Asymmetric Transition-Metal-Catalyzed Allylic Alkylations: Applications in Total Synthesis

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I. Considerations for Enantioselective Allylic Alkylation

A. Introduction

Development of asymmetric metal-catalyzed reactions has played a significant role in allowing synthetic access to biologically important molecules. While the most widely utilized reactions involve hydrogenation, epoxidation, or dihydroxylation, these reactions form only one type of bond, either a C−H or C−O bond, and normally involve only one mechanism for enantiodiscrimination, differentiating enantiotopic faces of a prochiral olefin or carbonyl group. There are two important characteristics that distinguish asymmetric allylic alkylations from essentially all other methods of asymmetric induction: first, the number of mechanisms for enantiodiscrimination and, second, the diversity of bond types that can be formed.[1] In the asymmetric allylic alkylation reaction, the chiral elements can be set at the nucleophile, the electrophile, or both. Since the first example of the chiral element being set at the electrophile in an asymmetric allylic alkylation reaction, numerous examples of all three outcomes have been observed. Approaches that simultaneously set the chiral elements at both the electrophile and nucleophile, however, have only recently been developed.

In contrast to most metal-catalyzed enantioselective processes, asymmetric allylic akylations involve net reaction at sp^3 instead of sp^2 centers. The ability to transform achiral, prochiral, or chiral racemic material to enantiopure material under similar conditions is unique to the asymmetric allylic alkylation (AAA) reaction. Furthermore, conversion of chiral racemic material to a single enantiomer, either through a *meso* intermediate or through a dynamic kinetic asymmetric transformation (DYKAT), is infrequently observed or not often possible in other types of asymmetric transformations.

The general catalytic cycle of the AAA reaction offers at least five opportunities for enantiodiscrimination[2], and in some instances, more than one mechanism is operative when chiral elements at the electrophile and nucleophile are set in the same reaction. The cycle involves olefin complexation, subsequent ionization of a leaving group, and then nucleophilic addition and decomplexation (Scheme 1). Except for decomplexation of the olefin from the palladium−ligand system, where the chirality has already been set, each of these steps provides an opportunity for enantioselection. In the π-allyl inter-

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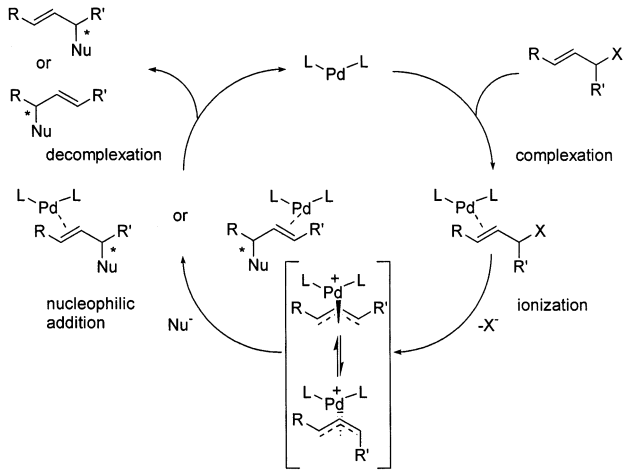
Born in Philadelphia, PA, in 1941 where, in 1959, he began his university training at the University of Pennsylvania (BA degree, 1962), Barry Trost obtained his Ph.D. degree in Chemistry just three years later at the Massachusetts Institute of Technology (1965). He directly moved to the University of Wisconsin, where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor of Chemistry in 1982. He joined the faculty at Stanford University as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In recognition of his many contributions, Professor Trost has received numerous awards, a few of which are the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), the Guenther Award in the Chemistry of Essential Oils and Related Products (1990), the Dr. Paul Janssen Prize (1990), 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 Yamada Prize (2001), and the ACS Nobel Laureate Signature Award for Graduate Education in Chemistry (2002). Professor Trost's research interests include the invention and development of new synthetic reactions largely based upon catalysis using transition-metal complexes and their use to define strategies that result in the total synthesis of complex molecules largely of biological importance.

Matthew L. Crawley was born in Suffern, NY, in 1976. He obtained his B.A. degree from Williams College with a double major in political economy and chemistry under the guidance of Professor J. Hodge Markgraf. In 1998 he started his graduate studies with Professor Barry M. Trost at Stanford University, where his work has focused on the development of asymmetric palladium-catalyzed reactions with application in total synthesis. After completion of his Ph.D. degree in the spring of 2003, he will join the Medicinal Chemistry department at Incyte Corporation in Delaware.

mediate, the complex may be syn-syn, syn-anti, or anti-anti (Figure 1). As shown in the catalytic cycle, the complexes that result from *E* olefins prefer the syn-syn configuration, while cyclic substrates are necessarily locked into the anti-anti geometry.

In the olefin complexation step, if one complex leads to ionization at a rate significantly faster than the other, and nucleophilic capture of that dia-

Scheme 1. Catalytic Cycle in Palladium-Catalyzed Asymmetric Allylic Alkylations



stereomer is fast relative to $\pi-\sigma-\pi$ equilibration, then enantiopic olefin face complexation becomes the enantiodetermining step (mechanism A). In a case where there are two potential leaving groups on a *meso* or on an achiral *gem*-disubstituted system, enantiotopic ionization of leaving groups is the enantiodetermining step (mechanism B). If the starting allylic system is a chiral racemic moiety but ionization leads to a *meso* π-allyl intermediate, differentiation of enantiotopic allyl termini is the enantioselection event (mechanism C). When the initial olefin coordination is rapid and reversible, two diastereomeric palladium complexes can form. These complexes can equilibrate through a $\pi-\sigma-\pi$ equilibration step, where either the more abundant (assuming similar rates of reaction) or the more reactive diastereomeric complex leads to product (mechanism D).[3] This type of selection, when the starting material is chiral racemic, constitutes a dynamic kinetic asymmetric transformation. Additionally, the chiral element may be set at the nucleophile, and with an achiral allyl complex, enantioface discrimination by

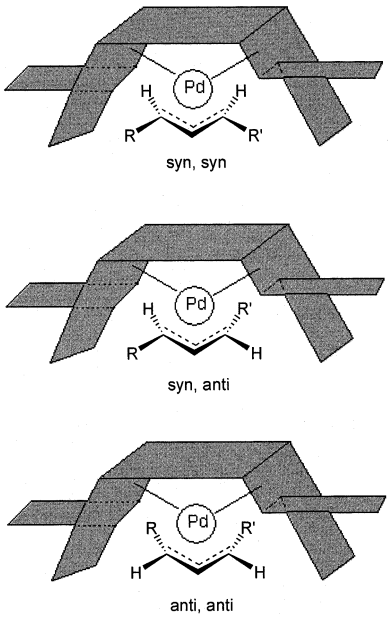


Figure 1. Palladium/ligand cartoon.

prochiral nucleophiles is the enantiodetermining step (mechanism E).

This review will be generally limited in scope to reactions that either provide a new mechanistic insight or synthetic advantage in asymmetric allylic alkylations, particularly those reactions that have been utilized in complex molecule total synthesis. Special attention will be given to syntheses that achieved otherwise difficult to target asymmetric transformations.[4]

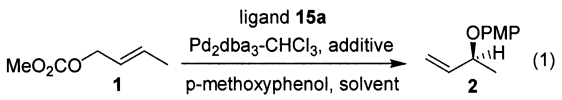
B. Mechanisms for Enantiodiscrimination

1. Preferential Ionization via Enantioselective Olefin Complexation (Mechanism A)

As in many other catalytic asymmetric reactions, differentiation of enantiotopic olefin faces is an operative mechanism of enantioselection. When the olefin is not symmetrically substituted, the transition-metal−ligand complex must distinguish between the two prochiral faces of the olefin. While generally olefin complexation with palladium is considered rapid and reversible, the d^{10} metal−olefin complex stabilities vary widely.[5]

There are only limited instances where it appears that enantioselective olefin complexation is the enantiodetermining step in the transition-metal-catalyzed allylic alkylations. A combination of factors required for such selectivity include an achiral allylic substrate with kinetic ionization of one olefin complex over the other and nucleophilic capture of the resulting allyl system at a rate significantly greater than the rate of $\pi-\sigma-\pi$ equilibration of the diastereomeric complexes.

One example, the regio- and enantioselective allylic alkylation of crotyl carbonate **1** with 4-methoxyphenol affording adduct **2**, meets these criteria (eq 1).[6] An increase in chloride ion additive, which

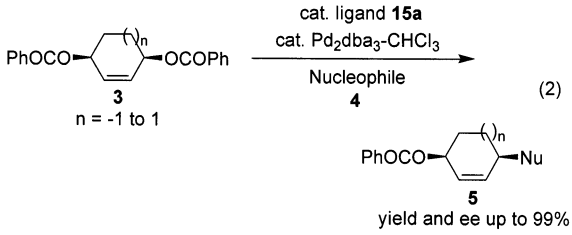


increases the rate of $\pi-\sigma-\pi$ equilibration of the diastereomeric complexes, drastically decreases enantioselectivity (Table 1, entry 2). This appears not to be a base-catalyzed effect, as the use of hindered bases has no impact on or increases the enantioselectivity. Furthermore, lowering the concentration, which should presumably decrease the rate of Pd(0)−Pd(0) S_N2-like exchange, actually increases the % ee of the adduct. Even more striking, a change to the branched chiral racemic carbonate gives the branched regioisomer of product but with low enantioselectivity. All of these findings strongly suggest that enantiotopic olefin face coordination is the enantiodetermining event in this AAA reaction.

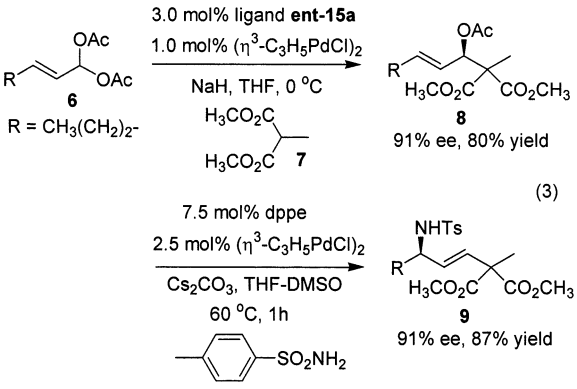
2. Enantiotopic Ionization of Leaving Groups (Mechanism B)

Selective ionization of enantiotopic leaving groups to induce specific stereochemistry during substitution is a mechanism that has been exploited in a large array of total syntheses. There are two electrophile types for this mechanistic class: 1,4-bisacyloxy-2-enes and allylic geminal dicarboxylates.

The ready accessibility of *meso* 2-alkene-1,4-diol intermediates promotes use of the first type of intermediates in total synthesis. This reaction is illustrated by the desymmetrization of diol derivative **3** with nucleophile **4** using ligand **15a** to afford adduct **5** (eq 2). The transformation generally proceeds with high enantioselectivity and yield.[7]



Allylic *gem*-diacetates serve as excellent substrates for the AAA reaction. The mechanistic evidence supports enantiotopic ionization of one of the prochiral acetate leaving groups as the enantiodetermining step. An example of this transformation involves the reaction of gem-diacetate **6** with the sodium salt of dimethyl methylmalonate **7**. This afforded adduct **8** in high yield (80%) and 91% ee (eq 3).[8] As in the case



of the traditional *meso* diesters, the product is still an allyl ester capable of undergoing another allylic alkylation reaction with tosylamine, where steric

Table 1. Asymmetric Allylic Alkylation of 4-Methoxyphenol with Crotyl Carbonate

entry	Pd_2dba_3 (mol %)	ligand (mol %)	conditions	% yield	branched:linear	% ee
1	1.0	3.0	CH_2Cl_2, 0 °C, 0.5 M	78	92:8	71
2	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M, 30% Bu_4NCl	86	97:3	31
3	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M	75	95:5	81
4	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M, TMG	72	94:6	80
5	0.25	0.75	CH_2Cl_2, 0 °C, 0.5 M, K_2CO_3	75	93:7	81
6	0.25	0.75	toluene, 0 °C, 0.1 M	95	96:4	90
7	0.25	0.75	branched SM, as entry 4	92	96:4	32

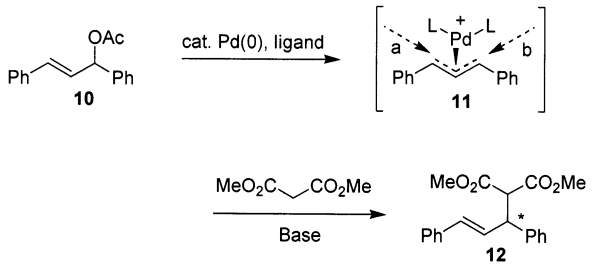
factors dictate a net S_N2' displacement, giving 100% transfer of chirality to generate adduct **9**.

3. Attack at Enantiotopic Termini of the Allyl Complex (Mechanism C)

If a chiral allylic substrate generates a *meso* π-allyl intermediate after ionization, then the two allylic termini of the complex are enantiotopic. This allows for the enantioselectivity with respect to the product to be determined by the regiochemistry of the nucleophilic addition to the allyl complex. Both stabilized and unstabilized nucleophiles may lead to enantiomeric products through control of regioselectivity induced by the chiral ligand.

The most extensively studied example of such a system is 1,3-diphenylallyl acetate **10**, which when ionized creates a *meso* complex **11**. This complex may subsequently be attacked by the conjugate base of dimethyl malonate at either termini (path a or path b), which subsequently affords chiral adduct **12** (Scheme 2).[9,10] Although this reaction has become a benchmark system for exploration of new ligands, the results from this system do not necessarily translate into high enantioselectivity for other substrates.[1,2,5]

Scheme 2. Desymmetrization of a meso-π-Allyl Intermediate with Malonate Nucleophile

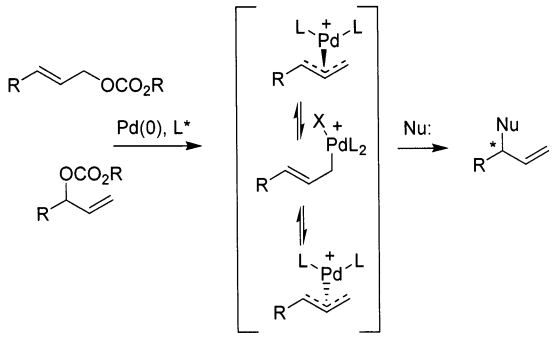


4. Enantioface Exchange in the η^3-Allyl Complex (Mechanism D)

Enantiotopic olefin face coordination or enantiotopic ionization may not be the enantioselection step in an AAA reaction if the diastereomeric π-allylmetal intermediates interconvert faster than nucleophilic capture. In this type of mechanistic scenario, there are several issues that complicate the picture. Not only enantioselectivity but regioselectivity of nucleophilic addition becomes a consideration. This mechanism can be grouped into two categories based on substrate: one with an achiral allylic ester and one starting with a chiral racemic ester. Reaction in the latter case constitutes a dynamic kinetic asymmetric transformation as both enantiomers of starting material are converted to a single enantiomer of product. The level of asymmetric induction can be derived either from the relative abundance of each diastereomeric intermediate if their rates of reaction are similar or more likely from the differential rates of reaction of the two interconverting diastereomeric intermediates.

In the case of an achiral substrate, generally a linear allylic carbonate, the two diastereomeric complexes that result from ionization can interconvert through $\pi-\sigma-\pi$ equilibration on the terminal carbon of the allyl system, where the sigma complex is achiral with respect to electrophile (Scheme 3). In this case, however, the initial amount of each diastereomeric complex formed may not be equal.

Scheme 3. Asymmetric Allylic Alkylation via Enantioface Exchange of Allylpalladium Complex

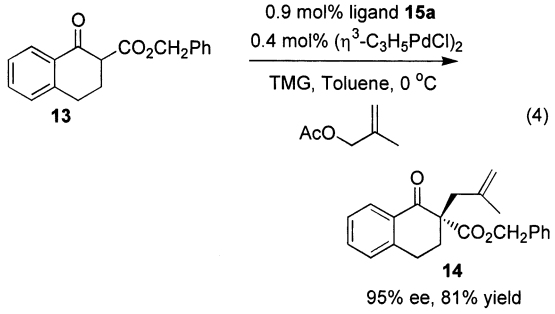


When starting with a chiral racemic allylic carbonate, the same type of equilibration via $\pi-\sigma-\pi$ interconversion occurs. However, in this case a 1:1 mixture of diastereomeric intermediate palladium complexes is initially formed (Scheme 3). The allyl intermediates must equilibrate through a terminal sigma carbon−bound complex so that the initial chirality with respect to carbon is erased or through the palladium complex shifting to a heteroatom with the same net effect (this phenomenon is discussed later in the syntheses of aflatoxin B lactone and (+)-brefeldin A).

5. Differentiation of Prochiral Nucleophile Faces (Mechanism E)

Enantioselection can occur when the π-allyl-ligand complex differentiates between the prochiral faces of the nucleophile. In this mechanism, where the nucleophile attacks on the face of the π-allyl system opposite to that of the chirality inducing metal−ligand complex, the induction of asymmetry appears to be quite a challenge.

The use of ligands that can impose a good enough chiral environment around prochiral nucleophiles, such as salts of β-diketones and β-diesters, can overcome these demands and give excellent enantioselectivity with allyl acetates. An example of a reaction that derives enantioselectivity from discrimination of prochiral nucleophile faces is the alkylation of tetralone **13** with 1-acetoxy-2-methyl-2-propene to give quaternary-substituted adduct **14** in high yield (81%) and 95% ee (eq 4).



C. Chiral Ligands

A feature that is unique to transition-metal-catalyzed asymmetric allylic alkylation reactions is

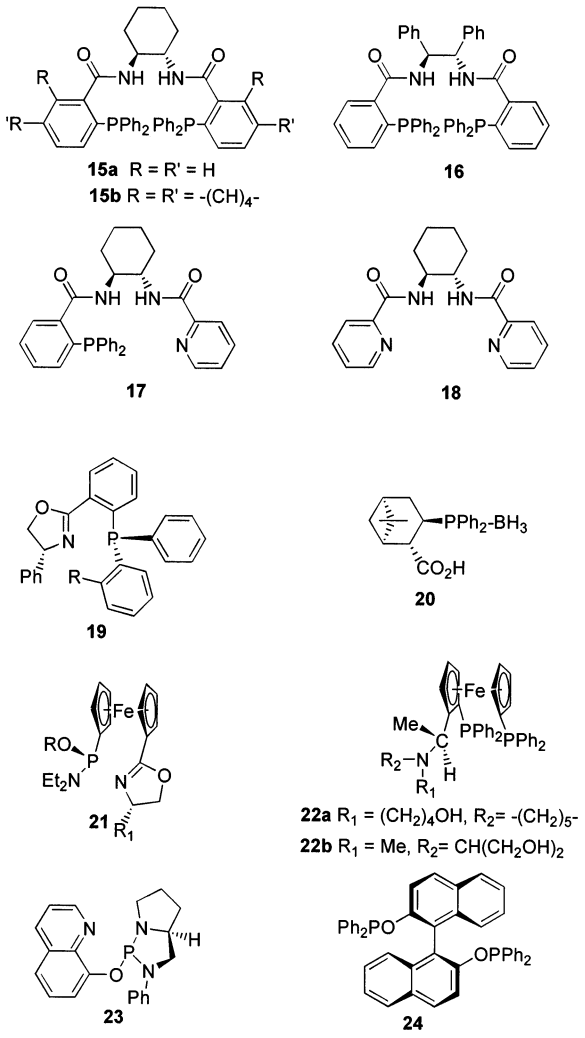


Figure 2. Chiral ligands utilized in total synthesis.

their ability to convert very different starting materials with a range of symmetry types—chiral racemic, *meso*, and achiral—to enantiomerically pure material. The types of ligands to effect this transformation have followed three general concepts in design: (1) creating chiral space with an array of groups whose conformational bias originates from primary stereogenic centers;[11] (2) electronic desymmetrization on the donor atoms of the ligand where different bond lengths on each side of the chiral space promote differential reactivity at each terminus;[12] (3) attaching a tether to coordinate the incoming nucleophile.[13] Figure 2 lists those ligands which are most prevalent in AAA-driven natural product total synthesis.

II. Carbon–Carbon Bond Formation: Synthetic Applications and Developments

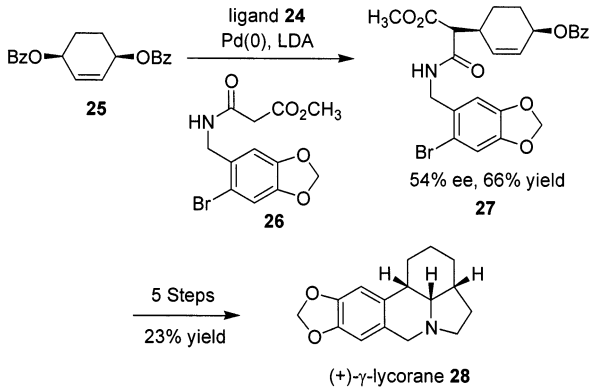
Asymmetric carbon−carbon bond formation has been an ongoing challenge in synthetic organic chemistry. In the AAA reaction, good enantioselectivity at the nucleophile and electrophile and diastereoselectivity with respect to both has been achieved with soft carbon nucleophiles on cyclic and acyclic electrophiles. The range of selectivity is demonstrated in the access afforded to a wide range of natural products. New developments with metals other than palladium for AAA carbon−carbon bond formation are also highlighted.

A. Total Syntheses with Carbon Nucleophiles

1. Malonate Type Nucleophiles

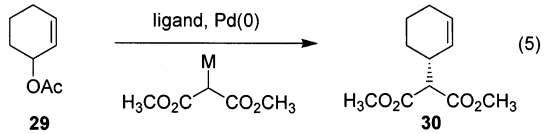
While there are several instances of acyclic electrophiles utilized with carbon nucleophiles in AAA reactions, the majority of applications in total synthesis are with cyclic electrophiles, particularly those involving five- or six-membered rings. Desymmetrization of *meso*-diester **25** with amide **26** afforded adduct **27** in 66% yield with up to 54% ee (Scheme 4).[14] The chirality was derived from the (*S*)-BINAPO

Scheme 4. Total Synthesis of (+)-γ-Lycorane



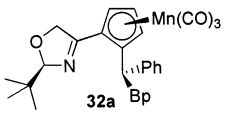
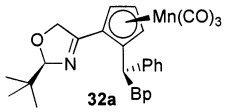
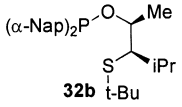
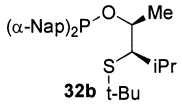
ligand **24**, first developed for Pd-catalyzed AAA reactions in the Trost group.[9] It should be noted that such desymmetrization usually proceeds with more than 95% ee utilizing the Trost−Van Vranken ligands.[15] The amide from the initial adduct was then cyclized in a diastereoselective AAA reaction using base with achiral ligands. After decarboxylation, the intermediate was subjected to a Heck cyclization and was then transformed to (+)-γ-lycorane **28** in 23% overall yield.

Several of the cyclic substrates utilized for total synthesis ionize to symmetrical π-allyl fragments, where the ligand allows for differentiation of enantiotopic termini of the intermediate. The synthesis of (−)-wine lactone **33** takes advantage of this type of process.[16] Starting with racemic acetate **29**, the lithium anion of dimethyl malonate is used as nucleophile to deracemize **29**, affording enantioenriched derivative **30** (eq 5). While the authors utilized ligand

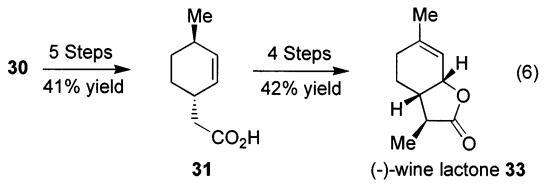


20 affording adduct **30** in 95% ee and 91% yield, many ligands and conditions provide comparable results[17−19] (See Table 2). Intermediate **30** was subsequently decarboxylated, cyclized via iodolactonization, opened with S_N2' cuprate substitution to adduct **31** in a 92:8 ratio to the undesired "syn" addition adduct. The carboxylic acid **31** was subsequently

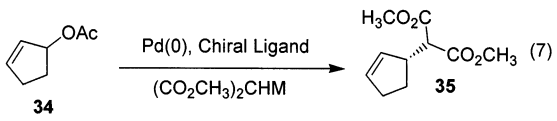
Table 2. Asymmetric Alkylation of Cyclic Allyl Acetates

Entry	Acetate	Ligand	Conditions	% Yield	% ee	Ref
1	**29**	**20**	$LiCH(CO_2CH_3)_2$, THF, rt	91	95	16
2	**34**	**15**	$NaCH(CO_2CH_3)_2$, $(Hex)_4NBr$, CH_2Cl_2, 0 °C	81	98	17
3	**29**	**15**	$NaCH(CO_2CH_3)_2$, $(Hex)_4NBr$, CH_2Cl_2, 0 °C	86	96	17
4	**34**	 **32a**	$NaCH(CO_2CH_3)_2$, THF, rt	73	96	18
5	**29**	 **32a**	$NaCH(CO_2CH_3)_2$, THF, rt	62	93	18
6	**34**	 **32b**	$KCH(CO_2CH_3)_2$, BSA, CH_2Cl_2, -20 °C	94	94	19
7	**29**	 **32b**	$KCH(CO_2CH_3)_2$, BSA, CH_2Cl_2, -20 °C	90	94	19

transformed in four steps and 42% yield to (−)-wine lactone **33** (eq 6).



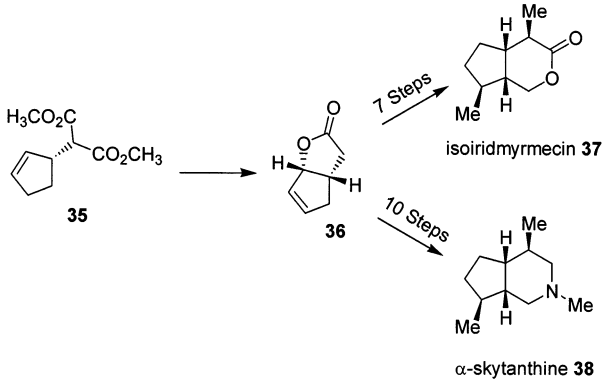
A similar palladium-catalyzed deracemization of the cyclopentene substrate **34** with the anion of dimethyl malonate as nucleophile with a number of ligands proceeds to adduct **35** in excellent yields and up to 98% ee (eq 7) as summarized in Table 2.



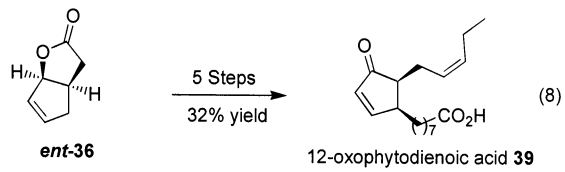
The unsaturated lactone **36** is derived from a similar alkylation followed by iodolactonization and elimination.[20] Lactone **36** was transformed to isoiridomyrmecin **37** in 7 steps and to α-skytanthine **38** in 10 steps (Scheme 5). The key step in both series was a diastereoselective S_N2' cuprate addition to introduce a side chain which would later be cyclized to form the second ring.

The enantiomer of intermediate **36** was utilized in an enantioselective synthesis of jasmonoids, a class

Scheme 5. Completion of the Total Syntheses of Isoiridomyrmecin and α-Skytanthine

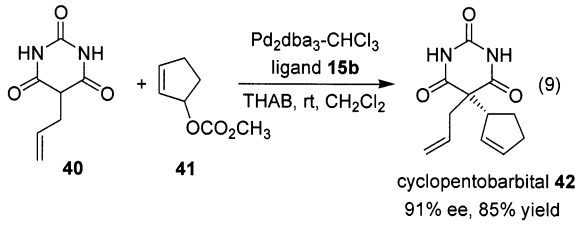


of cyclopentanones that participate in signaling of a variety of biological processes.[21] For example, an adduct *ent*-**36** was transformed to 12-oxophytodienoic acid **39** in five steps with 32% overall yield (eq 8).



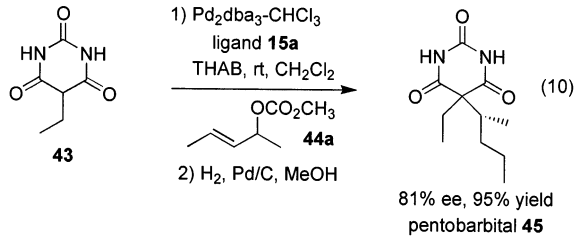
The AAA reaction with cyclic allylic electrophiles further demonstrates utility in the total synthesis of barbituric acid derivatives. Asymmetric allylic alkyl-

ation utilizing barbituate derivative **40** as nucleophile with simple allylic carboxylate **41** as electrophile afforded cyclopentobarbital **42** (5-allyl-5-cyclopent-2-enylbarbituric acid) in 85% yield and 91% ee (eq 9).[22]



This transformation utilized the dinaphthyl ligand **15b**, palladium dibenzylidene acetone chloroform complex as the palladium source, and tetrahexylammonium bromide as additive, the combination of which completely suppressed the typical N-alkylation reaction.

Pentobarbital (5-ethyl-5-(1-methyl-1-butyl)-barbituric acid) **45** was also synthesized in two steps in 81% ee through an AAA of carbonate **44** with barbituate **43** followed by hydrogenation (eq 10). In



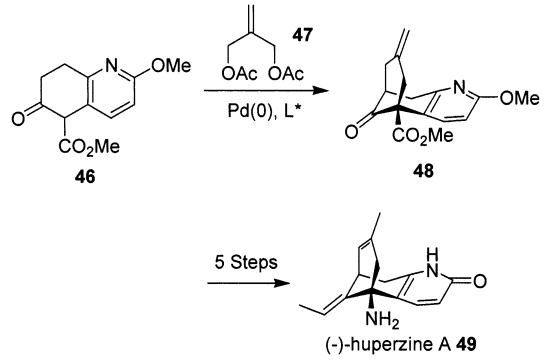
contrast to cyclopentobarbital, the key alkylation required ligand **15a** instead of the more sterically encumbered ligand **15b**.

Efforts toward (−)-huperzine A **49** utilizing an asymmetric allylic alkylation of symmetrical 2-methylene-1,3-propanediol diacetate **47** in which the enantiodiscriminating event involves differentiating the prochiral faces of the nucleophile have been ongoing for the last several years. This lycopodium alkaloid, isolated from the Chinese traditional medicinal herb *Huperzia serrata*, is a potent, selective, and reversible inhibitor of acetylcholinesterase.[23,24,25] It has been approved as a drug for the treatment of Alzheimer's disease, further stimulating synthetic efforts.

Three syntheses were published nearly simultaneously describing the similar asymmetric palladium-catalyzed bicycloannulation of β-keto ester **46**[26−28] as the key step to afford adduct **48** (Scheme 6). This alkylation is an example where differentiation of prochiral faces of the enolate is the enantioselection event. A recent effort with new ligands utilized the same nucleophile and electrophile and ultimately led to the highest levels of enantioselectivity.[29]

Extensive studies were conducted by the authors to optimize for a variety of conditions, with particular attention given to ferrocenylphosphine ligands and sterically encumberd amine bases. The earlier efforts achieved maximum selectivity between 52 and 64% ee. However, new ligand design involving variation of the R group of ligand **22a** led to ee's up to 90% (when $R_1 = (CH_2)_4OH$ and R_2 = cyclopentyl). In all

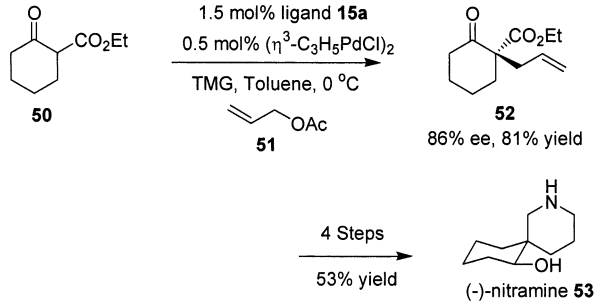
Scheme 6. Total Synthesis of (−)-Huperzine A



of these efforts, the key intermediate **48** was transformed to (−)-huperzine A **49** in five steps according to literature protocol (Scheme 6).

An asymmetric synthesis of the spiro-alkaloid (−)-nitramine **53** was reported using a β-ketoester nucleophile **50** with allyl acetate **51** as an electrophile (Scheme 7).[30] This is another example where chirality is set at the nucleophile, and the enantioselection must clearly derive from enantiodiscrimination of prochiral nucleophile faces. The AAA reaction affords adduct **52** in 81% yield and 86% ee. The tetrasubstituted derivative **52** was transformed in four steps and 53% overall yield to (−)-nitramine **53**, the key step entailing a novel diastereoselective ketone reduction accompanied by alkene hydration.

Scheme 7. Asymmetric Synthesis of (−)-Nitramine

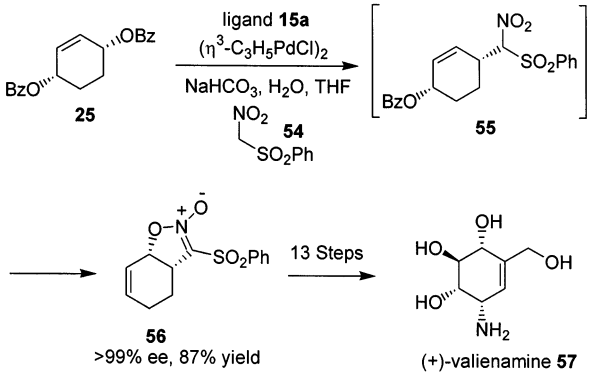


2. Other Stabilized Carbanions as Nucleophiles

Nucleophiles other than dimethyl malonate and related derivatives have played a crucial role in exploiting the power of the AAA reaction in total synthesis. Phenylsulfonyl-nitroalkane derivatives have been successfully utilized in the syntheses of (+)-valienamine **57**, a glycosidase inhibitor, *C*-2-*epi*-hygromycin A **63**, and (+)-cyclophellitol **77**.

The total synthesis of (+)-valienamine **57** derived its chirality from the desymmetrization of *meso* enedibenzoate **25** with sulfonylnitroalkane **54**. This enantioselective double-substitution reaction proceeds through intermediate **55** and affords cyclized product **56** in 87% yield with >99% ee (Scheme 8).[31] The initial alkylation was completed rapidly at ambient temperature, while the cyclization was significantly slower, likely due to the "mismatched" ionization required for the second alkylation. This gave the net equivalent of an asymmetric cis-hydroxycarboxylation after subsequent transformations. The bicyclo adduct **56** was transformed in 13

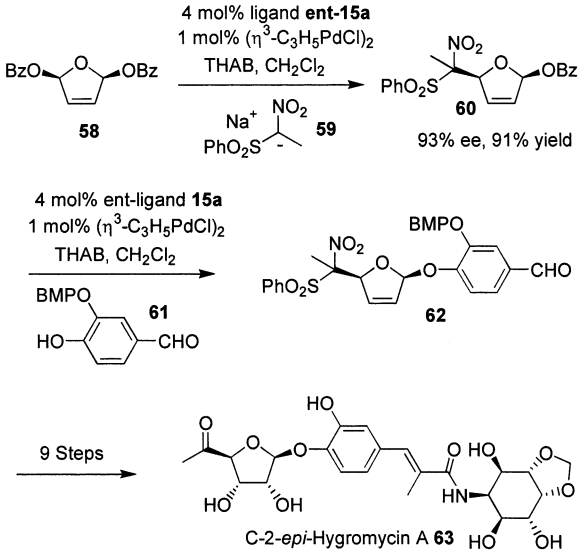
Scheme 8. Total Synthesis of (+)-Valienamine



steps to (+)-valienamine **57**, with the key step a palladium(0)-catalyzed net regioselective cis-hydroxyamination from the reaction of an intermediate cyclic vinyl epoxide with an isocyanate.

Asymmetric desymmetrization of 2,5-diacyloxy-2,5-dihydrofurans using a Pd-catalyzed alkylation has afforded access to several natural products. All of the stereochemistry in the furan moiety of *C*-2-*epi*-hygromycin A **63** was derived from a desymmetrization of 2,5-dibenzoyloxy-2,5-dihydrofuran **58** using a Pd-catalyzed AAA with the sodium salt of 1-phenylsulfonyl-nitroethane **59**.[32] This transformation, achieved in 93% ee with the Trost ligand **15a**, afforded dihydrofuran fragment **60** in 91% yield (Scheme 9).[33] A second allylic alkylation, with the

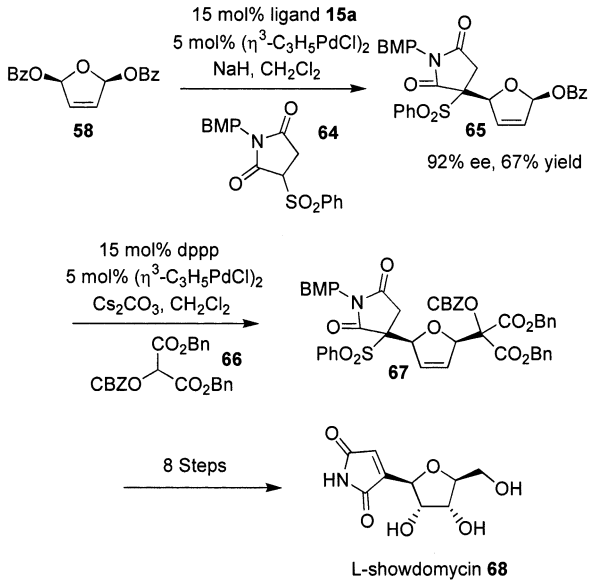
Scheme 9. Total Synthesis of C-2-epi-Hygromycin A



enantiomer of ligand **15a**, using phenol **61** as nucleophile afforded adduct **62** in 75% yield. While, in principle, chiral ligands are not required for this second alkylation since control of regio- and diastereoselectivity is only required, the higher reactivity of the chiral palladium complexes sometimes makes them the catalysts of choice. Adduct **62** was transformed in nine steps with diastereocontrolled elaboration of the 3,4-olefin to complete the synthesis of *C*-2-*epi*-hygromycin A **63**.

A synthesis of L-showdomycin **68** employs a desymmetrization of 2,5-dibenzoyloxy-2,5-dihydrofuran

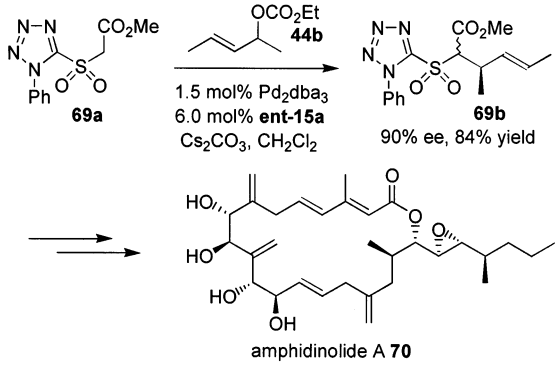
Scheme 10. Total Synthesis of L-Showdomycin



58 as the first step. The *meso*-dihydrofuran **58** was transformed into adduct **65** using imidosulfone **64** with ligand **15a** in 67% yield and 92% ee (Scheme 10).[34] The monoalkylated adduct **65** was alkylated again, with malonate-like nucleophile **66** using achiral palladium(0) complex with 1,3-bisdiphenylphosphinopropane to afford key intermediate **67**. This was transformed to L-showdomycin **68** in a total of eight steps. Obviously, access to the natural D-showdomycin only entails changing the chirality of the ligand in the initial allylic alkylation. Equivalent access to either enantiomer is clearly one of the benefits of asymmetric catalysis where both enantiomers of the catalyst are equally readily available.

In a total synthesis of the proposed structure of amphidinolide A **70**, a novel 20-membered macrolide with antitumor activity,[35] the chiral side chain was formed by employing a desymmetrization of *meso*-carbonate **44b** with sulfone ester **69a** (Scheme 11).[36]

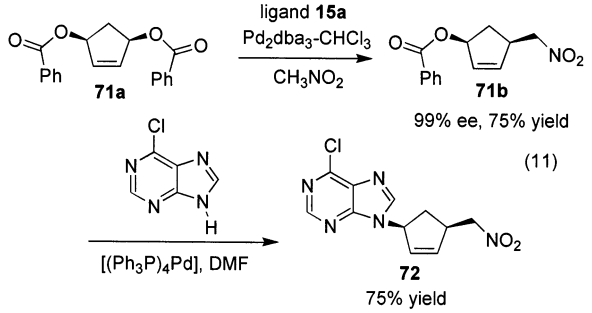
Scheme 11. Total Synthesis of Amphidinolide A



The reaction afforded product **69b** as a 1:1 mixture of diastereomers in 90% ee with 84% yield. Fragment **69b** was decarboxylated and later attached to the core structure through an *E*-selective Julia olefination. This fragment with others led to an efficient synthesis of amphidinolide A **70**.

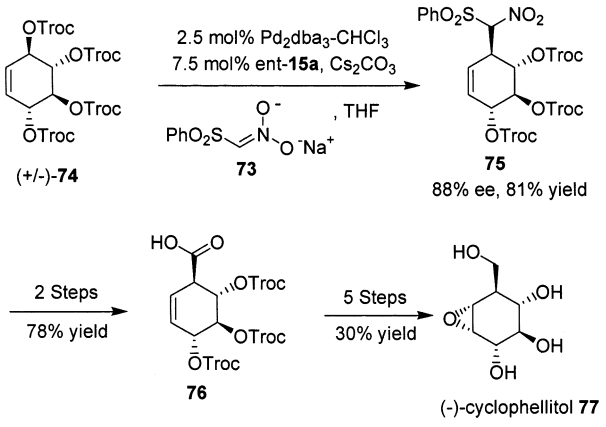
Though not yet utilized in a completed total synthesis, simple nitroalkanes serve as excellent

nucleophiles in asymmetric allylic alkylations.[37] Desymmetrization of *meso*-bisbenzoate **71a** with nitromethane utilizing ligand **15a** afforded **71b** in 99% ee and 75% yield (eq 11). Subsequent alkylation with heterocyclic amine nucleophile gives the known carbanucleoside intermediate **72** in 75% yield.



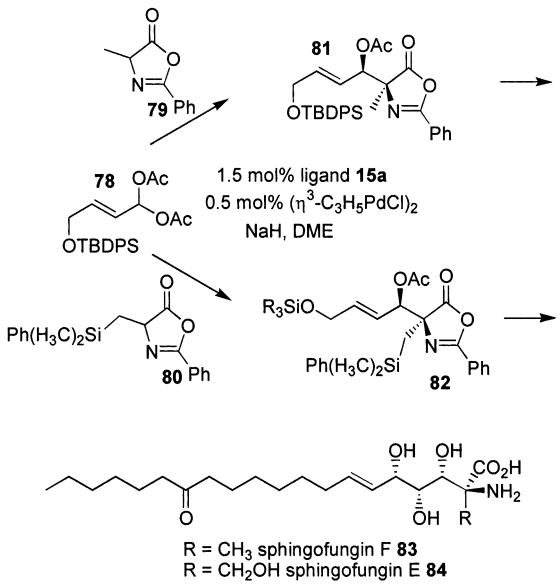
A second-generation synthesis of (−)-cyclophellitol **77**, a potent inactivator of β-glucosidase and inhibitor of HIV,[38] utilized the sodium salt of (phenylsulfonyl)-nitromethane **73** as nucleophile in the dynamic kinetic asymmetric transformation of troc-tetraester **74**.[39] (Scheme 12) The resulting adduct **75**, afforded in 81% yield and 88% ee, was readily converted in two steps with 78% yield to carboxylic acid derivative **76**. Thus, the salt of (phenylsulfonyl)nitromethane served as an equivalent of an alkoxylcarbonyl anion. Derivative **76** was converted in five steps and 30% overall yield to (−)-cyclophellitol **77**.

Scheme 12. Total Synthesis of (−)-Cyclophellitol



Several AAA reactions have managed to achieve stereoselectivity at both the nucleophile and the electrophile, giving rise to high enantioselectivity and diastereoselectivity in the formation of the adducts. In the total syntheses of sphingofungins F **83** and E **84**, such control was used advantageously. Prochiral *gem*-diacetate **78** was available in three steps from commercial 2-butyn-1,4-diol in a sequence involving silyl protection, a ruthenium-catalyzed redox isomerization,[40] and subsequent acetal formation from the aldehyde using ferric-chloride-catalyzed addition of acetic anhydride. The *gem*-diacetate **78** and the sodium anion of azlactone **79** with ligand **15a** and π-allylpalladium chloride dimer as catalyst produced an 11:1 mixture of diastereomers (major **81**) isolated in 70% and 5% yields, respectively, both with 89% ee (Scheme 13).[41] Azlactone **80**, differing from **79** only

Scheme 13. Total Synthesis of Sphingofungins E and F



in having a dimethylphenylsilylmethylene substituent instead of a methyl group, afforded adduct **82** as the major diastereomer (2.4:1.0) with 96% ee.[42] In both instances the enantiodetermining step must involve both discrimination between enantiotopic faces of the nucleophile and enantiotopic ionization of prochiral acetate leaving groups. The synthesis of sphingofungin F **83** was completed in 15 total steps and 17% overall yield, highlighted by a diastereoselective dihydroxylation and stereoselective palladium(II)-catalyzed 1,3-allylic transposition. The synthesis of sphingofungin E **84** was completed utilizing a similar strategy in 17 total steps with 5.1% overall yield.

B. AAA with Other Transition-Metal Catalysts

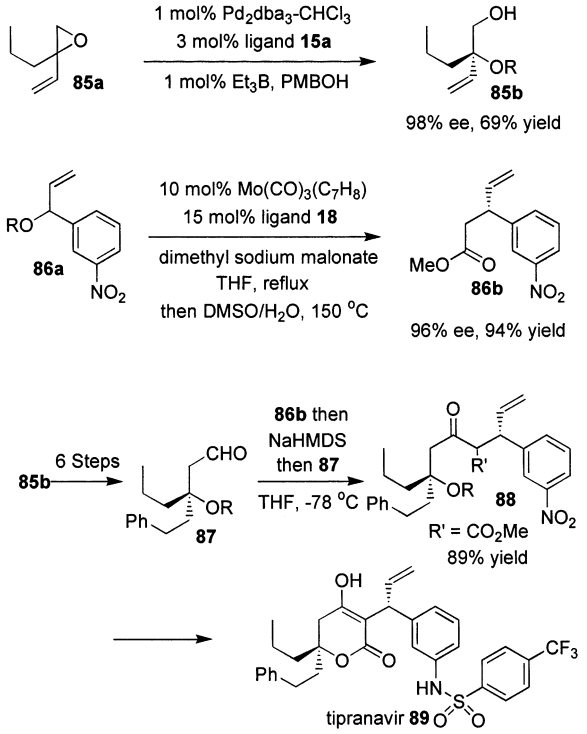
Metals other than palladium have successfully been employed in the AAA reaction with carbon nucleophiles. However, with the exception of molybdenum, none have yet realized their full potential in application to the total synthesis of a complex natural product.

1. Molybdenum

Molybdenum-catalyzed AAA reactions function similarly to palladium-catalyzed AAA reactions, with one key difference. In most cases of palladium-catalyzed AAA reactions, when there is a choice without electronic bias between a primary and secondary carbon, the linear adduct is favored. However, with molybdenum-catalyzed AAA reactions the opposite is true and the branched product is favored. Thus, the molybdenum AAA reaction serves as regiocomplimentary to the palladium-catalyzed process.

Some methodology work using the molybdenum-catalyzed AAA, where the scope and limitations of the system were explored,[43] helped set the stage for a concise synthesis of tipranavir **89**.[44] This therapeutic agent used to combat the human immunodeficiency virus (HIV), currently in phase IIb clinical trials, provides two stereogenic centers, one tetra-

Scheme 14. A Concise Enantioselective Total Synthesis of Tipranavir



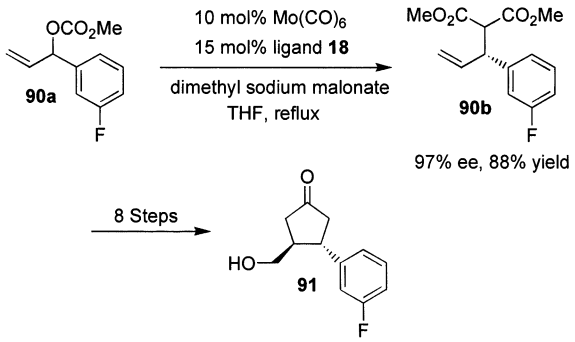
substituted, as well as a highly functionalized lactone as a synthetic challenge. The tetrasubstituted center was set from a regio- and enantioselective palladium-catalyzed boron-cocatalyzed DYKAT reaction of vinyl epoxide **85a** with 4-methoxybenzyl alcohol to afford adduct **85b** (Scheme 14) (DYKAT reactions with epoxides are discussed later). The stereogenic tertiary center was formed through a molybdenum-catalyzed AAA in a DYKAT of carbonate **86a** with dimethyl malonate to afford adduct **86b** after decarboxylation. Adduct **85b** was transformed to **87** and subsequently coupled in an aldol reaction employing sodium bistrimethylsilylamide as base to afford adduct **88**. Subsequent transformations afforded tipranavir **89** in a high 25% overall yield.

Another application of the AAA with molybdenum was reported by researchers at Merck laboratories in the synthesis of **91**, an advanced intermediate in the preparation of an investigational new drug candidate.[45] Asymmetric alkylation of racemic carbonate **90a** with dimethyl malonate using ligand **18** afforded chiral adduct **90b** in 97% ee and 88% yield (Scheme 15). Equilibration of the diastereomeric intermediate molybdenum complexes through $\pi-\sigma-\pi$ transitions must occur, and one complex reacts significantly faster (see section I.B), leading to adduct **90b** with high selectivity. This reaction was extremely robust and has been run on kilogram scale.[46] The AAA adduct **90b** was subsequently transformed to the key intermediate **91** in eight steps and 23% overall yield.

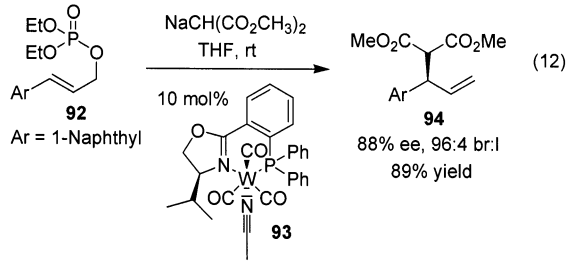
2. Tungsten

Though use of tungsten in the AAA reaction has not yet been applied in a total synthesis, applications with high enantioselectivity have recently been real-

Scheme 15. Synthesis of an Advanced Drug Intermediate



ized using a catalyst system based on the phosphinoaryloxazoline ligand **93**. In this case, alkylation of 3-aryl-2-propenyl phosphate **92** with sodium dimethyl malonate gave excellent enantioselectivity with high regioselectivity for the branched product **94**, which like molybdenum is complimentary to that of the palladium system (eq 12).[47]



3. Other Metals (Iridium, Nickel, and Platinum)

Iridium, nickel, and platinum have not been utilized in total syntheses yet, though their continued development will likely soon allow for this type of application. Recent advances in iridium-catalyzed processes[48,49] have allowed malonate-type nucleophiles to react with allylic acetates to give the branched product with ee's as high as 91%.

Nickel- and platinum-catalyzed AAA reactions, differing from the other metals in the use of "hard" nucleophiles with less reactive allylic ethers, have achieved great enantioselectivity in many cases. The process gives a net inversion of the allylic stereogenic center. This can be rationalized by assuming an inner-sphere reductive elimination mechanism, similar to that with palladium involving "hard" nucleophiles. Though the platinum AAA reaction has not been developed since efforts in the early 1980s,[50] progress has been made in nickel-catalyzed reactions using Grignard reagents as nucleophiles and allylic ethers with enantioselectivity often reaching over 80%.[51−53]

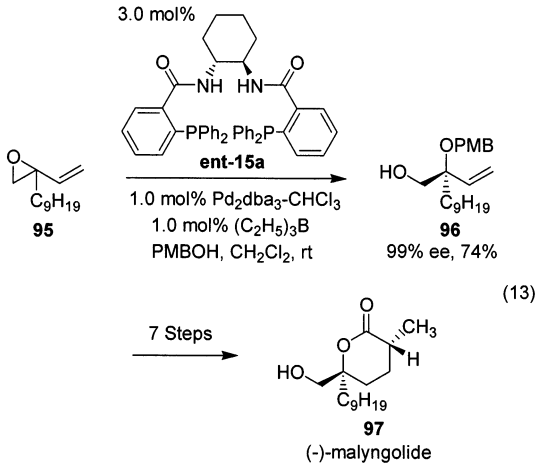
III. Syntheses Employing Asymmetric Carbon−Oxygen Bond Formation

The power of the palladium-catalyzed allylic alkylation is well demonstrated in carbon−oxygen bond-forming reactions utilized in total syntheses. Over a dozen biologically active molecules with diversity from (−)-malyngolide to callipeltoside have been synthesized using oxygen nucleophiles in the AAA

reaction. Syntheses using primary alcohols, carboxylates, and phenols are discussed in detail.

A. Primary Alcohols as Nucleophiles

Methodology to efficiently synthesize tetrasubstituted centers asymmetrically can play a key role in total synthesis of complex molecules. In this regard, dynamic kinetic asymmetric transformations in asymmetric allylic alkylation has created numerous possibilities for total synthesis, such as that utilized in the synthesis of (−)-malyngolide **97**. This compound is a naturally occurring antibiotic possessing significant activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes*. Beginning with chiral racemic 3-nonyl-3,4-epoxybut-1-ene **95**, an AAA reaction in a DYKAT with *p*-methoxybenzyl alcohol **3** as nucleophile with ent-ligand **15a**,-catalyzed by palladium and regiodirected by boron, afforded chiral allylic ether **96** in 74% yield with 97−99% ee (eq 13).[54] The chiral building block **96** was subsequently

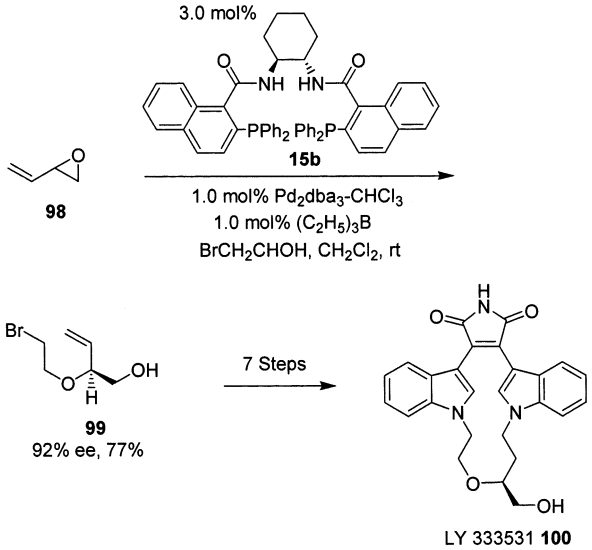


(13)

converted in seven steps to (−)-malyngolide **97**, highlighting a diastereoselective enolate protonation in the final step of the sequence.

Selective protein kinase C inhibitors, in particular Lilly drug LY 333531 **100**, provides a target that could utilize a DYKAT to set the key stereogenic center. Butadiene monoepoxide **98** and commercially available 2-bromoethanol were reacted in an asymmetric allylic alkylation using the Trost naphthyl ligand **15b** in a DYKAT to afford bisalkylating agent **99** (Scheme 16).[55] The choice of ligand **15b** which tightens the chiral pocket to slow the rate of nucleophilic attack increases both regio- and enantioselectivity by ensuring full equilibration of the intermediate diastereomeric complexes. This intermediate was transformed in seven steps to LY 333531 **100**.

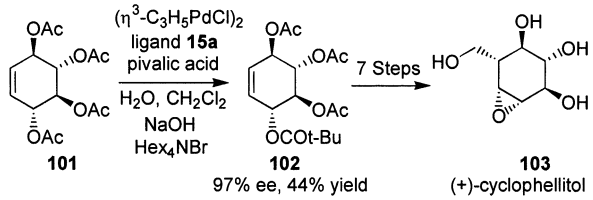
Scheme 16. Total Synthesis of Lilly Drug LY 333531



B. Carboxylates as Nucleophiles

Cyclic electrophiles are generally compatible with a broad range of nucleophiles including carboxylates. In the first-generation total synthesis of (+)-cyclophellitol **103**, an inhibitor of the HIV virus, a kinetic resolution of conduritol B **101** with the anion of pivalic acid as nucleophile gave adduct **102** in 44% yield (88% brsm) and 97% ee (Scheme 17).**56** The

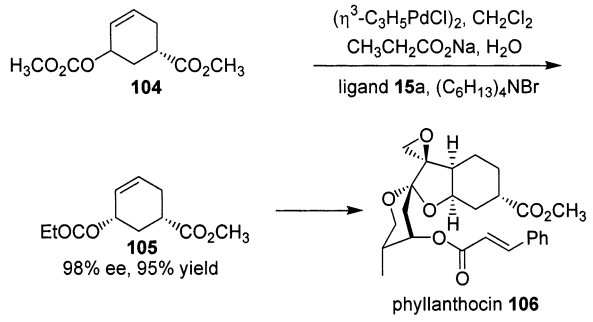
Scheme 17. Total Synthesis of (+)-Cyclophellitol



resolution also afforded resolved starting material in 99% ee after recrystallization. Differentiation between the hydroxyl groups in intermediate **102** allowed its transformation to (+)-cyclophellitol **103**.

The use of carboxylate nucleophiles in the AAA reaction may constitute the equivalent of a deracemizaton reaction. Deracemization of chiral racemic cyclic allyl carboxylate **104** gave a *meso*-π-allyl intermediate that was desymmetrized by sodium propionate to afford intermediate **105** in excellent ee (98%) and 95% yield (Scheme 18).[57] This product was the key building block for the synthesis of the antitumor agent phyllanthocin **106**.[58]

Scheme 18. Total Synthesis of Phyllanthocin



Dynamic kinetic asymmetric transformation of conduritol B tetracarboxylates facilitated a synthesis of D-*myo*-inositol 1,4,5-triphosphate **110**.[59] Racemic tetracarbonate **107** was transformed in an AAA using standard ligand **15a** with carboxylate nucleophile **108** to afford enantiopure (>99% ee) disubstituted product **109** in 80% yield (Scheme 19). The adduct **109** is then dihydroxylated with osmium tetroxide

Scheme 19. Synthesis of D-*myo*-Inositol

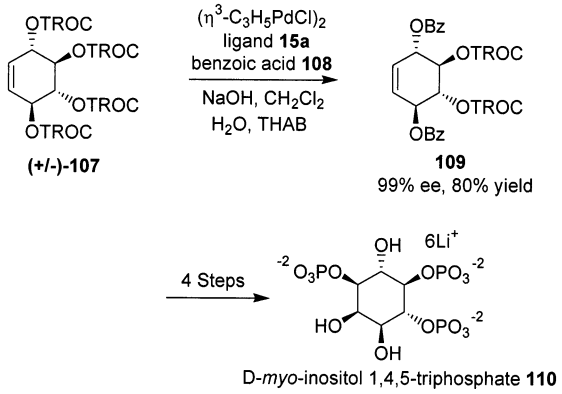


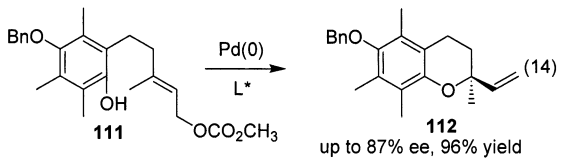
Table 3. Intramolecular Pd(0)-Catalyzed Allylic Alkyation

entry	additive	molarity	% ee	% yield
1	none	0.5	35	98
2	none	0.01	80	89
3	Et_3N	0.01	86	89
4	$EtN^{(i}Pr)_2$	0.01	87	86
5	H_2O	0.01	62	95
6	Bu_4NCl	0.01	38	41

utilizing *N*-methylmorpholine-*N*-oxide as the stoichiometric reoxidant, cleaved to the tetraol with zinc in acetic acid, and finally transformed in two additional steps to D-*myo*-inositol 1,4,5-triphosphate **110**.

C. Alkylations with Phenols

Phenols have demonstrated exceptional utility as nucleophiles in a number of total syntheses. A strategy toward the vitamin E core **112** employs a Pd-catalyzed AAA that derives enantioselectivity through palladium−ligand complex discrimination of the enantiotopic alkene faces of intermediate **111**.[60] This substrate was a synthetic target because lipophilic antioxidants continue to be of interest, particularly analogues of vitamin E.[61] The intramolecular cyclization affords the vitamin E core **112** with up to 87% ee and 96% yield (eq 14, Table 3). The regiochemistry in the cyclization is controlled (six-*exo* vs eight-*endo*) by the length of the tether.



The mechanism of enantiodiscrimination was established by studying the effects of concentration and additives. More dilute concentration, disfavoring equilibration, increases % ee. Additives such as tetraalkylammonium salts that increase η^3 to η^1 exchange decrease % ee. Bases that increase the rate of cyclization relative to equilibration also increase % ee. Starting with the branched carbonate, the regioselectivity stays the same but the enantioselectivity plummets. Thus, it seems clear this cyclization is one of the few known cases in AAA reactions where enantiotopic olefin coordination is the enantiodetermining event in the alkylation.

Interestingly, a similar substrate shows that the olefin geometry can be critical in maximizing enantioselectivity when olefin coordination is the enantiodetermining event. When phenol derivative **113** was utilized, only 84% ee was achieved in formation of product **115**. However, when the *Z* olefin derivative **114** rather than *E* **113** was employed, the enantioselectivity jumped to 97%, with no reduction in yield (eq 15). This can be explained by the mnemonic (see

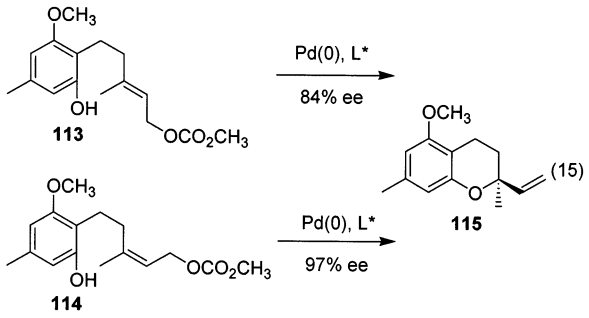
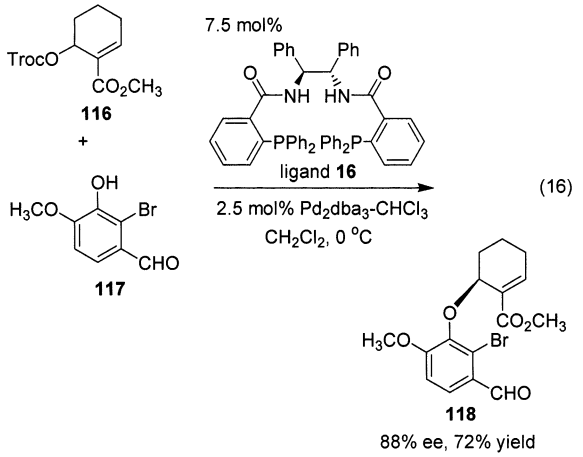


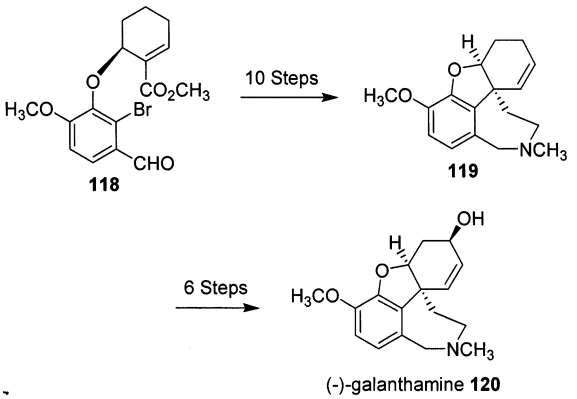
Figure 1);[62] large *anti*-substituents are better accommodated by the chiral ligand than large *syn*-substituents. Thus, the *Z*-alkene has a better fit in the chiral pocket.

Another important example of phenols as nucleophiles was in the total synthesis of (−)-galanthamine **120**, a selective acetylcholinesterase inhibitor used in the treatment of Alzheimer's disease.[63] This route took advantage of classical deracemization of a chiral racemic substrate **116**, available in two steps from glutaraldehyde, with ligand **16** to form a *meso*-π-allyl intermediate complex, which was regioselectively alkylated with phenol **117**, derived in one step from vanillin, to afford aryloxy intermediate **118** in 88% ee and 72% yield (eq 16).[64]

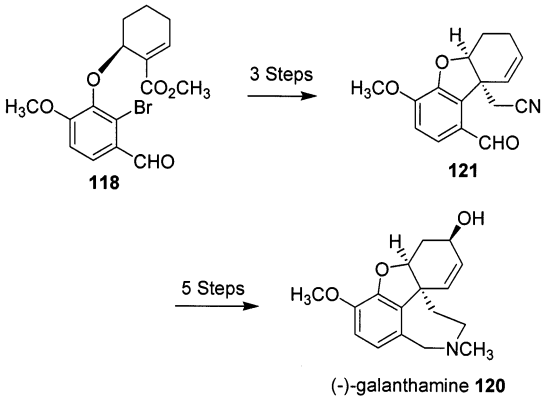


Given the *ortho*-disubstitution of the phenol and the trisubstitution of the substrate, the high enantioselectivity is notable. Furthermore, the absolute stereochemistry obtained in this reaction is opposite to that derived from AAA reactions of disubstituted cyclohexenyl carbonates. This presumably can be attributed to ester oxygen coordination with the palladium, changing the orientation of the π-allyl complex in the ligand chiral pocket.[60] After further

Scheme 20. Completion of the Total Synthesis of (−)-Galanthamine



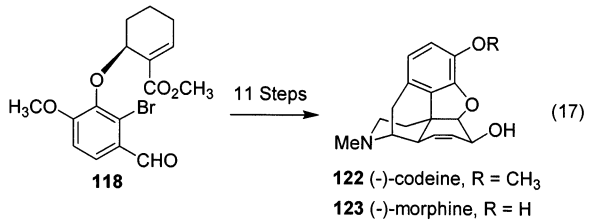
Scheme 21. A Second-Generation Total Synthesis of (−)-Galanthamine



elaboration of **118**, an intramolecular Heck reaction and intramolecular reductive amination proved key in obtaining tetracyclic core **119**, which was subsequently transformed in six steps to (−)-galanthamine **120** (Scheme 20).

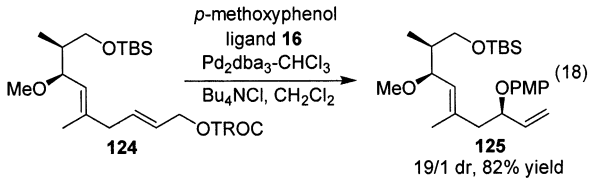
A second-generation synthesis of (−)-galanthamine **120** followed that considerably shortened the original route.[65] Starting from the same aryloxy intermediate **118**, the tricycle **121** was available in three straightforward steps. A diastereoselective allylic oxidation with selenium dioxide installed the requisite hydroxyl group (Scheme 21). Subsequently, in one pot, imine formation followed by reductive amination afforded (−)-galanthamine **120** in a concise eight steps from intermediate **118** with high overall yield (14.8%).

While 2002 is the 50th anniversary of the first synthesis of morphine **123** by Marshal Gates, great interest in this synthetic goal continues. The utility of chiral adduct **118** was then demonstrated in a very short asymmetric total synthesis of (−)-codeine **122** and a formal synthesis of (−)-morphine **123** (eq 17).[66] The synthesis forms the last ring, the piperidine, by a novel intramolecular hydroamination of an alkene.



(17)

Callipeltoside A **127**, a natural product that is difficult to isolate and possesses high antitumor activity,[67] was synthesized using a convergent strategy that employed a Pd-catalyzed AAA as one of the key steps.[68] The advanced intermediate **124**, generated from ruthenium-catalyzed alkene−alkyne coupling, was screened in AAA reactions with 4-methoxyphenol utilizing a number of chiral bisphosphine ligands. The best result was obtained with the diphenyl ligand **16** that gave a 3/1 branched/linear ratio with excellent (19/1) diastereoselectivity (eq 18).



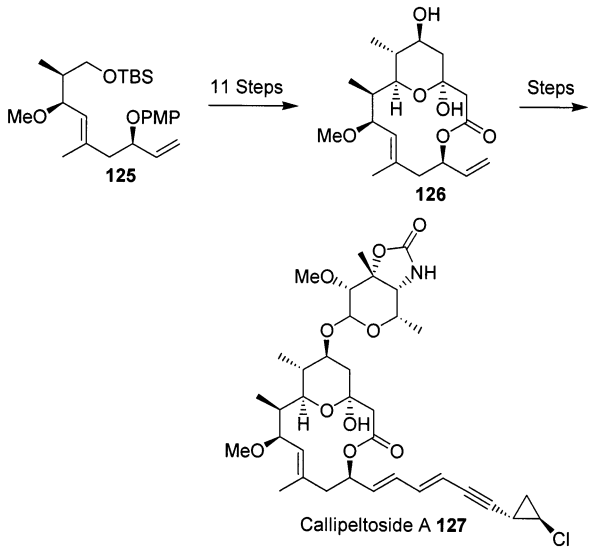
(18)

In this case, the mechanism of reaction must involve diastereofacial exchange of the palladium−allyl complex, as evident by the addition of chloride ion, promoting η^3 to η^1 exchange. Presumably, one of the interconverting diastereomeric complexes is more reactive and leads to product.

The stereochemistry obtained from this AAA was surprisingly opposite from what was expected.[69] One explanation might be that the steric bulk adjacent to the π-allyl system caused the preferred intermediate to be the "anti" rather than the "syn" complex.[70] The better ability of the chiral space created by these ligands to accommodate bulky ligands in an anti π-allyl−palladium complex supports this explanation.

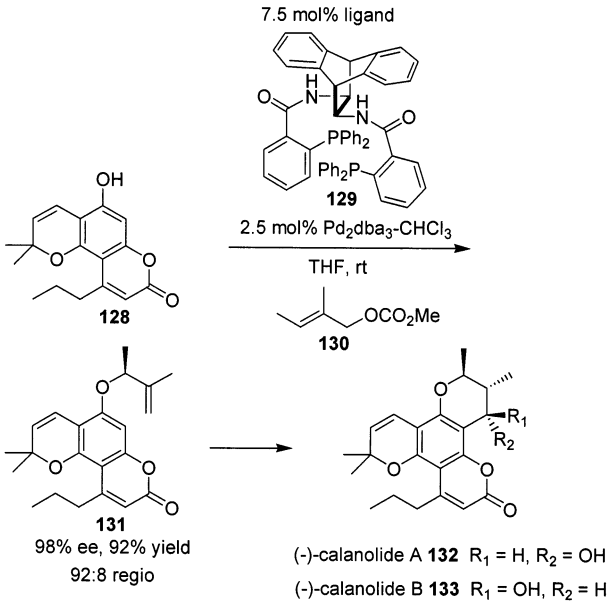
The allylic aryloxyether product **125** was transformed in 11 steps to the callepeltoside core **126**, with key transformations including two diastereoselective aldol reactions and a macrolactonization. The cyclopropyl ene−yne side chain is attached to the core via a cross olefin metathesis followed by a Stille coupling, which takes advantage of the terminal vinyl group created in the AAA. The aglycon is glycosylated with the sugar, and subsequent global deprotection affords callipeltoside A **127** (Scheme 22).

Scheme 22. Total Synthesis of Callipeltoside A



The use of unsymmetrical allylic carbonates as electrophiles presented the opportunity to achieve regio- and enantioselective allylic alkylation with phenolic nucleophiles. Such reactions require the reversal of the intrinsic regioselectivity observed using achiral ligands with phenol nucleophiles. They favor alkylation at the primary rather than the secondary carbon of the π-allyl complexes with achiral catalysts. Highly functionalized phenol **128** undergoes reaction with tiglyl methyl carbonate **130** to afford the secondary ether **131** in excellent regio- (92:8) and enantioselectivity (98% ee) using the right chiral ligand (Scheme 23).[71] The bisphosphine ligand

Scheme 23. Total Synthesis of (−)-Calanolides A and B

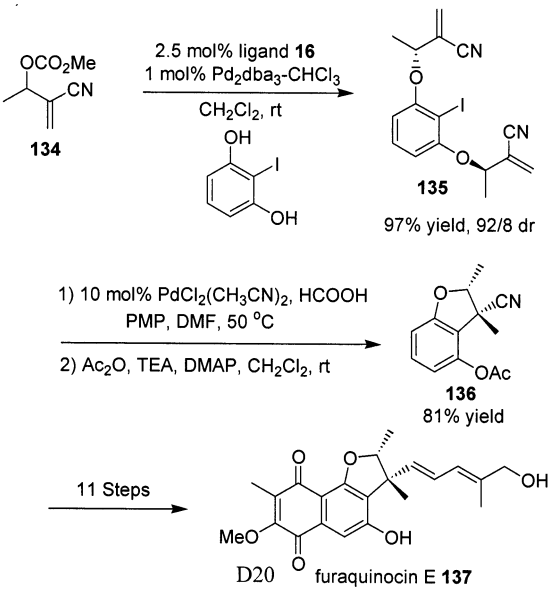


15a in this case did not provide the optimum regioselectivity, so a new class of ligands was utilized. The very bulky ligand **129** was able to overwhelm the inherent bias of bulky phenol allylation for linear product and provided primarily the branched adduct (br.:l = 10:1). Adduct **131** was in turn transformed to the anti-HIV compounds (−)-calanolide A **132** and (−)-calanolide B **133** (the enantiomers of the natural products) in four and six steps, respectively.

The greatest challenge in AAA reactions with phenol nucleophiles involves a dynamic kinetic asymmetric transformation, where a chiral racemic substrate is transformed to enantiopure product through an achiral non-*meso* electrophile intermediate. Despite difficulties, inherent to such a pathway, successful realization of this process has proved useful in the design of synthetic strategies to significant targets.

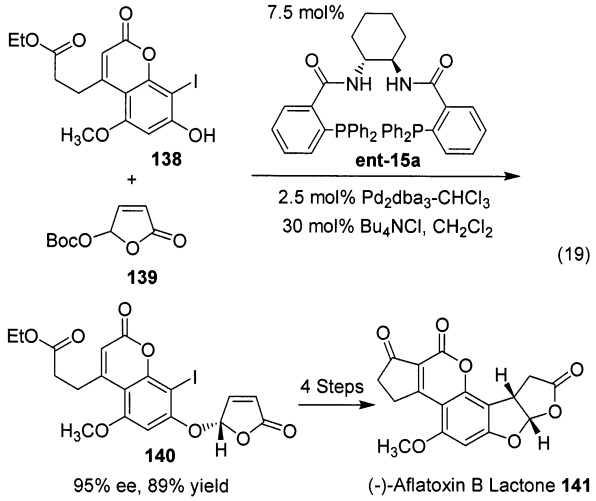
Furaquinocin E **137**, an antitumor antibiotic isolated from the fermentation broth of *Streptomyces sp.* KO-3998,[72] provided an opportunity for utilization of enantioselective allylic alkylation in a dynamic kinetic transformation as a key step. Alkylation of Baylis−Hilman adduct allylic carbonate **134** with 2-iodoresorcinol afforded the desired adduct **135** in excellent yield (97%) and good diastereoselectivity

Scheme 24. Concise Total Synthesis of Furaquinocin E



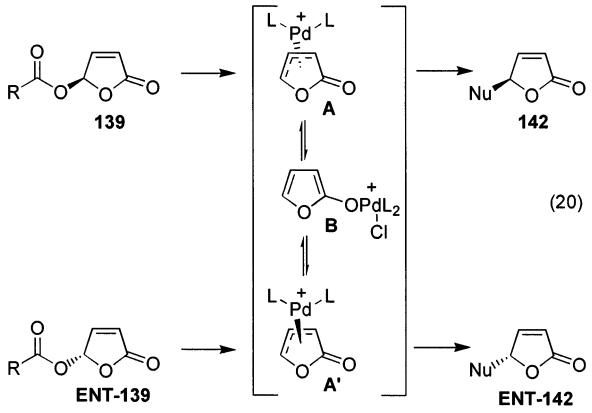
(92/8) (Scheme 24).[73] Thus, it is not necessary to effect an asymmetric Baylis−Hillman addition, since the racemate converges to a single enantiomeric product as a result of the palladium AAA. The intermediate **135** was cyclized in a Heck reaction setting the quaternary stereocenter, the resulting free phenol acylated, and the acetate product recrystallized to >99% ee (adduct **136**). This intermediate was transformed in 11 steps to furaquinocin E **137**.

Another synthesis that employed a palladium-catalyzed dynamic kinetic asymmetric transformation was the enantioselective synthesis of (−)-aflatoxin B lactone **141**. 5-Acyloxy-2-(5*H*)-furanone **139** was alkylated with substituted phenol derivative **138** to afford adduct **140** in 95% ee and 89% yield (eq 19).[74] Subsequent reductive Heck cyclization to



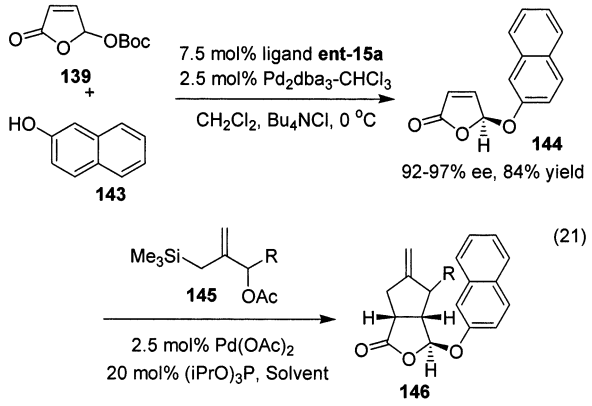
form the B ring followed by scandium triflate-catalyzed formation of the E ring afforded the pentacyclic aflatoxin B lactone **141**.

In this AAA, the interconversion of diastereomeric intermediates was through a furan-like intermediate (eq 20). The sigma complex **B** may explain the driving



force for η^3 to η^1 exchange and suggests a reason such exchange is faster than nucleophilic capture by the phenol. If the interconversion is fast relative to nucleophilic addition and if one of the diastereomeric complexes undergoes reaction significantly faster than the other, then an effective dynamic kinetic asymmetric transformation results. The enantiodiscrimination then derives from the differential rate constants for **A** to give product **B** compared to that for **A′** to give the mirror image ent-**B**.

The utility of this AAA reaction in a dynamic kinetic asymmetric transformation with 5-acyloxy-2-(5*H*)-furanone **139** was further demonstrated in the total synthesis of (+)-brefeldin A **150**. Transformation of chiral racemic butenolide **139** with 2-naphthol **143** as nucleophile afforded adduct **144** with 92−97% ee and 84% yield (eq 21).[75]



The resulting "chiral aldehyde" equivalent served as an excellent scaffold for diastereoselective Pd(0)-catalyzed TMM cycloadditions to adducts **146** (Table 4). These cycloadditions proceeded with complete control of regio- and diastereofacial selectivity. In the case of the cyano-substituted TMM reaction (entry b), the exocyclic double bond of the initial product isomerized to the endocyclic position. The solvent effect on the facial selectivity in this case is also noteworthy—i.e., higher diastereoselectivity in toluene than THF even though the former is at considerably higher temperature. While the epimeric ratio with respect to the methyl group in entry c was 1:1, the ratio in the phenyl case increased to 4:1 (entry d).

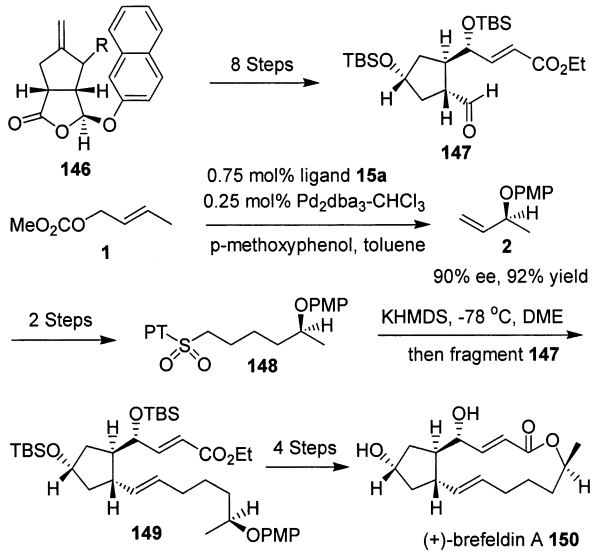
This cycloadduct **146** (R = H) was elaborated in eight steps to aldehyde core **147** and then coupled with lower side chain **148** in a *trans*-selective Julia olefination (Scheme 25). The chirality of fragment **148** was derived in turn from an AAA reaction of crotyl carbonate **1** and *p*-methoxyphenol (also see eq 1). The chiral building block **2** was transformed to the lower side chain **148** in two steps: an olefin cross metathesis followed by a Pd-catalyzed hydrogenation.[76] The brefeldin A carbon skeleton **149** was then transformed in four steps to (+)-brefeldin A **150**.

Table 4. TMM Cycloadditions to 4-Naphthoxybutenolide

entry	R	conditions	yield	dr[a] (epi)[b]
a_1	H	toluene, 100 °C, 12 h	93	>98/2
a_2	H	THF, 60 °C, 24 h	93	>98/2
b_1	CN[c]	THF, 60 °C, 12 h	94	5.5/1
b_2	CN[c]	toluene, 100 °C, 6 h	91	94/6
c	Me	toluene, 100 °C, 48 h	60	>98/2 (1/1)
d	Ph	toluene, 100 °C, 24 h	79	>98/2 (4/1)

[a] All diastereomeric ratios are of the crude mixture. All diastereomers were separable by column chromatography. [b] Stereogenic center substituted with R group. [c] Olefin isomerized into conjugation with the nitrile.

Scheme 25. Completion of the Total Synthesis of (+)-Brefeldin A



IV. Nitrogen Nucleophiles in AAA Total Synthesis

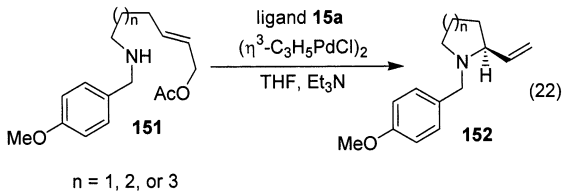
Stereoselective carbon−nitrogen bond formation is a major challenge in organic synthesis, making AAA reactions with nitrogen nucleophiles especially interesting. Since the first reported AAA reaction with a nitrogen nucleophile by the Trost group,[11] alkylamines, azides, amides, imides, and heterocyclic amines have all been employed as nucleophiles via cyclic and acyclic, hindered and unhindered π-allyl complexes as intermediates in catalytic cycles.

A. Alkylamines as Nucleophiles

Amines as nucleophiles in asymmetric allylic alkylations have proven to be a challenge because of three main considerations: mono- vs bisalkylation, regioselectivity of reaction, and rate of nucleophilic addition to diastereomeric complexes vs $\pi-\sigma-\pi$ equilibration of the allyl complex. While several notable discoveries have increased the viability of asymmetric

alkylation with amine nucleophiles in recent years, no AAA-based total synthesis has yet employed a primary alkylamine as the nucleophile.

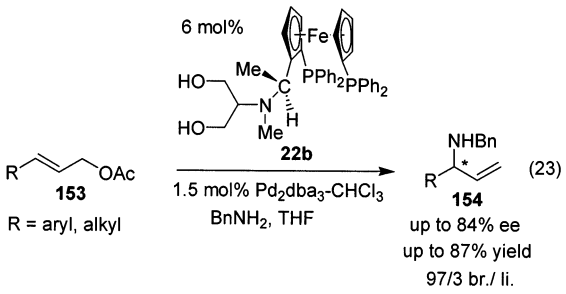
Unfavorable regioselectivity initially thwarted attempts to use primary and secondary alkylamines as nucleophiles with unsymmetrical substrates. One resolution of this problem was achieved by tethering the amine nucleophile. PMB-protected amine **151** (n = 1) undergoes a 5-*exo* cyclization to afford pyrrolidine derivative **152** with 91% ee in essentially quantitative (97%) yield (eq 22).[77] Tethering the



(22)

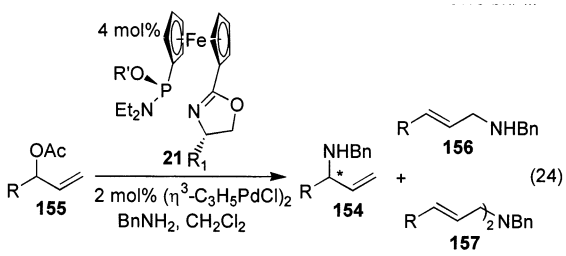
system allows it to overcome its intrinsic intermolecular reaction bias for nucleophiles to attack at the less substituted terminus. Interestingly, in this case, the enantioselectivity must be determined by asymmetric recognition in the complexation step.

The more complex problem of performing a reaction where the mechanism involves both regio- and enantiodiscrimination with amine nucleophiles has been addressed in several cases. Some of the earliest work done with amine nucleophiles on unsymmetrical substrates utilized ferrocencyl ligand **22b** that gave rise to benzylamine substituting at the more substituted allyl terminus to give branched adduct **154** (97/3) with 87% yield and 84% ee (eq 23).[78]



(23)

Recently, use of a novel mixed *P,N* ferrocene ligand **21** (when R′ = Me) allowed an even greater regioselective and enantioselective amination of the unsymmetrical allylic acetates (eq 24).[79] These reactions proceeded to give branched/linear product ratios up to 97/3 with % ee of adduct **154** up to 98% and yields greater than 90%.



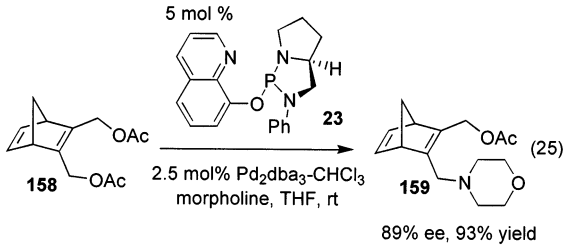
(24)

Classical *meso*-substrates have also been desymmetrized with secondary amines. Bicyclo[2.2.1] derivative **158** underwent an asymmetric amination with morpholine using a chiral pyridine−phosphine ligand that gave rise to **159** in 89% ee and 93% yield (eq 25).[80]

Table 5. Pd-Catalyzed Allylic Alkylation with Benzyl Amine

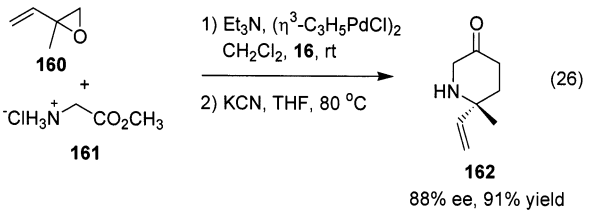
entry	substrate, R	time	% yield[a]	**154/156/157**[b]	% ee[c]
1	**155a**, phenyl	7	94	95/3/2	98
2	**155b**, 1-naphthyl	8	87	94/6/-	97
3	**155c**, 4-Meo-Ph	8	86	87/13/-	94
4	**155d**, 4-Me-Ph	6	89	94/6/-	95
5	**155e**, 4-Cl-Ph	3	76	86/9/5	97
6	**155f**, 2-thienyl	8	85	90/9/1	98
7	**155g**, methyl	4	78	>97/3/-	84

[a] Yield after chromatography. [b] Determined by GC of the crude product after chromatography. [c] Determined by chiral HPLC.



(25)

Regio- and enantioselective alkylation of isoprene monoepoxide **160** with glycine methyl ester **161** followed by subsequent intramolecular transesterification afforded cyclic adduct **162**.[81] Choice of ligand was important; the enantiomer of the more flexible diphenyl ligand **16** gave a high yield (91%) and enantiomeric excess (88% ee) (eq 26).



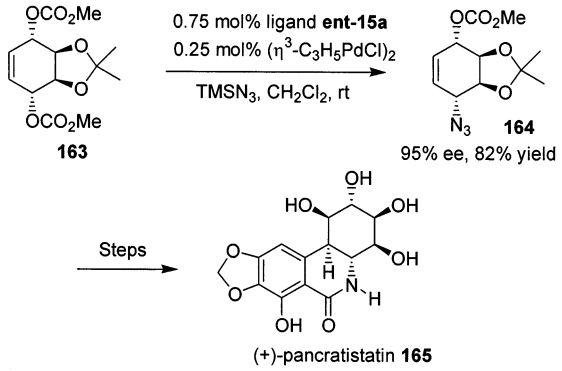
(26)

B. Azides as a Nucleophile

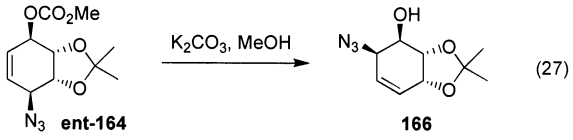
Azides are an interesting class of nucleophiles that have been employed with great success in the AAA reaction. The total synthesis of (+)-pancratistatin was the first that demonstrated the utility of azide nucleophiles in AAA-driven natural product strategy.[82] Desymmetrization of the *meso*-biscarbonate **163** with azide affordd adduct **164** in 82% yield and 95% ee. The remaining allyl ester then participated in a S_N2' cuprate addition of an aryl nucleophile. Lactam formation followed by diastereoselective net *trans*-dihydroxylation completed the total synthesis of (+)-pancratistatin **165** (Scheme 26). It is important to point out that the reaction conditions in the AAA were mild enough to suppress the typical [3,3]-sigmatropic rearrangement that allylic azides have a propensity to undergo.

The aminocyclitols represent an important class of compounds because of their biological activity. Their

Scheme 26. Asymmetric Synthesis of (+)-Pancratistatin

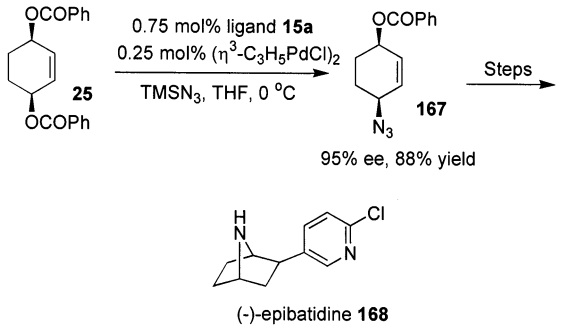


properties encouraged an asymmetric synthesis of the aminocyclohexitol unit of hygromycin A.[83] This sequence involved a desymmetrization strategy with a *meso* electrophile and azide nucleophile as described in the synthesis of (+)-pancratistatin, except in this case the other enantiomer of starting material was utilized. By using slightly elevated temperature during the carbonate hydrolysis, a [3,3] sigmatropic rearrangement of the initial allylic azide alkylation adduct was promoted. The position of this equilibrium is apparently favored by the hydrogen bonding between the proximal hydroxyl and azide groups. The net process then represents an enantiodesymmetrization via a S_N2'-type process to produce adduct **166** in 70% overall yield (eq 27).



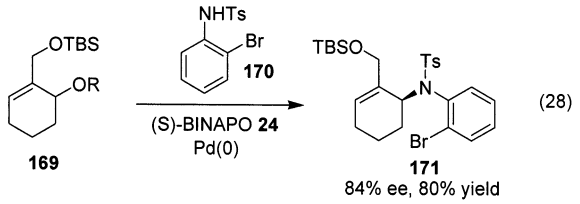
A palladium-catalyzed desymmetrization of *cis*-1,4-dibenzoyloxy-2-cyclohexene **25** using azide as the nucleophile played a pivotal role in the synthesis of (−)-epibatidine **168**.[84] This unusual alkaloid is a significant synthetic target in part because of its biological properties, which include analgesic activity that is 500 times higher than morphine but without the opiate activity. The mild conditions involved in the AAA reaction with azide nucleophiles prevented [3,3] sigmatropic rearrangement. The intermediate **167**, obtained in excellent yield and ee (95%), was transformed in seven steps to the desired product **168** (Scheme 27).

Scheme 27. Total Synthesis of (−)-Epibatidine



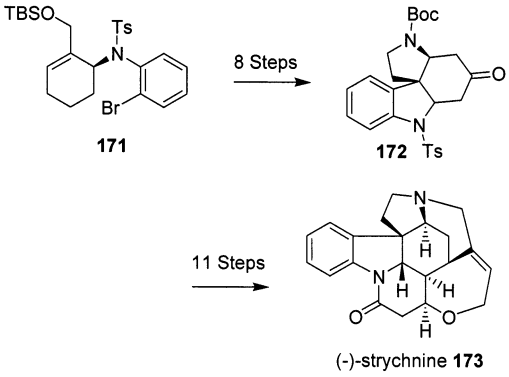
C. Sulfonamide Nucleophiles

A recent total synthesis of the alkaloid (−)-strychnine demonstrates the power of sulfonamides in AAA reactions.[85] This classic molecule, first synthesized by Woodward, has been the subject of intense synthetic study for the last 50 years. The approach focused on enantioselective formation of the indoline core utilizing sulfonamide derivative **170** with the trisubstituted allylic carbonate electrophile **169** (eq 28). The use of cyclohexenyl substrates



bearing a bulky substituent at the central allyl carbon was best performed using (*S*)-BINAPO **24** as a ligand. This alkylation allowed for high enantioselectivity (84%) despite the steric congestion of the system and obtained product **171** in 80% yield. The intermediate was subsequently transformed in 11 steps to (−)-strychnine **173** via key intermediate **172** (Scheme 28).

Scheme 28. Total Synthesis of (−)-Strychnine



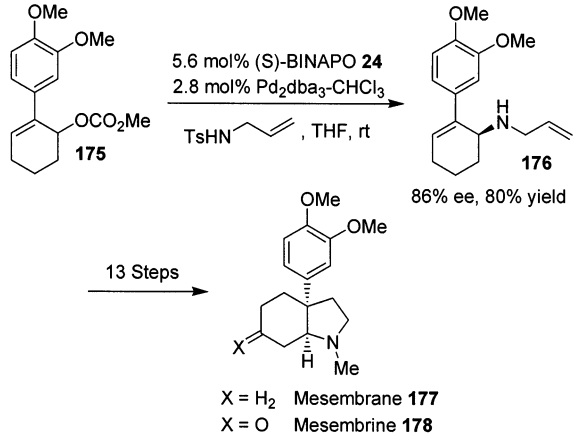
Intermediate **172** was also used to access the natural product (−)-tubifoline (Scheme 29).[86] The latter steps of this approach utilized a diastereoselective intramolecular Heck reaction to form the E ring system, followed by subsequent functional group transformations to afford (−)-tubifoline **174** in six steps.

Scheme 29. Total Synthesis of (+)-Tubifoline

Another application of sulfonamide nucleophiles was in the total syntheses of (−)-mesembrane **177** and (−)-mesembrine **178**. These natural products, differing in structure only at C(3), were approached via an intermolecular alkylation using *N*-tosylallylamine as a nucleophile.[87] (S)-BINAPO ligand **24** was

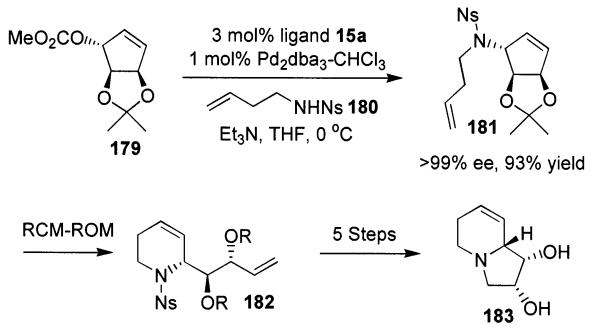
employed with the cyclic carbonate electrophile **175** affording adduct **176** in 86% ee and 80% yield (Scheme 30). Zirconium-promoted cyclization and subsequent synthetic transformations completed the synthesis in 13 steps.

Scheme 30. Efficient Total Synthesis of Mesembrine



Homoallylnosylamine as a nucleophile has been used in two total syntheses. In the first example, the synthesis of indolizidine alkaloid **183** was achieved after a desymmetrization of the π-allyl complex resulting from carbonate **179** with homoallylnosylamine **180**.[88] The cyclopentene system **181** was transformed to a hexahydropiperidine **182**, which was subsequently converted to 1,2,3,5,6,8a-hexahydroindolizine-1,2-diol **183** utilizing a ring-opening−ring-closing metathesis as the key step (Scheme 31).

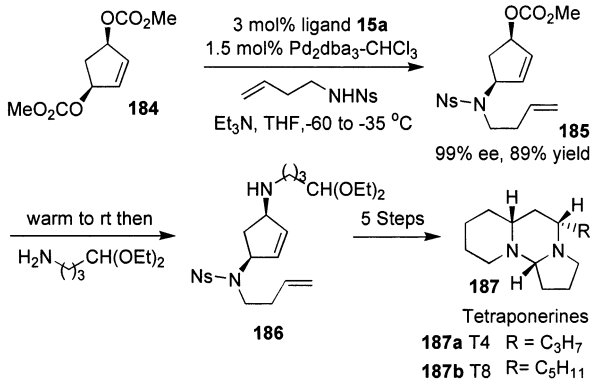
Scheme 31. Synthesis of an Indolizidine Alkaloid



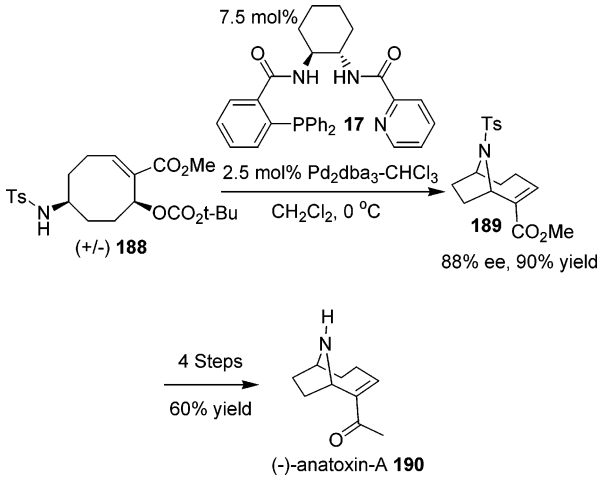
Utilizing the same amide nucleophile and ligand **15a**, *meso*-biscarbonate **184** was desymmetrized affording the initial adduct **185** in 99% ee and subsequently reacted in the same pot with a second amine nucleophile to give a single enantiomer and diastereomer **186** (Scheme 32).[89] The intermediate was then transformed over a series of steps including a ROM−RCM to afford access to several tetraponerines, including T4 **187a** and T8 **187b** as illustrated.

An intramolecular AAA with a sulfonamide nucleophile was reported for an enantioselective total synthesis of (−)-anatoxin-A **190**, the "very fast death factor" (Scheme 33). In studies toward the synthesis of this molecule, the initial bisphosphine ligands **15a** and **15b** proved to be too restrictive for the steric demands of the substrate. This promoted investigation of new ligands that diminished the steric constraints of the chiral space resulting in ligand **17**. With this new ligand, the Pd(0) AAA reaction proceeded smoothly to deracemize the eight-membered ring substrate **188**.[90] The resultant bicyclo[4.2.1]-nonane **189** was afforded in 88% ee and 90% yield and then transformed to (−)-anatoxin-A **190** in four steps and 60% yield.

Scheme 32. Total Synthesis of the Tetraponerines T4-T8



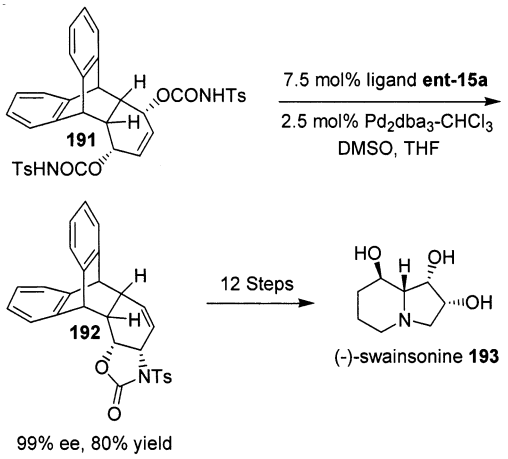
Scheme 33. Total Synthesis of (−)-Anatoxin-A



D. Imide Nucleophiles

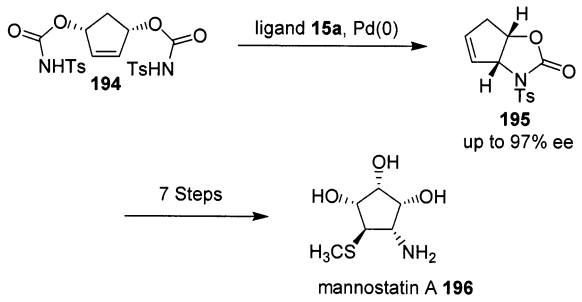
Imide nucleophiles, like the sulfonamides, have been employed widely in syntheses utilizing the AAA reaction. The availability of phthalimide, an excellent primary amine surrogate, has promoted extensive investigation of reactions with a long list of allylic carbonate electrophiles. However, only those applications that resulted in successful total syntheses will be discussed here. Imide nucleophiles other than phthalimide itself have also been utilized, particularly in intramolecular reactions. In the total synthesis of (−)-swainsonine **193**, a compound with anticancer, antiviral, and immunoregulatory properties, the key step was desymmetrization of a *meso*-2-en-1,4-diol **191** in an intramolecular fashion with an imide nucleophile (Scheme 34).[91] Diastereoselective dihydroxylation dictated by the dihydroanthracene unit sets the four stereogenic centers of swainsonine. This route provides (−)-swainsonine **193** in an efficient 12 steps, rendering the complete synthesis in a total of 15 steps and 15% overall yield.

Scheme 34. An Asymmetric Total Synthesis of (+)-Swainsonine



Mannostatin A **196**, isolated from *Streptoveticillum verticillus*, is a highly specific nanomolar inhibitor of α-D-mannosidase.[92] It was synthesized using a desymmetrization strategy that started with *meso*-bisimide derivative **194** which was cyclized in an intramolecular AAA reaction to adduct **195** (Scheme 35).[93] While the initial results with *(S)*-BINAPO **24**

Scheme 35. An Efficient Synthesis of Mannostatin A

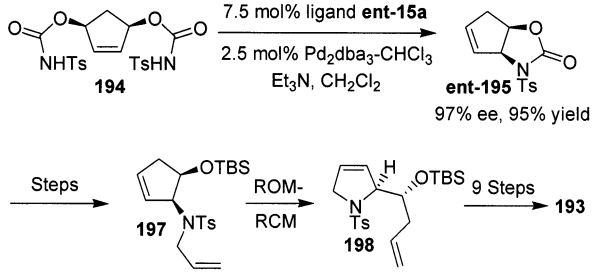


gave modest enantioselectivity, the use of ligand **15a** allowed for formation of **195** in up to 97% ee.[15] The synthesis was then completed in seven steps highlighted by a diastereoselective reduction and epoxidation.

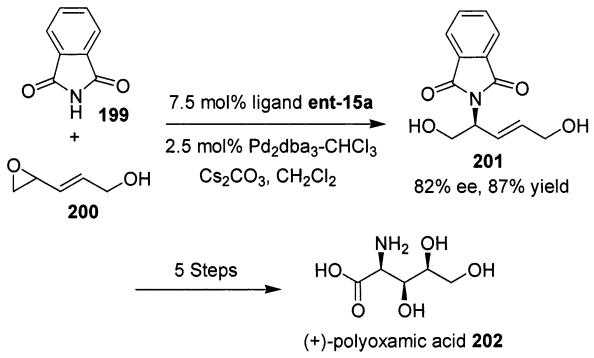
A second synthesis of (−)-swainsonine **193** also set the key chiral centers utilizing palladium catalysis. Utilizing the previously reported desymmetrization[11,94] that created asymmetry from an intramolecular imide nucleophile alkylation, the intermediate was transformed to diene **197**, which was subjected to metathesis conditions to give the pyrrolidine **198**. This intermediate was subsequently transformed to (−)-swainsonine **193** (Scheme 36).[95]

A total synthesis of the antifungal agent (+)-polyoxamic acid had as the key asymmetric step an enantioselective alkylation of vinyl epoxide **200** with phthalimide **199** (Scheme 37).[96] This transformation involves a *meso* intermediate derived from chiral racemic material that is desymmetrized by addition of the imide. Subsequent steps on adduct **201** involving diastereoselective dihydroxylation, imide cleavage, and finally oxidation−deprotection afforded (+)-polyoxamic acid **202** from epoxide **200** in 30% overall yield.

Scheme 36. An Alternate Total Synthesis of (+)-Swainsonine

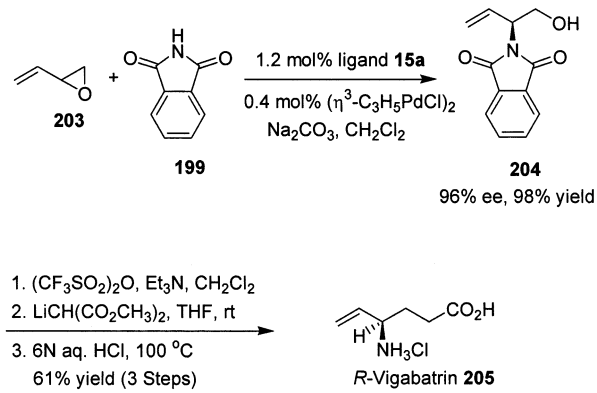


Scheme 37. Synthesis of (+)-Polyoxamic Acid

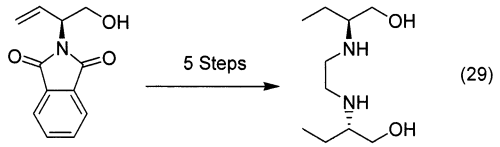


The first example of an AAA reaction with an imide nucleophile in a total synthesis was reported in the asymmetric synthesis of vigabatrin.[97] Vigabatrin is an irreversible inhibitor of GABA transaminase and is used in the treatment of dyskinesia, schizophrenia, and epilepsy. It can additionally be used to help alleviate drug dependency on addictive drugs including nicotine.[98] A concise four-step route involves alkylation starting with racemic butadiene monoepoxide **203**. Unlike in the case of (+)-polyoxamic acid, this AAA reaction involves issues of both enantioselectivity and regioselectivity. The catalyst−ligand system employed allows for a dynamic kinetic asymmetric transformation of the chiral racemic substrate. The alkylation affords adduct **204** in 98% yield with 96% ee, crystallized to enantiopurity, and that adduct is subsequently transformed in three steps to *R*-vigabatrin **205** in 61% overall yield (Scheme 38). An advantage of this route is that it gives access to either enantiomer, i.e., use of the opposite enantiomer of ligand gives access to *S*-vigabatrin in comparable yield and % ee.

Scheme 38. Total Synthesis of Vigabatrin



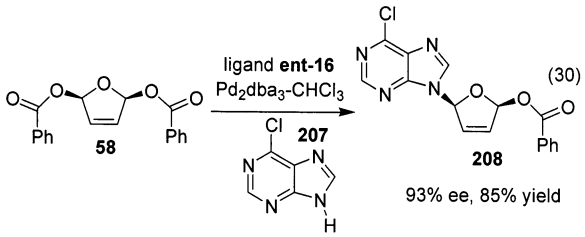
The same intermediate **204** additionally served as an intermediate in the total synthesis of *S*,*S*-ethambutol **206**, a tuberculostatic drug.[99] The enantiopurity (>99%) is quite important in this instance from a drug development standpoint, as the other enantiomer can cause blindness in people. The enantiopure substrate **206** was liberated to the amine salt with ethylenediamine, dimerized with oxalyl chloride, and subsequently reduced in two steps to the natural product with an overall yield of 43% (eq 29).



204 *S*,*S*-ethambutol **206**

E. Heterocyclic Amine Nucleophiles

In contrast to alkylamines, heterocyclic amines have been utilized in a number of total syntheses including those of carbo-nucleosides and indolocarbazole pro-aglycons. The first reported examples of such use were in the syntheses of *ent*-adenosine acetonide **209** and of the polyoxin/nikkomycin nucleoside core **212/ 213**.[100] In the approach toward the adenosine derivative, the key step involved the alkylation of a *meso*-benzoate **58** with a purine base **207** (eq 30). In this instance, the classical methods



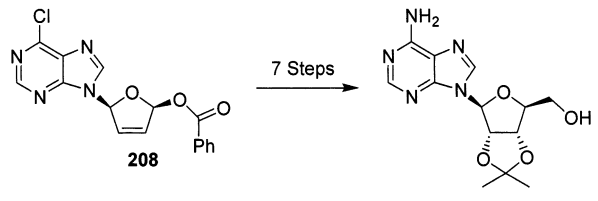
58 **207** **208**

93% ee, 85% yield

of enzymatic desymmetrization used for cyclopentene systems would be ineffective. Selective hydrolysis of one benzoate would afford the hemiacetal, which is chemically unstable and self-destructs.

This alkylation afforded derivative **208** in 85% yield with 93% ee, which was subsequently recrystallized to enantiopure adduct. Furthermore, the combination of desymmetrization and substitution as a one-step AAA reaction process rather than as two separate operations demonstrates the general efficiency of this route, even for carbocyclic substrates. The intermediate **208** is subsequently transformed in seven steps to the *ent*-adenosine acetonide **209** for a total of nine steps and 18% overall yield starting from furan (Scheme 39).

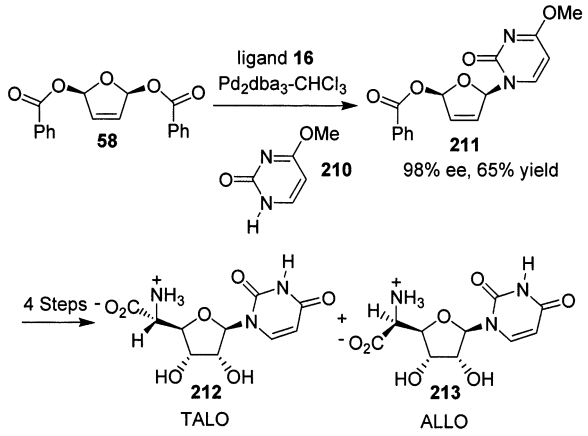
Scheme 39. Total Synthesis of *ent*-Adenosine Acetonide



208 *ent*-adenosine acetonide **209**

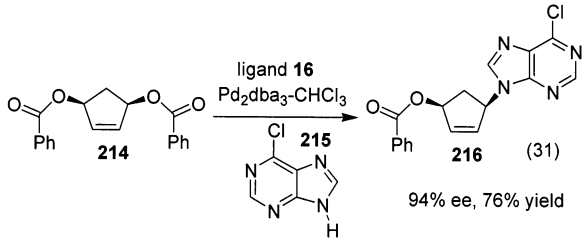
In another example with the same electrophile, utilization of a uracil equivalent as the nucleophile in the enantiodiscriminating step allowed access to the chiral building block **209**. The adduct, whose ee was determined to be greater than 98%, was subsequently transformed in a concise four steps to the polyoxin-nikkomycin nucleoside core **212/213** in 39% overall yield (Scheme 40).[99] It is noteworthy that the

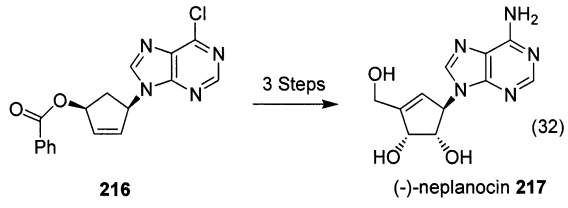
Scheme 40. Synthesis of the Polyoxin-Nikkomycin Nucleoside Core



AAA approach sharply contrasts with chiral-pool methods, where access to various enantiomers is limited by the availability of starting materials.

Shortly after the first reports of these heterocyclic amines as nucleophiles, a total synthesis of (−)-neplanocin A **217** was reported.[101] The strategy employed the same desymmetrization strategy as in the synthesis of *ent*-adenosine as discussed earlier (eq 31). The carbon analogue of the bisbenzoate **214**



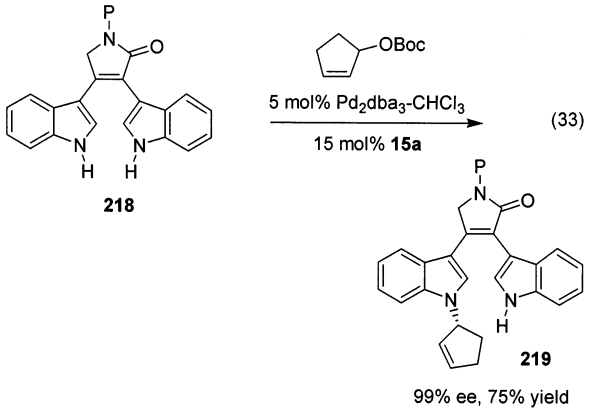


216 (-)-neplanocin **217**

was alkylated with 6-chloropurine **215** under similar conditions to those previously reported for the oxo-analogue. This intermediate was then diastereoselectively epoxidized and transformed to (−)-neplanocin **217** in nine steps with high overall yield.

The most recent example of palladium-catalyzed asymmetric allylic alkylation with heterocyclic amines was in the synthesis of indolocarbazole pro-aglycons **219**.[102] This family of natural products exhibits nanomolar PKC and topoisomerase inhibitory activity and thus has been the focus of intense synthetic

study. Such intrinsic bias provides new challenges for the AAA reaction. In order for the strategy to be viable, it had to achieve chemo-, regio- and enantioselective allylation of one of the two indole nitrogens in the lactam precursor **218**. Alkylations utilizing cyclopentyl carbonate with the standard ligand and sugar-derived electrophiles with racemic ligand afforded *distal* indole nitrogen functionalization (i.e., **219**) (eq 33).



The utility of this methodology was further highlighted by establishment of conditions to allow the indole nitrogen *proximal* to the lactam **218** to react chemo- and enantioselectively with the allylic carbonate. A change in ligand to the binaphthyl system **15b** accompanied by a change to a glyoxamide as nucleophile allowed for the desired change in chemoselectivity.

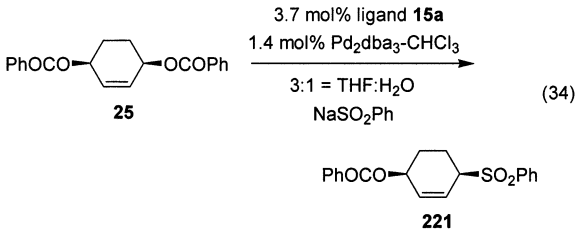
The ability to chemo-, regio-, and enantioselectively functionalize heterocyclic amine systems with allylic carbonates illustrates the power of this methodology in total synthesis. The applications of asymmetric allylic alkylations with amines will likely continue to grow. Nitrogen nucleophiles in AAA-driven synthesis have demonstrated that otherwise difficult to achieve chiral intermediates can be derived from achiral or racemic material in high % ee and yield. The fact that in the past decade nearly 20 asymmetric syntheses using this subclass of asymmetric allylic alkylations have emerged is testimony to the utility of the AAA in complex molecule total synthesis.

V. Sulfur Nucleophiles

Allylic sulfones are exceptionally versatile intermediates in organic synthesis because of the ability of the sulfone to impart both nucleophilic and electrophilic properties to the α-carbon. If the allyl sulfone is chiral, the functionalization of adjacent atoms can proceed diastereoselectively.

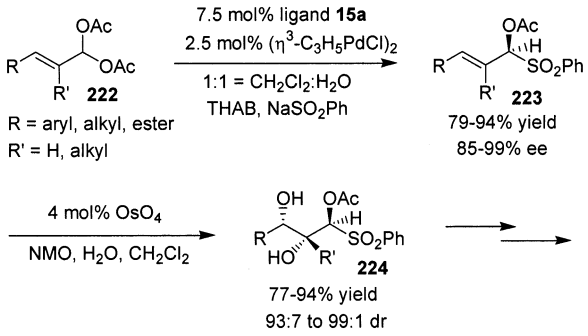
Sulfones were first introduced to the AAA reaction (using sodium benzenesulfinate) in desymmetrization of *meso*-2-ene-1,4-diols **25** to give chiral adduct **221** in 85% yield as a single enantiomer (eq 34).[103] This intermediate was subsequently transformed to useful chiral building blocks for synthesis.

Recently, sodium benzenesulfinate was used in a AAA reactions with allylic *gem*-diacetates **222** to give enantiopure α-acetoxysulfones **223** (Scheme 41).[104]



These building blocks **223** serve as "chiral aldehyde" equivalents and can be dihydroxylated with high diastereoselectivity to diols **224**. Total syntheses utilizing these intermediates are currently under development.[105]

Scheme 41. α-Acetoxysulfones as "Chiral Aldehyde" Equivalents



VI. Summary and Conclusions

Since the first realization of high enantioselectivity in transition-metal-catalyzed asymmetric allylic alkylations nearly a decade ago, the use of this process has become a vibrant area of study. The nucleophile, allyl unit, or sometimes both have been the site for asymmetric induction in reactions that can derive enantioselectivity from five different mechanisms. Recently both palladium- and molybdenum-catalyzed reactions have achieved dynamic kinetic asymmetric transformations of chiral racemic substrates to enantiopure products, without the 50% yield limitation that is inherent to kinetic resolutions or kinetic asymmetric transformations. Taking advantage of the exceptional versatility of the AAA reaction to control C−C, C−O, C−N, and C−S bond formation, over 50 total syntheses have emerged with this reaction as the central strategy. As demonstrated by this review, the potential of the asymmetric alkylation reaction continues to grow with the development of new ligands, nucleophiles, and processes. It is noteworthy that over one-half of the syntheses reviewed in this article have been published only in the last three years and that the number of reported AAA reactions in total synthesis has grown steadily year by year. It is likely that research in this area will continue to develop and will result in new efficiencies in total synthesis.

VII. Acknowledgments

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would like to thank the extensive efforts of an outstanding group of collaborators who have helped to realize the potential of these powerful methods in these laboratories. They are individually acknowledged in the references. We would also thank Mike Ameriks, Oliver Thiel, and Vince Yeh for their help in the editing of this review.

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