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Supplementary Material Available: Experimental procedures and characterization data for new ligands, details for determination of enantiomeric excesses, and absolute configurations of the diols (5 pages). Ordering information is given on any current masthead page.

Selective Asymmetric Dihydroxylation of Dienes

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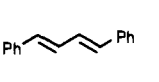
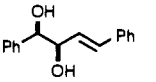
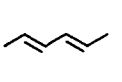
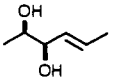
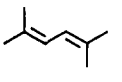
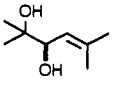
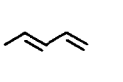
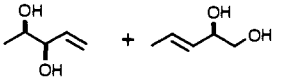
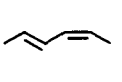
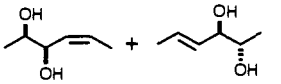
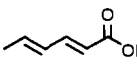
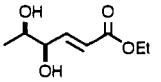
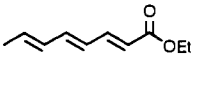
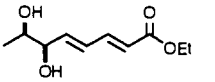
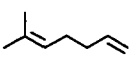
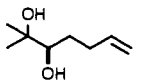
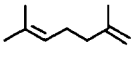
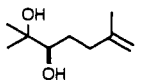
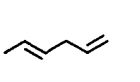
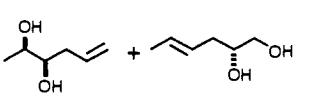
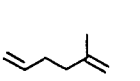
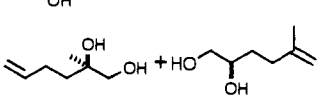
With recent advances, the catalytic asymmetric dihydroxylation (AD) of olefins has reached unprecedented levels of enantioselectivity and simplicity.[1] As part of our continuing effort to broaden the scope of the AD reaction for synthetic applications, the selective mono-dihydroxylation of dienes is a desirable goal. Success in this area would deliver valuable synthetic intermediates, ene diols, with high enantiomeric purity and also address the largely unexplored issues of the regioselectivity of the AD.[2,3]

We selected a symmetrical conjugated diene, 1,4-diphenylbutadiene, as the test substrate, anticipating that the mono-dihydroxylation product ene diol would be sufficiently deactivated by the electron-withdrawing adjacent hydroxyl groups. Using the usual 3 molar equiv of $K_3Fe(CN)_6$ (the normal amount used in AD-mix[1]) as the stoichiometric oxidant and $(DHQD)_2$-PHAL [1,4-bis(9-*O*-dihydroquinidinyl)phthalazine][4] as the ligand, the corresponding ene diol was obtained in 84% yield and very good ee (99%), in excellent agreement with our proposal. Encouraged by this initial result, the AD of a number of conjugated and nonconjugated dienes with different substitution patterns was examined. The results are summarized in Table I.

All of the conjugated dienes gave uniformly high yields of the expected ene diols except *trans*-piperylene (entry 4), which afforded the corresponding diols in moderate yields due to the volatility and water solubility of the products. The tetrol products, if formed, represented only trace amounts in these reaction mixtures. For unsymmetrical conjugated dienes, osmylation occurred preferentially at the more electron-rich double bond. For example, AD of piperylene (entry 4) gave a 3:1 mixture of the ene diols with the diol from the 1,2-disubstituted olefin found in excess. The preference for a trans over a cis olefin is significant and is exemplified by the AD of *trans,cis*-hexadiene, which gives predominately the ene diol corresponding to the dihydroxylation of the trans double bond (entry 5).[5] Similarly, AD of ethyl sorbate (entry 6) gave the 4,5-diol ester as the only isolated product; it is interesting to note that the same product was obtained only in poor yield using the NMO system.[6] Entry 7 nicely illustrates that mono-dihydroxylation of a conjugated trienoic ester can also be achieved with a regioselectivity similar to that for the related dienoic ester.

Table I[a]

	olefin	product(s)[b]	% yield, (% ee)[c]
1.			84(≥99)[d]
2.			78(93)
3.			94(93)[d]
4.			48(90,72) 3:1
5.			88 (98) 15:1
6.			78 (92)
7.			93 (95)
8.			73(98)
9.			70(98)
10.			56(94) 13:1
11.			42(74) 5:1

[a] The AD was run as described in ref 1 with 0.2-1.0 mol % of OsO_4. See the supplementary material for experimental details. [b] All of the absolute configurations, except that of 2-methyl-5-hexene-1,2-diol (entry 11), are tentatively assigned by using the mnemonic device described in ref 1. [c] The % ee's were determined by GLC analysis of the MTPA esters or by direct injection of the diol on a CDX-B β-cyclodextrin GLC column or a Chiralcel OD HPLC column. The indicated % ee is for the major product, except for entry 4 where both were determined. See the supplementary material for experimental details. [d] This reaction was run at room temperature.

The selectivity observed with nonconjugated dienes is substantial. Entries 8 and 9 reveal the strong preference for trisubstituted over terminal olefins in the AD. No products resulting from oxidation of the terminal olefins were observed in these reactions. The selectivity dropped when less substituted olefins were placed in competition with a terminal olefin: (*E*)-1,4-hexadiene gave a 13:1 preference for the 1,2-disubstituted diol (entry 10), and 2-methyl-1,5-hexadiene, which contains a 1,1-disubstituted olefin, gave only a 5:1 ratio in competition with a monosubstituted olefin (entry 11).[7] This drop in selectivity is always accompanied by a drop in the yield of the ene diol due to tetrol formation (cf. entries 8,9 and 10,11).

The selective ene diol formation from conjugated dienes observed in this study is in sharp contrast to the earlier results reported from our laboratories which showed that dihydroxylation of conjugated dienes employing catalytic amounts of OsO_4 and 1 equiv of NMO gave mainly tetrols and unreacted starting

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(4) The structures of our latest ligands, $(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL, are found in ref 1. These ligands are available from Aldrich Chemical Company, Inc.
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(7) The use of chiral ligand has been shown to have little effect on the regioselectivity in this study.

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material.[7] One possible explanation proposed to account for the tetrol formation in the NMO system involves the "second cycle" process, a scenario in which the preferential oxidation of the ene diol over the parent diene is due to a rather strong affinity of the trioxo Os(VIII) glycolate for the ene diol.[8b,9,10] However, selective ene diol formation in the $K_3Fe(CN)_6$-based system appears to be determined only by the electronic nature of the ene diol and the corresponding parent diene, consistent with our earlier finding that using $K_3Fe(CN)_6$ as the stoichiometric oxidant in place of NMO excludes the "second cycle" in the catalytic process.[11]

In conclusion, we have shown that the AD of dienes, and by implication higher polyenes, is highly selective and favors oxidation of the more electron-rich olefin when $K_3Fe(CN)_6$ is used as a stoichiometric oxidant. The high selectivity of this reaction makes effective control of the AD to a mono-dihydroxylation stage possible. The resulting chiral ene diol products should prove useful in asymmetric synthesis.

Acknowledgment. Financial support was provided by the National Institutes of Health (GM 28384-12).

Supplementary Material Available: Listings of experimental procedures and physical and analytical data (^1H NMR, ^{13}C NMR, HRMS, HPLC, and GLC retention times of the diols or their MTPA esters and the optical rotations) of the diols (6 pages). Ordering information is given on any current masthead page.

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Matrix-Assisted Laser Desorption/Ionization of Capillary Electrophoresis Effluents by Fourier Transform Mass Spectrometry

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Capillary electrophoresis (CE) is a powerful separation technique capable of rapid and efficient separation of complex biological mixtures.[1] With CE, separation efficiencies in excess of 10^6 theoretical plates have been achieved in times as short as a few minutes.[2] Additionally, the small sample volumes required make possible the investigation of many biological processes at the cellular level.[3] The major limitation of this method lies in detection of the eluted analytes.[4] Ideally, the detector should have sufficient sensitivity to record the passage of an analyte zone as it migrates through the capillary. Sub-attomole detection limits can be achieved using laser-induced fluorescence[5-7] or electrochemical detection.[8-10] Unfortunately, both techniques lack specificity. An ideal complement, capable of providing the desired molecular specificity, is mass spectrometry. Zare and co-workers[11] have demonstrated on-line CE matrix-assisted laser desorption/ionization (MALDI)[12,13] using an ice/nicotinic acid matrix and time-of-flight (TOF) mass analysis for the analysis of unspecified quantities of bovine insulin, albeit with exceptionally poor mass resolution. Off-line CE-MALDI, for picomole quantities of bovine trypsinogen, with TOF analysis has also been reported.[14]

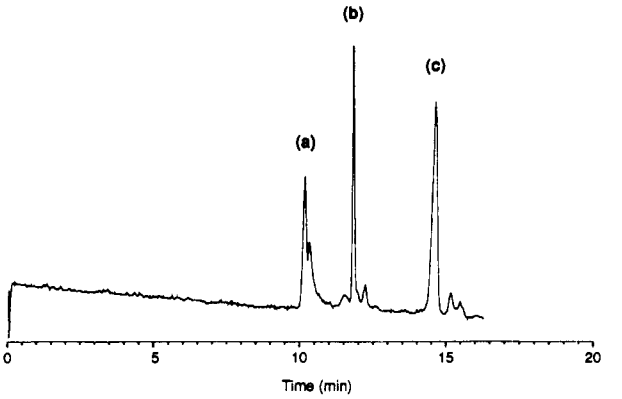

Figure 1. Ultraviolet detector electropherogram for the capillary zone electrophoresis of (a) somatostatin; (b) equine myoglobin; and (c) bovine insulin.

A previously unexplored alternative is to employ a Fourier transform mass spectrometer (FTMS) as the mass analyzer. The high-resolution spectra made available by this device (typically between 10^4 and 10^6, even for high-mass species[15,16]) and the potential for performing high-resolution MS/MS experiments offer the promise of dramatic improvements in the determination of structures of high molecular weight compounds separated by CE. Although high mass resolution has not yet been obtained (typically 50–100 for the CE application), nevertheless, off-line CE-MALDI with Fourier transform mass spectrometry analysis can provide highly accurate mass measurements for large biomolecules at the sub-picomole level. Until recently,[17] it was thought[18] that MALDI analysis of large molecules would be difficult with FTMS, possibly requiring unusually high trapping voltages to succeed at all. After the recent successful development of a means for accomplishing MALDI-FTMS, it seemed logical to explore its promising potential for off-line CE analysis. Accordingly, a concentric flow deposition interface with post-column matrix solution introduction was designed and fabricated. This device permits deposition of CE effluents *concurrently with matrix solution* upon an indexed stepper-motor-controlled laser desorption probe tip, which can be transferred to the FTMS system for mass spectrometric analysis.[19]

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