M. Shiro, S. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419; j) A. V. Malkov, M. Orsini, D. Pernazza, K. W. Muir, V. Langer, P. Meghani, P. Kocovsky, *Org. Lett.* **2002**, *4*, 1047.

[3] J. W. A. Kinnaird, P. Y. Ng, K. Kubota, X. Wang, J. L. Leighton, *J. Am. Chem. Soc.* **2002**, *124*, 7920.

[4] The cyclohexane diamine is treated with the appropriate substituted benzaldehyde to give the bis-Schiff base, which is reduced to the bis-(*p*-X-benzyl)diamine. The diamine is then treated with allyltrichlorosilane to give the active reagent. See the Supporting Information.

[5] a) M. T. Reetz, K. Kesseler, A. Jung, *Tetrahedron Lett.* **1984**, *25*, 729. For a comprehensive discussion regarding the tendency of β-alkoxyalkanals to favor the *anti* diastereomer in allylation and aldol reactions, see: b) D. A. Evans, M. J. Dart, J. L. Duffy, M. G. Yang, *J. Am. Chem. Soc.* **1996**, *118*, 4322.

One-Step Route to Tetrahydrofurans

A General Oxidative Cyclization of 1,5-Dienes Using Catalytic Osmium Tetroxide**

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The oxidative cyclization of 1,5-dienes to produce tetrahydrofurans has been known for some time, and is a unique method for making these heterocycles. The reaction is

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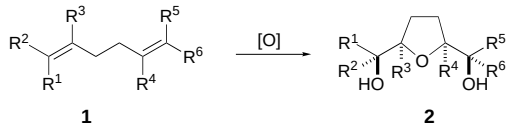
particularly powerful because it involves the stereospecific suprafacial addition of two oxygen atoms across each of the two alkenes, coupled with the steroselective formation of a *cis*-substituted tetrahydrofuran ring (Scheme 1). Typically,

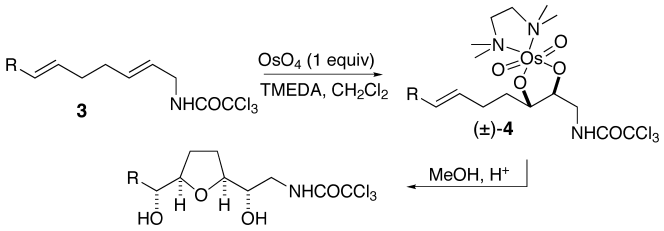


1 2

Scheme 1. Stereoselective formation of *cis*-tetrahydrofurans. [O] = $KMnO_4$, OsO_4, RuO_4.

this type of oxidation requires stoichiometric amounts of powerful oxidants such as $KMnO_4$[1] or CrO_3 derivatives,[2] which usually leads to low yields because of over-oxidation. Recently, conditions have been reported for accomplishing this reaction using catalytic osmium tetroxide[3] or ruthenium tetroxide[4] in conjunction with $NaIO_4$ reoxidant. However, while both of these processes are admirable, neither is particularly general or high yielding. For example, oxidation of geranyl acetate using Picialli's conditions (cat. OsO_4, $NaIO_4$, DMF[3]) gave 55% yield of a tetrahydrofuran, and a slightly lower yield with the isomeric neryl substrate (see entries 3 and 4, Table 1, see below); in our experience, these two substrates are often the ones that give the highest yields. In contrast, catalytic ruthenium tetroxide gave the same products as above from both geranyl and neryl acetates in 61 and 31% yield, respectively, but was not completely stereoselective for *cis*-tetrahydrofurans.

Our own work in this area had concentrated on the use of osmium tetroxide, which we believe is the oxidant with the most potential for the oxidative cyclizations of dienes. Initial results using the combination of OsO_4/tetramethylethylenediamine (TMEDA) with a diene had yielded an osmate ester **4**, which could be persuaded to cyclize (by adding the RO–Os=O unit across a distal alkene) under acidic conditions (Scheme 2).[5]

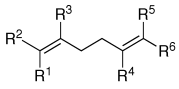


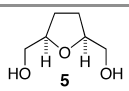
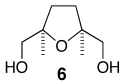
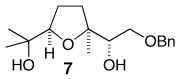
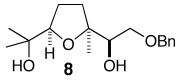
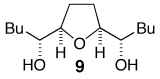
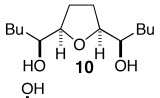
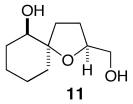
Scheme 2. Acid-promoted cyclization of osmate esters.

Although the yields of oxidative cyclization were good using this protocol (typically, 60–80%), the use of stoichiometric transition metals was unattractive and we sought out catalytic variants. Our early work had clearly shown that it was the acidic conditions that promoted cyclization of the osmate ester **4** to form the five-membered ring. Therefore, we examined the oxidative cyclization of a range of 1,5-dienes using catalytic OsO_4 (5%), Me_3NO (4 equiv), and either camphorsulfonic acid (CSA; 6 equiv) or trifluoroacetic acid (TFA; excess) to lower the pH. Remarkably, the dihydroxylation/oxidative cyclization sequence worked very well and provided several stereochemically defined tetrahydrofurans in good yield (Table 1), and as single stereoisomers. The conditions reported here are general for a range of 1,5-diene substrates and are a broad solution to the problems of yield and applicability, as outlined above. In fact, the lowest yield in Table 1 (60%) is a consequence of the volatility of the diene starting material (see entry 1). The stereoselective oxidation of both *cis* and *trans* isomers (compare entries 3 with 4 and 5 with 6, Table 1) is also noteworthy.[6]

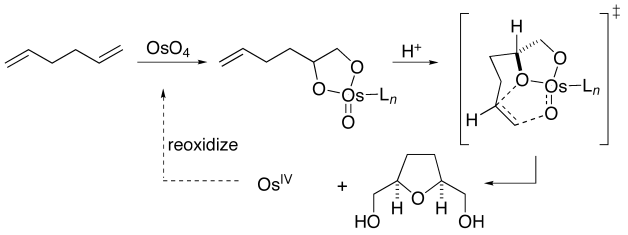
In terms of mechanism, we suggest a similar scheme to that described above in Scheme 2. The initial reaction is dihydroxylation of the diene to yield an osmate ester (Scheme 3); this may then be cyclized to a tetrahydrofuan before the osmium is reoxidized back to

Table 1: Osmium-catalyzed cyclizations of 1,5-dienes.



Entry	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield [%]
1	H	H	H	H	H	H	 **5**	60[a]
2	H	H	Me	Me	H	H	 **6**	72[a]
3	Me	Me	H	Me	H	CH_2OBn	 **7**	88[b]
4	Me	Me	H	Me	CH_2OBn	H	 **8**	95[b]
5	H	Bu	H	H	H	Bu	 **9**	78[b]
6	Bu	H	H	H	Bu	H	 **10**	81[b]
7	H	$-(CH_2)_4-$	H	H	H	H	 **11**	71[a]

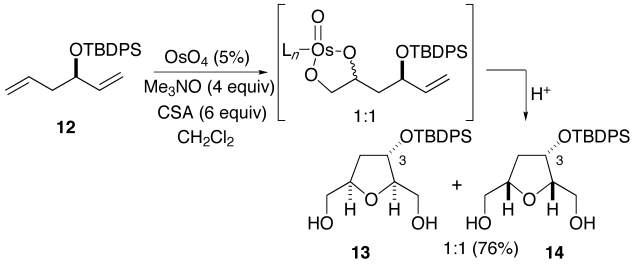
[a] CSA conditions in CH_2Cl_2. [b] TFA conditions in acetone/water (9:1). Bn = benzyl.



Scheme 3. Possible mechanism of oxidative cyclization.

Os^{VIII}.[7] The exact role of the acid in promoting cyclization is unknown, but we suggest that it protonates an oxo ligand on the osmium center, making it a more electron-deficient partner in the ensuing cycloaddition.

Our next objective was to search for methods of making these products enantiomerically pure.[8] We turned our attention to the role of stereodirecting groups on the diene backbone, between the two alkene groups: this is the first time that this possibility has been explored. The oxidation of substrate **12** is instructive for two reasons (Scheme 4). First, it

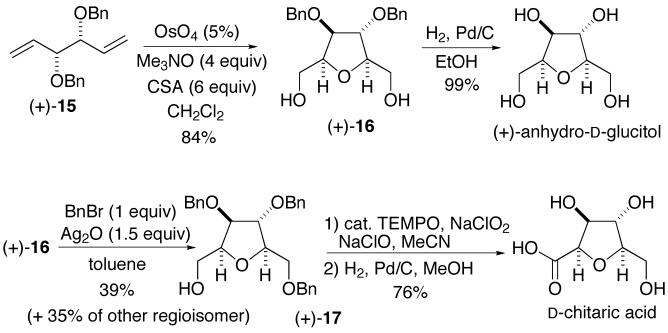


Scheme 4. Oxidation of substrate **12**. TBDPS = *tert*-butyldiphenylsilyl.

indicates that bulky silyl protecting groups are compatible with the oxidative regimen. Second, the lack of stereoselectivity with respect to the initial chiral center probably means that the reaction initiates through dihydroxylation of the unsubstituted alkene to give a mixture of osmate esters[9] (presumably, this reaction is nonstereoselective because the chiral center is too far removed). However, the presence of two *cis*-tetrahydrofuran products, **13** and **14,** means that the penchant for forming *cis* stereochemistry during cyclization clearly overrides any bias imposed by the substituent at C3. Hence, two *cis* isomers are formed in equal amounts, one from each isomer of the osmate ester.[10]

One consequence of this mechanism is that the readily available C_2-symmetric compound (+)-**15**[11] should be oxidized to give a single stereoisomer, whatever the outcome from the initial dihydroxylation (Scheme 5). This was indeed the case, and compound (+)-**16** was isolated pure in 84% yield from the oxidation reaction.

The utility of this substrate was illustrated when compound (+)-**16** was deprotected (H_2, Pd/C) to give (+)-anhydro-D-glucitol,[12] or then monoprotected with BnBr/Ag_2O to yield (+)-**17**. When compound **17** was oxidized to the carboxylic acid, and deprotected by hydrogenolysis, (+)-D-chitaric acid[13] was produced in a short sequence (Scheme 5).



Scheme 5. Synthesis of anhydro-D-glucitol and D-chitaric acid. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl.

To conclude, we report here for the first time a general and high-yielding oxidative cyclization of 1,5-dienes to *cis*-tetrahydrofurans. Our method is particularly attractive because it uses catalytic quantities of transition metal, in conjunction with an amine oxide as reoxidant and an acid to promote cyclization. Moreover, the potential of internal substituents on the diene backbone to act as stereodirecting groups has been explored and a short synthesis of highly functionalized enantiopure tetrahydrofuran natural products has been developed.

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[1] E. Klein, W. Rojahn, *Tetrahedron* **1965**, *21*, 2353; J. E. Baldwin, M. J. Crossley, E.-M. M. Lehtonen, *J. Chem. Soc. Chem. Commun.* **1979**, 918; D. M. Walba, M. D. Wand, M. C. Wilkes, *J. Am. Chem. Soc.* **1979**, *101*, 4396.

[2] Chromium-promoted cyclization of diols derived from 1,5-diene give the same THF products, see: D. M. Walba, G. S. Stoudt, *Tetrahedron Lett.* **1982**, *23*, 727.

[3] V. Piccialli, *Tetrahedron Lett.* **2000**, *41*, 3731.

[4] P. H. J. Carlsen, T. Katsuli, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936; V. Piccialli, N. Cavallo, *Tetrahedron Lett.* **2001**, *42*, 4695.

[5] T. J. Donohoe, J. J. G. Winter, M. Helliwell, G. Stemp, *Tetrahedron Lett.* **2001**, *42*, 971.

[6] Compound **5** is known, see: M. E. Jung, I. D. Trifunovich, A. W. Sledeski, *Heterocycles* **1993**, *35*, 273. Compound **6** was derivatized to a bis-Moshers ester that was no longer symmetrical; compounds **8, 10**, and **11** were characterized by X-ray crystallography. The structure of **7** is assigned by analogy to that of **8**, while compound **9** was converted into an authentic sample of **10** by a double Mitsunobu inversion/hydrolysis sequence.

[7] Preliminary experiments have shown that both first and second cycle osmium species are capable of undergoing the oxidative cyclization reaction and therefore we find it difficult to discriminate between the two.

[8] The pH of these oxidation reactions has been measured at <1; in this range we do not (nor would we expect to) observe asymmetric induction from a chiral cinchona alkaloid ligand. Previous attempts to make the cyclization products enantiopure have used acyl-derived auxiliaries, see: D. M. Walba, C. A. Przybyla, C. B. Walker, Jr., *J. Am. Chem. Soc.* **1990**, *112*, 5624; P. J. Kocienski, R. C. D. Brown, A. Pommier, M. Procter, B. Schmidt, *J. Chem. Soc. Perkin Trans. 1* **1998**, 9; A. R. L. Cecil, R. C. D. Brown, *Org. Lett.* **2002**, *4*, 3715; R. C. D. Brown, C. J. Bataille, R. M. Hughes, A. Kenney, T. J. Luker, *J. Org. Chem.*

  1433-7851/03/4208-0950 $ 20.00+.50/0

2002, *67*, 8079; or chiral phase-transfer catalysis, see: R. C. D. Brown, J. F. Keily, *Angew. Chem.* **2001**, *113*, 4628; *Angew. Chem. Int. Ed.* **2001**, *40*, 4496.

[9] Based on Sharpless' rate data, we estimate that the C1–C2 alkene unit is approximately ten times less reactive than the other towards dihydroxylation: H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483. Using OsO_4/TMEDA we have been able to isolate the two (inseparable) osmate ester diastereosiomers shown in Scheme 4 and show that they cyclize to a mixture of **13** and **14**.

[10] The structures of **13** and **14** were proven by protection of the primary hydroxy groups, desilylation, and oxidation to the C3 ketone. Both **13** and **14** gave the same ketone, which showed reciprocal NOE enhancements between H(C2) and H(C5).

[11] S. D. Burke, G. M. Sametz, *Org. Lett.* **1999**, *1*, 71.

[12] The spectroscopic data from our material matched exactly that in the literature, see: R. Persky, A. Albeck, *J. Org. Chem.* **2000**, *65*, 5632.

[13] E. Hardegger, F. Lohse, *Helv. Chim. Acta* **1957**, *40*, 2383; H. C. Cox, E. Hardegger, F. Kögl, P. Liechti, F. Lohse, C. A. Salemink, *Helv. Chim. Acta* **1958**, *41*, 229; E. Hardegger, H. Furter, J. Kiss, *Helv. Chim. Acta* **1958**, *41*, 2401.