**Review**

# Pd Asymmetric Allylic Alkylation (AAA). A Powerful Synthetic Tool

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**Palladium catalyzed asymmetric allylic alkylations represent a challenging problem because the mechanism of the reaction places the chiral environment distal to the bond breaking or making events responsible for the asymmetric induction. Furthermore, unlike virtually every other asymmetric process, many strategies can be employed for introduction of asymmetry and many different types of bonds can be formed. While over 100 different ligands have been designed, a family of ligands derived from 2-diphenylphosphinobenzoic or 1-naphthoic acid and chiral scalemic diamines have been successful in inducing excellent enantioselectivity by five different enantiodiscriminating events. These methods have already provided practical strategies towards numerous biological targets—some of which are adenosine and its enantiomer, aflatoxin B, aristeromycin, calanolide A and B, carbovir, cyclophellitol, ethambutol, galanthamine, mannostatin, neplanocin, phyllanthocin, sphingofungins E and F, tetraponaines, vigabatrin, and valienamine.**

**Key words** palladium catalysis; asymmetric synthesis; allylic alkylation; total synthesis; chiral ligand; dynamic kinetic asymmetric transformation

Chiral compounds have many applications. None are more important than those related to biological targets. The chiral nature of biological receptors make chiral ligands common objectives as pharmaceuticals and agrichemicals. Thus, developing efficient synthetic methods to such compounds represents an important challenge. In spite of great advances, resolution methods still frequently represent the most economical method for commercial production in spite of the fact that the theoretical yield of the single desired enantiomer cannot exceed 50% unless the opposite enantiomer can be converted to the desired one. Using starting materials from the chiral pool also constitutes a common strategy. More recently, attention has shifted to inducing chirality into achiral precursors. Two tacts have been explored. In one, chiral auxiliaries, normally emanating from the chiral pool, are covalently attached to prochiral substrates.[1)] The advantage of this approach is the high degree of success in transmitting chiral information in this more controlled strategy. However, it suffers from numerous drawbacks. First, it requires stoichiometric amounts of the chiral auxiliary which ultimately is not part of the final product. It also requires additional steps to add and subsequently remove the chiral auxiliary. Clearly, the conceptually most attractive strategy is employing asymmetric catalytic reactions.[2)]

Some of these have achieved great success. Two of the most successful have been asymmetric catalytic hydrogenation and asymmetric catalytic oxidation of alkenes, notably epoxidation. These two reactions, in addition to virtually every other asymmetric catalytic reaction, share a common feature— the enantiodiscriminating event involves recognizing the enantiotopic faces of a prochiral $\pi$-unsaturation such as a carbonyl group or a double bond. Furthermore, each of these reactions also involve formation of just one bond type—a C–H bond in the case of hydrogenation and a C–O bond in the case of oxidation.

Catalytic asymmetric allylic alkylation differs from virtually all other catalytic processes in two important ways. In the first, there are many enantiodiscriminating mechanisms, not just one. As shown in Fig. 1, there are at least five such mechanisms. As in most other catalytic asymmetric reactions, differentiating the enantiotopic faces of a $\pi$-unsaturation is one mechanism (Fig. 1, A). A second mechanism is differentiating enantiopic leaving groups (Fig. 1, B). Mechanism C involves differentiating enantiotopic termini of a $\pi$-allylmetal intermediate. Since this intermediate derives from a chiral racemic precursor in which the chirality of the substrate is lost, this deracemization constitutes a dynamic kinetic asymmetric transformation (DYKAT). Mechanism D is a varient of mechanism A wherein the $\pi$-allylmetal intermediates interconvert faster than they are attacked by a nucleophile and asymmetric induction derives from differential rates of reaction of the two diastereomeric intermediates. This mechanism allows employment of either an achiral precursor or a racemic chiral precursor—the latter then corresponding to a DYKAT. All of the foregoing involves creation of chirality at the $\pi$-allyl fragment. Mechanism E involves discriminating between the enantiotopic faces of the nucleophile.

Besides the multitude of mechanisms for asymmetric induction, another major benefit is the diversity of bond types that potentially can be formed. In addition to formation of C–H and C–O bonds, C–N, C–S, C–P and, most importantly, C–C bonds, all can be formed.[3)]

A major stumbling block in this approach arises because of the mechanism of the catalysis.[4)] In catalytic hydrogenation and oxidation, the substrates are coordinated to the metal. The bond forming events between the prochiral $\pi$-system and hydrogen or oxygen occur within the coordination sphere of the metal. The situation in metal catalyzed allylic alkylation is quite different as revealed in Fig. 1. Both the ionization[5)] and nucleophilic addition[6)] events involve bond cleavage and formation, respectively, that occur outside the coordination sphere of the metal and thus distal to the chiral ligands. Thus, chiral information must be transmitted from one face of the substrates to that on the side opposite to the metal. In types A and B, the metal induced ionization of the leaving group represents the enantiodiscriminating step; whereas, in types C and D, nucleophilic addition constitutes

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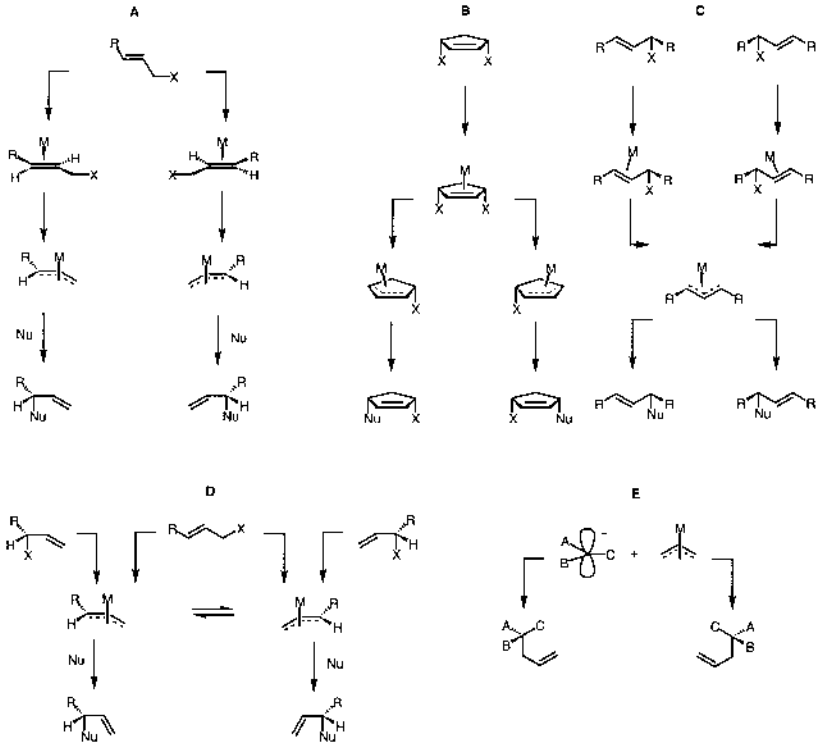


Fig. 1. Various Enantiodiscriminating Events in AAA

the enantiodiscriminating step. Type C involves a chiral precursor and type D may involve one. When chiral substrates have the potential of being completely converted into a single enantiomer of the product, the process should be referred to as a DYKAT. An interesting aspect would be the ability of the chiral inducing element to extend beyond the $\pi$-allyl moiety and influence the induction of chirality at the nucleophile.[7,8] The remoteness of the chiral inducing ligands with respect to the nucleophile make such a process even more challenging.

In order to induce asymmetry through such distances, a number of models can be envisioned.[9] An electronic model for type C discrimination is depicted in **1**. In this approach, two different types of atoms that can serve as coordinating groups to the metal are employed. A chiral environment can be created in the scaffold connecting the two binding atoms or at one or both of the coordinating atoms. The difference in reactivity of the resultant diastereomeric complexes or in their concentration then accounts for the asymmetric induction. Two examples of this approach include a P, N (*e.g.*, **2**)[10—12] and a P, S (*e.g.*, **3**)[13] system. An alternative strategy invokes steric effects. A biomimetic approach envisions the creation of chiral space in analogy to the active site of an enzyme in which the ability of the substrate to fit and move within the chiral space of the active site accounts for the ability of the chiral space to influence enantioselectivity.

In designing complexes to function as catalysts *via* this latter mechanism, a large bite angle $\theta$ (*e.g.*, **4**) was envisioned to help extend the chiral space to more effectively embrace the substrate.[14] Increasing the chain length of the tether may have such an effect. Support for this interpretation came from comparing BINAP (**5**) and BINAPO (**6**) in a type C process as illustrated in Eq. 1, a reaction that subsequently became the standard reaction for testing new ligands.[14a] The

Born in Philadelphia in 1941, he received his bachelor's degree from the University of Pennsylvania in 1962, and his Ph. D degree from Massachusetts Institute of Technology in 1965. He directly moved to the University of Wisconsin where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor in 1982. He joined the faculty of Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. He has already published two books and over 650 scientific articles and was Editor-in-Chief of a nine volume compendium entitled "Comprehensive Organic Synthesis." His work has been characterized by a very high order of imagination, innovation and scholarship. He has ranged over the entire field of organic synthesis, particularly emphasizing extraordinarily novel methodology. Further, he has repeatedly demonstrated how his innovative methodology allows for the simplification of many complex target oriented syntheses leading to natural products of high biological activity. In recognition of his many contributions, he has received a number of awards, including the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), Arthur C. Cope Scholar Award (1989), the ACS Roger Adams Award (1995), the Presidential Green Chemistry Challenge Award (1998), the Herbert C. Brown Award for Creative Research in Synthetic Methods (1999), the Nichols Medal (2000), and the Yamada Prize (2001).

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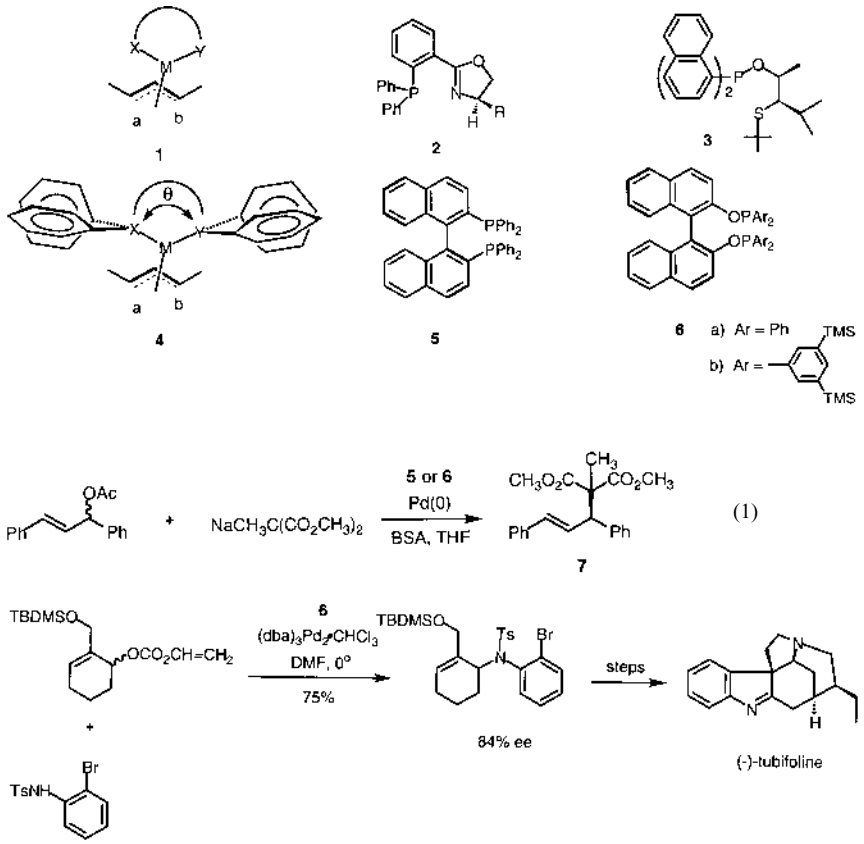
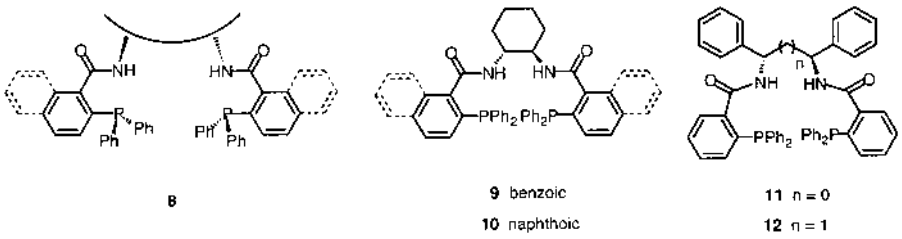



ee of **7** increased from 50% with **5** to 68% with BINAPO (**6a**). Even better results are obtained with cyclic systems wherein a further enhancement occurred with a 3,5-disubstituted analog **6b**. Recent work that built from these observations demonstrates the utility of this ligand for 2-substituted-3-acyloxycyclohexenes as has been shown in a synthesis directed towards the *Strychnos* indole alkaloid (−)-tubifoline (Eq. 2).[15)]

Creation of chiral space can borrow the basic principles from nature's prime catalysts, the enzymes, wherein primary chirality is transformed into conformational chirality that creates the catalytic active site. The ability of the substrate to fit and move within the chiral space of the active site imprints its chirality on the product. A modular design that mimics these basic principles was envisioned to derive from diamides generated from chiral diamines and 2-diphenylphosphinobenzoic[16)] or naphthoic acid[17)] (**8**).[18)] The long, rather rigid tether connecting the two metal binding posts was envisioned to impose a larger than normal bite angle (*i.e.*, >90°). This proposal has been verified in the "invertomer" series wherein the amide is simply inverted—*i.e.*, the ligands derive from a chiral dicarboxylic acid and 2-diphenylphosphinoaniline.[19)] The primary chirality of the diamine scaffold would be translated into the conformational chirality of the bis-triarylphosphino moieties.[20)] These moieties create chiral grooves similar to those of propeller. A cartoon depicting the chiral space associated with a complex derived from ligand **11** is depicted in Fig. 2. The walls and flaps lining the chiral space are formed by the aryl rings on the phosphorus and the roof is defined by the chiral scaffold. This model serves as a valuable guide in understanding and predicting the reactivity of this chiral system.

Ligand stereochemistry correlates with product stereochemistry in a predictable fashion as summarized in Fig. 3. The ligands can be defined as clockwise (cw) or counterclockwise (ccw) type which characterizes the orientation of the two phosphines with respect to each other in an extended Newman-type projection. In an ionization, the movement of the metal with respect to the substrate in going from $\eta^2$ to $\eta^3$ coordination is a cw type. The products then derive from a kinetic capture of the diastereomeric $\pi$-allyl complexes. In looking at the cartoons of Fig. 2, this motion corresponds to



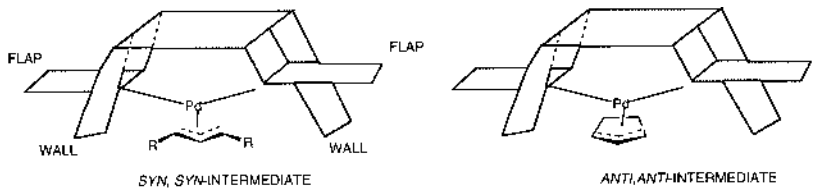



Fig. 2. Cartoon of Chiral Space

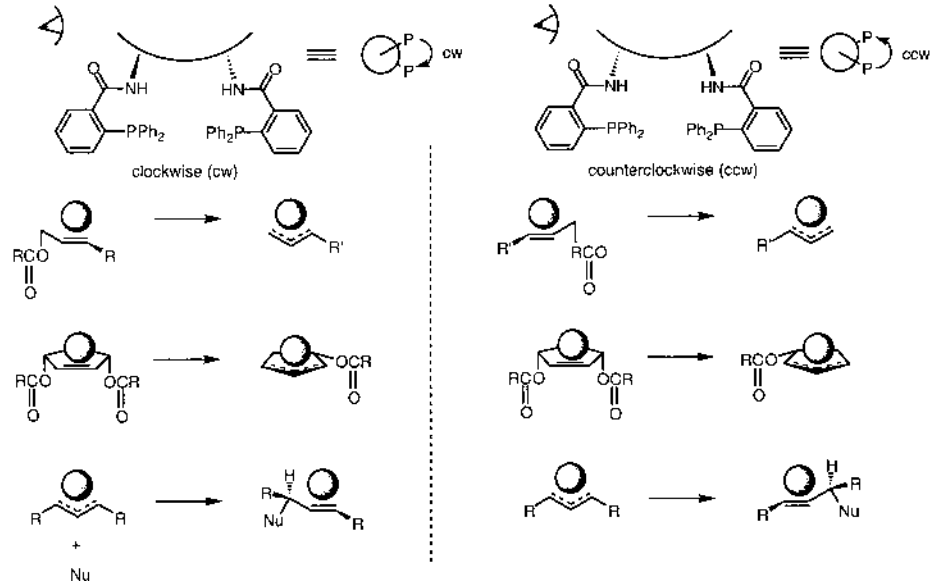



Fig. 3. Correlation of Ligand and Product Stereochemistry

the leaving group departing in the sterically most unencumbered region of space—*i.e.*, under the flap rather than through the wall. The nucleophilic addition is the microscopic reverse of the ionization—*i.e.*, a ccw motion between the metal and the allyl fragment is preferred. According to the cartoon, addition of the nucleophile *via* the sterically least encumbered area proximal to the flap occurs. The ccw ligands invoke the mirror image motions as depicted.

**Type A Enantiodiscrimination**

Because type A enantiodiscrimination involves both regio- and enantioselectivity, overcoming the intrinsic bias for nucleophiles to attack at the least hindered terminus led to focussing on intramolecular processes. Simply exposing **13** to the chiral catalyst generated from ligand **9** produced the vinylpyrrolidine and piperidine in very good yields and enantioselectivities (Eq. 3).[21] On the other hand, the chiral racemic substrates **15a**, **b** gave the same cyclized product with only 4—6% ee. This difference between the achiral and chiral precursors supports the interpretation that the enantiodiscrimination is the ionization event. Furthermore, the absolute configuration is predicted by the model of Fig. 2 wherein a *syn* complex is generated and captured by the amine prior to any equilibration.

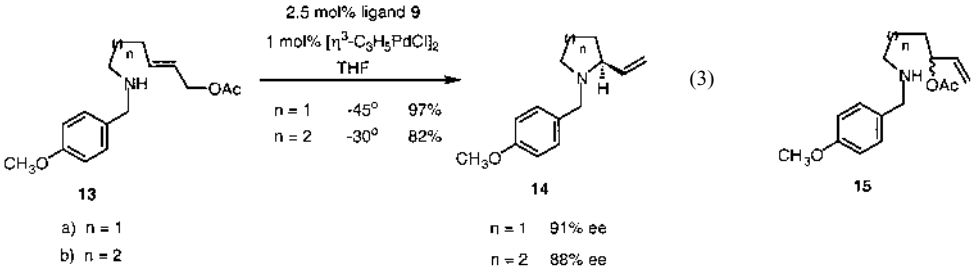
A synthesis of the chromane core of vitamin E takes advantage of this phenomenon.[22] As shown in Eq. 4, the cyclization of achiral carbonate **16** proceeded in excellent yield and very good ee in the presence of either base (triethylamine) or acid (acetic acid) to form chromane **17**. That the enantiodiscrimination likely stemmed from the ionization step derived from the observations that 1) the chiral racemic substrate **18** produced racemic product and 2) introducing additives to speed up equilibration of $\pi$-allyl intermediates lowers the ee. The absolute configuration of the chromane obtained with ligand **9** is enantiomeric to the natural vitamin. The stereochemistry of the chromane stereogenic center is the most important of the natural vitamin for highest biological activity.[23]

The reaction showed a dependence on the geometry of the starting alkene. As illustrated in Eq. 5, the *Z*-alkene **19** gave significantly higher ee than the *E*-alkene **20**.[24] Examination of the cartoons of Fig. 2 suggests that large *anti* substituents are better accommodated by these ligands than large *syn* substituents. Thus, the *Z*-alkene **20** better fits into the chiral space.

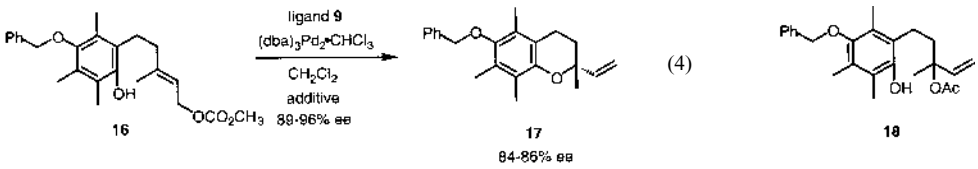
**Type B Enantiodiscrimination**

The desymmetrization of *meso*-diols represents an excellent strategy for asymmetric induction. The cyclization of the dicarbamate **21**, generated *in situ* from the diol and *p*-toluenesulfonyl isocyanate, gave the oxazolidin-2-one **22** in excellent yield and enantioselectivity (Eq. 6).[16,25] The compound served as a key intermediate in the synthesis of the glucosidase inhibitor mannostatin A.[26]

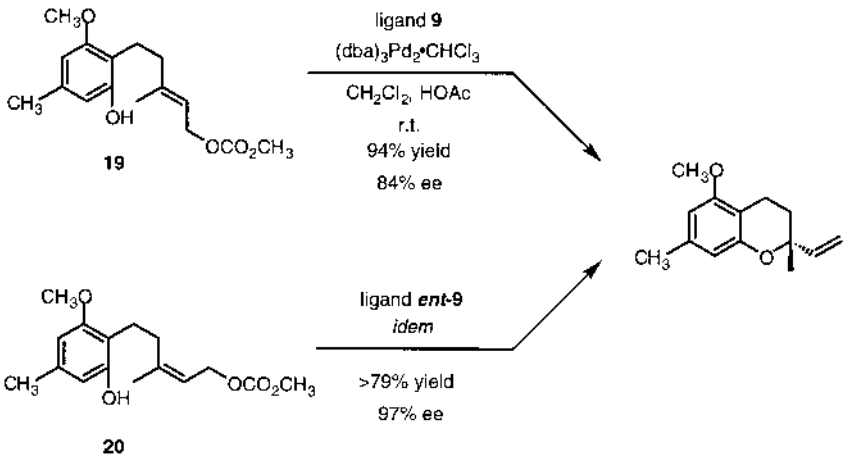
Nitrogen nucleophiles also serve in intermolecular reactions. A sulfonamide **24** reacted with the bis-carbonate **23** to provide the product **25** of 99% ee (if isolated 89% yield) (Eq. 7).[27] This compound need not be isolated but can undergo a


2.5 mol% ligand 9
1 mol% [η3-C3H5PdCl]2
THF
n = 1 -45° 97%
n = 2 -30° 82%
13
a) n = 1
b) n = 2
14
n = 1 91% ee
n = 2 88% ee
15

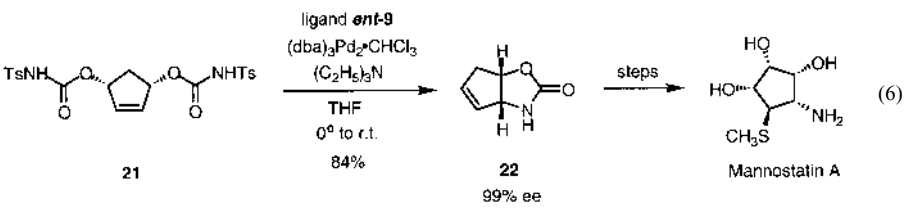
(3)


ligand 9
(dba)3Pd2•CHCl3
CH2Cl2
additive
89-96% ee
16
17
84-86% ee
18

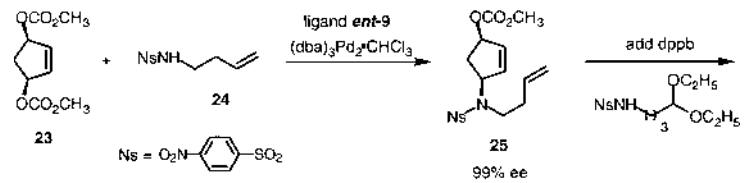
(4)


19
ligand 9
(dba)3Pd2•CHCl3
CH2Cl2, HOAc
r.t.
94% yield
84% ee
20
ligand ent-9
idem
>79% yield
97% ee

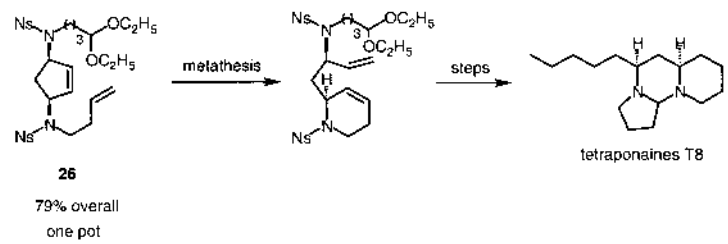
(5)


21
ligand ent-9
(dba)3Pd2•CHCl3
(C2H5)3N
THF
0° to r.t.
84%
22
99% ee
steps
Mannostatin A

(6)


23
24
Ns = O2N SO2
ligand ent-9
(dba)3Pd2•CHCl3
25
99% ee
add dppb

(7)

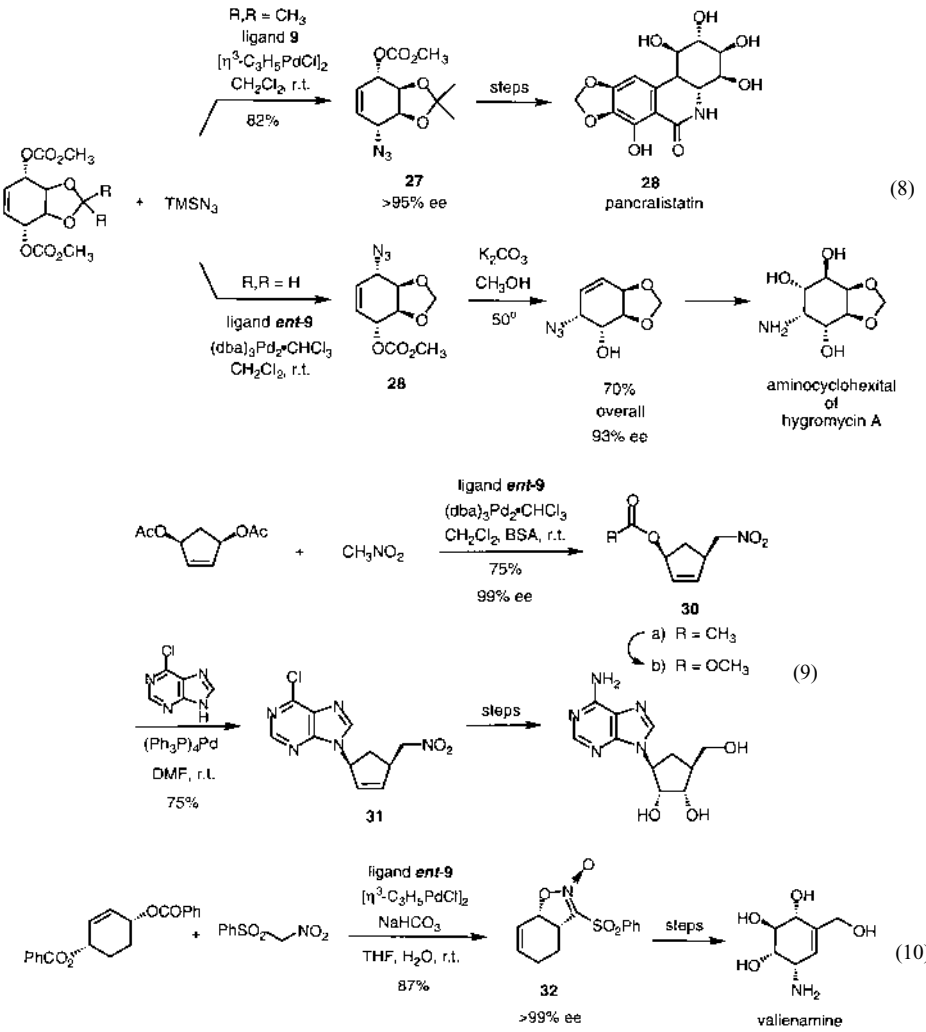

26
79% overall
one pot
metathesis
steps
tetraponaines T8

second regio- and diastereoselective palladium catalyzed alkylation in the same pot to provide the bis-substituted compound **26**. Metathesis sets the stage for a facile synthesis of the poisonous constituents of the venom of the New Guinean ant.

Azides are an interesting class of nitrogen nucleophiles.[28] As illustrated in Eq. 8, the initial allylic azide **27** can be isolated in excellent yield and enantioselectivity.[29] This azide served as a key intermediate in an efficient synthesis of the antitumor agent pancratistatin. A similar reaction also led to a concise synthesis of the powerful analgesic (−)-epibatidine.[30] On the other hand, simple hydrolysis of the initial adduct at temperatures slightly elevated above room temperature gave the [3.3] sigmatropic rearrangement azidoalcohol **29** in excellent yield and enantioselectivity.[31] This sequence led to the aminocyclohexitol portion of hygromycin A, an effective agent for control of swine dysentery (Eq. 8).[32] Purines and pyrimidines have also been successfully employed and has led to the synthesis of numerous carbanucleosides including carbovir, aristeromycin, and neplanocin A.[33,34] In work directed towards the synthesis of prostacyclin analogs, oxygen nucleophiles (phenols) have been successfully employed.[35]

Carbon nucleophiles work equally well.[36,37] For example, nitroalkanes participated well in such reactions (Eq. 9) wherein the monoalkylation product **30** was produced virtually enantiomerically pure (99% ee).[38] Subsequent palladium catalyzed regio- and diastereoselective substitution using a purine base gave the carbonucleoside intermediate **31** which would lead to *ent*-aristereomycin. A sulfonylnitroalkane proved to be a quite interesting nucleophile and may lead to double substitution[34] (Eq. 10).[39] The enantiomerically pure novel heterocycle **32** was isolated in 87% yield and >99% ee. This compound was utilized in an asymmetric synthesis of valienamine, a component of novel glycosidase inhibitors, one of which is useful in the treatment of diabetes. It should be noted that use of enzymes in desymmetrization of six-membered ring *meso*-diols is generally a poor reaction.[40] In contrast, the palladium catalyzed reaction is useful independent of ring size.

The heterocyclic *meso* diester **33** cannot be desymmetrized by enzymatic methods since the hydrolysis product is chemically unstable. On the other hand, there is no problem in performing the normal asymmetric allylic alkylation (AAA) with this heterocycle[41] which is available in one step from furan. Heterocycles like the typical pyrimidines and purines of the nucleosides participated well as illustrated by 4-chloropurine. A second regio- and diastereoselective palladium catalyzed reaction introduces a carbon side chain which ultimately could be converted by standard methods to both a carboxylic acid as well as a hydroxymethyl side chain. A major advantage of this approach is equivalently facile ac-



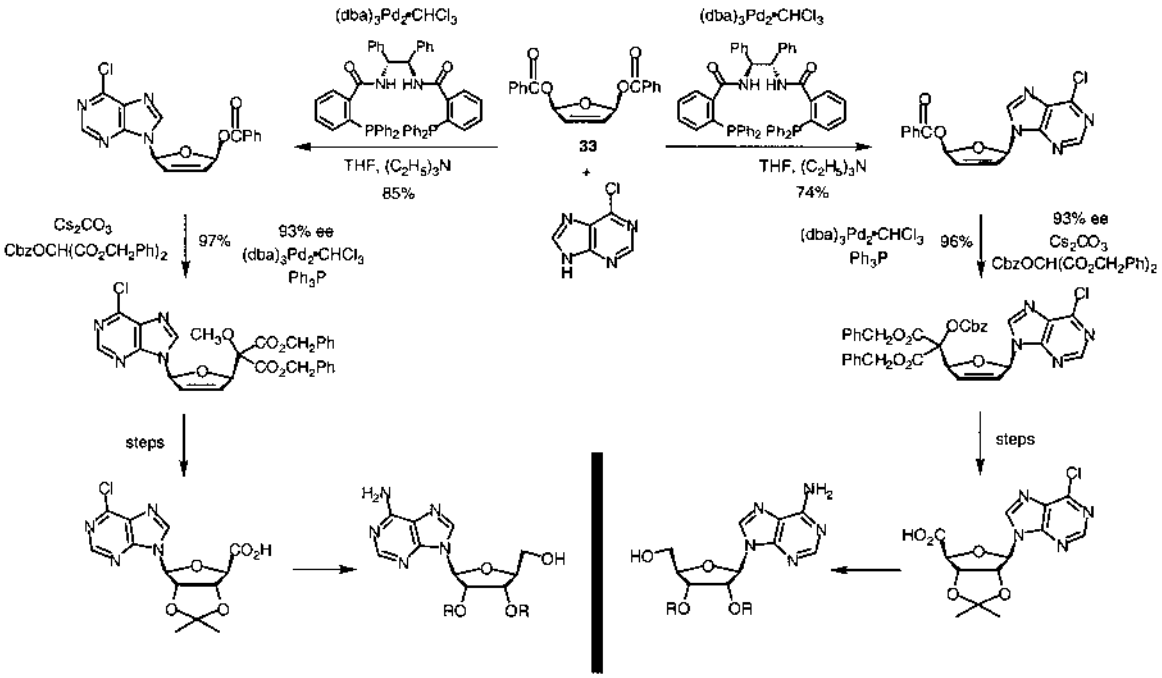


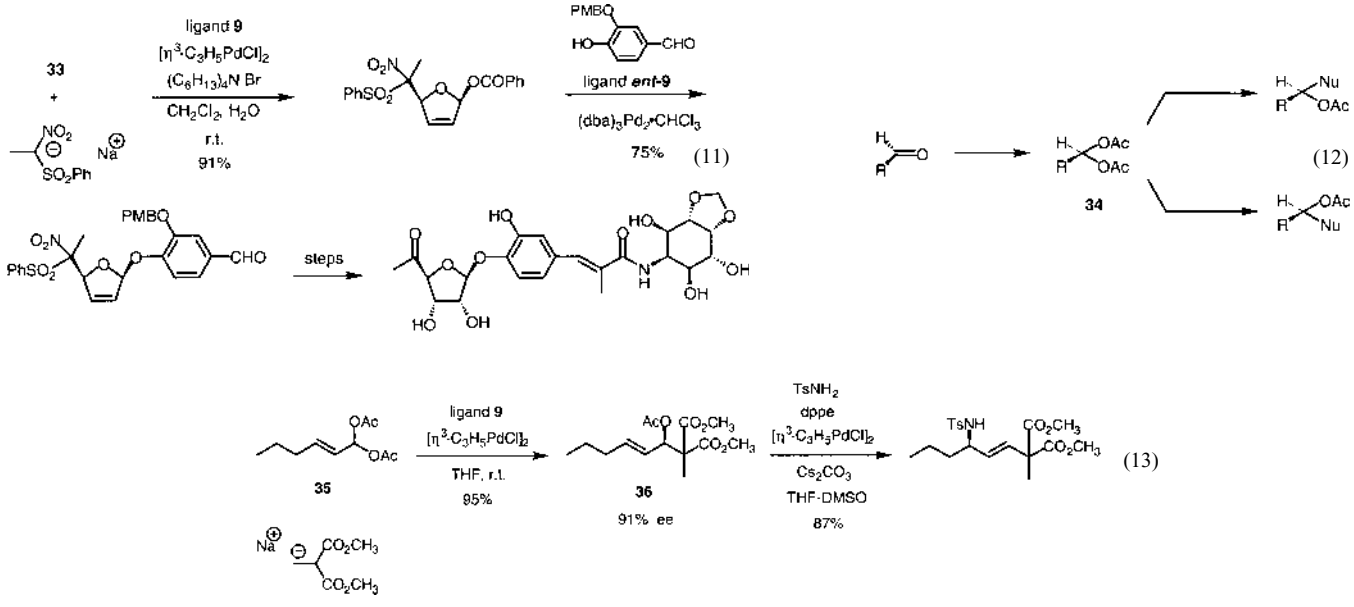
Chart 1. A Non-Carbohydrate Nucleoside Synthesis

cess to either D- or L-nucleosides by simple choice of the chiral ligand.

A reverse strategy wherein the carbon side chain is introduced prior to the heterocyclic substituent can also be employed. This strategy was applied to a synthesis of 2-epi-hygromycin A as outlined in Eq. 11.[42] In this case, the glycosylation step involved a phenol as a nucleophile. Thus, the ability to desymmetrize dibenzoate **33** provides a very concise route to the tetrahydrofuran moiety. The AAA also provided the aminocyclohexitol (see Eq. 8) which was directly coupled with the acid to give 2-epihygromycin A. Thus, all the chirality derived from palladium AAA.

Gem-diacetates **34** readily available by the Lewis acid catalyzed addition of acetic anhydride to an aldehyde constitute an unusual type of substrate for desymmetrization. The two acetates are prochiral (see Eq. 12). Substitution of either one selectively then is equivalent to nucleophilic asymmetric addition to one of the prochiral faces of the aldehyde. Since symmetric additions of stabilized nucleophiles of the type utilized in AAA are not possible directly, this strategy becomes an important new way to achieve this result.[43]

As shown in Eq. 13, the gem diacetate **35** underwent smooth alkylation to give malonate **36** of high ee. As with all the other *meso* diesters, the product is still an allyl ester capable of undergoing a second palladium catalyzed allylic alkylation. Steric factors dictate the second alkylation proceeds in a net $S_N2'$ mode and with 100% chirality transfer. Here too, enzymatic desymmetrization fails since the product of enzymatic hydrolysis, a hemiacetal, spontaneously collapses to a carbonyl partner.



Beyond the examples wherein enzymatic desymmetrization fails, the palladium catalyzed AAA has other advantages over the enzymatic strategy. Production of either enantiomer is simpler since both enantiomeric ligands are equally accessible—a situation clearly not the case with enzymes. The desymmetrization step is not an extra step in a synthetic sequence in an AAA. The synthetic step of alkylation is integrated with the desymmetrization. In the case of the enzymatic desymmetrization, the alkylation event is an extra step (or more) subsequent to the desymmetrization.

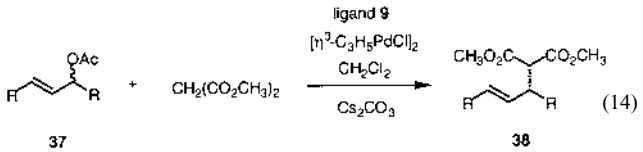
**Type C Enantiodiscrimination**

The classical AAA involves the conversion of racemic allylic esters like **37** into chiral products like **38** at 100% conversion. In constrast to most asymmetric ligands used for asymmetric induction, this reaction, utilizing ligands of type **9** and its relatives, does not proceed well for bulky R groups like phenyl but, very significantly, proceeds extremely well for small substituents like methyl which normally do not give good ee's with other ligands. This behavior is easily understood by the cartoons of Fig. 2. Thus, alkylated malonate **38** (R=$CH_3$) of 92% ee was obtained in 98% yield.[44] Since both enantiomers of the starting material are converted to the same product, the reaction constitutes a DYKAT. An unusual example is illustrated in Eq. 15. The epoxide **39** derived from cyclopentadiene in two steps—singlet oxygen oxidation followed by sodium borohydride reduction.[45] Using relatively standard conditions, the phthalimide **40** was obtained in excellent yield and ee. It served as a precursor to polyoxamic acid, the novel amino acid moiety of the polyoxine and nikkomycin antifungal agents. After conversion of the phthalimide to a Boc, it also constitutes a formal asymmetric synthesis of kainic acid.[46]

Cyclic substrates are generally excellent with broad ranges of nucleophiles including carbon, sulfur, nitrogen, and oxygen.[47] Illustrative of carbon nucleophiles is the DYKAT of 3-acyloxycycloheptene with malonate (Eq. 16, path a)[47] and nitroalkanes (Eq. 16, path b).[38] Racemic conduritol B (**41a**) was easily accessed in three steps from benzoquinone.[48] A DYKAT of the tetraester **41b** with phenylsulfonylnitromethane gave an 81% yield of **42** which, in four steps, was converted to the glycosidase anti-human immunodeficiency virus (HIV) agent (−)-cyclophellitol, the enantiomer of the natural product.[49] The natural enantiomer can easily be accessed by simply switching the ligand. Using an oxygen nucleophile, an asymmetric synthesis of D-myo-inositol 1,4,5-triphosphate was performed.[50]

These reactions require ionization of both enantiomers of the substrate with an enantiomerically pure catalyst. By definition, the substrate enantiomers will react at different rates. Thus, a kinetic resolution or a kinetic asymmetric transformation (KAT) is also possible. In fact, the tetraacetate **41c** underwent a nearly perfect kinetic resolution or KAT using pivalic acid as the nucleophile (Eq. 18).[51] The KAT product **43** was transformed into the natural enantiomer of (+)-cyclophellitol.

The use of carboxylates as nucleophiles constitute a most interesting reaction that can be likened to a deracemization.[52] Thus, both enantiomers of **44** react with a carboxylic acid to regenerate an ester **45** which is now virtually enantiomerically pure (Eq. 19). This product was the key building block for the synthesis of the antitumor agent phyllanthocin.[53]



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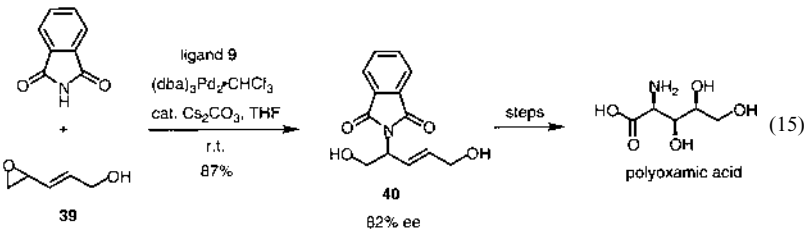

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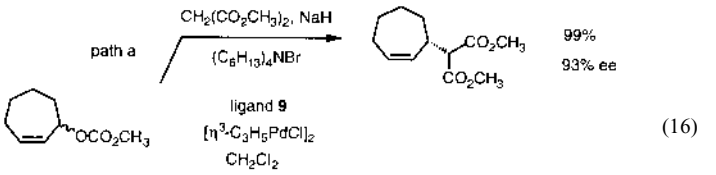

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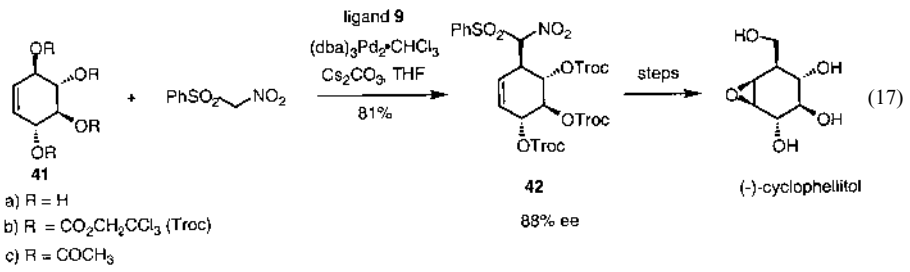

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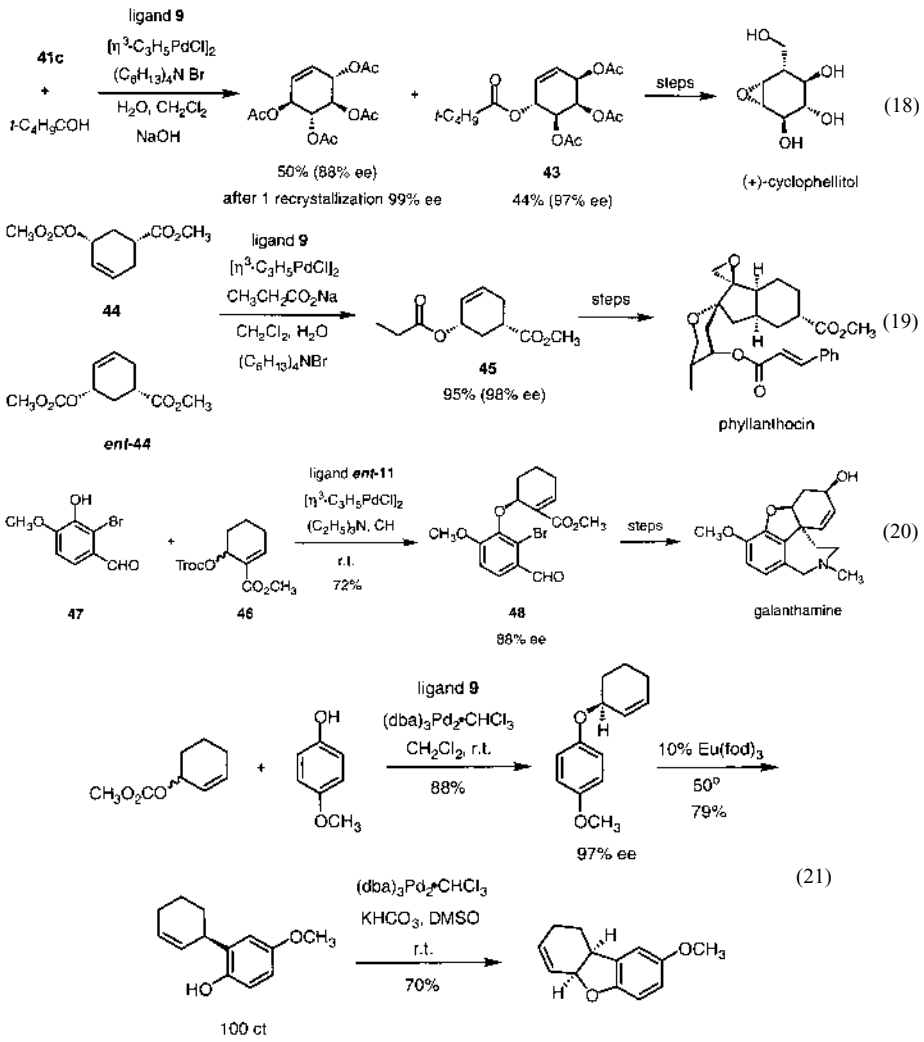
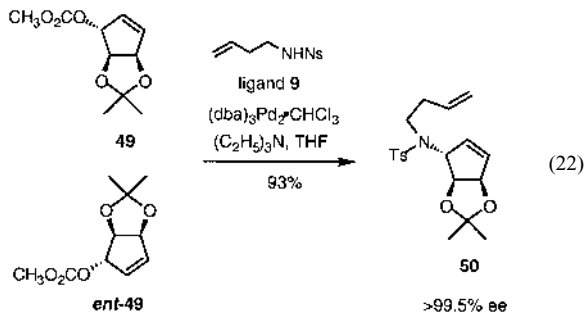


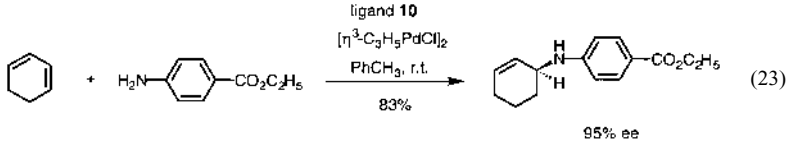

Phenols are especially interesting nucleophiles.[54] Thus, the ester **46** reacted with phenol **47** to provide the allyl phenyl ether **48** in good yield and ee (Eq. 20).[55] This is one of the very rare examples where the mnemonic fails to predict the observed absolute configuration which derived from the presence of the ester substituent on the central carbon of the allyl unit. The resultant product **48** served as a useful precursor of galanthamine, an agent under development for the treatment of Alzheimer's disease.

The asymmetric creation of the allyl phenyl ether sets the stage for the Claisen rearrangement to create the equivalent of an asymmetric ortho alkylation of phenols.[54] Equation 21 illustrates this aspect as well as an alternative approach to benzofurans of the type found in galanthamine. A lanthanide was employed to catalyze the Claisen rearrangement with complete chirality transfer (ct). A palladium catalyzed allylic oxidation completes the sequence.[56]

Nitrogen nucleophiles also have found useful applications. Simple amines function well as do hydroxamic acids, imides, and sulfonamides.[47,57] Substrate **49** is quite significant since it requires the palladium to approach the face of the alkene proximal to the acetonide.[58] Nevertheless, racemic **49** reacted well to give a 93% yield of enantiomerically pure **50**, a building block for the indolizidine alkaloids.[59]

In these reactions, the $\pi$-allylpalladium intermediate is generated by the ionization of an allylic leaving group. An alternative strategy to the same type of intermediate employs a hydropalladation of a diene. Indeed, asymmetric hydroamination of cyclohexa-1,3-diene occurred with the naphtho ligand **10** (Eq. 23).[60]



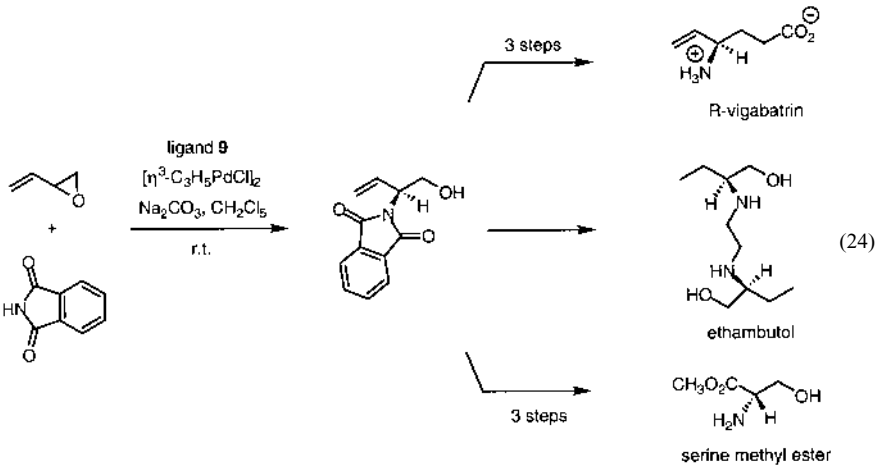
**Type D Enantiodiscrimination**

In this type of enantiodiscrimination, both regio- and enantioselectivity issues arise. To minimize problems of regioselectivity, vinylepoxides like epoxybutadiene (EpB) were employed to help direct nucleophilic attack to the internal carbon by coordination to oxygen.[61] Indeed, phthalimide underwent smooth addition to EpB with excellent regio- and enantioselectivity using the naphtho ligand **10** (Eq. 24).[17] The obtained vinylglycinol served as a pivotal intermediate towards the anti-epileptic vigabatrin, the tuberculostatic agent ethambutol, and the amino acid serine.[62] Since both enantiomers are converted to the same enantiomeric product, this reaction is a DYKAT.

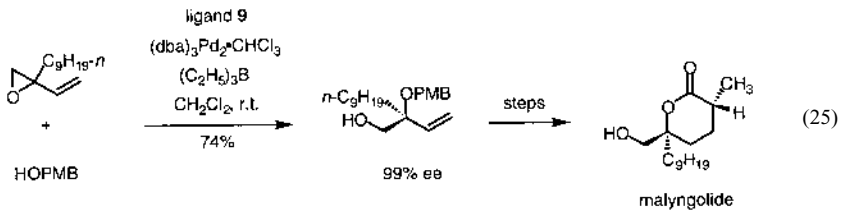
With boron co-catalysts, primary alcohols serve as excellent nucleophiles with racemic epoxides.[63] Even the formation of a quaternary center occurred with excellent regio- and enantioselectivity (Eq. 25). The adduct in this case served as a precursor of the antibiotic malyngolide.[64] Using carbonic acid salts (carbonate and bicarbonate) under similar conditions provided vinylglycidols.[65]

The success of vinylepoxides in a DYKAT depends upon a mechanism for rapid equilibration of the intermediate diastereomeric complexes. This equilibration is possible by a well-known dynamic property of $\pi$-allylmetal complexes involving an $\eta^3$ to $\eta^1$ equilibrium. A quite different class of substrates, the butenolides **51**, requires an almost unknown equilibration mechanism depicted in Eq. 26. This process requires the normal $\pi$-allylpalladium complexes **52** and *ent*-**52** ultimately to pass through the sigma complex **53** in order to provide access to either enantiomer of the product.[66] Thus, a Curtin–Hammett situation must prevail—*i.e.*, the enantiodiscrimination will depend upon the magnitude of the differences in the relative rates of $k_1$ to $k_2$ of Eq. 26. The issue of regioselectivity is resolved by the electronics of the system—the presence of the carbonyl group strongly favors nucleophilic addition at the $\gamma$-position. As shown in Eq. 27, addition of chloride or fluoride ion to speed upon conversion of the $\eta^3$-complexes **52** to the $\eta^1$-complex **53** accomplishes this task well.[67] By deracemizing the butenolide to form the product with high enantiomeric purity, the stage is set for elaboration of the double bond diastereoselectively. The example of Eq. 27 optimized the use of the DYKAT and sets the stage for an efficient synthesis of aflatoxin wherein the AAA is coupled with a reductive Heck cyclization to form the core furanofuran moiety.

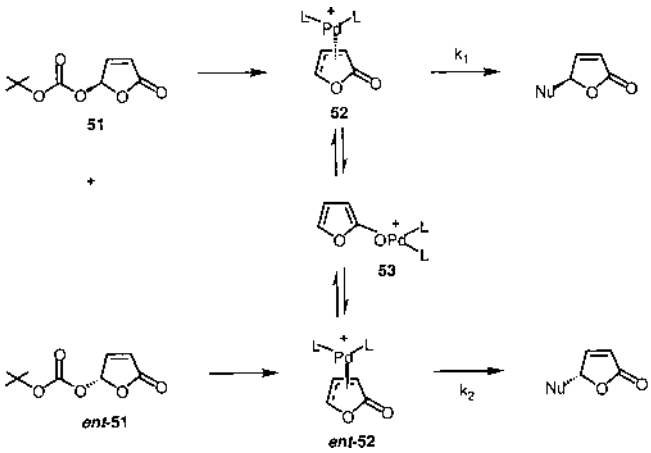
The case of a non-biased unsymmetrical $\pi$-allyl system



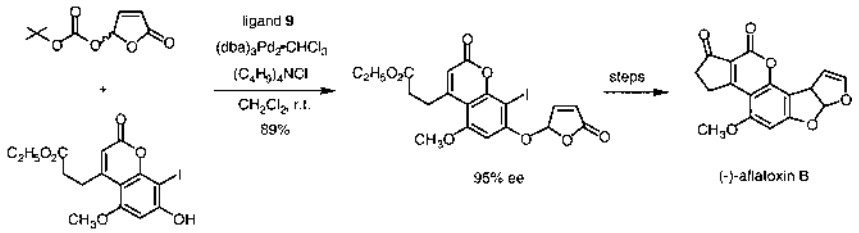

(24)




(25)




(26)

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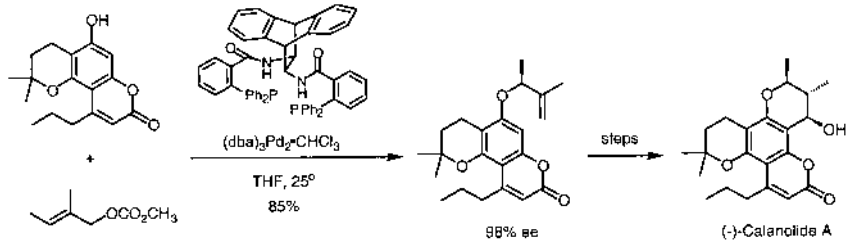


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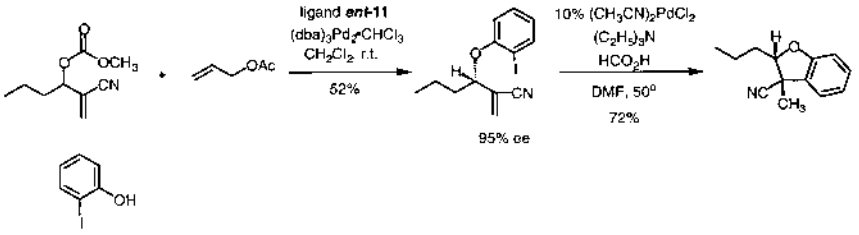



(29)

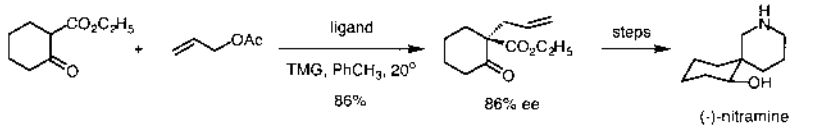
with respect to regioselectivity is intrinsically much more difficult. Nevertheless, the cartoons of Fig. 2 make a case that in any unasymmetrical $\pi$-allyl system involving attack at either a secondary or even tertiary center *vs.* a primary one, the former should be intrinsically preferred because of the nature of the chiral pocket.[68,69] Indeed, even with crotyl carbonate, a 98 : 2 ratio favoring attack at the secondary carbon with *p*-methoxyphenol is preferred and the product can be obtained having about 90% ee.[68,70] This process allowed the development of a practical approach to the non-nucleoside reverse transcriptase inhibitor calanolide system (Eq. 28).[71] While the synthesis of the enantiomer of the natural product is being depicted, it should be apparent that simply switching the enantiomer of the ligand in the AAA generates the natural enantiomer since all of the remaining stereogenic centers derive from the first one.

A novel application of this process is the deracemization of Baylis–Hillman adducts (Eq. 25) which occurs with excellent regio- and enantioselectivity.[72] Use of *p*-methoxyphenol as the nucleophile allowed its oxidative removal to regenerate the free OH of the Baylis–Hillman adduct—a sequence that effects the true deracemization. An alternative shown in Eq. 29 makes use of the phenol nucleophile to achieve an asymmetric synthesis of dihydrobenzofurans, a key structural unit of numerous bioactive natural products such as the furaquinocins.

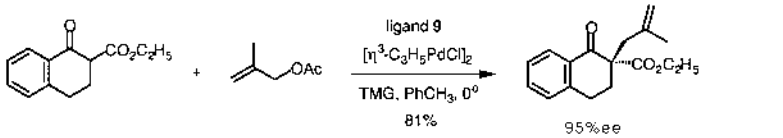
**Enantiodiscrimination of Type E**

All of the preceding sections deal with induction of asymmetry at the allyl fragment itself—the most practical approach to use metal catalyzed allylic alkylations for asymmetric since it is most intimately associated with the metal and thus the chiral ligands. Given the mechanism of the process wherein the nucleophile attacks on the face of the $\pi$-allyl unit opposite that of the metal, induction of asymmetry by differentiation of the prochiral faces of a nucleophile appears quite remote.[73,74] In spite of the demands, excellent enantioselectivity can be observed with $\beta$-keto esters.[75] In the simplest case (Eq. 30) using allyl acetate, an 86% ee in the alkylation was achieved. The product served as a precursor to the spiroalkaloid (−)nitramine. Using a more substituted allylating agent, the ee rose to as high as 99% (cf. Eq. 31).

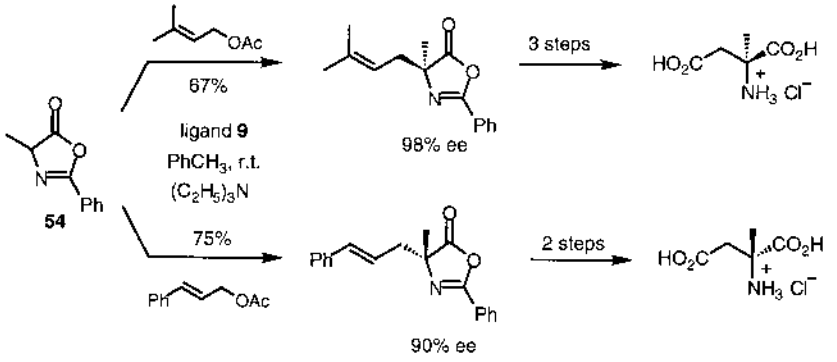
Azlactones provide access for an asymmetric synthesis of



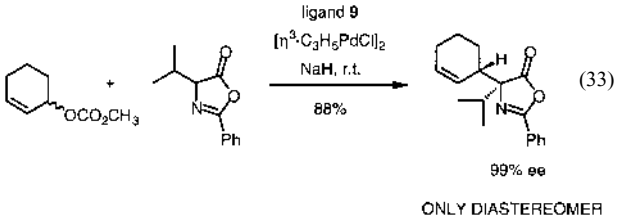

(30)




(31)




(32)

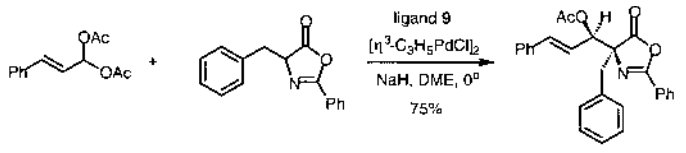



(33)

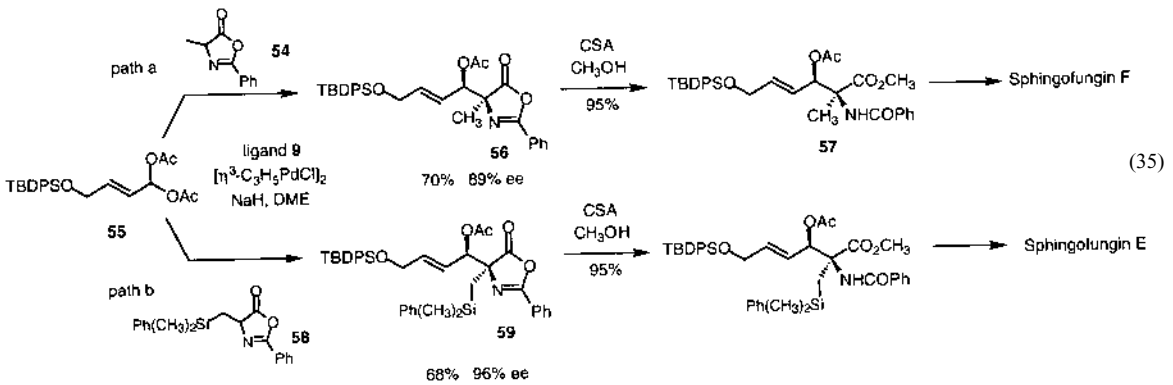
unusual amino acids.[76] Thus, quaternary amino acids, which cannot be accessed by catalytic hydrogenation, are readily accessed by this methodology. Among the applications of the allylated amino acids is the oxidative cleavage of the alkene. This represents the shortest synthesis of $\alpha$-methylaspartic acid. Remarkably, either enantiomer is available from the same enantiomer of the ligand by simply changing the allylating agent from prenyl to cinnamyl acetate. Although such unexpected behavior can be rationalized by models derived from the cartoons, it would have been quite difficult to predict it in advance. Using allyl systems that also develop stereogenic centers in the product can lead to high de as well as ee (Eq. 33).

An interesting prochiral allyl partner is the gem-dicarboxylates. They participate quite well to generate novel serine analogues as shown in Eq. 34.[77] The crude product had a dr of 15 : 1 from which the major diastereomer was isolated in 75% yield and had a 99% ee. This reaction formed the basis of a general strategy to the sphingofungins and related compounds like myriocin and mycestericin.[77,78] The gem-diacetate **55**, available in a two step atom economical sequence involving a ruthenium catalyzed redox isomerization[79] of the monosilyl ether of 2-butyn-1,4-diol followed by a ferric chloride catalyzed addition of acetic anhydride to the resultant aldehyde, produced a 11 : 1 dr of alkylated products with azlactone **54** from which the major diastereomer **56** of 89% ee was isolated in 70% yield. Chemoselective methanolysis of the azlactone produced the amido ester **57** which culminated in a synthesis of sphingofungin F. The efficiency of this synthesis is highlighted by the fact it required only fifteen steps from commercially available materials and proceeded in 17% overall yield. Increasing the steric bulk of the azlactone substituent increased the ee. Thus, the sphingofungin E precursor **59** of 96% ee was isolated in similar yield although the diastereoselectivity using azlactone **58** was only 2.4 : 1. Nevertheless, the total synthesis still only required seventeen steps and proceeded in 5% overall yield.

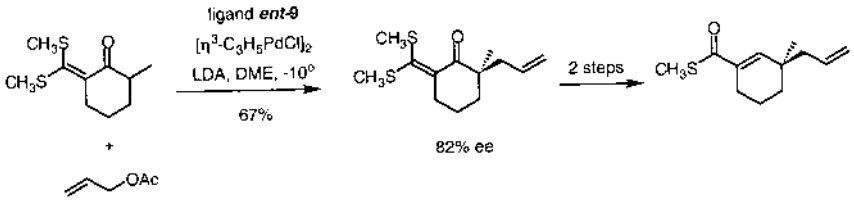
The stabilized nucleophiles utilized so far are typical for palladium catalyzed allylic alkylation. On the other hand, simple ketone enolates are not generally satisfactory partners in such processes. Interestingly, with catalysts derived from the chiral ligands under development, the scope of the reaction has expanded to include this heretofore unsatisfactory partner (Eq. 36).[80,81]




(34)




(35)




(36)

## Conclusion

Metal catalyzed asymmetric allylic alkylations is a vibrant area of investigation. The enormity of the oppotunity mandates development of this fruitful bond forming process. The ability of the catalyst by choice of both metal and ligand to imprint the chemo-, regio-, diastereo-, and enantioselectivity on formation of so many different bond types is the reward. This article focused on just one ligand design out of over one hundred. With this ligand system, all five types of enantiodiscrimination have been realized. While kinetic resolutions have normally been avoided due to their intrinsic limitation, they can also be performed if desired. The utility of this methodology for the synthesis of a diverse array of molecular targets of biological relevance have already been demonstrated. In implementing these syntheses, the advent of this new methodology to provide new synthetic strategies, that previously did not exist have led to enhanced efficiencies. In spite of the advances to date, these must be considered only the beginning of what ultimately may be possible.

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