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Asymmetric dihydroxylation of disubstituted allenes

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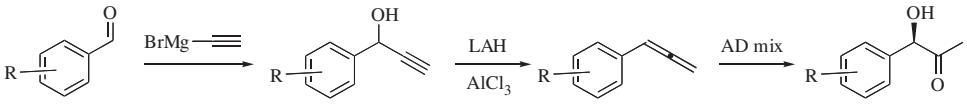
Abstract—Asymmetric dihydroxylation of 1,1-disubstituted and 1,3-disubstituted allenes can be used to synthesize chiral α-hydroxy ketones. We have also obtained α,α′-dihydroxy ketones with high enantioselectivity from 1,3-disubstituted allenes. Low conversion of the dihydroxylation of chiral allenes can be used as a kinetic resolution of sterically hindered allenes.

We recently reported the asymmetric dihydroxylation (AD) of arylallenes as a synthetic methodology for the formation of α-hydroxy ketones.[1] We were impressed by the complete regioselectivity and the high degree of stereoselectivity in the synthesis of chiral α-hydroxy ketones using this methodology (see Scheme 1). This procedure can be considered along with the other methods for asymmetric synthesis of α-hydroxy ketones.[2] Other metal-catalyzed oxidation reactions of allenes have been reported, which lead to racemic α-hydroxy ketones.[3]

In order to determine the utility of this reaction we have explored the AD reaction with disubstituted allenes. We expected that the 1,1-disubstituted allene would be as regioselective as the mono-substituted examples. The fact that the resulting tertiary alcohol would be stereogenic and non-epimerizable was an attractive feature. We also were drawn to the 1,3-disubstituted case because that class of allenes is chiral and there was potential for kinetic resolution using the AD reaction at low conversion. This was intriguing for mechanistic purposes, but it also has significant potential as a method for obtaining optically active allenes.[4]

The synthesis of the 1,1-disubstituted allenes (**1**, **2**, and **3**) shown in Scheme 2 was performed using the same procedure as the mono-substituted allenes reported in our previous paper. That is, ethynyl Grignard was added to the corresponding ketone and the resulting propargyl alcohol was reduced with LAH in an S_N2' fashion.[5]

We found that the S_N2' reaction was successful for formation of allenes **4** and **5** from their corresponding alkynols, which were formed by addition of the anion of 1-octyne to the corresponding aldehydes.[6] The alkyne needed for the synthesis of the *tert*-butyl substituted allene **6** was not readily available, so the procedure of Jiang and Si[7] was used and it gave the necessary propargyl alcohol in good yield. Use of the LAH reaction on the alkynol for the formation of **6** was not successful. Fortunately, reaction with tin hydride under radical conditions as described by McGrath and co-workers gave allene **6**.[8] Synthesis of 1,3-diphenylallene (**7**) using this tin hydride procedure was complicated by undesired by-products. Its synthesis was performed as described by Bergman and co-workers.[9] This method involves an S_N2' addition of a phenyl anion onto the mesylated propargyl alcohol. Although this gives a good yield of



Scheme 1. Dihydroxylation of arylallenes.

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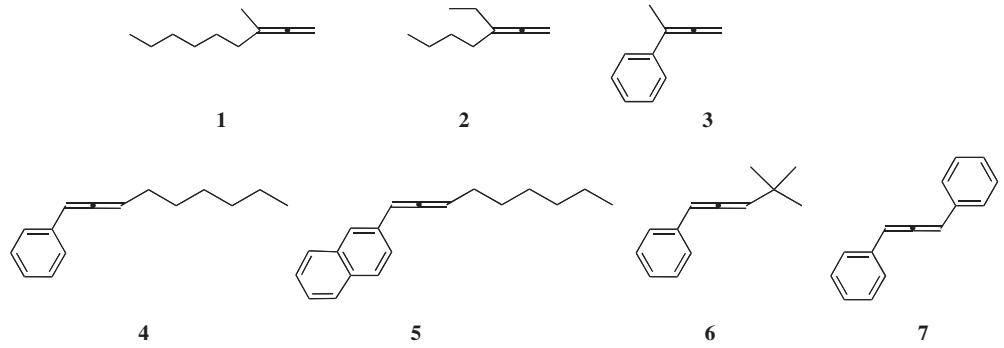


Scheme 2. Allenes **1**–**7**.

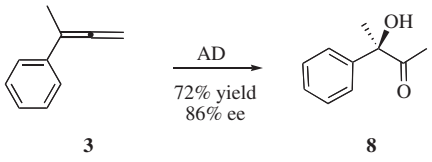
the allene, we have found that this particular allene (**7**) is not very stable.

Our results for the asymmetric dihydroxylation are shown in Table 1. The major product for the dihydroxylation of allenes **1**, **2**, and **3** was the corresponding hydroxy methyl ketone of each. That is, the oxidation occurs regioselectively across the more substituted alkene as expected. The enantioselectivity, however, was not very impressive. We have found that the best % ee for these non-aryl substituted allenes was on the order of 20%, but typically it was much less. The AD was more well behaved in the reaction with 3-phenyl-1,2-butadiene (**3**). In this case the Sharpless β-AD mix gave the tertiary α-hydroxy ketone (**8**) in good yield and excellent enantioselectivity (see Scheme 3). The identity of the resulting hydroxy ketone was verified by spectroscopic data.[10] The enantiomeric excess for the chiral *R* hydroxy ketones obtained from the allenes were determined by chiral column chromatography. The α-AD mix is less selective[1] but does form the enantiomeric α-hydroxy ketone in each case. Both AD mixes are reported to be >95% optically pure.[11] The only undesired product (<5%) for the dihydroxylation of **1** or **2** was the result of over-oxidation, which gave a 1,3-dihydroxy ketone. There was no over oxidation product noted in the AD reaction of allene **3**.

Table 1. Asymmetric dihydroxylation of allenes

Allene	% Recovered allene (% ee)	% Hydroxy ketone	% ee[a] (config)	Over-oxidized products
1	20	29	50 (*R*)	<5
2	19	28	<5	<5
3	<10	72	86 (*R*)	—
4	25 (37)	29	79 (*R*)	25
5	24 (15)	40	89 (*R*)	20
6	18 (99)	40	64 (*R*)	48
7	29 (98)	not obsd	—	60

[a] % ee from β-mix reaction based on Chiracel OD (for alcohols) or chiral shift reagent[12] (for allenes).

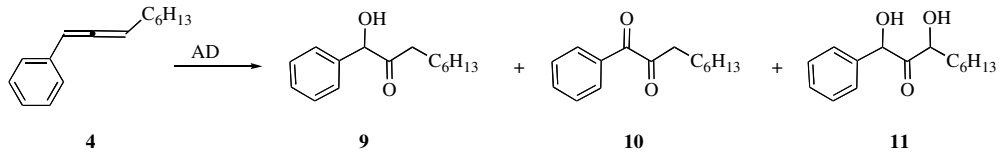


Scheme 3. Asymmetric dihydroxylation of allene **3**.

Dihydroxylation of the 1,3-disubstituted allenes presented an interesting challenge. Our previous experience with aryl substituted allenes led us to believe that we would be able to control the regioselectivity of the oxidation. We expected that the more nucleophilic double bond of the allene would react first. Although our results were consistent with this prediction, we also found numerous over-oxidation products in these examples. Allene **4** gave a good yield of 1-hydroxy-1-phenyl-2-nonanone (**9**).[13] Unless considerable care was taken, the over-oxidized 1-phenyl-1,2-nonadione (**10**) was also obtained. We were familiar with the diketone because it is a minor product in the asymmetric dihydroxylation of the mono-substituted allenes. In addition to compound **10**, however, we also obtained the dihydroxyketone **11** (see Scheme 4). The stereochemical relationship between the hydroxyl groups in diol **11** is not known at this time. The two over-oxidized products are not formed in high yield and several attempts to selectively form the diol in preference to dione **10** have failed. We are continuing to explore the possibility of controlling the formation of two stereocenters with the single step oxidation by intentionally over-oxidizing 1,3-disubstituted allenes with the Sharpless β-mix.

The naphthyl substituted allene (**5**) behaved similarly to the phenyl compound. The major product was the desired α-hydroxy ketone and the over-oxidized products were also observed. Presumably the yields of α-hydroxy ketone formation for the naphthyl compound are better because of the increased π-stacking that exists in the chiral ligand.

We synthesized allene **6** in order to maximize the steric preference for one enantiomer of the allene over the other. It follows that this would allow for kinetic resolution of the allene. Indeed we found that the bulkiness of the *tert*-butyl group was sufficient to stop the oxidation of one of the enantiomers. Even with prolonged reaction times the less reactive enantiomer was only slightly consumed. Instead the additional oxidant reacted to give the further oxidized product of the reactive enantiomer (see Table 2). The major oxidized product was 1-hydroxy-4,4-dimethyl-1-phenyl-2-pentanone.[14]

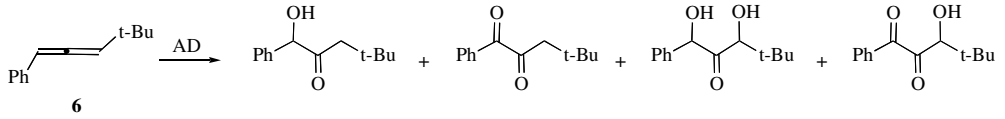


4 9 10 11

Scheme 4. Asymmetric dihydroxylation of 1-phenyl-1,2-nonadiene.

Table 2. Asymmetric dihydroxylation of 4,4-dimethyl-1-phenyl-1,2-pentadiene (**6**)

Amount of oxidant	AD mix	% Allene (% ee)	% α-Hydroxy ketone (% ee)	% α,α′-Dihydroxy ketone (% de)	3-Hydroxy pentanedione (% ee)
0.004 equiv Os	β	29 (59)	15 (<5)	12 (34)	6 (54)
0.008 equiv Os	β	18 (>99)	40 (64)	28 (53)	20 (34)
0.008 equiv Os	α	11 (>94)	20 (45)	10 (21)	9 (10)



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Scheme 5. Asymmetric dihydroxylation of 1-phenyl-4,4-dimethyl-1,2-pentadiene.

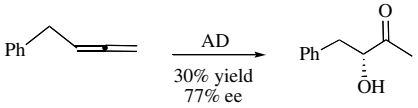
This α-hydroxy ketone was isolated at best in yields around 40%, consistent with the selective reaction with only one enantiomer of the allene (see Scheme 5). The electron rich aryl-substituted alkene was the more reactive site. We also obtained trace amounts of the 1,2-pentanedione and the 1,3-dihydroxy-2-pentanone as in the AD reaction of allenes **4** and **5**. A fourth product isolated in this reaction was 3-hydroxy-4,4-dimethyl-1-phenyl-1,2-pentanedione.

We were pleased to find that the Sharpless AD mixes were able to resolve the sterically hindered allene **6**. When the reaction was performed with a limiting amount of oxidant, the recovered allene was found to be nearly pure enantiomer (see Table 2). Using the AD β-mix results in recovery of the *R* enantiomer of **6** and the α-mix allows isolation of the *S* enantiomer.[8b] The kinetic resolution of allenes has been reported previously.[15] Few examples exist that compare to the procedure we report here. Although utility is limited since we were unable to perform complete kinetic resolution on allenes **4** or **5** using this methodology. The enantiomeric enrichment of unreacted allene, when the oxidant was the limiting reagent, was typically <40% for these allenes.

We were intrigued by the possibility of resolving 1,3-diphenyl-1,2-propadiene (**7**), we expected that the chiral environment would be very selective for this compound. The limited solubility and the inherent instability of this compound made it more challenging to find the best conditions for asymmetric dihydroxylation, but we were finally successful in obtaining an excellent kinetic resolution of the chiral diphenyl allene. The best results were obtained when the reaction was run at 0 °C and to 70% conversion. The recovered allene was obtained in 98% ee as shown by HPLC analysis.

In light of the poor reactivity of the alkyl substituted allenes **1** and **2** with the AD mixes, we chose to extend the survey of mono-substituted allenes. We examined the reactivity of 1,2-octadiene and 4-phenyl-1,2-butadiene.[16] The results of the octadiene were consistent with the other alkyl substituted allenes. Very poor enantioselectivity was observed in the formation of 3-hydroxy-2-octanone (28% yield, 58% ee). But much to our surprise, the benzyl substituted allene gave very good enantioselectivity of 3-hydroxy-4-phenyl-2-butanone (see Scheme 6).[17] This single result does more to clarify the selectivity of the Sharpless reagent than any of the 14 other allenes we have studied. It is apparent that there is a π-stacking component to the phthalizine and/or quinoline substrates of the AD mix that facilitates the oxidation process. Although we previously argued this fact, we also felt that the styryl nature of the phenyl substituted allenes was a major factor. But this result indicates that although a stabilized carbocation helps in the yield of dihydroxylation, it is not essential for an enantioselective reaction.

In summary, we have established that the asymmetric dihydroxylation of allenes is a suitable method for enantioselective formation of α-hydroxy ketones. We have explored the scope of this methodology with respect to 1,1-disubstituted and 1,3-disubstituted allenes. We also have found that AD can be used for kinetic resolution of sterically hindered allenes.



Scheme 6. Asymmetric dihydroxylation of 4-phenyl-1,2-butadiene.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.138.

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14. Spectral data for 1-hydroxy-4,4-dimethyl-1-phenyl-2-pentanone are: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (9H, s, $3CH_3$), 2.24 (2H, ABq, $J = 15.5$ Hz, CH_2), 4.43 (1H, d, $J = 4$ Hz, OH), 5.02 (1H, d, $J = 4$ Hz, CH), 7.26–7.38 (5H, m, Ar); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 209.03, 131.64, 130.41 (2C), 129.28 (2C), 128.83, 80.85, 50.19, 31.48, 29.82 (3C); HRMS calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1310; HPLC 64% ee (Chiracel OD; 10% isopropyl alcohol in hexane; 1 ml/min) $t(R) = 6.06$ min $t(S) = 7.25$ min.
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