Published in final edited form as:

Tetrahedron. 2015 September 2; 71(35): 5708–5733. doi:10.1016/j.tet.2015.06.044.

Metal Catalyzed Allylic Alkylation: Its Development in the Trost Laboratories

Barry M. Trost

Department of Chemistry, Stanford University, Stanford, CA 94305, USA, bmtrost@stanford.edu, phone: 650-723-3385, fax: 650-725-0002

1. Introduction

I am highly honored to be the co-recipient of the Tetrahedron Prize for 2014 with Professor Jiro Tsuji for our work on metal catalyzed allylic alkylation, notably that using palladium. In the context of this award, this report deals only with the evolution of our work. Nevertheless, it is important to note that innumerable groups around the world have and are playing essential roles metal catalyzed allylic alkylations. The reader can find citations to such work in the references to our work that appears in this report. My involvement with this field derived from work in my laboratory dealing with the structure determination and synthesis of the insect juvenile hormone.¹ The juvenile hormone is one of three hormones that control the stages of insect development from the pupae to the larvae and finally to the adult. Thus, these hormones, most notably the juvenile hormone that prevented molting was targeted as a potentially more environmentally benign insecticide. The structural relationship of the insect juvenile hormone and methyl farnesoate suggests a possible biosynthetic pathway may be involving the homologation of two of the olefinic methyl groups to ethyl groups. Such an approach, if feasible, would be very attractive, short, and potentially very practical. Unfortunately, such a synthetic protocol did not exist – a fact that intrigued me. While the reactions of the oxygen analog wherein alkylation at the carbon adjacent to the π -unsaturated carbonyl group is one of the most important synthetic reactions, the inability of the all carbon analog to undergo a similar transformation was very attractive.

2. Methodology of palladium processes

We initiated studies by dividing the objective of allylic alkylation into two stages – the first involving the cleavage of the allylic C-H bond and the second being the C-C bond forming step.^{2,3} Treatment of an olefin such as 2-ethylidenenopinane **1**, which was a mixture of geometric isomers, gave

(1)

a single π -allylpalladium complex **2** (eq 1).⁴ A broad range of di- and tri-substituted olefins reacted well. Most interestingly, the presence of a carbonyl group in the substrate did not interfere. Mono-substituted double bonds are apparently not nucleophilic enough, a fact that led to poor reactivity with palladium chloride. Using a more electrophilic palladium salt such as palladium trifluoroacetate allowed the reaction to proceed under much milder conditions and in higher yields.⁵ Furthermore,

(2)

monosubstituted alkenes reacted well too (eq 2). We observed that the alkylation step did not proceed upon addition of a nucleophile. This lack of reactivity was overcome by the addition of a phosphine wherein a much more electrophilic cationic π -allylpalladium complex forms *in situ* and can now readily react with appropriate nucleophiles.² The stereochemistry of the alkylation step was established to occur with inversion of configuration wherein the nucleophile attacked the π -allylpalladium species on the face opposite from where the palladium resided as shown in eq 1.⁴

This new concept of allylic alkylation led to the creation of a prenylation protocol as shown in Scheme 2 for the prenylation of methyl farnesoate to geranylgeraniol.^{6,7} The chemoselectivity of the palladation reaction is noteworthy. Use of methyl phenylsulfinylacetate as nucleophile led to a one pot synthesis of dienates (Scheme 3).⁷ The overall sequence is an alkene version of an allylic olefination. Since Pd(0) is the product of the alkylation reaction but Pd(+2) is required for the formation of the π -allylpalladium species, a catalytic version requires an oxidation of Pd(0) to Pd(+2) under the reaction conditions. On the other hand, an alternative method to generate π -allylpalladium intermediates is the oxidative addition of an allylic ester with a Pd(0) complex. The advantage of this approach is that Pd(0)

(3)

both initiates ionization and is the product of the alkylation, thus being catalytic in palladium.⁸ We therefore turned our attention to the development of this catalytic allylic

alkylation. Olefination of estrone methyl ether generates the ethylidene product **3** with high Z-alkene selectivity. Using the stoichiometric allylic alkylation protocol, the angular methyl substituent directs the metal to the face of the alkene anti to the methyl group to give π -allylpalladium complex **4**. The approach of the nucleophile on the face distal to the metal then generates **5**. On the other hand, epoxidation of the same alkene **6** followed by base promoted epoxide opening generates allylic ester diastereomer **6** selectively. Its alkylation leads to the diastereomeric product **7**. Thus, the stereochemistry of palladium catalyzed allylic substitution proceeds with overall net retention of configuration, a stereochemical complement to normal non-catalyzed substitution processes which proceed with inversion. The unprecedented switch in stereochemistry led us to verify further this conclusion as shown in Scheme 5.⁹ In each case, the product stereochemistry was the same as the stereochemistry of the starting material within experimental error. Given that the stereochemistry of the nucleophilic attack on the π -allylpalladium species occurred with inversion of configuration, the overall net retention of the process therefore stipulates that the ionization of the allylic ester also proceeds with inversion. Thus, the net retention must derive by a double inversion mechanism.

The regioselectivity proved to be much more complicated. The generalization that Pd promotes nucleophilic attack on the least hindered allyl terminus of an unsymmetrically substituted π -allylpalladium species (eq 4, path a) is an oversimplification. There are multiple factors that control the

(4)

regioselectivity. Considering the π -allyl intermediate **8**, steric factors favor attack at the less substituted terminus to give **9**. On the other hand, stability of the initially formed olefin-Pd(0) complexes favors the less substituted olefin **10** (eq 4, path b) due to its lower LUMO making back-bonding from Pd(0) to olefin more favorable. Thus, an early transition state especially with a more bulky nucleophile should favor path a of eq 4; whereas, a late transition state with not too sterically demanding nucleophile should favor path b of eq 4. In accord with this generalization, the product of the reaction of neryl acetate with malonate anion favors attack at the more substituted carbon (eq 5, path a) but the less substituted carbon

(5)

(eq 5, path b) with the anion derived from methyl benzenesulfonylacetate.⁹

While allylic esters and the related carbonates are the most widely used substrates, other ionizable groups have proven effective. For example, vinylepoxides have proven to be very versatile (eq 6).¹⁰ Under typical base catalyzed nucleophilic alkylation, the product of direct substitution with

(6)

inversion of configuration results (eq 6, path a). The $\text{Pd}(0)$ catalyzed reaction occurs under neutral conditions to the $\text{S}_{\text{N}}2^1$ product with net retention of configuration (eq 6, path b). The fact that the reaction between pro-nucleophiles and epoxides is a simple addition represents an example of an ideal synthetic reaction in terms of atom economy. A particularly intriguing leaving group is a sulfone.

(7)

Indeed, the allylsulfone **12** undergoes typical $\text{Pd}(0)$ catalyzed substitution at the less hindered allyl terminus with overall retention of configuration to malonate **13** as depicted in eq 7.¹¹ The benefit of the sulfone is the utility of the sulfone group to acidify the C-H bonds on the carbon bearing the sulfone. Thus, the allyl sulfone **11b**, can be readily methylated via an intermediate metalated sulfone. Thus, the allylsulfone **11b** functions as a functional equivalent of a 1,3-dipole **11a**. Allyl sulfones may be termed “chemical chamelions” since the carbon bearing the sulfone functions as a nucleophile in the presence of base but as an electrophile in the presence of a catalytic amount of palladium.

The most atom economic option is not to have a leaving group. We, therefore, examined whether we can form π -allylpalladium complexes by hydrometalation of 1,3-¹² or 1,2-

dienes.¹³ Indeed, treatment of 1,3-dienes with the pro-nucleophiles in the presence of a Pd(0) source gives the simple adduct of net

(8)

1,4-addition across the diene (eq 8). The addition across a 1,2-diene occurs under significantly milder conditions with extraordinary chemoselectivity. Thus, base promoted standard alkylation proceeds

(9)

completely by simple iodide displacement (eq 9, path a). On the other hand, the Pd catalyzed process proceeds totally by addition to the allene (eq 9, path b).

Malonates had proven to be the archetypical pro-nucleophile for these reactions. Presumably, the nucleophile can coordinate to the metal and, since the metal is much more electron deficient than any of the allyl carbons, that process is likely the kinetically fastest process. However, for nucleophilic addition to the allyl unit to occur, the nucleophile coordination to metal must be reversible so that nucleophilic attack outside the coordination sphere of the metal, as was shown to be required, can indeed occur. Thus, malonates and related carbon nucleophiles like β-ketoesters, α-sulfonyl and α-sulfinyl esters, 1,3-diketones, etc all represent good pro-nucleophiles. On the other hand, simple ketones normally gave poor results. In the best case, the reaction of vinyl epoxide with cyclopentanone gave only a 20% yield

(10a)

(10b)

of the desired alkylated product (eq 10a).¹⁰ “Softening” the ketone enolate by the addition of a phenylthio group improved the process considerably (eq 10b). Alternatively, enol stannanes proved to be effective enolate surrogates and allowed normal reactivity without problems of polyalkylation as well

(11)

(eq 11).¹⁴ Amines are excellent nucleophiles. With primary amines, polyalkylation can complicate the process.

Using a sterically bulky amine **14** as nucleophile gave the monoalkylated amine **15**.¹⁵

(12)

Curiously, amines, in contrast to carbon nucleophiles, have a propensity to give a diastereomeric mixture of allylated products even though the starting allyl ester was a single diastereomer (eq 12). The mechanism of stereochemical equilibration is unclear. Interestingly, using a Pd(0) complex supported on solid phosphinylated beads avoids this problem.¹⁶ Not only did the benzhydryl amine **14** avoid polyalkylation, this benzhydryl substituent can be readily removed with conc. formic acid. As shown in eq 12, the unusual amino acid gabaculine was unmasked readily. This benzhydryl amine also serves as an ammonia surrogate since ammonia fails to react at all. Vinyl epoxides offer a unique way to introduce a nitrogen nucleophile. Addition of an isocyanate to an epoxide serves to

regioselectively install the nitrogen adjacent to oxygen as shown in eq 13.¹⁷ Interestingly, changing the N substituent

(13)

of the isocyanate from Ts to aryl, in particular 2-methoxy-1-naphthyl, the relative stereochemistry of the oxazolidin-2-one switched from *trans* as shown in eq 13 to *cis* **16a** exclusively as shown in eq 14.¹⁸ CAN chemoselectively removes the aryl group from the nitrogen to give the simple oxazolidinone **16b**.

(14)

Thiol nucleophiles proved erratic; sometimes reaction proceeded readily, whereas other times the catalyst was poisoned. The problem ultimately stemmed from adventitious oxidation of the thiol to the disulfide which is a very effective poison for Pd(0). Using the trimethylsilyl thioether readily resolved this irreducibility problem as shown in eq 15.¹⁹ In contrast to amine nucleophiles, no loss of diastereoselectivity is observed. This example also illustrates the use of carbonates as alternatives to

(15)

carboxylates which are both more robust since deacylation processes are less likely and more reactive as a leaving group. The use of the (dba)₃Pd₂-CHCl₃ complex as pre-catalyst allows facile choice of optimum ligand which, in this case, proved to be a phosphite.

The hardness of alkoxides and the poor nucleophilicity of alcohols has generally hindered the development of alcohol nucleophiles. Muting the hardness by forming a tin ether allowed alkylation of vicinal diols with vinyl epoxides using Pd catalysis (eq 16).²⁰ The failure of water serving as a

(16)

nucleophile has the benefit of allowing Pd catalyzed allylic alkylations to proceed under aqueous conditions. Softening hydroxide as a nucleophile by using a siloxide provides a nice way to install a simple hydroxyl group (eq 17).²¹

(17)

In the absence of a suitable nucleophile, loss of a proton can ensue to generate 1,3-dienes. The problem with this method is regioselectivity. The ready availability of vinyl β -hydroxycarboxylic acids via addition of carboxylate enolates to α,β -unsaturated aldehydes suggested the feasibility of a decarboxylative elimination to control the regioselectivity of the diene. As shown in eq 18, the reaction not only gave a single regioisomer but it also maintained the geometry of the double bond of the

(18)

substrate as illustrated by the synthesis of the insect pheromone bombykol (**17b**).²²

3. Cyclizations with palladium catalysis

In attempts to effect cyclizations of β -ketoester pronucleophiles, we noted that alkylation

(19)

proceeded preferentially at oxygen rather than carbon (eq 19). On the other hand, subjecting the enol vinylogous ester to Pd(0) in DMSO at 120°C effected O to C rearrangement to the cyclopentanones favoring the Z geometry.²³ An alternative synthesis of the enol vinylogous ester by conjugate addition of an alcohol onto an ynoate followed by Pd catalyzed O to C isomerization provided ready access to

(20)

prostanoids (eq 20). With a non- β -keto ester as the pro-nucleophile, typical cyclization by C-C bond formation occurs (eq 21).²⁴ In an acyclic substrate, **20**, a most astonishing regioselectivity was observed.

(21)

Whereas either a 6- or 8-membered ring could form by attacking of the anion on either terminus of the

(22)

allyl Pd intermediate, the 6-membered product **21** would be expected to overwhelmingly dominate because 1) 6 membered rings form over 10^4 times faster than 8 membered rings, 2) the intermediate π -allylpalladium favors the syn isomer which would require forming a highly strained *trans* double bond in an eight membered ring and 3) the stereoelectronics favors a 6-exo-trig over a 8-endo-trig nucleophilic attack. Remarkably, experimentally, the 8-membered ring lactone **22** was strongly favored 93:7 **22:21**. This example is the only reported case of 8-membered ring dominating over 6-membered ring formation. In the analogous case of 7 vs 9-membered ring formation, the 9-membered ring, obtained in 60% yield, was the exclusive product!

Formation of 8 and 9-membered rings are typically the most difficult rings to form in large measure due to ring strain evolved from transannular interactions. Larger rings should form at least as well if not better. Indeed, the 12-membered lactone **23** formed as the exclusive product (eq 23) on the way to recifeiolide. The 16-membered ring of exaltolide also formed with equal efficiency (eq 24).

(23)

(24)

These observations bode well for the ability to effect macrocyclization utilizing Pd catalyzed allylic alkylation for forming C-C bonds. The vinyl epoxides proved to be particularly effective electrophilic partners wherein cyclizations are simple isomerizations.²⁵ For example, eight (eq 25) and nine (eq 26) membered rings form efficiently with phosphite ligands. While such reactions typically

(25)

(26)

require rather dilute solutions ($\sim 0.01\text{M}$), these cycloisomerizations could be carried out at high concentrations ($> 0.1\text{M}$) when a solid supported Pd(0) catalyst was employed (eq 27). Under these

(27)

conditions, the effective concentration of the substrate at the active site due to the heterogeneity of the catalyst is quite low mitigating polymerization. Perhaps the most remarkable example of this cycloisomerization strategy is the ability to form the 26-membered ring of the tetrin antifungal agent (ie

(28)

23) in near quantitative yield (eq 28)!²⁶ Furthermore, the juxtaposition of functionality sets the stage for use of a Pd(0) catalyzed bis-elimination reaction of the diene precursor **24** to form the thermodynamically more stable all *E* tetraene **25**.

Macroheterocycles were also readily obtained under the conditions of allylic alkylation using a heteroatom nucleophile.²⁷ In these cases, the macrocyclization is carried out in the absence of base,

(29)

thereby generating the cyclized ammonium acetate salt and thus constitutes a macro-cycloisomerization. Neutralization upon work-up then liberates the free amine (eq 29) on the way to the spermidine alkaloid inandenin-12-one.

Switching from a substrate bearing an allylic leaving group to protonating a 1,2-diene (an allene) to form the π -allyl complex proved extremely efficient in macrocyclization. Thus, the 16-member all carbocycle formed in 68% yield even at 0.01M (eq 30).²⁸ Medium sized rings form even in higher

(30)

yields as shown for the 10-membered rings (eq 31). For these smaller rings the presence of both an acid

(31)

and a base are required. As noted for the more standard cyclizations involving substrates bearing an allylic leaving group, in the case of 7 vs 9-membered ring formation using an allene precursor, only the

(32)

9-membered ring product was observed (eq 32).

4. Enantioselectivity

A significant benefit of transition metal catalytic processes is the prospect of using chiral ligands to induce asymmetry. This potential was realized early in the asymmetric hydrogenation wherein a prochiral π -unsaturation undergoes reduction with spectacular generality and levels of enantioinduction. However, transferring the concept from hydrogenation to Pd catalyzed alkylation was highly challenging. In the asymmetric hydrogenation, transfer of hydrogens to the π -unsaturation occurs within the coordination sphere of the metal. Since the chirality derives from the chiral ligands, the bond forming reaction occurs in close proximity to the chirality of the ligands wherein the ligand chirality can greatly influence the asymmetry. On the other hand, the stereochemistry of the Pd catalyzed allylic alkylation process indicates the bond breaking and bond making events in which chirality is created occur outside the coordination sphere of the metal. Examination of Fig. 1 reveals that the metal and its attendant ligands (see Fig 1) are on opposite sides of the allyl unit and quite distant from the ligands L bound to Pd. How can chirality at the ligands L influence the stereochemistry of reactions proceeding in such a fashion and for which there was no precedent?

A second aspect that differentiates the modes for asymmetric induction for the Pd catalyzed reaction compared to processes like asymmetric hydrogenation is the mechanisms for asymmetric induction. In hydrogenation, there is essentially only one mechanism for asymmetric induction, that is differentiation of enantiotopic faces. As shown in Fig 2, that mechanism also exists in Pd catalyzed asymmetric allylic alkylation (AAA) as shown in Fig 2-A. However, the kinetically formed π -allyl complexes in this mechanism can shift to a Curtin-Hammett situation wherein the difference in rate of nucleophilic addition to the

interconverting diastereomeric π -allyl complexes determines the ee as in Fig 2-B. An interesting prospect arises wherein the substrate is chiral but mechanistically can lose its chirality during the course of the reaction. In one iteration, Fig 2-C, the π -allyl subunit has a plane of symmetry. In a second iteration, Fig 2-D, the π -allylpalladium intermediate can interconvert between the two faces of the η^3 -allylpalladium species via a σ -O-bound enolate which again creates a Curtin-Hammett situation. Fig 2-E illustrates that an achiral symmetrical substrate can undergo enantioselective ionization. Finally, the nucleophile may also have prochiral faces (Fig 2-F). Thus, both partners in the Pd catalyzed allylic alkylation may undergo asymmetric induction.

This difficulty was made immediately evident in the initial studies.²⁹ Using mechanism Fig 2-B, the *cis* isomer of allyl acetate **26** undergoes allylation using DIOP, a chiral ligand that gives high

(33)

enantioinduction in hydrogenations, in only 24% ee (eq 33). Poorer results were obtained with many other common achiral ligands such as DIPAMP and CAMPHOS. In a related reaction utilizing lactone **27**, switching from DIOP to BINAP improved the ee from 16% to 31% (eq 34).³⁰ We

(34)

hypothesized that high asymmetric induction would require the creation of chiral space, akin to the active site of an enzyme. Increasing the size of the palladocycle from 7 as in BINAP to 9 as in BINAPO (**27b**) should indeed increase the differential recognition. While that occurred to a small extent, we envisioned we could extend it further by making the aryl rings more sterically bulky as in BINAPO analog **27c**. Indeed, the ee jumped to 69%.

At this point, we decided that a totally new ligand design would be required. We wanted a modular ligand that would be simple to synthesize and systematically vary. Ligand **28** nicely filled our requirements being composed of a chiral diol or diamine scaffold, a linker, and binding posts each of which could be independently varied.³¹ The chiral C_2 -symmetric diols

or diamines (see Table 1) were also readily available. Further, if such ligands could serve as bidentate ligands to a single metal thereby creating a single ring, the resultant macrocycle would create a highly asymmetric chiral environment reminiscent of an enzyme. To minimize complications associated with the impact of the structure of the nucleophile on asymmetric induction, we examined the desymmetrization of meso-diols as substrates wherein ionization was the enantio-discriminating event as shown in eq 35.³² The diester ligands L_{2a} and

(35)

L_{2b} gave decent levels of enantioselectivity. Remarkably, whereas L_{2c} , $\text{X}=\text{O}$, is achiral and, by necessity, must generate racemic product, simply converting $\text{X}=\text{O}$ to $\text{X}=\text{NH}$ not only creates a chiral ligand but it provides a product of higher ee than the corresponding chiral diester L_{2b} . Thus, in a nearly racemic scaffold the presence of an amide had a very high influence.

Switching to diamides did indeed improve the ee as expected. In particular, the design of the chiral scaffold had a significant impact. Increasing the N-C-C-N dihedral angle in going from $L_{2\text{STD}}$ to L_{2A} which, in turn, creates a larger P-Pd-P bite angle improves the chiral recognition.³¹ Thus, we focused on the diamide family of ligands. In optimizing the ee, we discovered that simple addition of triethylamine improved the ee to 99%!³³ Indeed, $L_{2\text{STD}}$ became our “standard” ligand. However, the corresponding diamide from stilbene diamine L_{2S} and ligand L_{2A} wherein the dihedral N-C-C-N angles and P-Pd-P bite angles are enlarged have had significant benefits in subsequent work. A reliable mnemonic to rationalize and predict the absolute configuration of the product based upon the enantiomer of the ligand was also developed.³⁴

The desymmetrization of meso diols has proven to be generally broadly applicable including inter- as well as intramolecular processes. Thus malonate reacts using the standard ligand to give the monoalkylated product only (eq 36, path a).³⁵ Indeed, ionization of the remaining allyl ester is very slow

(36)

with the chiral ligand $R,R\text{-}L_{2\text{STD}}$ since that represents a “mismatched” ionization. Indeed, to get the remaining ester to ionize, a switch to an achiral ligand is required. As shown in eq

36, path a, the malonate introduced in the first step then can function as the nucleophile in an intramolecular reaction to constitute an asymmetric synthesis of cyclopropanes.

This desymmetrization extends to amine nucleophiles (eq 36, path b).³⁶ For high ee, the chiral scaffold required was developed from the stilbene diamine wherein the resultant ligand L_5 encompassed aromatic rings that may engage in π -stacking to enhance the chiral space. A particularly exciting nitrogen nucleophile is azide which, as shown in eq 36, path c, gives enantiomerically pure allyl azide at -20° !³⁷

N-Heterocycles also serve as excellent nucleophiles in this desymmetrization. As shown in eq 37, pyrroles provided nucleoside analogs of interest as anti-viral and anti-tumor analogs.³⁸ Most

(37)

(38)

interestingly, the meso diester derived from furan also smoothly participates without complications of aromatization of the π -allylpalladium intermediate (eq 38). This adduct was converted to the enantiomer of the adduct that would derive from natural ribose, an analog not readily obtainable from natural sources. Obviously, either enantiomer is available by the Pd AAA method simply by using one or the other of the enantiomeric ligands.

A most exciting application of this desymmetrization of diester **29** involves a nitronate nucleophile which undergoes O rather than C alkylation. It then undergoes a Cope-type elimination to

(39)

form enone **30a** directly in one pot (eq 39).³⁹ This product retains an allyl ester which undergoes subsequent Pd allyl substitution with retention of stereochemistry.⁴⁰ Using the

silyl ether of N-benzylaminoethanol provides the alkylated amine **30b** which can undergo cyclization to the chiral morpholine **31**.

A sulfur nucleophile, benzenesulfinate anion, participates in Pd AAA reactions wherein attack occurs at sulfur not oxygen (eq 40).⁴¹ The utility of chiral sulfones as building blocks led to the use of

(40)

sodium benzenesulfinate whereby allylic sulfone **32** was available in >96% ee. As shown in eq 40, the initial product allows propagation of the chirality by effecting subsequent transformations to form C-O and C-C bonds with high diastereoselectivity.

A novel pro-chiral substrate involving gem-diacetates provides the equivalent of an asymmetric addition to a carbonyl group utilizing nucleophiles that typically do not add enantioselectively to such groups.⁴² Thus, the diacetate **33**, undergoes desymmetrization with the standard ligand in high ee (eq 41).

(41)

Interesting is the use of sodium benzenesulfinate which generates an unprecedented “chiral carbonyl” equivalent (eq 42). This “chiral carbonyl” equivalent induces excellent stereocontrol on additions to the

(42)

double bond as depicted for dihydroxylation.⁴³

Enantioselectivity via discriminating enantiotopic faces of the double bond of the allyl ester (Fig. 2 A) is limited since the regioselectivity of alkylation more commonly generates the achiral product wherein the nucleophile attacks the less substituted carbon. Tethering the nucleophile to the allyl ester overcomes this issue. Thus, formation of N-heterocycles leads exclusively to the “branched” product in

(43a)

(43b)

high ee (eq 43a and 43b).⁴⁴ Mechanistic studies support the proposed mechanism for enantio-discrimination. The substrate for eq 43b is made by the Ru catalyzed alkene-alkyne coupling. In fact, these two steps can be merged into a one pot process wherein the initial Ru catalyzed process is performed in acetone after which a methylene chloride solution of the Pd catalyst is simply added.⁴⁵ The use of oxygen nucleophiles was examined in the context of a chromane synthesis (eq 44).⁴⁶ Thus, the *E*

(44)

isomer **34** provides the chromane in high ee. Consistent with the enantioselectivity arising from enantiodiscrimination of enantiotopic alkene faces is the fact that the *Z* isomer **35** generates the same enantiomeric product by using the enantiomeric ligand.

An asymmetric Wagner-Meerwein shift induced by chiral π -allylpalladium intermediates also proceeds by this mechanism as shown in eq 45.⁴⁷ The observation that the faster reacting cyclopropane

(45)

substrate exhibits higher selectivity than the slower reacting cyclobutane substrate supports the mechanistic interpretation that the kinetic facial differentiation is enantiodetermining. An asymmetric Wagner-Meerwein shift initiated by hydropalladation of an allene also has led to excellent ee's most likely by discriminating between the preferential hydropalladation⁴⁸ of prochiral faces of the allene (eq 46).

(46)

The use of 1-alkoxy-allene to generate π -allylpalladium intermediates has also been used in intermolecular versions of AAA (eq 47). The alkoxy group directs the regioselectivity to give the chiral

(47)

branched product.⁴⁹ There is no direct evidence that this proceeds by either mechanism A or B of Fig. 2.

Substrates that typically react via mechanism in Fig 2B are vinyl epoxides.^{50a} Thus, butadiene monoepoxide reacts readily with both nitrogen (eq 48) and oxygen nucleophiles. Initial studies revealed that the regioselectivity depended upon choice of ligand wherein the ligands possessing 2-diphenylphosfinonaphthyl as the linker gave almost exclusive formation of the branched product. Using phthalimide as the pro-nucleophile and the racemic epoxide, a quantitative yield of the branched product virtually enantiopure was obtained (eq 48).^{50b} The result was a perfect dynamic kinetic asymmetric transformation (DYKAT). This is the easiest most practical route to vinylglycinol of either enantiomer, an aspect not available by the common route of starting from a natural amino acid. For use of oxygen based nucleophiles, catalytic triethylborane was used to help control the regioselectivity for attack at the more substituted allyl terminus to give the branched product.⁵¹ A practical asymmetric synthesis of either enantiomer of vinylglycidols resulted (eq 49). For butadiene monoepoxide, **36**, R=H, the use of sodium carbonate in a two phase methylene chloride-water system using *S,S*-L₂S and (C₄H₉)₄N Cl gave

(48)

(49)

excellent results.⁵² Under the conditions of the reaction, the catalyst remains in the organic layer but the product is formed as the sodium salt of an alkyl carbonate which is in the aqueous phase. Acidification of the aqueous phase after the separation of phases then gives the diol **37** (R=H). The organic phase can be simply recharged with epoxide, sodium carbonate, and phase transfer catalyst to give an equally effective reaction. Indeed, the organic phase containing the chiral phase was used for five cycles without any loss in yield or ee. Switching to isoprene monoepoxide, **36** (R=CH₃), simplified the protocol. Sodium bicarbonate sufficed, and, remarkably, the standard *S,S*-L_{STD} ligand proved satisfactory to give the tertiary alcohol with no detectable amount of the alternative regioisomer. Even a carbon nucleophile can be used in these DYKAT reactions to create a quaternary center as shown in eq 50.⁵³ Interestingly, the addition of a mild source of fluoride to speed up the racemization of the π -allylpalladium intermediate was required.

(50)

Vinyl aziridines act analogously to vinyl epoxides.⁵⁴ Thus, *N*-benzylvinylaziridine reacts with imides to give rise to the vicinal diamines (eq 51). As with the vinyl epoxides, the naphthyl linker gives highest regioselectivities. Since any kind of substituent can be on the aziridine nitrogen, use of the *N*-

(51)

homoallyl group provides the azepine core of the PKC inhibitor balanol (eq 52).⁵⁵ Use of *N*-heterocycles as nucleophiles has led to a facile synthesis of fused vinyl piperazinones (eq 53).⁵⁶

(53)

With a monosubstituted allyl system in a totally unconstrained case, a battle between kinetic and thermodynamic control exists. Usefully, starting with racemic chiral allyl substrate **38** allows obtention

(54)

of the branched product **39** (**39:40**, 80:20) in 80 % $\pm$ 3% ee (eq 54).⁵⁷ Thus, with a sterically non-hindered nucleophile, attack at the most electron-deficient substituted allyl terminus occurs. The presence of the quaternary ammonium halide salt assures equilibration of the two diastereomeric π -allylpalladium complexes is fast relative to nucleophilic attack.

This regioisomer was also observed in the case of Bayless-Hillman adducts (eq 55) with phenol nucleophiles.⁵⁸ Again equilibration of the π -allylpalladium complexes must be fast relative to

(55)

nucleophilic attack for high ee. The optimal results were obtained with the stilbene diamine ligand.

One of the most curious mechanisms is deracemization as shown in Fig. 2 C. The ease of availability and the potential for applications focused our early efforts on cyclic allyl esters **41** (eq 56).⁵⁹

(56)

A key to high ee for the alkylated product **42** is the choice of counterion. Tetramethyl and tetra-*n*-butyl ammonium counterions gave significantly lower ee's compared to tetra-*n*-hexyl. Similar results were obtained with nitroalkanes as nucleophiles, even in the case of 2-nitropropane wherein a tetrasubstituted carbon is created (eq 57).⁶⁰ This reaction also succeeded with an acyclic substrate as shown in eq 58.

(57)

Remarkably, the ee depended significantly on the catalyst loading. With 2 mol% Pd(0) precursor, only 3% ee was observed. Dropping the Pd(0) precursor loading to 0.5 mol% increased the ee to 86% and a further decrease to 0.25 mol% increased the ee to 91%. This effect of ee on load of catalyst may be explained by the need to allow the π -allylpalladium intermediates which are not C_2 symmetric to fully equilibrate so that they are functionally equivalent to being C_2 symmetric.

(58)

While examples illustrated the phenomenon with carbon nucleophiles, heteroatom nucleophiles also react quite well and with high asymmetric induction. Using carboxylates as oxygen nucleophiles, deracemization of allylic carbonates generates the corresponding allylic carboxylates in high ee (eq 59).⁶¹ The product **43** serves as a precursor to phyllanthocin and constitutes the most practical synthesis of this chiral subunit.⁶² A particularly striking example of this phenomenon is the

(59)

deracemization of the tetra ester **44** to give the dibenzoate **45a** (eq 60, path a).⁶³ Phenols also represent an interesting class of nucleophiles for desymmetrization. The use of vanillin illustrates the

(60)

chemoselectivity (eq 61).⁶⁴ The creation of an allyl phenyl ether **46** sets the stage for a Claisen rearrangement which proceeds with complete chirality transfer converting a chiral C-O bond to a chiral C-C bond **47**. Subjecting the resultant aldehyde to an intramolecular hetero- Alder ene reaction then generates the tricycle **48**. Note the high atom economy and rapid buildup of multi-stereogenic centers with high stereocontrol emanating from the AAA reaction.

(61)

Nitrogen nucleophiles participate equally well. Particularly noteworthy is the desymmetrization of eq 60, path b, wherein the monoamine **45b** is obtained with high yield and ee. Sulfur nucleophiles such as sulfinates serve as excellent nucleophiles as shown in eq 62.⁴¹ The resultant allyl sulfone serves

(62)

as a very useful building block.

So far, the electrophilic partner, the π -allylpalladium species, is the “natural” partner for asymmetric induction by use of chiral ligands. Their reaction partners, the nucleophiles, are

also potential prochiral partners. Keeping in mind the fact that the bond making and breaking events are outside the coordination sphere of the metal, the prochiral nucleophile places itself as far away from the chiral inducing structural elements, the so-called “chiral scaffold,” as possible as shown in Fig. 4. Thus, the probability of inducing asymmetry over such long distances appeared daunting. While the expectation was failure, the experiment was too simple not to do. Using a β -ketoester **49** as the prochiral nucleophile, the allylation proceeded excellently, giving the product with 95% ee (eq 63, path a).⁶⁵ Even more remarkable, using both partners as prochiral entities as in eq 63 path b gives both high dr and ee for the major diastereomer.

(63)

The conventional wisdom was that simple lithium ketone enolates were unsatisfactory nucleophilic partners for Pd catalyzed allylations while the addition of a tin additive allowed allylation to proceed. Nevertheless, their viability with the chiral complexes was important to compare. Using tetralone **50** as the test case, with LDA as base, using a tin additive gave a quantitative yield of allylated product of 88% ee (eq 64).⁶⁶ Without the tin additive nearly the same results were obtained (96% yield, 85% ee). Thus, the chiral ligands also form complexes that expand the scope of the Pd catalyzed allylic

(64)

alkylation. With α -arylated ketones as substrates, the sodium or cesium enolate in the absence of any additive performed best.⁶⁷ In many cases, the preferred ligand was that derived from the stilbene diamine L_s. For the β -tetralone **51**, the cesium enolate gave the highest enantioselectivity (eq 65). The product **52** could undergo a second intramolecular Pd catalyzed alkylation to generate the bridged tricycle **53**, an analog of the natural product huperzine A (eq 65).

(65)

An alternative method for enolate alkylation involves formation of enol allyl carbonates. Upon treatment with a Pd(0) complex, the substrates ionize and then lose CO₂ to form a π -allylpalladium enolate which combines to form the allylated ketone.⁶⁸ Initial studies showed that allylation of cyclic ketones to form both tertiary (eq 66) and quaternary (eq 67) centers works well.⁶⁹ The ligand of choice

(66)

(67)

is that which has the largest bite angle, the anthracenyl derived one L_A. Acyclic substrates work equally well.^{69,70} Enolate geometry controls facial selectivity as shown in eq 68 and 69 wherein switching from a *Z* to an *E* enolate inverts the stereochemistry of the newly formed stereocenter. No enolate equilibration occurs nor does any polyalkylation. In the case of enol allyl carbonates derived from 2-acylimidazoles,

(68)

(69)

the aryl imidazole group is primed for imidazole cleavage to a variety of carbonyl containing compounds including esters, acids, amides, and ketones as shown for the latter two in eq 70.⁷¹

(70)

Vinylogous esters and thioesters represent very versatile building blocks. The use of the allyl ester of a methylated β -ketoester as in eq 71, which derives by methylation of the unsubstituted β -

(71)

(72)

ketoester, works best when the enol substituent is phenoxy.⁷² Replacing phenoxy by phenylthio (**54**, eq 72, path b) gives an even better process. The most reactive substrate is enol thioether **55** which gives a quantitative yield of allylated product **56**. Scheme 6 illustrates the synthetic versatility of these vinylogous thioesters.

The enol esters of α -hydroxyketones represent formidable challenges for selectivity.^{73,74} These species are readily available in two steps from the alcohol that becomes the allylating agent and the α -hydroxy- or α -bromoketone. When the silyl ether **57** is subjected to Pd(0)

catalysis, the exclusive product is the aldehyde **60** (see eq 73). Alternatively, when the corresponding acetate **61** is subjected to the same conditions, the acetoxy ketone **63** is the exclusive product.^{74,75} This dichotomy can be understood by considering the structures of the intermediate ion pairs. In the case of silicon, the two regioisomeric enolates **58** and **59** can be considered to be in rapid equilibration due to a very low energy barrier for silicon transfer. The extended conjugation should also make enolate **59** more stable than **58**. Thus, enolate **59** reacts faster with the π -allylpalladium species to give aldehyde **60**. On the other hand, the acyl shift required in enolate **62** would be expected to have a higher energy barrier with the result that the kinetically formed enolate **62** reacts faster with the π -allylpalladium species than it equilibrates.

(73)

Another notable class of prochiral nucleophiles are azlactones, common intermediates in the synthesis of substituted amino acids. Whereas allyl and α -substituted allyl groups gave low enantioselectivity, 3-substituted allylating agents gave high ee's (eq 74).⁷⁶ Inducing stereochemistry at

(74)

both partners proved even easier to accomplish. Thus, discriminating enantiotopic leaving groups (eq 75) as well as deracemizing 1,3-disubstituted allylating agents (eq 76) gave excellent ee with our standard ligand.⁷⁷

(75, 76)

Indole related compounds are key intermediates in alkaloid chemistry. Oxindoles have proven to be particularly versatile building blocks. Indeed, the Pd catalyzed AAA proceeds to generate the quaternary stereocenter using the anthracenyl derived ligand L_A as the preferred ligand (eq 77).⁷⁸ The use of the atom economical version involving generation of the π -allyl species via protonation of an

(77)

(78)

allene also gave excellent results (eq 78).^{49,79} Interestingly, with 3,3-disubstituted allylating agents, the regioselectivity can be controlled to direct C-C bond formation to the disubstituted terminus of the π -allyl unit (eq 79).⁸⁰ This regioselectivity derives from attack of the nucleophile at the more electrophilic

(79)

terminus of the allyl unit combined with using the naphtho linker which favors the olefin – Pd(0) coordination in the initial alkylated product to the one possessing the least substituted olefin because of its lower LUMO energy allowing increased back-bonding from the low valent metal. The amazing aspect of this type of alkylation is the facility with which two adjacent quaternary stereocenters evolve from each partner in the allylic alkylation in high ee and de.

Indoles themselves have served as prochiral nucleophiles in asymmetric allylic alkylation (eq 80).⁸¹ Because this initial product is an indolenine which is reactive towards nucleophiles, an annulation protocol emerged. As illustrated in eq 80, having an appropriate side chain led to cyclizations to form

(80)

the tricycles **64** where $\text{X} = \text{O}, \text{N},$ or C .

Nitroalkenes have also proved to be good prochiral nucleophiles for allylic alkylation.⁸² Using

(81)

both a prochiral nitroalkane with a prochiral 1,3-dimethylallylating agent gave the resultant product in 59% yield (99% based upon recovered starting material), 12:1 dr, and 97% ee (eq 81).

How unstabilized a nucleophile can be employed? We turned to electron deficient nitrogen heterocycles like pyridine, pyridazine, etc.⁸³ In the case of nitrogen containing heterocycles, a methyl group at C-2 can be deprotonated and directly employed in AAA reactions. However, for the case of 2-substituted pyridines, pre-complexation with $\text{BF}_3 \cdot \text{O}(\text{C}_2\text{H}_5)_2$ ether is required (eq 82).

(82)

5. Oxidative allylic alkylation

The fundamental challenge to effect direct allylation of nucleophiles via C-H activation of the allylating agent, which started us on our path to Pd chemistry, was put "on hold" early on. Developments in our efforts to learn about the allylic alkylation of allylic alcohol and related derivatives consumed our attention because of our successes. We were lured more recently to return to make the process more efficient by directly replacing an allylic C-H bond by a C-C bond. Using a 1,4-diene in the presence of an oxidizing agent

(83)

(84)

and palladium did lead to pentadienylated products with reasonably stabilized nucleophiles; even a simple nitroalkane sufficed (eq 83).⁸⁴ Despite claims that phosphine ligands are incompatible in similar oxidative reactions, they proved, in our hands, to be superior to other ligands. Remarkably, an active methylene nucleophile can undergo classical allylation and oxidative allylic alkylation by mixing all 3 components together in the presence of a Pd complex (eq 84). The compatibility of phosphine based ligands being capable of serving in oxidative allylic alkylations led to the development of an

(85)

asymmetric version as well (eq 85).⁸⁵ This example is the only reported asymmetric allylic alkylation of any kind involving allylic C-H activation.

6. Total synthesis – achiral ligands

Initial efforts at using Pd catalyzed allylic alkylation were focused upon simple structural issues. For example, alkylation of amines by Pd(0) allylic alkylations (AA) occurs under very mild conditions with easy to prepare and handle alkylating agents as shown for the synthesis of gabaculine **65** (eq 86).¹⁵ The evolution of an α-alkoxyallyl ester, derived from addition of metalated ethyl vinyl ether to

(86)

aldehydes as an enolonium equivalent, a reactive intermediate not readily accessible previously, led to a simple synthesis of pyrenophorin B **66** (eq 87).⁸⁶ A geometrically controlled olefination protocol that

(87)

does not involve difficult to remove stoichiometric by-products has led to the synthesis of an insect pheromone bombykol (**17**, eq 18)²² and vitamin E ester **67** (eq 88).⁸⁷

(88)

The ability to control regioselectivity in the Pd catalyzed use of vinyl epoxides proved highly useful. The regioselectivity of such electrophiles under these conditions places the nucleophile distal to the departing oxygen as shown in **68** (eq 89).⁸⁸ A second Pd(0) catalyzed reaction occurs with

(89)

complete regio- and diastereoselectivity to ultimately provide the carbanucleoside aristeromycin **69**. Thus, the cis vicinal C-O bonds translates to cis 1,4-disubstituted C-C and C-N bonds. The mechanism for transfer of stereochemical information depends both on the

epoxide stereochemistry but also the geometry of the olefin as shown in our synthesis of pumiliotoxin **71** (eq 90) from epoxide **70**.⁸⁹ If the

(90)

nucleophile becomes tethered to the oxygen then a cis 1,2-disubstituted product ensues. Thus, in a synthesis of (+)-citroviral **72**, using CO₂ tethers the subsequent carbonate nucleophile⁹⁰ to give the

(91)

(92)

vicinal product (eq 91).⁹¹ Switching CO₂ to an isocyanate leads to aminoalcohols such as acosamine **73** (eq 92).^{18b}

Cyclizations have been particularly effective. For example a synthesis of the iboga alkaloids takes advantage of the intrinsic diastereoselectivity of the Diels-Alder reaction (eq 93).^{92–94}

(93)

particularly short synthesis of ibogamine **74** resulted.⁹⁴ A cyclization involving a carbon based nucleophile allowed carvone to serve as the precursor to set the stereochemistry in a synthesis of the

(94)

alkaloid dendrobine (eq 94).⁹⁵ This process has been particularly effective for macrocyclization. Thus, a facile synthesis of the twelve-membered macrolide receifiolide resulted (see eq 23). The enolonium equivalent **75** creates a perfect juxtaposition for common macrolide antibiotics as shown in the key steps

(95)

of the synthesis of antibiotic A26771 B, **76** (eq 95)⁹⁶ and aspochalasin **77** (eq 94).⁹⁷

Cycloisomerizations

(96)

of amines as nucleophiles have proven particularly effective as shown in a synthesis of the spermidine alkaloid inandenin-12-one **78** (eq 97).⁹⁸

(97)

7. Total synthesis – chiral ligands

Desymmetrizing meso diesters with Pd complexes containing chiral ligands in which enantioselectivity is created in the ionization step has proven to create expeditious synthetic routes to numerous targets. Table 1 lists the ligands developed in these laboratories, ones which have proven to be the most effective over the broadest range of substrates. The five membered ring meso-diester type of substrate such as **79a** has proven extraordinarily

promiscuous. In a synthesis of the novel aminoalcohol mannostatin **80** initial enantioselectivity proved promising (78% ee) (eq 98).⁹⁹ Realizing that ionization may be reversible unless the sulfonamide is made into a good nucleophile by deprotonating with base led to the addition of triethylamine whereupon the ee soared to 99%!¹³³ Placing an additional substituent

(98)

on the five membered ring as in **79b** under the original conditions gave a similar ee (70%). This product provided a very practical synthesis of allosamizoline **81** (eq 99).

Carbanucleosides are readily available. With diester **79c**, the first strategy introduces the one carbon unit to create the hydroxymethyl substituent followed by a second Pd(0) catalyzed process with

(99)

achiral ligands to introduce the base which resulted in a synthesis of carbosir **82** (eq 100, path a).¹⁰⁰ Revising the order of the two Pd(0) catalyzed processes reduces the total number of steps to four (eq 100, path b).¹⁰¹ The pyrrole **83** is particularly interesting since it undergoes chemoselective double

(100)

alkylation that provides (–)-agelastatin **84** in only 6 steps (eq 101).¹⁰² Table 2 summarizes the use of this desymmetrizing strategy to a number of bioactive targets. A most unusual nucleophile is a hindered nitronate which undergoes an O rather than C alkylation leading to an unprecedented oxidative

(101)

desymmetrization to enone **85** on the way to the enyne tricholomenyn A, **86**, eq 102.¹⁰⁹

(102)

The enantioselective ionization of a gem-dicarboxylate offers the opportunity to access highly elaborated serine systems as represented by the sphingofungins such as sphingofungin F, **87**, eq 103.¹¹⁰ Divinyl carbonate is available as a 1:1 diastereomeric mixture of the meso and d, l forms (see Table 2, entry 10). If 100% of the meso and 50% of the d, l forms react, a 75% yield of a single enantiomeric

(103)

product should result along with 25% unreacted starting material when using chiral Pd(0) catalysts of 100% enantioselectivity. Using phthalimide as nucleophile indeed provided a 72% yield (96% based upon 25% being non-reactive) of the monoalkylated product of 89% ee (see Table 2, entry 10). This intermediate led to the alkaloid australine^{108a} and the mitomycin analog 7-epi-(+)-FR900482.^{108b}

With allyl systems like **88**, the chiral product is **89** although the typically expected product with achiral ligands (eq 104) is **90**. Can the chiral ligand control both the regio- as well as enantioselectivity? The most assured way to control the regioselectivity is to tether the nucleophile to the electrophile. Chromane natural products are a “natural” for such methods since phenols are excellent nucleophiles in Pd AAA reactions and the elaboration of the acyclic precursor is greatly facilitated by the phenolic OH. Indeed, the chromane **91** is available from either the *E* or *Z* trisubstituted alkene wherein the same

(104)

absolute configuration of the chromane product is accessed by using enantiomeric ligands for each substrate (see eq. 105).⁴⁶ Both simple chromane (+)-clasifoliol and the more complex (–)siccanin¹¹¹ derive from this adduct.

(105)

The ready availability of racemic Morita-Baylis-Hilman adducts make them attractive substrates for deracemization if the regioselectivity can be controlled. Indeed, such a strategy proved effective in both an intra- (eq 106) as well as intermolecular (eq 107) fashion in asymmetric syntheses of

(106)

(107)

hippospongiol¹¹² and furaquinocin E¹¹³ respectively. In non-tethered uses similar to eq 107, the employment of a sterically demanding ligand like the naphthalene containing L_N

tilts the regioselectivity for non-sterically demanding nucleophiles like oxygen to favor the least electron rich terminus as in our synthesis of calanolide A (eq 108).¹¹⁴ Most remarkably, an oxindole carbon nucleophile even generated

(108)

vicinal quaternary centers using L_N in our synthesis of flustramines (eq 109).⁸⁰ On the other hand, the

(109)

stilbene diamine derived L_S proved more optimum in our use of this strategy to favor branched products in a synthesis of callipeltoside.¹¹⁵

The ability to favor branched regioisomers in the reactions of vinyl epoxides and vinyl aziridines has proven applicable to a range of targets as shown in Table 3. Oxygen and nitrogen nucleophiles allow excellent regio- and enantioselectivity which involves deracemization of the π -allyl palladium intermediate. The asymmetric synthesis of the phthalimide derivative of vinylglycinol (cf Table 3, entry 2), a widely used chiral building block, makes this two-step synthesis from commercially available starting materials particularly attractive since either enantiomer is equally accessible.⁴⁹ Thus, in addition to accessing vigabatrin (Table 3, entry 2a), the bacteriostatic antimycobacterial drug ethambutol was also synthesized.¹¹⁶

The deracemization of the vinyl epoxide **92** occurs by a completely different mechanism since the π -allylpalladium intermediate **93** is meso (ignoring the chirality of the ligands). Thus, preferential

(110)

attack of the nucleophile at one of the two diastereotopic termini of the π -allyl subunit establishes the absolute configuration in a synthesis of polyoxamic acid (eq 110).¹²⁶

Table 4 summarizes a number of applications of this mechanism for asymmetric induction. Entry 2 illustrates a catalyst, not substrate, controlled stereochemistry. This example also illustrates that the initial stereocontrol of C-O bond formation translates nicely to C-C stereocontrol since the juxtaposition of functionality allows a subsequent diastereoselective Claisen rearrangement. Entry 5 illustrates a kinetic resolution. Using better leaving groups allows the process to become a deracemization (entry 6) which led to D-myo-inositol-1,4,5-triphosphate. The strategy provided by this key process allowed the shortest synthesis of the potent antiviral Tamiflu (entry 7).¹³² An intramolecular

(111)

version required the design of a new ligand for a synthesis of potent toxin, (+)-anatoxin-a (eq 111).¹³³ The P,N ligand desymmetrizes the meso intermediate both electronically as well as sterically. The standard P,P ligands gave only low ee's.

Deracemization of butenolides provides a nice juxtaposition of functional groups for further elaboration.¹³⁴ For example, the synthesis of aflatoxin B illustrates a novel annulation by a sequence of two Pd catalyzed processes (eq 112).

(112)

The great variety of enantioselective alkylations of prochiral nucleophiles provides one of the most powerful AAA processes. Table 5 exemplifies the diversity of structures that can be created. Interestingly, simple ketones (entries 2–4) join β -ketoesters (entries 1 and 6) as suitable nucleophiles. Entry 5 illustrates how simple the processes can become since the alcohol itself serves as a leaving group and the N unsubstituted indoles serve as the nucleophiles.

Table 6 illustrates the use of the decarboxylative alkylation in synthesis. Entry 1 highlights the chemoselectivity allowing the simple secondary amides to be used – no protecting groups. The direct accessibility of 2-hydroxy ketones by C-C bond formation is noteworthy (entry 2). It should be noted that, in entries 2 and 3, good dr was also observed which provides a functional group handle for introducing additional substituents on the double bond.

Desymmetrizing prochiral nucleophiles is another strategy that looks promising. The use of 3, 3'-bis-indoles, which are simply available, then becomes a direct approach to the cyclotryptamine alkaloids (eq. 113).¹⁴¹

(113)

8. Summary

Metal catalyzed allylic alkylations opened a whole new way to create complex structures that enable transformations that previously eluded us. While, at first glance, it might be thought we had done so much that there can be little new to be discovered. Actually the opposite is the case. It continues to be an exciting avenue of pursuit with whole new dimensions coming. It is also the stimulus to see what other metals can do in catalytic allylic alkylations. In our labs, we have explored a number of metals, including molybdenum,¹⁴⁵ tungsten,¹⁴⁶ and ruthenium.¹⁴⁷ These metal catalysts favor bond formation to the more substituted allyl terminus. Other labs are revealing metals like rhodium and iridium have unique transformations.

The additions of these processes to our synthetic toolbox helps us to approach our fundamental objective of solving problems in our world that rely on designing and optimizing structure for function.

Acknowledgments

I am indebted to an extraordinary group of collaborators, undergraduate, graduate and postdoctoral, who have tirelessly pushed the frontiers through over forty years. Their willingness to participate in high risk endeavors and their partnership on pushing the frontiers culminated in the evolution of palladium catalyzed allylic alkylation as a powerful tool. I am also indebted to my family, notably my deceased wife, for the personal support without which the efforts required could not have been possible. We are grateful to the National Science Foundation and the National Institutes of Health for their generous support of our research programs. We are also indebted to Johnson Matthey for their generous gift of palladium compounds.

References

1. Trost BM. *Accounts Chem. Res.* 1970; 3:120.
2. Trost BM, Fullerton TJ. *J. Am. Chem. Soc.* 1973; 95:292. Trost BM, Dietsche TJ, Trost BM, Fullerton TJ. *J. Org. Chem.* 1974; 39:737. Trost BM, Strege PE. *Tetrahedron Lett.* 1974:2603.
3. Trost BM, Strege PE, Weber L, Fullerton TJ, Dietsche TJ. *J. Am. Chem. Soc.* 1978; 100:3407.
4. Trost BM, Weber L. *J. Am. Chem. Soc.* 1975; 97:1611. Trost BM, Weber L, Strege PE, Fullerton TJ, Dietsche TJ. *J. Am. Chem. Soc.* 1978; 100:3416.
5. Trost BM, Metzner PJ. *J. Am. Chem. Soc.* 1980; 102:3572.
6. Trost BM, Weber LJ. *Org. Chem.* 1975; 40:3617.
7. Trost BM, Conway WP, Strege PE, Dietsche TJ. *J. Am. Chem. Soc.* 1974; 96:7165. Trost BM, Weber L, Strege PE, Fullerton TJ, Dietsche TJ. *J. Am. Chem. Soc.* 1978; 100:3426.

8. Trost BM, Verhoeven TR. J. Am. Chem. Soc. 1976; 98:630. [PubMed: 1245689] Trost BM, Verhoeven TR. J. Am. Chem. Soc. 1978; 100:3435.
9. Trost BM, Verhoeven TR. J. Am. Chem. Soc. 1980; 102:4730.
10. Trost BM, Molander GA. J. Am. Chem. Soc. 1981; 103:5969.
11. Trost BM, Schmuff NR, Miller MJ. J. Am. Chem. Soc. 1980; 102:5979.
12. Trost BM, Zhi L. Tetrahedron Lett. 1992; 33:1831.
13. Trost BM, Gerusz VJ. J. Am. Chem. Soc. 1995; 117:5156.
14. Trost BM, Keinan E. Tetrahedron Lett. 1980; 21:2591.
15. Trost BM, Keinan E. J. Org. Chem. 1979; 44:3451.
16. Trost BM, Keinan E. J. Am. Chem. Soc. 1978; 100:7779.
17. Trost BM, Sudhakar AR. J. Am. Chem. Soc. 1987; 109:3792.
18. Trost BM, Sudhakar AR. J. Am. Chem. Soc. 1988; 110:7933.
19. Trost BM, Scanlan TS. Tetrahedron Lett. 1986; 27:4141.
20. Trost BM, Tenaglia A. Tetrahedron Lett. 1988; 29:2927. Trost BM, Tenaglia A. Tetrahedron Lett. 1988; 29:2931.
21. Trost BM, Ito N, Greenspan PD. Tetrahedron Lett. 1993; 34:1421.
22. Trost BM, Fortunak JM. J. Am. Chem. Soc. 1980; 102:2841.
23. Trost BM, Runge TA, Jungheim LN. J. Am. Chem. Soc. 1980; 102:2840. Trost BM, Runge TA. J. Am. Chem. Soc. 1981; 103:2485. Trost BM, Runge TA. J. Am. Chem. Soc. 1981; 103:7550. B M, Runge TA. J. Am. Chem. Soc. 1981; 103:7559.
24. Trost BM, Verhoeven TR. J. Am. Chem. Soc. 1977; 99:3867. Trost BM, Verhoeven TR. J. Am. Chem. Soc. 1980; 102:4743.
25. Trost BM, Warner RW. J. Am. Chem. Soc. 1982; 104:6112. Trost BM, Warner RW. J. Am. Chem. Soc. 1983; 105:5940.
26. Trost BM, Hane JT, Metz P. Tetrahedron Lett. 1986; 27:5695.
27. Trost BM, Cossy J. J. Am. Chem. Soc. 1982; 104:6881.
28. Trost BM, Michellys P-Y, Gerusz VJ. Angew. Chem. Int. Ed Engl. 1997; 36:1750.
29. Trost BM, Strege PE. J. Am. Chem. Soc. 1977; 99:1649.
30. Trost BM, Murphy DJ. Organometallics. 1985; 4:1143.
31. Trost BM, Van Vranken DL. Angew. Chem. Int. Ed. Engl. 1992; 31:228.
32. Trost BM, Breit B, Organ MG. Tetrahedron Lett. 1994; 35:5817.
33. Trost BM, Patterson DE. J. Org. Chem. 1998; 63:1339.
34. Trost BM, Machacek MR, Aponick A. Accounts Chem. Res. 2006; 39:747.
35. Trost BM, Tanimori S, Dunn PT. J. Am. Chem. Soc. 1997; 119:2735.
36. Trost BM, Van Vranken DL, Bingel C. J. Am. Chem. Soc. 1992; 114:9327.
37. Trost BM, Stenkamp D, Pulley SR. Chem. Eur. J. 1995; 1:568.
38. Trost BM, Osipov M, Dong G. Org. Lett. 2012; 14:2254.
39. Trost BM, Richardson J, Yong K. J. Am. Chem. Soc. 2006; 128:2540. [PubMed: 16492030]
40. Trost BM, Masters JT, Lumb J-P, Fateen D. Chem. Sci. 2014; 5:1354. [PubMed: 24761221]
41. Trost BM, Organ MG, O'Doherty GA. J. Am. Chem. Soc. 1995; 117:9662.
42. Trost BM, Lee C-B, Weiss JM. J. Am. Chem. Soc. 1995; 117:7247. Trost BM, Lee CB. J. Am. Chem. Soc. 2001; 123:3671. [PubMed: 11457099]
43. Trost BM, Crawley ML, Lee CB. J. Am. Chem. Soc. 2000; 122:6120. Trost BM, Crawley ML, Lee CB. Chem. Eur. J. 2006; 12:2171. [PubMed: 16402397]
44. Trost BM, Krische MJ, Radinov R, Zanoni G. J. Am. Chem. Soc. 1996; 118:6297.
45. Trost BM, Machacek MR. Angew. Chem. Int. Ed. 2002; 41:4693.
46. Trost BM, Shen HC, Dong L, Surivet J-P. J. Am. Chem. Soc. 2003; 125:9276. [PubMed: 12889940] Trost BM, Shen HC, Dong L, Surivet J-P, Sylvain C. J. Am. Chem. Soc. 2004; 126:11966. [PubMed: 15382932]
47. Trost BM, Yasukata T. J. Am. Chem. Soc. 2001; 123:7162. [PubMed: 11459498]

48. Trost BM, Xie J. J. Am. Chem. Soc. 2006; 128:6044. [PubMed: 16669667] Trost BM, Xie J. J. Am. Chem. Soc. 2008; 130:6231. [PubMed: 18429612]
49. Trost BM, Simas ABA, Plietker B, Jäkel C, Xie J. Chem. Eur. J. 2005; 11:7075. [PubMed: 16196061]
50. a) Trost BM, Bunt RC. Angew. Chem. Int. Ed. 1996; 35:99.b) Trost BM, Lemoine RC. Tetrahedron Lett. 1996; 37:9161.
51. Trost BM, McEachern E, Toste FD. J. Am. Chem. Soc. 1998; 120:12702.
52. Trost BM, McEachern EJ. J. Am. Chem. Soc. 1999; 121:8649.
53. Trost BM, Jiang C. J. Am. Chem. Soc. 2001; 123:12907. [PubMed: 11749552] Trost BM, Jiang C. Org. Lett. 2003; 5:1563. [PubMed: 12713324]
54. a) Trost BM, Fandrick DR. J. Am. Chem. Soc. 2003; 125:11836. [PubMed: 14505403] b) Trost BM, Fandrick DR. Org. Lett. 2005; 7:823. [PubMed: 15727450]
55. Trost BM, Fandrick DR, Brodman T, Stiles DT. Angew. Chem. Int. Ed. 2007; 46:6123.
56. Trost BM, Osipov M, Dong G. J. Am. Chem. Soc. 2010; 132:15800. [PubMed: 20949972]
57. Trost BM, Toste FD. J. Am. Chem. Soc. 1999; 121:4545.
58. Trost BM, Tsui H-C, Toste FD. J. Am. Chem. Soc. 2000; 122:3534. Trost BM, Brennan MK. Org. Lett. 2007; 9:3961. [PubMed: 17803313]
59. Trost BM, Bunt RC. J. Am. Chem. Soc. 1994; 116:4089.
60. Trost BM, Surivet JP. Angew. Chem. Int. Ed. 2000; 39:3122. Trost BM, Surivet JP. J. Am. Chem. Soc. 2000; 122:6291.
61. Trost BM, Organ MG. J. Am. Chem. Soc. 1994; 116:10320.
62. Trost BM, Kondo Y. Tetrahedron Lett. 1991; 32:1613.
63. Trost BM, Patterson DE, Hembre EJ. J. Am. Chem. Soc. 1999; 121:10834.
64. Trost BM, Toste FD. J. Am. Chem. Soc. 1998; 120:815.
65. Trost BM, Radinov R, Grenzer EM. J. Am. Chem. Soc. 1997; 119:7879.
66. Trost BM, Schroeder GM. J. Am. Chem. Soc. 1999; 121:6759.
67. Trost BM, Schroeder GM, Kristensen J. Angew. Chem. Int. Ed. 2002; 41:3492.
68. Trost BM, Xu J. J. Am. Chem. Soc. 2005; 127:2846. [PubMed: 15740108]
69. Trost BM, Xu J, Schmidt T. J. Am. Chem. Soc. 2009; 131:18343. [PubMed: 19928805]
70. Trost BM, Xu J. J. Am. Chem. Soc. 2005; 127:17180. [PubMed: 16332054]
71. Trost BM, Lehr K, Michaelis DJ, Xu J, Buckl AK. J. Am. Chem. Soc. 2010; 132:8915. [PubMed: 20550121]
72. Trost BM, Bream RN, Xu J. Angew. Chem. Int. Ed. 2006; 45:3109.
73. Trost BM, Xu J, Reichle M. J. Am. Chem. Soc. 2007; 129:282. [PubMed: 17212401]
74. Trost BM, Xu J, Schmidt T. J. Am. Chem. Soc. 2009; 131:18343. [PubMed: 19928805]
75. Trost BM, Xu J, Schmidt T. J. Am. Chem. Soc. 2008; 130:11852. [PubMed: 18710230]
76. Trost BM, Ariza X. Angew. Chem. Int. Ed. 1997; 36:2635.
77. Trost BM, Ariza X. J. Am. Chem. Soc. 1999; 121:10727.
78. Trost BM, Frederiksen MU. Angew. Chem. Int. Ed. 2005; 44:308.
79. Trost BM, Jäkel C, Plietker B. J. Am. Chem. Soc. 2003; 125:4438. [PubMed: 12683811] Trost BM, Xie J, Sieber JD. J. Am. Chem. Soc. 2011; 133:20611. [PubMed: 22070545]
80. Trost BM, Malhotra S, Chan WH. J. Am. Chem. Soc. 2011; 133:7328. [PubMed: 21520958]
81. Trost BM, Quancard J. J. Am. Chem. Soc. 2006; 128:6314. [PubMed: 16683785]
82. Trost BM, Surivet JP. J. Am. Chem. Soc. 2000; 122:6291.
83. Trost BM, O'Boyle BM. J. Am. Chem. Soc. 2008; 130:16190. [PubMed: 18989964] Trost BM, Thaisrivongs DA. J. Am. Chem. Soc. 2009; 131:12056. [PubMed: 19645450] Trost BM, Thaisrivongs DA, Hartwig J. J. Am. Chem. Soc. 2011; 133:12439. [PubMed: 21770467]
84. Trost BM, Hansmann MM, Thaisrivongs DA. Angew. Chem. Int. Ed. 2012; 51:4950. Trost BM, Thaisrivongs DA, Hansmann MM. Angew. Chem. Int. Ed. 2012; 51:5034.
85. Trost BM, Thaisrivongs DA, Donckele EJ. Angew. Chem. Int. Ed. 2013; 52:1523.

86. Trost BM, Gowland FW. *J. Org. Chem.* 1979; 44:3448.
87. Trost BM, Ornstein PL. *Tetrahedron Lett.* 1981; 22:3463.
88. Trost BM, Kuo GH, Benneche T. *J. Am. Chem. Soc.* 1988; 110:621.
89. Trost BM, Scanlan TS. *J. Am. Chem. Soc.* 1989; 111:4988.
90. Trost BM, Angle SR. *J. Am. Chem. Soc.* 1985; 107:6123.
91. Trost BM, Lynch J, Angle S. *Tetrahedron Lett.* 1987; 28:375.
92. Trost BM, Genet JP. *J. Am. Chem. Soc.* 1976; 98:8516.
93. Trost BM, Godleski SA, Belletire JL. *J. Org. Chem.* 1979; 44:2052.
94. Trost BM, Godleski SA, Genet JP. *J. Am. Chem. Soc.* 1978; 100:3930.
95. Trost BM, Tasker AS, Rühler G, Brandes A. *J. Am. Chem. Soc.* 1991; 113:670.
96. Trost BM, Brickner SJ. *J. Am. Chem. Soc.* 1983; 105:568.
97. Trost BM, Ohmori M, Boyd SA, Okawara H, Brickner SJ. *J. Am. Chem. Soc.* 1989; 111:8281.
98. Trost BM, Cossy J. *J. Am. Chem. Soc.* 1982; 104:6881.
99. Trost BM, Van Vranken DL. *J. Am. Chem. Soc.* 1993; 115:444.
100. Trost BM, Li L, Guile SD. *J. Am. Chem. Soc.* 1992; 114:8745.
101. Trost BM, Madsen R, Guile SD, Elia AEH. *Angew. Chem. Int. Ed. Eng.* 1996; 35:1569. Trost BM, Madsen R, Guile SD, Brown B. *J. Am. Chem. Soc.* 2000; 122:5947.
102. Trost BM, Dong G. *J. Am. Chem. Soc.* 2006; 128:6054. [PubMed: 16669672] Trost BM, Dong G. *Chem. Eur. J.* 2009; 15:6910. [PubMed: 19533707]
103. Trost BM, Madsen R, Guile SD. *Tetrahedron Lett.* 1997; 38:1707.
104. Trost BM, Shi Z. *J. Am. Chem. Soc.* 1996; 118:3037.
105. Trost BM, Cook GC. *Tetrahedron Lett.* 1996; 37:7485.
106. Trost BM, Pulley SR. *J. Am. Chem. Soc.* 1995; 117:10143.
107. Trost BM, Patterson DE. *Chem. Eur. J.* 1999; 5:3279.
108. a) Trost BM, Aponick A, Stanzl B. *Chem. Eur. J.* 2007; 13:9547. [PubMed: 17847148] b) Trost BM, O'Boyle BM. *Org. Lett.* 2008; 10:1369. [PubMed: 18318539] Trost BM, O'Boyle BM, Torres W, Ameriks MK. *Chem. Eur. J.* 2011; 17:7890. [PubMed: 21618622]
109. Trost BM, Masters JT, Lumb J-P, Fateen D. *Chem. Sci.* 2014; 5:1354. [PubMed: 24761221]
110. Trost BM, Lee CB. *J. Am. Chem. Soc.* 1998; 120:6818. Trost BM, Lee C. *J. Am. Chem. Soc.* 2001; 123:12191. [PubMed: 11734018]
111. Trost BM, Shen HC, Surivet J-P. *Angew. Chem. Int. Ed. Eng.* 2003; 42:3943.
112. Trost BM, Machacek MR, Tsui HC. *J. Am. Chem. Soc.* 2005; 127:7014. [PubMed: 15884945]
113. Trost BM, Thiel OR, Tsui H-C. *J. Am. Chem. Soc.* 2002; 124:11616. [PubMed: 12296725]
114. Trost BM, Toste FD. *J. Am. Chem. Soc.* 1998; 120:9074.
115. Trost BM, Gunzner JL, Dirat O, Rhee Y-H. *J. Am. Chem. Soc.* 2002; 124:10396. [PubMed: 12197742]
116. Trost BM, Bunt RC, Lemoine R, Calkins TL. *J. Am. Chem. Soc.* 2000; 122:5968.
117. Trost BM, Tang W. *Org. Lett.* 2001; 3:3409. [PubMed: 11594846]
118. Trost BM, Horne DB, Woltering MJ. *Chem. Eur. J.* 2006; 12:6607. [PubMed: 16807949]
119. Trost BM, Zhang T. *Org. Lett.* 2006; 8:6007. [PubMed: 17165916]
120. Trost BM, Tang W, Schulte JL. *Org. Lett.* 2000; 2:4013. [PubMed: 11112631]
121. Trost BM, Andersen NG. *J. Am. Chem. Soc.* 2002; 124:14320. [PubMed: 12452702]
122. Trost BM, Dong G, Vance JA. *J. Am. Chem. Soc.* 2007; 129:4540. [PubMed: 17343388] Trost BM, Dong G, Vance JA. *Chem. Eur. J.* 2010; 16:6265. [PubMed: 20411537]
123. Trost BM, Fandrick DR, Brodman T, Stiles DT. *Angew. Chem. Int. Ed.* 2007; 46:6123.
124. Trost BM, Osipov M, Dong G. *J. Am. Chem. Soc.* 2010; 132:15800. [PubMed: 20949972]
125. Trost BM, Fandrick DR. *Org. Lett.* 2005; 7:823. [PubMed: 15727450]
126. Trost BM, Krueger AC, Bunt RC, Zambrano J. *J. Am. Chem. Soc.* 1996; 118:3039.

127. Trost BM, Chisholm JD, Wroblewski SJ, Jung M. J. Am. Chem. Soc. 2002; 124:12420. [PubMed: 12381177] Trost BM, Wroblewski ST, Chisholm JD, Harrington PE, Jung M. J. Am. Chem. Soc. 2005; 127:13589. [PubMed: 16190724]
128. Trost BM, Toste FD. J. Am. Chem. Soc. 2000; 122:11262. Trost BM, Tang W. Angew. Chem. Int. Ed. 2002; 41:2795.
129. Trost BM, Tang W, Toste FD. J. Am. Chem. Soc. 2005; 127:14785. [PubMed: 16231933]
130. Trost BM, Hembre EJ. Tetrahedron Lett. 1999; 40:219. Trost BM, Patterson DE, Hembre EJ. Chem. Eur. J. 2001; 7:3768. [PubMed: 11575778]
131. Trost BM, Patterson DE, Hembre EJ. J. Am. Chem. Soc. 1999; 121:10834.
132. Trost BM, Zhang T. Angew. Chem. Int. Ed. 2008; 47:3759.
133. Trost BM, Oslob JD. J. Am. Chem. Soc. 1999; 121:3057.
134. Trost BM, Toste FD. J. Am. Chem. Soc. 1999; 121:3543.
135. Trost BM, Tang W. J. Am. Chem. Soc. 2003; 125:8744. [PubMed: 12862467]
136. Trost BM, Pissot-Soldermann C, Chen I, Schroeder GM. J. Am. Chem. Soc. 2004; 126:4480. [PubMed: 15070341] Trost BM, Pissot-Soldermann C, Chen I. Chem. Eur. J. 2005; 11:951. [PubMed: 15612053]
137. Trost BM, Dong Li, Schroeder GM. J. Am. Chem. Soc. 2005; 127:2844. [PubMed: 15740107] Trost BM, Dong L, Schroeder GM. J. Am. Chem. Soc. 2005; 127:10259. [PubMed: 16028937]
138. Trost BM, Quancard J. J. Am. Chem. Soc. 2006; 128:6314. [PubMed: 16683785]
139. Trost BM, Osipov M, Dong G. Org. Lett. 2010; 12:1276. [PubMed: 20148531]
140. Trost BM, Stiles DT. Org. Lett. 2007; 9:2763. [PubMed: 17592853]
141. Trost BM, Osipov M. Angew. Chem. Int. Ed. 2013; 52:9176.
142. Trost BM, Dudash J Jr, Dirat O. Chem. Eur. J. 2002; 8:259. [PubMed: 11822457]
143. Trost BM, Chupak LS, Lübbers T. J. Am. Chem. Soc. 1998; 120:1732.
144. Trost BM. Tetrahedron Lett. 1991; 32:1613.
145. Trost BM. Org. Proc. Res. Dev. 2012; 16:185.
146. Trost BM, Hung M-H. J. Am. Chem. Soc. 1983; 105:7757.
147. Trost BM, Rao M, Dieskau A. J. Am. Chem. Soc. 2013; 135:18697. [PubMed: 24245989]

Biography

Barry M. Trost

Born in Philadelphia, Pennsylvania in 1941 where he began his university training at the University of Pennsylvania (BA, 1962), he obtained a 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 in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In addition, he has been Visiting Professor of Chemistry in Germany (Universities of Marburg, Hamburg, Munich and Heidelberg), Denmark (University of Copenhagen), France (Universities of Paris VI and Paris-Sud), Italy (University of Pisa) and Spain (University of Barcelona). In 1994 he was presented with a *Docteur honoris causa* of

the Université Claude-Bernard (Lyon I), France, and in 1997 a *Doctor Scientiarum Honoris Causa* of the Technion, Haifa, Israel.

Professor Trost's work has been characterized by a very high order of imagination, innovation and scholarship. He has ranged over the entire field of organic synthesis, particularly emphasizing extraordinarily novel methodology. In recognition of his many contributions, Professor Trost has received a number of awards, including the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), the Baekeland Award (1981), the first Allan R. Day Award of the Philadelphia Organic Chemists' Club (1983), the Chemical Pioneer Award of the American Institute of Chemists (1983), the Alexander von Humboldt Stiftung Award (1984), MERIT Award of NIH (1988), Hamilton Award (1988), Arthur C. Cope Scholar Award (1989), Guenther Award in the Chemistry of Essential Oils and Related Products (1990), the Dr. Paul Janssen Prize (1990), the ASSU Graduate Teaching Award (1991), Pfizer Senior Faculty Award (1992), Bing Teaching Award (1993), 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 Belgian Organic Synthesis Symposium Elsevier Award (2000), the Nichols Medal (2000), the Yamada Prize (2001), the ACS Nobel Laureate Signature Award for Graduate Education in Chemistry (2002), the ACS Cope Award (2004), the City of Philadelphia John Scott Award 2004, Thomson Scientific Laureate (2007), the Kitasato Microbial Chemistry Medal (2008), the Nagoya Medal (2008), Israel Chemical Society Excellence in Medicinal Chemistry Award (2013), the Ryoji Noyori Prize (2013), the German Chemical Society's August-Wilhelm-von-Hofmann Denkmuenze (2014) and the International Precious Metal Institute Junichiro Tanaka Distinguished Achievement Award (2014). He has held a Sloan Fellowship, a Camille and Henry Dreyfus Teacher-Scholar grant and an American-Swiss Foundation Fellowship as well as having been the Julius Stieglitz Memorial Lecturer of the ACS-Chicago section (1980–81) and Centenary Lecturer of the Royal Society of Chemistry (1981–82). Professor Trost has been elected a Fellow of the American Academy of Sciences (1982) and a member of the National Academy of Sciences (1980). He has served as editor and on the editorial board of many books and journals, including being Associate Editor of the Journal of the American Chemical Society (1974–80). He has served as a member of many panels and scientific delegations, and served as Chairman of the NIH Medicinal Chemistry Study Section. He has held over 125 special university lectureships and presented over 270 Plenary Lectures at national and international meetings. He has published two books and over 930 scientific articles. He edited a major compendium entitled Comprehensive Organic Synthesis consisting of nine volumes and serves on the editorial board for Science of Synthesis and Reaxys.

Fig 1.
Stereochemistry of bond breaking and bond forming reactions

Fig 2.
Mechanism of enantioinduction

Fig 3.
Chiral ligand template

Figure 4.
Challenge of asymmetric induction at prochiral nucleophile

Scheme 1.

Structure and potential biosynthesis of insect juvenile hormone

Scheme 2.
Prenylation protocol

Scheme 3.
Conversion of alkenes into dienoates

Scheme 4.
Catalytic vs stoichiometric allylic alkylation

Scheme 6.
Versatility of alkylated vinylogous thioester

Table 1

Chiral ligands for palladium

Table 2

Bioactive targets derived from desymmetrizing meso-diester

Entry	Electrophile	Nucleophile	Ligand Pd Precatalyst	AAA Product	Target	Ref
1a			<i>S,S</i> - <i>L</i> _S (dba) ₃ Pd ₂ ·CHCl ₃			101
1b						101, 103
2			<i>R,R</i> - <i>L</i> _S (dba) ₃ Pd ₂ ·CHCl ₃			104
3		TMS-N ₃	<i>S,S</i> - <i>L</i> _S (dba) ₃ Pd ₂ ·CCl ₃			37
4			<i>S,S</i> - <i>L</i> _S (dba) ₃ Pd ₂ ·CCl ₃			104
5			<i>R,R</i> - <i>L</i> _{STD} [η ³ -C ₃ H ₅ PdCl] ₂			142
6			<i>S,S</i> - <i>L</i> _{STD} [η ³ -C ₃ H ₅ PdCl] ₂			143
7		TMS-N ₃	<i>R,R</i> - <i>L</i> _{STD} [η ³ -C ₃ H ₅ PdCl] ₂			105
8		TMS-N ₃	<i>R,R</i> - <i>L</i> _{STD} [η ³ -C ₃ H ₅ PdCl] ₂			106
9			<i>R,R</i> - <i>L</i> _{STD} (dba) ₃ Pd ₂ ·CCl ₃			107
10a			<i>R,R</i> - <i>L</i> _N [η ³ -C ₃ H ₅ PdCl] ₂			108a
10b			<i>R,R</i> - <i>L</i> _N [η ³ -C ₃ H ₅ PdCl] ₂			108b

Table 3

Deracemizations of vinyl epoxides and vinyl oxaziridines

ENTRY		Nucleophile	Ligand, Pd(0) source	Adduct	Target	Ref
1		HO-CH ₂ -Br	<i>R,R</i> - <i>L_N</i> (dba) ₃ Pd ₂ ·CHCl ₃			117
2a			<i>R,R</i> - <i>L_N</i> [η ³ -C ₃ H ₅ PdCl] ₂			50, 116
2b						118
2c						118
2d						118
3		C ₂ H ₅ O ₂ C-CH ₂ -CH=CH-OH	<i>S,S</i> - <i>L_N</i> (dba) ₃ Pd ₂ ·CHCl ₃	C ₂ H ₅ O ₂ C-CH ₂ -CH=CH-OR		118
		CH ₃ O-C ₆ H ₄ -CH ₂ -OH	<i>R,R</i> - <i>L_{STD}</i> (dba) ₃ Pd ₂ ·CHCl ₃	n-C ₉ H ₁₉ OPMB		120
5		CH ₃ O-C ₆ H ₄ -CH ₂ -OH	<i>S,S</i> - <i>L_{STD}</i> (dba) ₃ Pd ₂ ·CHCl ₃			121
6			<i>R,R</i> - <i>L_{STD}</i> (dba) ₃ Pd ₂ ·CHCl ₃			122
7		Ph-O-C(=O)-NH-C(=O)-O-Ph	<i>S,S</i> - <i>L_N</i> [η ³ -C ₃ H ₅ PdCl] ₂			123
8		Br-NH-CO ₂ Me	<i>R,R</i> - <i>L_{STD}</i> [η ³ -C ₃ H ₅ PdCl] ₂			124
9			<i>S,S</i> - <i>L_N</i> [η ³ -C ₃ H ₅ PdCl] ₂			55

Table 4

Deracemization of 1, 3-disubstituted allyl precursors

Entry	Electrophile	Nucleophile	Ligand	Adduct	Target	Ref
1			S,S-L _S (dba) ₃ Pd ₂ ·CHCl ₃			127
2			S,S-L _S (dba) ₃ Pd ₂ ·CHCl ₃			122
3a			S,S-L _S (dba) ₃ Pd ₂ ·CCl ₃			128
3b						129
4			S,S-L _S ³ C ₃ H ₅ PdCl ₂			144
5			R,R-L _{STD} ³ C ₃ H ₅ PdCl ₂			130
6			S,S-L _{STD} ³ C ₃ H ₅ PdCl ₂			131
7			R,R-L _{STD} ³ C ₃ H ₅ PdCl ₂			132

Table 5

Enantiodiscrimination of pro-chiral nucleophiles-intermolecularly.

ENTRY	allyl	Nucleophile	ligand	Pd source	Target	Ref
1			<i>R,R</i> - <i>L</i> _{STD} [η^3 -C ₃ H ₅ PdCl] ₂		NITRAMINE	65
2			<i>R,R</i> - <i>L</i> _N [η^3 -C ₃ H ₅ PdCl] ₂		METAZOCINE	135
3			<i>R,R</i> - <i>L</i> _{STD} [η^3 -C ₃ H ₅ PdCl] ₂		HAMIGERAN B	136
4			<i>S,S</i> - <i>L</i> _{STD} [η^3 -C ₃ H ₅ PdCl] ₂		ERINACIN A	137
5			<i>S,S</i> - <i>L</i> _A (dba) ₃ Pd ₂ ·CHCl ₃		R=CH₃ ESERMETHOLE R=CONHPh PHENSERINE	138
6			<i>R,R</i> - <i>L</i> _A [η^3 -C ₃ H ₅ PdCl] ₂
7			<i>R,R</i> - <i>L</i> _S (dba) ₃ Pd ₂ ·CHCl ₃		RANIRESTAT	139

Table 6

Enantioselectivity of decarboxylative alkylation

Entry	Substrate	Ligand, Pd source	Adduct	Target	Ref
1		<i>S,S</i> - <i>L</i> _{STD} (dba) ₃ Pd ₂ •CHCl ₃			140
				SPIROTRYPROSTATIN	
2		<i>R,R</i> - <i>L</i> _A (dba) ₃ Pd ₂ •CHCl ₃			73
				(S)-OXYBUTYNIN	
3		<i>R,R</i> - <i>L</i> _A (dba) ₃ Pd ₂ •CHCl ₃			71
				CETIEDIL	