Deracemization of Cyclic Allyl Esters

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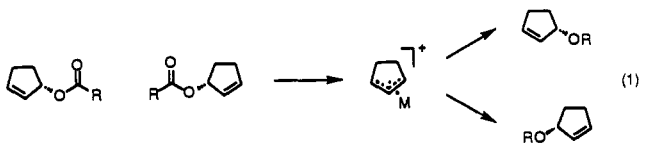
Obtention of enantiomerically pure compounds has grown in importance by the focus on using pure enantiomers for biological purposes rather than racemates. Methods to achieve this aim utilizing abiological or biological catalysis wherein only a truly catalytic amount of an asymmetric agent is required represent the most desirable solutions. Among targets of practical significance stand allyl alcohols because of their importance as building blocks *via* numerous reactions exemplified by Claisen rearrangements,[1] cuprate coupling,[2] epoxidations,[3] and various cycloadditions.[4] Asymmetric reduction of simple cycloalkenones has not been shown to be generally useful.[5] Base-"catalyzed" opening of epoxides requires a stoichiometric amount of "catalyst" and also shows an *important* dependence on ring size.[6] Kinetic resolutions of cycloalkenols by either transition metal[7] or enzymatic catalysis[8] suffer from a theoretical yield of 50%. Amino alcohol catalyzed additions of stoichiometric organozinc compounds to aldehydes appear promising.[9] We wish to record a new strategy for the preparation of cycloalkenols of high ee by the deracemization of the corresponding esters.

The achievement of a catalytic deracemization of a racemic chiral allylic ester mandates its conversion to an achiral intermediate which will become chiral only in a chiral environment. A π-allyl metal complex constitutes such an intermediate in which chirality is reintroduced by selective attack by an oxygen nucleophile at one of the allylic termini as shown in eq 1. The



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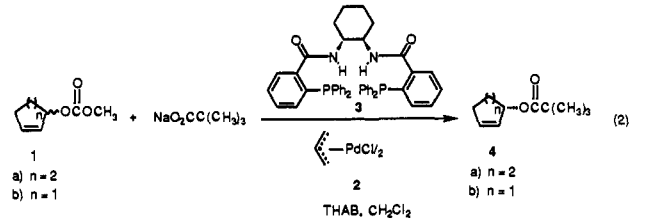
question of the appropriate oxygen nucleophile becomes critical. While a siloxide[10] or a carboxylate[11] would be ideal because of their ease of subsequent manipulation, they have only served as nucleophiles in the Pd(0)-catalyzed reactions of vinyl epoxides, not in simple substitutions.[12] Of the two, the carboxylate appeared preferable since the resultant esters are frequently the derivative of the allyl alcohol actually desired. The problem to be overcome is the differential rate of reaction of the starting ester compared to the product ester since, to the extent to which the product serves as a substrate, it ultimately will be equilibrated to the racemate. Thus, this approach envisions a kinetic trapping of the achiral π-allyl metal unit. The problem is more severe than it appears at first glance since the chiral nonracemic ligand forms a matched and a mismatched pair with the racemic substrate but only a matched pair with the initial product. Thus, the rate of reaction of the mismatched pair of the substrate must be significantly greater than that of the matched pair of the product.

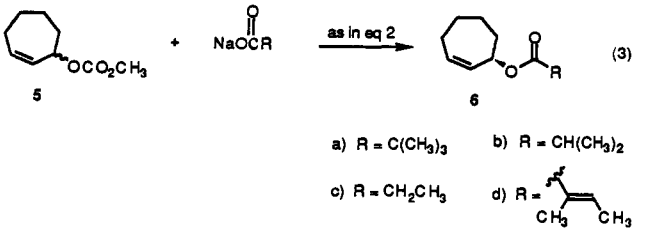
We initially chose the methyl carbonate of cyclohexen-3-ol (**1a**) and sodium pivalate with the notion that a bulky carboxylate would fix the conformation of the product wherein this substituent was pseudoequatorial thereby disfavoring its rate of ionization. Under our standard conditions of 2.5 mol % π-allylpalladium chloride dimer (**2**), 7.5 mol % chiral ligand **3**,[13] 1.3 equiv of tetrahexylammonium bromide (THAB),[14] and 1.3 equiv of sodium pivalate (generated *in situ* from 1.3 equiv of NaH and 1.6 equiv of pivalic acid) in methylene chloride, the reaction of carbonate **1a** gave a 94% yield of pivalate **4a**[15] of 91% ee, which increased very slightly to 92% ee at −20 °C (eq 2). The reaction was sluggish



(2)

at temperatures below −25 °C. The five-membered-ring substrate **1b** (eq 2) showed a more dramatic temperature effect. Remarkably, the reaction proceeds readily even at −78 °C, at which temperature a 91% yield of pivalate **4b**[15] of 97% ee was obtained. The ee fell to 80% at −72 °C.

The choice of ester, specifically the exploration of any special requirement of pivalate, was explored in the context of the seven-membered-ring substrate **5** (eq 3). Systematic variation of the



(3)

steric bulk of the R group of the carboxylate by replacing methyl by hydrogen (i.e., pivalate to isobutyrate to propionate) revealed

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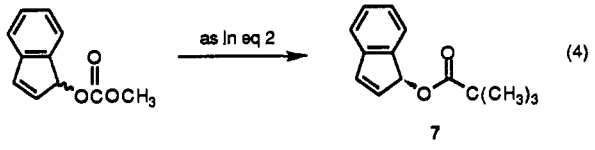
no correlation with steric size (eq 3). Esters **6a**, **6b**, and **6c**[15] were obtained in ee's of 98% (76–98% yield), 94% (94% yield), and 98% (91% yield) with reactions being performed at ambient temperature. It appears that any carboxylate is a satisfactory nucleophilic partner. To illustrate diversity and synthetic application, an unsaturated carboxylate, tiglate, was employed with excellent results (eq 3, **6d**,[15] 95% ee, 84% yield). The resultant product is primed for conjugate addition–*in situ* Claisen rearrangement.[16]

The presence of indane units in drug candidates such as an AIDS protease inhibitor[17] induced us to explore the indenyl system. Following the standard protocol, indenyl pivalate (**7**)[15] was obtained in 91% yield and 98% ee (eq 4).



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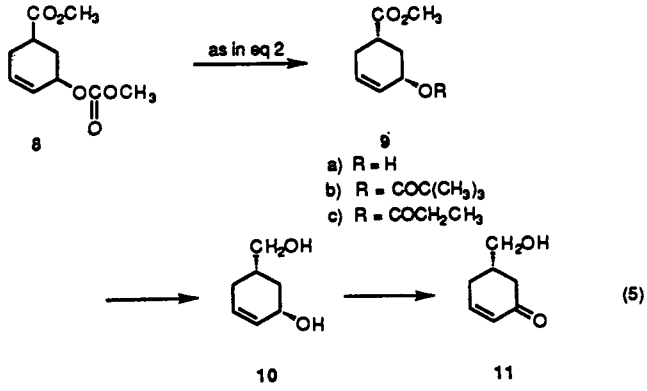
The hydroxy ester **9a** has served as an important building block in the synthesis of bioactive natural products exemplified by the antitumor agent phyllanthocin[18] and the insect sex excitant periplanone B.[19] A variety of approaches for its synthesis in enantiomerically enriched form has been employed,[20] with the most successful involving an initial asymmetric Diels–Alder reaction using stoichiometric chiral auxiliaries.[18,19] Following the standard protocol, deracemization of the *cis* allylic carbonate **8** with sodium pivalate gave **9b**[15] in 93% ee (98% yield), which



(5)

8 **9** **10** **11**

increased to 98% ee (95% yield) with sodium propionate forming **9c**.[15] The corresponding hydroxy ester **9a** served as approximately one-half of phyllanthocin.[18] Reduction (LAH, THF, 99% yield) to **10**[19,20] and chemoselective oxidation of the allylic hydroxyl group (MnO_2, CH_2Cl_2, 82% yield) gave the periplanone B building block **11**.[19,20] For all cases, the ee's were established by NMR using a chiral shift reagent [(Eu(hfpc)$_3$] and correlation to known products.

In considering enzymatic processes, enzymes bring both chiral recognition and enhanced kinetics to bear on the chemical reaction. These amide ligands impart similar behavior to the Pd(0) templates they form with **1**. As already noted, the cyclopentenyl substrate reacted at –78 °C in less than 20 min. This reactivity may be contrasted with an achiral ligand like 1,2-bis(diphenylphosphino)ethane, which failed to effect reaction (eq 2 but achiral ligand to give racemic product) with sodium pivalate at room temperature or even above. On the other hand, adding a racemic mixture of ligand **3** to the above reaction at room temperature led to virtually instantaneous reaction to racemic product. Thus, both rate enhancement and chiral recognition characterize this transition metal catalyzed reaction, justifying drawing a parallel to enzymatic processes. As the results demonstrate, formation of the ester by alkyl–oxygen bond formation rather than acyl–oxygen bond formation removes the problem of steric hindrance associated with the carboxylic acid in the normal esterifications. The required difference in reactivity between ester substrate and ester product toward these catalysts appears to be independent of structure of the allyl or carboxylate units. Thus, any carboxylic acid should function well. However, it is necessary to monitor time and sometimes temperature to minimize racemization. The temperature effect on the cyclopentyl substrate appears to result from racemization of product, an effect not noted in six- and seven-membered-ring cases. In contrast to other strategies, ring size plays no role with five-, six-, and seven-membered-ring substrates giving equally high ee's. This new method should prove a useful approach for the asymmetric synthesis of cyclic allylic alcohols and esters.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs and NSERC (Canada) for a fellowship for partial support of M.G.O. Mass spectra were provided by the Mass Spectrometry Facility, University of California—San Francisco, supported by the NIH Division of Research Resources.

Supplementary Material Available: A representative experimental procedure and characterization data for **4a,b**, **6a–d**, **7**, and **9b,c** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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