Pure & Appl. Chem., Vol. 68, No. 4, pp. 779–784, 1996.
Printed in Great Britain.

Asymmetric introduction of heteroatoms

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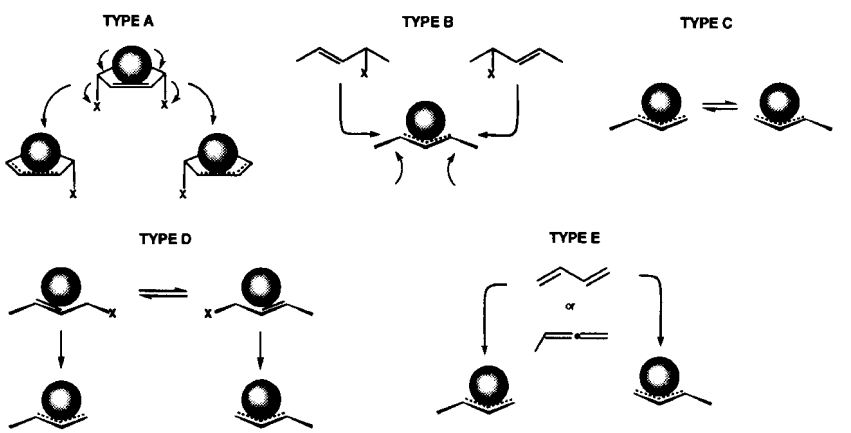
Abstract: Selective introduction of heteroatom substituents represents one of the continuing challenges for new methodology. Asymmetric introduction of oxygen, nitrogen, and sulfur substituents via palladium catalyzed allylic alkylations becomes possible in three different ways—1) desymmetrization of meso-2-ene-1,4-diol diesters, 2) deracemization of allylic esters via meso η^3-allyl intermediates, and 3) deracemization of an unsymmetrical allyl system wherein racemization occurs via an η^3-η^1-η^3-isomerization mechanism. Applications of this methodology have resulted in numerous total syntheses including asymmetric syntheses of pancratistatin, carbanucleosides, nucleosides, amino acids, phyllanthocin, and vinylglycinol among others.

Heteroatom substituents represent critical adornments on carbon skeleta to impact function and to serve as selectivity control agents. Their introduction in diastereo- and enantiocontrolled fashion represents a continuing important challenge. Enantioselective introduction of oxygen and nitrogen via epoxidation, dihydroxylation, aziridination etc. via asymmetric catalysis which involve additions to prochiral alkenes has proven to be increasingly important. Palladium catalyzed allylic alkylations embraces substitution chemistry as an approach for asymmetric introduction of heteroatoms.

The applicability of asymmetric allylic alkylation requires a symmetrization pathway to simply avoid effecting a kinetic resolution which limits the chemical yield to 50%. Five strategies achieve such a goal (see Scheme 1). The first approach differentiates between enantiotopic leaving groups (type A). The second involves conversion of chiral allylic isomers to meso-η^3-allylpalladium complexes wherein asymmetric induction involves preferential addition to one of the two enantiotopic termini (type B). A third approach invokes kinetic discrimination between interconverting enantiomeric η^3-allyl complexes (type C). Alternatively, discrimination in complexation of enantiotopic faces of an alkene either by ionization (type D) or by addition of a proton to a prochiral 1,3- or 1,2-diene may generate one of the two enantiomeric complexes (type E). These latter two types of chiral discrimination can revert to a type C case.



Scheme 1. Displacement Strategies for Asymmetric Introduction of Heteroatoms

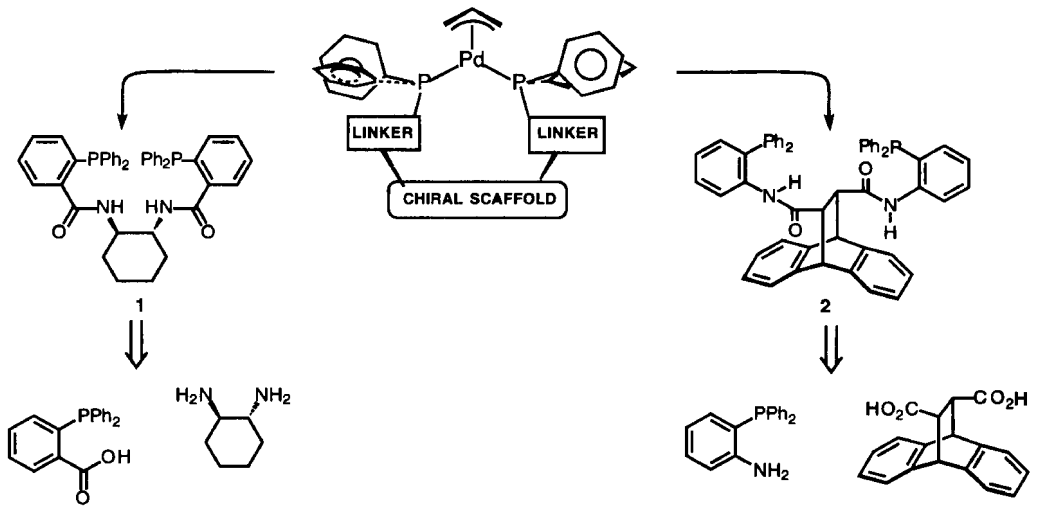
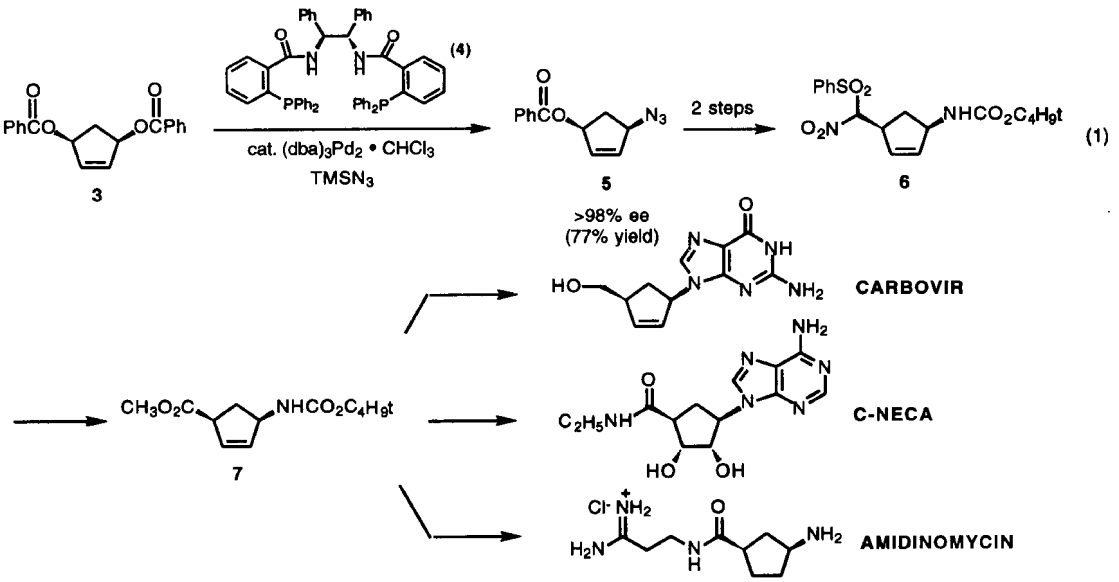


Figure 1. Model for Ligand Design

Asymmetric induction of types A, B, and C require transmitting stereochemical information from one face of a η^3-allyl unit to the other—i.e. distal to the asymmetric inducing moieties, the chiral ligands. The concept of a chiral pocket evolved to transmit stereochemical information for such cases. The design illustrated in Figure 1 borrowed a general concept from enzymes in which primary chirality (i.e. stereogenic centers) create "chiral space" by inducing conformational chirality. In the case of metal coordination, the primary chirality of a scaffold is converted into conformation chirality of a bidentate ligand defined by the edge-face conformation of a diarylphosphino moiety.[1,2] In this way, two platforms emerged. In the first,chiral C_2 symmetric diamines (or diols) are converted into diamides (or diesters)[2] with 2-diphenylphosphinobenzoic acid illustrated by diamide **1**. In the second, chiral C_2 symmetric diacids are converted into chiral diamides with 2-diphenylphosphinoaniline illustrated by diamide **2**.[3]

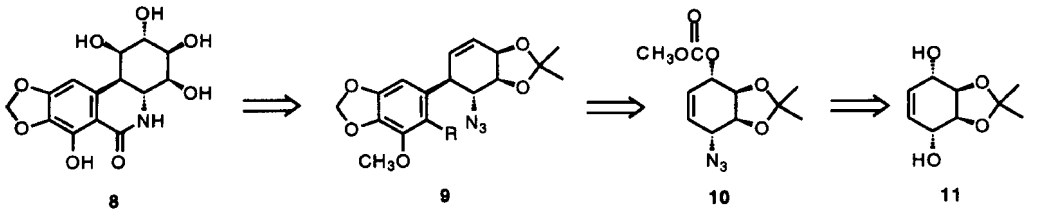
Desymmetrization of Meso-Diesters

The dibenzoate **3** undergoes smooth alkylation with an azide source in the presence of diamide **4** to introduce a nitrogen in the form of the very versatile azide as in **5** with >98% ee (eq 1)[4]. For example, it is chemoselectively reduced to the amine which is immediately protected as its t-BOC derivative. Palladium catalyzed allylic alkylation permits replacement of the second benzoate with



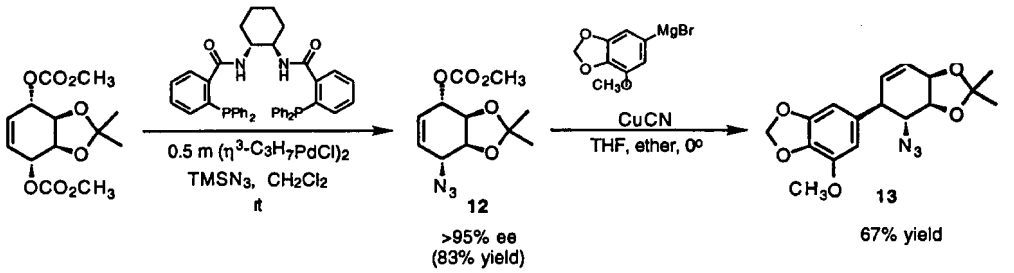
complete regio- and diastereo- (with retention of configuration!) selectivity to give the very versatile intermediate **7** which serves as an important building block for the synthesis of carbanucleosides, the coronary vasodilator C-NECA, and the antiviral agent amidinomycin among others.

The promising anti-tumor agent (+)-pancratistatin (**8**) represents a challenging target for diastereo- and enantioselective introduction of heteroatoms. Equation 2 illustrates a retrosynthetic analysis in which the alkene **9** can be readily envisioned to derive from lactamization and *trans*-



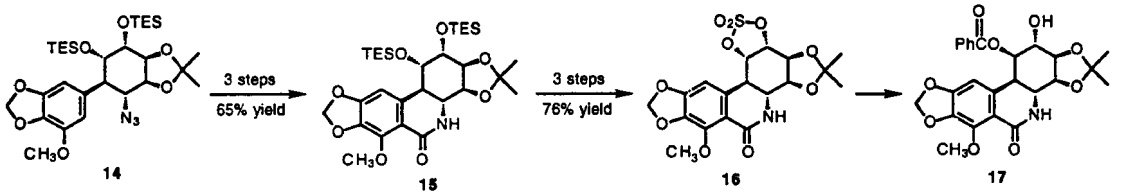
8 9 10 11 (2)

dihydroxylation for conversion into the target **8**.[5] The regio- and diastereocontrolled introduction of the aryl group from an allylic ester as in **10** can be envisioned via organocuprate chemistry. Desymmetrization of a diester derived from the well-known and readily available diol **11** (69% overall yield from benzoquinone) becomes an obvious route. Equation 3 outlines the realization of two key steps—the desymmetrization and arylation. It is noteworthy that the the dicarbonate gives enantiopure azide **12** in this substituted case—given the earlier work on the unsubstituted ring systems wherein dibenzoates were required as leaving groups for high ee's.



(3)

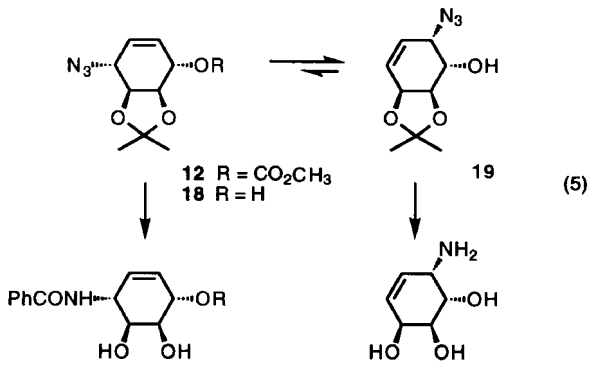
Using straightforward chemistry, the diol **14** as its bis TES ether readily derives from alkene **13**. A novel new lactamization protocol involves conversion of the azide to its isocyanate followed by *in situ* metal-halogen exchange to generate the aryllithium to give **15**. The final stage requires conversion of the



(4)

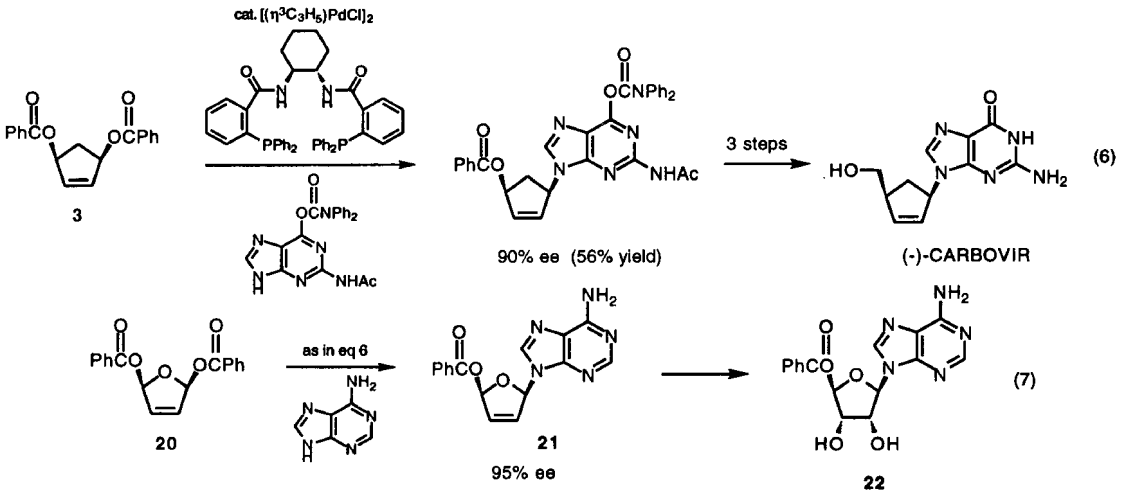
1-isopancratistatin stereochemistry to that of pancratistatin which involves an inversion of configuration. Although unusual in the present case since it involves a *trans* diequatorial ring opening of a cyclic sulfate if proceeding via a chair conformation, it proceeds completely regioselectively to the benzoate **17** which is readily deprotected to the natural product.

A special advantage of the azide **12** is its ability to participate in a [3.3] sigmatropic rearrangement. If the carbonate is hydrolyzed at 80^0, a 7-8:1 ratio of **19** to **18** is obtained. Thus, from the one desymmetrization either regioisomeric allylic azide is available. In the present instance, the initial azide serves as a precursor to conduramine A; whereas, that derived from the thermal isomerization leads to conduramine E.



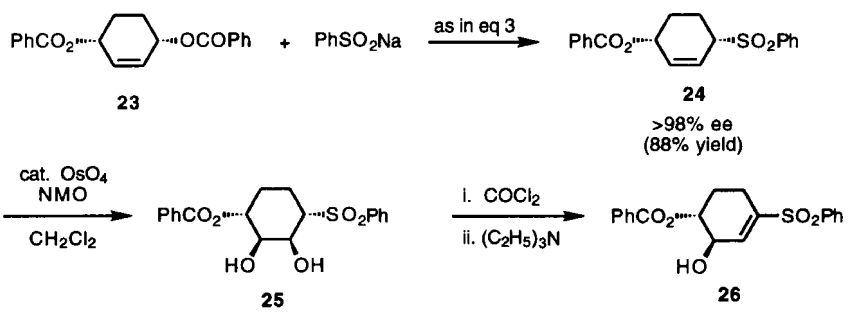
N-BENZOYLCONDURAMINE A-1 CONDURAMINE E

Many nitrogen nucleophiles ranging from simple amines to heterocycles may be employed in this desymmetrization. Of particular value are the purines and pyrimidines which provide entries to nucleosides and their analogues. For example, a four step synthesis of (-)-carbovir from dibenzoate **3** becomes possible.[6] The availability of the *cis*-dibenzoate **20** by direct oxidation of furan leads to a



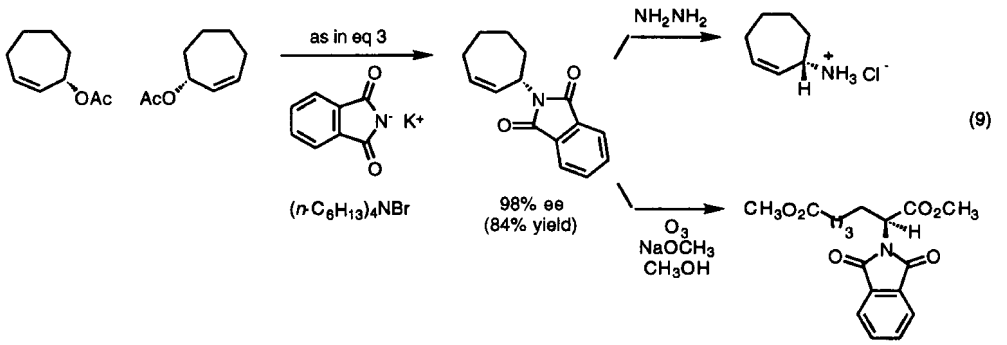
protocol for the synthesis of nucleosides and their analogues. Using adenine as the pronucleophile, the alkylation product **21** is available in >95% ee.[7] Simple diastereoselective cis-hydroxylation of **21** provides a synthesis of the nor-adenosine **22** in only three steps from furan.

Other heteroatoms may be introduced with equal enantioselectivity since, to a first approximation, the enantiorecognition is independent of nucleophile. The sulfinate anion proves to be quite interesting in light of the use of allylsulfones in synthesis.[8] Desymmetrization of the dibenzoate **23** produces the sulfone **24** with >98% ee. Diastereoselective dihydroxylation to **25** followed by elimination transfers the chirality in an allylic fashion to produce the enantiomerically pure trans-diol derivative **26**.



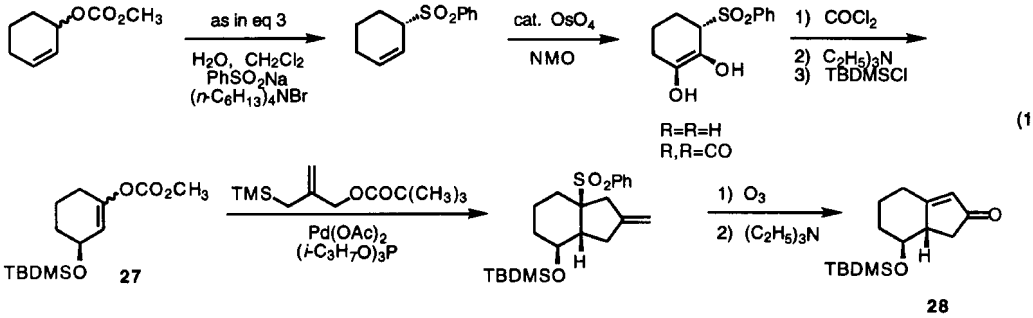
Deracemization of Allylic Esters

Since η^3-allylpalladium complexes are meso, racemic allylic esters may undergo allylic alkylation to form enantioenriched products (type B asymmetric induction). Using phthalimide as nucleophile, smooth alkylation occurs to give the allylic product in excellent ee as illustrated for the case of a seven membered ring substrate (eq 9).[9] Hydrazinolysis produces the allylic amines; whereas, ozonolysis provides access to unusual amino acids.



(9)

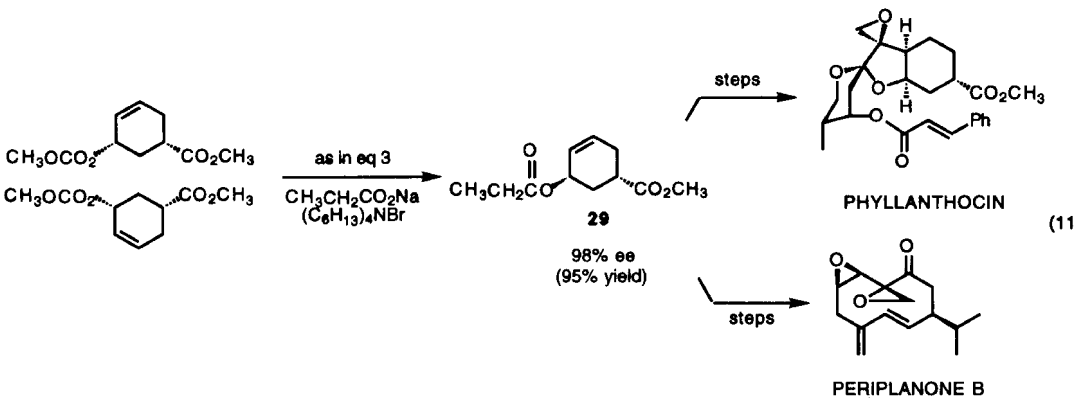
Unlike type A asymmetric induction, the involvement of the nucleophile in the enantiodiscriminating step may make its nature quite important in determining the ee. Remarkably, the nature of the anion, which ultimately becomes bonded to the allylic unit in the product, is less important than the cation. Equation 10 illustrates the use of a sulfinate anion in the presence of the tetrahexylammonium cation giving the allylic sulfone in 98% ee.[8] Once again, transfer of the chirality from the carbon bearing the sulfone to those of the double bond by diastereoselective *cis*-dihydroxylation followed by dehydration provides the enantiomerically pure γ-hydroxy-α,β-unsaturated



(10)

sulfone **27**, very versatile asymmetric building blocks. As one illustration, cycloaddition via TMM-PdL_2 followed by ozonolysis creates an asymmetric synthesis of the polyhydroindenone **28**.

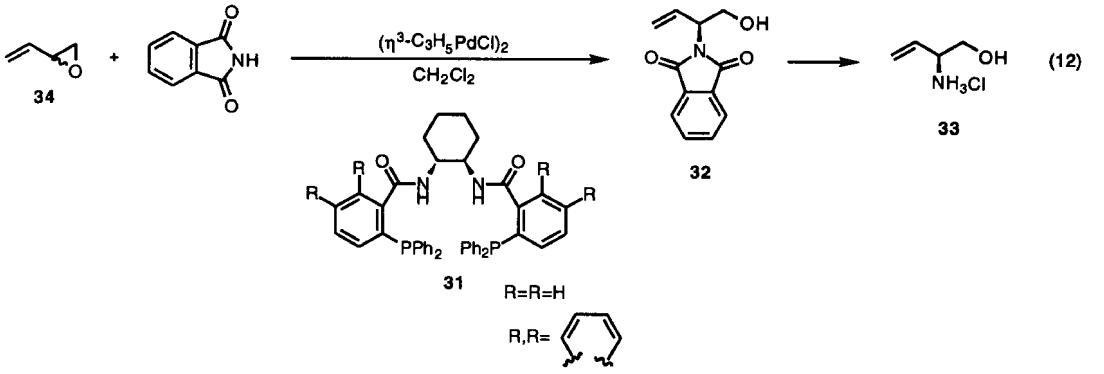
Remarkably, using an oxygen nucleophile, enantiomerically pure allylic esters result (eq 11).[10] The resultant allylic alcohol derivative in the example illustrated serves as a valuable building block exemplified by the antitumor agent phyllanthocin and the insect sex excitant periplanone B.



(11)

Deracemization of an Unsymmetrical Allyl System

Employing racemic butadiene monoepoxide **30** as substrate typifies type C asymmetric induction in which the intermediate η^3-allylpalladium intermediate must undergo racemization faster than alkylation.[11] This example requires resolution of a second issue of selectivity as well—regioselectivity—since alkylation normally occurs at the primary carbon. With the normal DPPBA type ligand (**31**, R=R=H), the desired vicinal regioisomer is indeed major (9:1) but the ee is only 76%. By



restricting the rotational freedom of the carboxamide group as in the naphthyl ligand **31**, R,R=CH=CH-CH=CH, the regioselectivity jumped to >70:1 as did the enantioselectivity to >98%. Thus, in two steps from butadiene monoepoxide, enantiomerically pure vinylglycinol is easily available..

Conclusions

Allylic alkylation reactions may serve as important approaches for the asymmetric introduction of heteroatoms. By doing so, simplified approaches to a variety of biologically important targets result. While the results to date are exciting, much opportunity remains untapped. For example, types D and E asymmetric induction have not even been broached yet. A rather limited number of reactants within types A-C asymmetric induction have only been examined. Understanding the basis of this asymmetric induction remains to be established. From such understanding, new generations of chiral ligands to control every type of asymmetric induction should become possible.

ACKNOWLEDGMENT

This work is generously supported by the National Institutes of Health and the National Science Foundation. I am indebted to my oustanding group of coworkers, individually identified in the references, who are truly responsible for the realization of this dream of asymmetric allylic alkylation begun by Paul Strege, Dennis Murphy, and Daniel Singleton.

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