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Asymmetric dihydroxylation of allenes ☆

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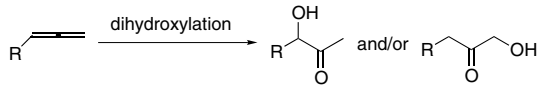
Abstract—We have used asymmetric dihydroxylation (AD) of allenes in order to synthesize chiral α-hydroxy ketones. This methodology has been applied to several aryl-substituted allenes. We have found that electron donating groups on the aromatic ring increase the efficiency of the reaction.

We have been interested in synthetic methodology for the formation of α-hydroxy ketones. The literature describes many procedures for generating this type of functional group.[1] We were intrigued by the potential for asymmetric dihydroxylation of allenes as a novel approach to the synthesis of chiral α-hydroxy ketones. Literature examples of allene oxidation are limited,[2] so we wanted to expand on the generality of the procedure. In addition, we felt that several mechanistic questions[3] might be addressed by analysis of allene dihydroxylation. Finally, although there are a few methods for asymmetric synthesis of α-hydroxy ketones[1,4] and α-hydroxy acid derivatives,[5] there clearly is potential for a new, efficient alternative.

We chose to perform the allene oxidation using the Sharpless asymmetric dihydroxylation (AD) mix. The Sharpless group[6] has rationalized their observed regio and stereoselectivity of alkene dihydroxylation using the AD mix in terms of electronic and steric factors. The unique nature of the allene group may afford an opportunity to evaluate these variables further. Of course, the regioselectivity of oxidation will be a critical factor, since dihydroxylation of the terminal end of a monosubstituted allene will result in an achiral product (see Scheme 1).



Scheme 1. Potential products for monosubstituted allene dihydroxylation.

This report describes the AD reaction of six arylallenes. Each of the allenes was synthesized by addition of ethynylmagnesium bromide to an aryl aldehyde (see Scheme 2). The resulting aryl-substituted propargyl alcohols were reduced using LAH and $AlCl_3$ in an S_N2' fashion.[7] The allenes were purified by chromatography and their spectral data were found to be identical to literature values for each and the new substances were verified spectroscopically.[8] Dihydroxylation of the allenes was then performed using the Sharpless AD mixes (α and β).

Our results are shown in Table 1. In all cases, the major product for the dihydroxylation step resulted from addition of the osmium tetroxide across carbons 1 and 2 of the allenes. Moreover, the enantioselectivity for the oxidation is excellent. The resulting hydroxy ketones were spectroscopically compared with the corresponding known substances and the new compounds were verified by spectroscopic data.[9] The optical rotations for the chiral *R*-hydroxy ketones obtained from allene oxidation using the Sharpless β-AD mix were consistent with chiral column chromatography.[10] The α-AD mix gave the *S*-enantiomers in a slightly lower % ee (78–85% ee). The only undesired product (<5%) in either of the dihydroxylations was the result of over-oxidation of the

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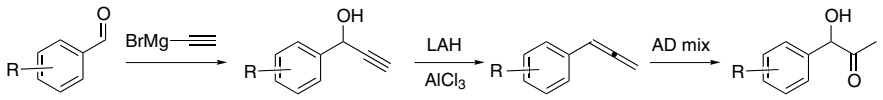


Scheme 2. Synthesis of arylallenes.

Table 1. Percent yield for three steps in synthetic scheme

Ar	Alkynol	Allene	Hydroxy ketone	% Ee[a] (configuration)
Ph–	94	63	45	88 (*R*)
4-MePh–	90	56	49	89 (*R*)
4-MeOPh–	94	58	79	92 (*R*)
4-ClPh–	95	28	58	82 (*R*)
2-MePh–	94	44	52	88 (*R*)
2-Naph–	94	40	63	92 (*R*)

[a] % Ee based on results from β-mix.

α-hydroxy ketone, which produced the 1-aryl-1,2-diketone. This may be a result of simple air oxidation of the benzylic alcohols, an oxidation pathway, which has been previously reported.[11]

A comparison of the yields shown in Table 1 and the preferred regioselectivity found in each oxidation is consistent with a reaction pathway that involves an alkene nucleophile adding to the osmium tetraoxide electrophile (i.e., electronic control). An alternative explanation is that the aromatic pi-system of the arylallene orients itself with respect to the osmium ligand in such a way that the only possible approach for the tetroxide is at the C1–C2 alkene (steric control). We are more inclined to believe that electronic influence is the major contribution to the regioselectivity, which is consistent with the observation that the 4-methoxyphenylallene results in a higher yield of dihydroxylation. In addition, the 2-methylphenylallene does not show any result of steric impact on the dihydroxylation step. One might expect steric control to be sensitive to bulk at the *ortho*-position of the pi-system. Also, the size of the naphthyl group does not adversely effect the selectivity of the dihydroxylation. Pi-stacking is likely the major factor controlling the enantioselectivity observed in this reaction. One would expect the *ortho*-methyl group to reduce the observed % ee due to the nonplanarity of the arylallene. Since no significant reduction was observed, the pi-stacking region must be relatively open.

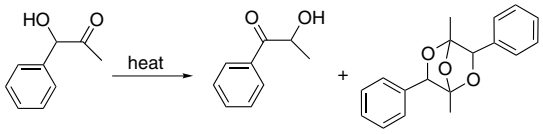
We have optimized the yields for the alkynol and allene steps shown in Scheme 1 and those isolated yields are listed in Table 1. Addition of ethynyl magnesium bromide gives the corresponding alkynol in excellent yield. Formation of the allene by hydride addition is a reliable reaction, but the allenes that are formed in each case are relatively volatile. This fact impacts the yield for the second step of this sequence. Although one could probably use the allene without removal of the solvent, the yields that are reported here are following purification. An additional factor is that the LAH reaction is known to give multiple products.[12] The dihydroxylation procedure was uniformly followed to allow for comparison of the substituent effects. The percent conversion for each run was approximately 90%. Longer reaction times resulted in over-oxidation of the hydroxy ketones. The low isolated yields for the ADH reaction reported in Table 1 may be due to the inefficient recovery of the relatively volatile starting material (yields are not based on recovered starting material) and/or loss of material after the extensive chromatographic effort required to obtain the hydroxy ketone sufficiently pure for determination of optical activity. However, our HPLC analysis of the unpurified ADH reactions using the β-AD mix confirms the enhanced yield for the methoxy substituted allene.

The enantiomeric excess is excellent for these arylallenes, particularly for the β-AD mix. Comparison of the literature values for optical rotations to the values we have obtained and then factoring in our results from chiral chromatography, we can see that the literature rotation for Ar=4-methylphenyl (−385 for the *R*-isomer)[9b] and for Ar=4-methoxyphenyl (−344 for the *R*-isomer)[9c] closely agree with our data. In the case of Ar=4-chlorophenyl our observed rotation (−332) is considerably higher than the literature value.[9d] The rotation we obtained for Ar = 2-methylphenyl is −363 (*c* 0.25, $CHCl_3$) and −101 (*c* 0.08, $CHCl_3$) for Ar=2-naphthyl. We can compare our results with the known procedures for synthesis of 1-hydroxy-1-phenyl-2-propanone (see Table 2). Although our approach does not yield the highest % ee, it does represent a direct route to the α-hydroxy ketone functional group comparable to the other stereoselective methods. The yields for the α- and the β-mixes are similar but the % ee for the reactions was higher for the β-mix in each case. It is interesting to note that this is consistent with the observation Sharpless has made concerning the use of his AD mixes.[6]

Finally, we did not observe enolization nor dimerization of the hydroxy ketones under the conditions of the dihydroxylation. The process shown in Scheme 3 is reported to occur,[13] but only after prolonged time at elevated temperatures. For example, the 1-(4-chlorophenyl)-1-hydroxy-2-propanone reaches equilibrium with the isomer 1-(4-chlorophenyl)-2-hydroxy-1-propanone and its dimer (see Scheme 3) after 168 h at 55 °C. Warren et al. also described the air oxidation of the 1-aryl-1-hydroxy-2-propanone, which produces the same 1,2-diketone that we observed as mentioned above. We have observed a slow degradation of the hydroxy

Table 2. Asymmetric synthesis of 1-hydroxy-1-phenyl-2-propanone

Method (reference)	(%) Yield	% Ee
Oxaziridine addition (4a)	61	95
Enzymatic reduction (4c)	83	86
Allene ADH (this work)	45	88



Scheme 3. Enolization and dimerization of α-hydroxy ketones.

ketones and it appears that this process is an oxidation pathway rather than enolization or dimerization. It does result in loss of optical activity.

In summary, we have established that the asymmetric dihydroxylation of allenes is a suitable method for enantioselective formation of the α-hydroxy ketones. We are continuing to explore the scope of this methodology particularly with respect to the chemistry of disubstituted allenes.

Supplementary material Supplementary data including ^{1}H NMR, ^{13}C NMR, and HRMS is available online with the paper in ScienceDirect.

Acknowledgements

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