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Asymmetric Dihydroxylation of Aryl Allyl Ethers

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Abstract: Asymmetric dihydroxylation of substituted aryl allyl ethers is described. Para-substituents are shown to favor high enantioselectivity (89-95%ee), while ortho-groups have a deleterious effect (28-63%ee). Four medicinal agents were prepared: guaifenesin (expectorant), mephenesin (muscle relaxant), chlorphenesin (antifungal) and propranolol (β-blocker).

Many members of the substituted glycerol family of molecules have useful bioactivity.[1] These substances, especially when required in enantiopure form, are now commonly prepared from enantiomerically enriched glycidol or related chiral three carbon synthons.[2] With the advent of the asymmetric dihydroxylation (AD) process,[3] aryl allyl ethers became attractive starting materials for important members of this class of compounds.

This brief note discloses the relationship between the %ee and variation of the substituents in the aromatic ring when aryl allyl ethers are subjected to AD (Table). Commercially available AD-mix-β was used and the yields were excellent (85-95%) in all cases.[4] With para substitution, both electron donating and withdrawing groups seem to slightly enhance the enantioselectivity over the unsubstituted case (entry 5), as one notes that the ee's are generally good to excellent (89-95%, entries 1-4).

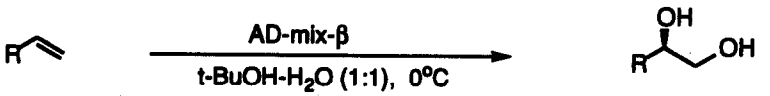
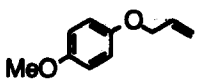
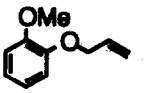
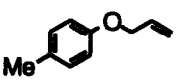
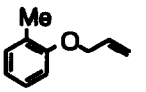
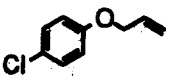
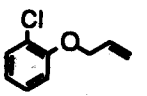
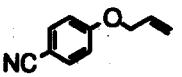
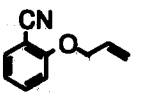
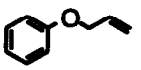
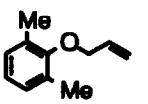
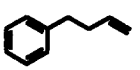
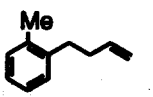
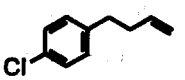
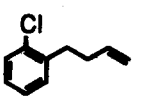


Table The %ee[a] of the diols produced by asymmetric dihydroxylation (AD)

Entry	Olefins[b]	Diol (config.) % ee	Entry	Olefins[b]	Diol (config.) % ee
1		(S)-1 90	8		(S)-8 63
2		(S)-2 89	9		(S)-9 56(94)[c]
3		(S)-3 92	10		(S)-10 29
4		(S)-4 95	11		(S)-11 28
5		(S)-5 88	12		(S)-12 36
6		(R)-6 84	13		(R)-13 81
7		(R)-7 82	14		(R)-14 77

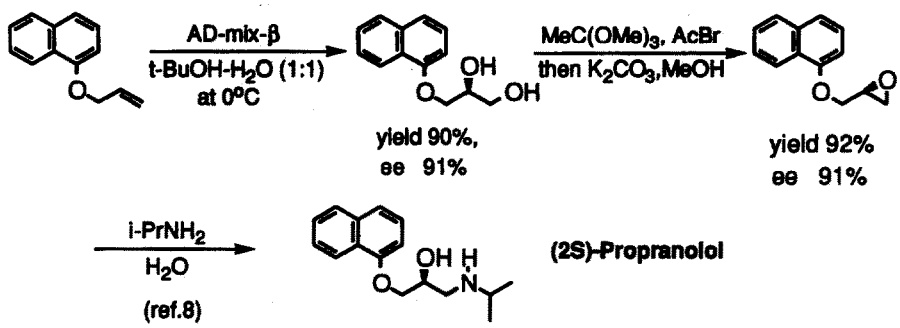
a) Enantiomeric excesses of the diols from the aryl allyl ethers were determined by HPLC analysis of the diols or the derived diacetates on chiralcel OD or OD-H columns. Enantiomeric excesses of the diols from the 4-aryl-1-butenes were determined by HPLC analysis of MTPA esters of the diols on a Pirkle 1-A column. b) Aryl allyl ethers were prepared by refluxing a mixture of the substituted phenol, allyl bromide (1.5eq.) and K_2CO_3 (1.5eq.) in acetone. The 4-Aryl-1-butenes were obtained by coupling the appropriate benzylic bromide with allylmagnesium bromide in THF at room temperature.[5] c) After recrystallization from water (50% recovery).

However, there is surprising sensitivity to substituents in the ortho position, where the enantio-selectivities range from poor to fair (28-63%, entries 8-12). Particularly noteworthy is the para-CN case which gives the highest ee (95%, entry 4),[3b] while the ortho-CN isomer (entry 11) goes to the other extreme (28%ee). Also included in the Table for comparison are several hydrocarbon analogs where a methylene group has been substituted for the ether oxygen (entries 6, 7, 13 and 14). In these cases varying the substituent from ortho-H to ortho-Me or ortho-Cl results in negligible enantioselectivity changes. Apparently, for these non-ether analogs the ee's are almost invariant with substitution at either the ortho or para positions.

Any discussion of the origin of these subtle (steric?) effects would be pure speculation until a better understanding of the mechanism of the AD process is achieved. The only purpose of this report is to give the synthetic chemist a feeling for which aryloxy allyl cases are good candidates for AD and which are not.

So far in our experience the most useful follow up to the AD process is to convert the diol to the epoxide by a simple one-pot procedure via the acetoxonium ion.[6] The application of this sequence in a β-blocker synthesis[7] is shown below:

Scheme



Finally, a few of the aryloxy diols in the Table are pharmaceutical agents and the active enantiomer is (S) in each case: guaifenesin (8),[9,10] chlorphenesin (3),[10,11] and mephenesin (9).[12]

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4. The general procedure: A stirred solution of AD-mix-β (1.4g) in 10mL of 1:1 tert-butyl alcohol-water (5mL of each) was cooled to 0°C, and the appropriate aryl allyl ether (1mmol) was added. The mixture was stirred at 0°C overnight, then 1.5g of Na_2SO_3 was added and stirring continued at r.t. for 30 mins. The tert-butanol layer was separated and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated. After flash chromatography on silica gel eluting with 1:1 ethyl acetate-hexane the diol was obtained in 85-95% yield. Optical rotations for the aryloxy diols: **1**: $[\alpha]_D$+5.9° (c 1.22, EtOH) and $[\alpha]_D$+7.5° (c 1.1, MeOH); **2**: $[\alpha]_D$+14.7° (c 0.49, EtOH); **3**: $[\alpha]_D$+46.9° (c 0.32, EtOH) and $[\alpha]_D$+8.1° (c 1.50, MeOH); **4**: $[\alpha]_D$+28.2° (c 0.44, EtOH); **5**: $[\alpha]_D$+8.6° (c 1.1, EtOH); **8**: $[\alpha]_D$+12.9° (c 1.21, EtOH) and $[\alpha]_D$+5.8° (c 1.10, MeOH); **9**: $[\alpha]_D$+4.0° (c 0.96, EtOH) and $[\alpha]_D$ -11.5° (c 0.91,hexane - 2-propanol (4:1)); **10**: $[\alpha]_D$+2.7° (c 1.18, EtOH); **11**: $[\alpha]_D$+9.4° (c 0.49, EtOH); **12**: $[\alpha]_D$+27.4° (c 0.46, EtOH). All these diols are assumed to be (S)-configured since AD-mix-β was used in all cases. This assignment is certain for 3-(methoxyphenoxy)-1,2-propanediol (**1**) [lit[13] $[\alpha]_D$+7.79° (c 1.03, MeOH) and the three medicinal agents: guaifenesin (**8**) [lit[10] $[\alpha]_D$+8.3° (c 1.18, MeOH)], chlorphenesin (**3**) [lit[10] $[\alpha]_D$+7.9° (c 1.45, MeOH)], mephenesin (**9**) [lit[12] $[\alpha]_D$-19.3° (c 0.9, hexane - 2-propanol (4:1)], where the absolute configurations are established.
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