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Asymmetric Dihydroxylation of Tertiary Allylic Alcohols

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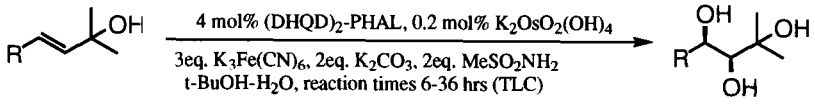
Abstract: *The asymmetric dihydroxylation (AD) of tertiary allylic alcohols is examined. Good to excellent ee's are obtained with trans-di- and tri-substituted tertiary allylic alcohols of different substitution patterns except for a trisubstituted case where the tertiary carbinol substituent is on the disubstituted olefinic carbon.*

Due to recent improvements[1] in asymmetric dihydroxylation (AD) reaction, we have been engaged in efforts to expand the scope of the process and report here that some tertiary allylic alcohols can be added to the list of good substrates.

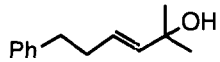
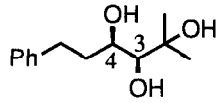
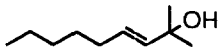
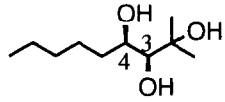
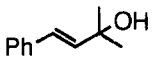
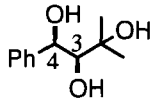
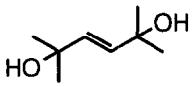
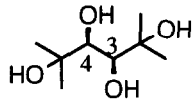
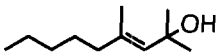
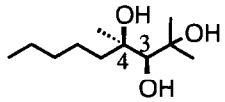
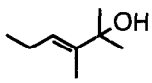
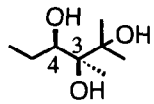
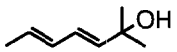
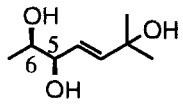
We first examined the AD of **1a** and found that the reaction was very slow at 0°C with AD-mix-β. Nearly half the starting material remained unchanged after 48 hrs. When the reaction was run at room temperature and using 4 mol% of ligand instead of the 1 mol% present in the standard AD-mix, it was complete within 36 hrs. Therefore, we chose 4 mol% of ligand and 0.2 mol% of $K_2OsO_2(OH)_4$ as the modified conditions[2] with which to investigate the AD of these hindered allylic alcohols. If one desires faster reactions, then we recommend use of more osmium catalyst (up to the 1 mol% level). The olefins investigated and the results obtained are summarized in the Table.

The enantioselectivity levels observed in the AD of **1a**, **1b** and **1e** are somewhat lower, but generally in line with previous results with trans-disubstituted and trisubstituted olefins.[1]



1 2

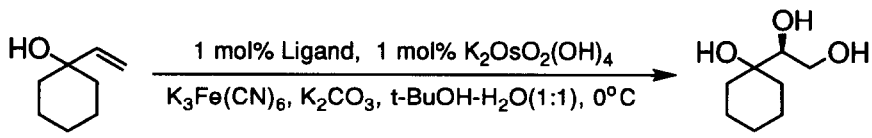
Table: Results for the AD of tertiary allylic alcohols

Entry	Substrate	Triol[2]	Yield	ee[a]	abs. config[b]
a			83%	91%	3S, 4R
b			87%	90%	3S, 4R
c			83%	77%	3S, 4R
d			50% (70%)[d]	90%	3S, 4S
e			91%	79%	3R, 4R
f			75%	36%[c]	3S, 4R[c]
g			50% (74%)[d]	93%	5R, 6R

a) Enantiomeric excesses were determined by HPLC analysis of the triols (**2a**, **2c**), the 3,4-dibenzoate of **2b** and the 4-monobenzoate of **2f** on Chiralcel OD, the 3,4-dibenzoate of **2d** on Chiralcel OD-H and 5,6-dibenzoate of **2g** on Chiralcel OG columns (Daicel Chemical Industries, LTD). Enantiomeric excess of **2e** was determined by GLC analysis of the triol on CDX-B (β-cyclodextrin) column (J & W Scientific). b). The absolute configuration of **2c** and **2d** were determined by comparison with authentic samples prepared from methyl (2S,3R)-2,3-dihydroxy cinnamate. and (S,S)-diethyl tartrate, respectively, by addition of excess MeLi. For the other triols, the absolute configurations are assigned according to the AD face-selection rule.[1] c) The low ee renders the configurational assignment (based in this case on the AD face selection rule) highly uncertain. *d)* 5 mmol scale.

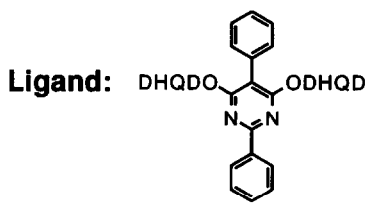
The poor ee for **1f** is surprising and cannot be rationalized at present. Questions as to whether the hydroxy group also plays a role (positive or negative) in the stereocontrol of the AD process for allylic alcohols, and related hydrogen bonding substrates, are being studied.[3]

The AD of conjugated diene **1g** is regioselective as well as highly enantioselective (93% ee), preferring the double bond distal the tertiary alcohol group. We also found that 1-vinylcyclohexan-1-ol (**3**) is a good substrate for the AD reaction with the new pyrimidine ligand **5**:[1b]



3 **4**[4]

after chromatography	Yield: 88%	e.e.: 90%
after recrystalization	recovered: 65%	e.e.: 97%



5

The crude ee of 90% is readily increased to 97% upon recrystallization from pentane-diethyl ether. The importance of the new pyrimidine ligand **5** is that it compensates for a weakness in the phthalazine ligand, the latter does poorly with monosubstituted terminal olefins with branching in the R group.[1b]

In conclusion, it has been shown that good ee's can be obtained in the AD of tertiary allylic alcohols with different substitution patterns. Only substitution on the carbon bearing the iso-propoxyl group seems to have a deleterious effect on the enantioselectivity.

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

References and Note:

1. a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. -S.; Kwong, H. -L.; Morikawa, K.; Wang, Z. -M.;, Xu, D.; Zhang, X. -L., *J. Org. Chem.*, **1992**, *57*, 2768. b) Crispino, G. A.; Jeong, K. -S.; Kolb, H. C.; Wang, Z. -M.; Xu, D.; Sharpless, K. B., *J. Org. Chem.*, **1993**, *58*, 3785.
2. The general procedure: To a well-stirred solution of $(DHQD)_2$-PHAL (32 mg, 4 mol%), $K_2OsO_2(OH)_4$ (0.74 mg, 0.2 mol%), $K_3Fe(CN)_6$ (988 mg, 3 mmol), K_2CO_3 (415 mg, 3 mmol), and $CH_3SO_2NH_2$ (190 mg, 2 mmol) in 1:1 *tert*-butyl alcohol-water at room temperature the appropriate allylic alcohol (1 mmol) was added. After the reaction was finished (TLC), 1.5 g of Na_2SO_3 was added and stirring was continued for 30 min. The layers were separated and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layers were washed with a 1N KOH , 5% aq. HCl and brine, and then dried over $MgSO_4$ and concentrated. The crude triol was purified by flash chromatography on silica gel. **2a**: $[\alpha]_D$ +4.4° (c 1.02, EtOH). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.31 (m, 3H), 7.20 (m, 2H), 4.00 (t, J= 8 Hz, 1H), 3.16 (br, 1H), 2.81 (br, 3H), 2.74 (m, 2H), 2.00 (m, 1H), 1.86 (m, 1H), 1.30 (s, 3H), 1.25 (s, 3H), ppm. **2b**: $[\alpha]_D$ -3.8° (c 0.71, EtOH). ^1H NMR ($CDCl_3$) δ: 3.97 (dt, J= 12 Hz, J= 4 Hz, 1H), 3.14 (d, J= 4 Hz, 1H), 2.70 (br, 1H), 2.62 (br, 1H), 1.64 (m, 1H), 1.52 (m, 1H), 1.32 (br, 6H), 1.30 (s, 3H), 1.29 (s, 3H), 0.90 (t, J= 7.2 Hz, 3H), ppm . **2c**: $[\alpha]_D$ -47.2° (c 1.05, EtOH). ^1H NMR ($CDCl_3$) δ: 7.34 (m, 5H), 4.99 (d, J= 2 Hz, 1H), 4.00 (br, 1H), 3.44 (d, J= 2 Hz, 1H), 2.95 (br, 2H), 1.33 (s, 3H), 1.22 (s, 3H), ppm. **2d**: $[\alpha]_D$ -6.1° (c 1.20, EtOH). ^1H NMR ($CDCl_3$) δ: 4.85 (br, 2H), 3.91 (br, 2H), 3.51 (br, 2H), 1.21 (br, 12H), ppm. **2e**: $[\alpha]_D$ +6.9° (c 1.87, EtOH). ^1H NMR ($CDCl_3$) δ: 3.50 (d, J= 6.6 Hz, 1H), 3.33 (br, 1H), 3.22 (d, 6.3 Hz, 1H), 3.12 (br, 1H), 1.73 (m, 1H), 1.51 (m, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.32 (br, 6H), 0.89 (t, J= 7.2 Hz), ppm. **2f**: $[\alpha]_D$ +17.6° (c 1.00, EtOH). ^1H NMR ($CDCl_3$) δ: 3.80 (t, J= 5 Hz, 1H), 3.40 (br, 1H), 3.07 (br, 1H), 3.02 (br, 1H), 1.61 (m, 2H), 1.33 (s, 3H), 1.27 (s, 3H), 1.05 (s, 3H), 1.02 (t, J= 7.2 Hz, 3H), ppm. **2g**: $[\alpha]_D$ +30.5° (c 1.39, EtOH). ^1H NMR ($CDCl_3$) δ: 5.85 (dd, J= 15.7 Hz, J= 0.8 Hz, 1H), 5.60 (dd, J= 15.7 Hz, J= 7.1 Hz, 1H), 4.07 (br, 1H), 3.81 (dd, J= 7.1 Hz, J= 6.7 Hz, 1H), 3.61 (dt, J= 6.7 Hz, J= 6.4 Hz, 1H), 3.48 (br, 2H), 1.29 (br, 6H), 1.30 (d, J= 6.4 Hz, 3H), ppm.
3. Xu, D.; VanNieuwenhze, M. S.; Sharpless, K. B., unpublished results.
4. **4**: $[\alpha]_D$ -5.6° (c 0.50, EtOH). ^1H NMR ($CDCl_3$) δ: 3.83 (m, 2H), 3.46 (t, J= 2 Hz, 1H), 2.84 (br, 1H), 2.27 (br, 2H), 1.52 (m, 10H). The enantiomeric excess was determined by HPLC analysis of the bis-benzoate of **4** on a Chiralcel OF column.

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