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Asymmetric Hydrogenation of Acyclic Enol Esters

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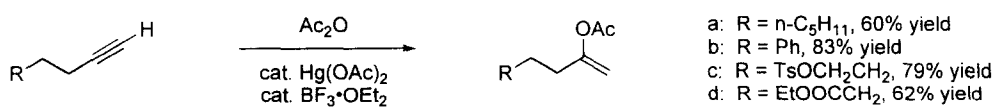
Abstract: High enantioselectivity has been observed for the catalytic asymmetric hydrogenation of enol esters bearing a vinylic (≥94% ee) or acetylenic (>97% ee) substituent using a rhodium-chiral bisphosphine catalyst. This is at variance with the hydrogenation of enol esters bearing a saturated substituent, which are hydrogenated with only moderate enantioselectivity under the same conditions.

The preparation of esters of chiral alcohols by the enantioselective asymmetric hydrogenation of enol esters has been reported for a variety of systems.[1,2] Although products with high enantiomeric purity were obtained in some cases (especially if there were conformational restraints such as in cyclic enol ester substrates),[1b,e] in general enol ester hydrogenations proceed with moderate enantioselectivity. A notable exception involved the use of a rhodium(I) catalyst which was complexed with a DuPHOS bis-phospholane ligand.[2] In this case the asymmetric hydrogenation of enol esters with varying substituents afforded the product saturated esters in high optical purity. However, the substrates had significant steric differentiation, and in no cases afforded simple straight-chain alcohol derivatives.

Saturated alcohol derivatives are in themselves not particularly attractive targets for asymmetric catalysis, as they have limited utility for further transformations. Allylic alcohol derivatives, however, are significantly more desirable, since the olefin imparts diverse synthetic potential by either direct or remote functionalization. We report here the preparation of allylic alcohol derivatives in high enantiomeric purity by the asymmetric hydrogenations of both dienyl and especially enynyl esters and compare these results with the corresponding hydrogenations of simple enol esters.

The asymmetric hydrogenations of acyclic enol esters with saturated substituents were investigated first to understand the inherent enantioselectivity. Several simple enol acetates **2a-d** were prepared by reaction of the corresponding acetylene **1** with acetic anhydride in the presence of catalytic amounts of mercuric acetate and boron trifluoride etherate.[3]



1 **2**

a: R = n-C_5H_{11}, 60% yield
b: R = Ph, 83% yield
c: R = $TsOCH_2CH_2$, 79% yield
d: R = $EtOOCCH_2$, 62% yield

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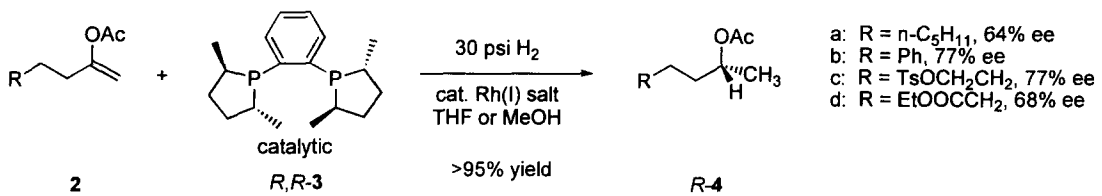
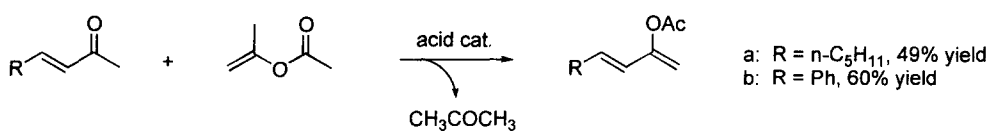
The asymmetric hydrogenations of these enol acetates were performed at ambient temperature under approximately 30 psig of hydrogen, with identical results obtained using either methanol or tetrahydrofuran as the solvent.[4] The catalyst was a rhodium(I) species prepared *in situ* from bis(1,5-cyclooctadiene)-rhodium(I) tetrafluoroborate and the methyl DuPHOS ligand *R,R*-**3**. This bis-phospholane was chosen because that type of ligand afforded clearly superior results for the hydrogenations of other enol esters.[2] The hydrogenations proceeded rapidly (<2 h) and cleanly to afford the saturated acetate in high yield (>95%) but with only poor to moderate enantioselectivity. For example, *R*-**4a**[5] was obtained in a disappointingly low 64% ee[6] from the hydrogenation of **2a**. Similarly poor enantioselectivities were obtained with various substituents on the aliphatic chain, including *R*-4-phenyl-2-butyl acetate[7] (*R*-**4b**, 77% ee from 4-phenyl-1-buten-2-yl acetate [**2b**]),[6] 5-acetoxyhexyl tosylate (**4c**, 77% ee from 5-acetoxy-5-hexenyl tosylate [**2c**]),[8] and ethyl 5-acetoxyhexanoate (**4d**, 68% ee from ethyl 5-acetoxy-5-hexenoate [**2d**]).[6]



2 *R,R*-**3** *R*-**4**

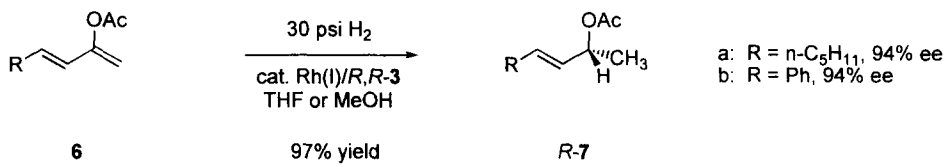
This poor enantiotopic discrimination was not a result of simply a poorly matched catalyst, as substituting the *R*-BINAP ligand for **3** in this case led to a significantly lower enantioselectivity (32% ee) for the hydrogenation of **2d**. It appeared instead that a saturated alkyl substituent was detrimental to this particular transformation. Thus the target of investigation shifted to the desired dienyl ester systems **6**, in the hope that the olefinic portion of the substituent would provide better enantiodiscrimination than the corresponding methylene units of the saturated derivative. The most satisfactory preparation, albeit in moderate yield, of these dienyl acetate substrates (apparent single *E* isomer according to ^{1}H NMR coupling constants) involved acid-catalyzed enolization of the corresponding enone **5** and capture of the enol with isopropenyl acetate.[9]



5 **6**

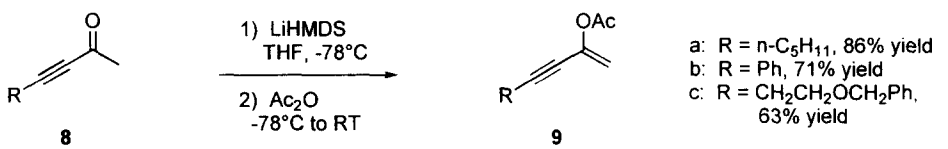
The asymmetric hydrogenations of *E*-dienyl acetate substrates **6** were performed in the same manner as the reactions with enol acetates **2**.[4] It was gratifying to find that the reactions of **6**, while proceeding in the same configurational sense as for **2**, afforded greatly enhanced enantioselectivities. For example, the catalytic asymmetric hydrogenation of *E*-1,3-nonadien-2-yl acetate (**6a**, a direct analog of **2a**) under standard conditions afforded *R*-*E*-3-nonen-2-yl acetate[5] (**7a**) of 94% ee,[6] a greatly improved enantioselectivity as compared to **4a** from **2a** (64% ee). This high enantioselectivity was not limited to this particular substrate, as indicated by the

catalytic asymmetric hydrogenation of *E*-4-phenyl-1,3-butadien-2-yl acetate (**6b**), which afforded *R*-*E*-4-phenyl-3-buten-2-yl acetate[7] (**7b**) in 94% ee[6] (as compared to 77% ee for hydrogenation of the saturated analog **2b**).



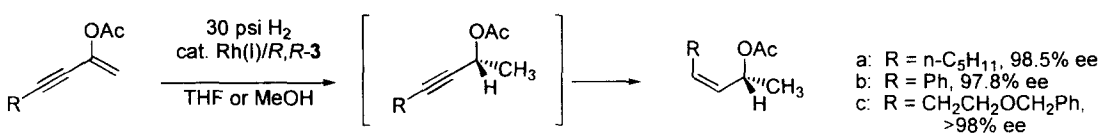
6 97% yield *R*-**7**

The source of the improved enantioselectivities observed with the additional unsaturation was not completely clear. Possible explanations include a reduced substrate steric size close to the metal center or an additional or alternative substrate binding site (the distal olefin) with the metal. The investigation of the asymmetric reduction of a substrate with an acetylenic substituent such as that in enynyl ester **9** would provide an interesting comparison. Certainly this type of substituent would have even smaller steric size than the olefinic substituent, while the potential binding geometry of the acetylene would be significantly different than the allylic olefin of **6**. The enynyl acetates **9** were prepared from the corresponding α,β-acetylenic ketones **8** by enolate formation followed by capture with acetic anhydride.



8 **9**

Under the standard asymmetric hydrogenation conditions[4] a bimodal reduction was observed, initially affording propargylic acetate **10** which was subsequently further reduced to afford the *Z*-allylic acetate **11** (olefin configuration determined by ^{1}H NMR coupling constants). The sense of asymmetry was the same for these reactions as for those with the enol and dienyl acetates, but the enantioselectivity observed in this reduction was extraordinarily high, and is apparently general for substrate structural type **9**. For example, non-1-en-3-yn-2-yl acetate (**9a**) was hydrogenated to *R*-*Z*-non-3-en-2-yl acetate (*R*-**11a**)[5] in 98.5% ee,[6] 4-phenyl-1-buten-3-yn-2-yl acetate (**9b**) was hydrogenated to *R*-*Z*-4-phenyl-3-buten-2-yl acetate (*R*-**11b**)[7] in 97.8% ee,[6] and 6-benzyloxyhex-1-en-3-yn-2-yl acetate (**9c**) was hydrogenated to *Z*-6-benzyloxyhex-3-en-2-yl acetate (**11c**) in >98% ee.[6]



9 >97% yield **10** **11**

The intermediacy of **10** was determined by halting the hydrogenation of **9b** at early reaction times. In this case, **10b** was the sole product observed, and was obtained with the same enantioselectivity as **11b**. These results demonstrated two important points with regard to this transformation. First, the enantioselectivity of the asymmetric reduction followed a trend of $sp > sp^2 > sp^3$ for the carbon next to the reacting olefin, a trend which matches the size of the substituent. Second, the slow reduction of the triple bond compared to the enol olefin indicates that the latter likely preferentially complexes to the metal center.

Thus we have found that enynyl esters are preferred substrates for asymmetric hydrogenation using a Rh-DuPHOS catalyst, affording products with extremely high (>97% ee) enantiomeric purities. These substrates are reduced with greater enantioselectivity than the corresponding olefinic and especially saturated species. This type of substrate is more versatile as well, since by choice of reaction conditions it can afford either a propargylic or allylic acetate as the product. Either of these species can be transformed into a number of useful materials.

References and Notes

1. (a) Koenig, K. E.; Bachman, G. L.; Vineyard, B. D. *J. Org. Chem.* **1980**, *45*, 2362. (b) Selke, R.; Pracejus, H. *J. Mol. Cat.* **1986**, *37*, 213. (c) Brown, J. M.; Murrer, B. A. *J. Chem. Soc. Perkin Trans. 2* **1982**, 489. (d) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491. (e) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Tayaka, H. *J. Org. Chem.* **1995**, *60*, 357.
2. Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518.
3. Hrudlik, P. F.; Hrudlik, A. M. *J. Org. Chem.* **1973**, *38*, 4254.
4. All of the asymmetric hydrogenations were performed under the same conditions. A typical procedure is exemplified for the preparation of **11a**. Bis(cyclooctadienyl)rhodium tetrafluoroborate (10 mg; 0.025 mmol; 0.02 equiv)) and *R,R*-MeDuPHOS (*R,R*-**3**, 9 mg; 0.03 mmol; 0.024 equiv) were combined in a pressure tube under argon. The tube was evacuated and filled with argon five times and degassed THF (5 mL) was added to afford a yellow-orange solution. Enynyl acetate **9a** (225 mg; 1.25 mmol) dissolved in 5 mL of degassed THF was then added. The reaction mixture was evacuated and filled with argon five times and then evacuated and filled with hydrogen three times. The reaction mixture was placed under 30 psi of hydrogen and stirred until hydrogen uptake had ceased (2 h). The vessel was vented and flushed with nitrogen, and the reaction mixture was concentrated to afford 0.26 g of the crude **11a**. The enantiomeric excess of the product (98.5% ee) was determined without further purification.
5. The absolute configuration was determined by correlation with *R*-2-nonanol: Mori, K.; Ogita, H. *Leibigs Ann. Chem.* **1994**, 1065.
6. The enantiomer ratio was determined by chiral capillary GC using a Cyclodex-B column (J&W Scientific).
7. The absolute configuration was determined by correlation with *R*-4-phenyl-2-butanol: Burgess, K.; Jennings, L. D. *J. Am. Chem Soc.* **1991**, *113*, 6129.
8. The enantiomer ratio was determined by deacetylation and derivatization to the MTPA ester followed by ^{1}H NMR analysis: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
9. Karlsson, J. O.; Frejd, T. *J. Org. Chem.* **1983**, *48*, 1921.