# Predicting the Stereochemistry of Diphenylphosphino Benzoic Acid (DPPBA)-Based Palladium-Catalyzed Asymmetric Allylic Alkylation Reactions: A Working Model

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**ABSTRACT**
Palladium-catalyzed asymmetric allylic alkylation has proven to be a powerful method for the preparation of a wide variety of chiral compounds and the rapid assembly of complex molecular architecture from simple starting materials. While many types of catalyst systems have been successfully employed with certain systems, diphenylphosphino benzoic acid (DPPBA) based ligands have found use over a broad range of substrate classes. This Account highlights the mechanistic aspects considered when designing reactions with DPPBA-based ligands and presents a working model for the a priori prediction of their stereochemical outcome.

## Introduction

Palladium-catalyzed asymmetric allylic alkylation (Pd AAA) has been demonstrated to be an extremely powerful method for asymmetric synthesis.[1] Asymmetric allylic allylation distinguishes itself from other catalytic methods such as hydrogenation and oxidation in its ability to form multiple types of bonds such as C−C, C−O, C−S, C−N, and C−H. When this versatility is coupled with both wide functional group tolerance and mild reaction conditions, the potential of this process is clear.

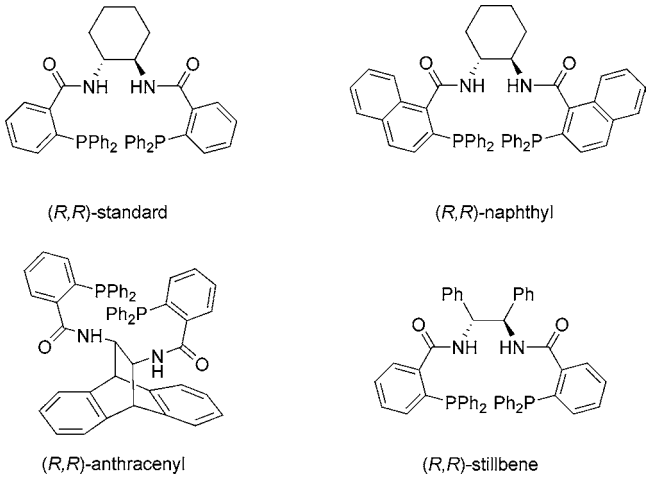


**FIGURE 1.** $C_2$-symmetric ligands.

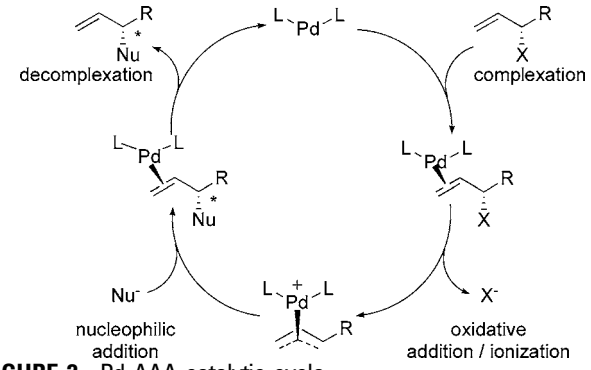


**FIGURE 2.** Pd AAA catalytic cycle.

Most metal-catalyzed asymmetric reactions derive their selectivity by differentiation of the enantiotopic $\pi$ faces of an unsaturated system. In contrast, Pd AAA has multiple mechanisms for enantiodiscrimination. Fortunately, a great deal of work has been devoted to developing a mechanistic understanding of diphenylphosphino benzoic acid (DPPBA) based Pd AAA.[2] Furthermore, the Trost group has coupled this mechanistic insight with a working model for predicting the stereochemical outcome of allylation reactions using a family of $C_2$-symmetric ligands.[2a,b] This Account will cover the issues inherent in devising a successful Pd AAA. The reaction mechanism and the basis for enantiodiscrimination will be discussed in the context of asymmetric induction using the family of $C_2$-symmetric ligands that have been developed in our laboratories (Figure 1).

## Mechanistic Considerations of Allylic Alkylation

Each step of the catalytic cycle illustrated in Figure 2 is an opportunity for inducing asymmetry. For example, the

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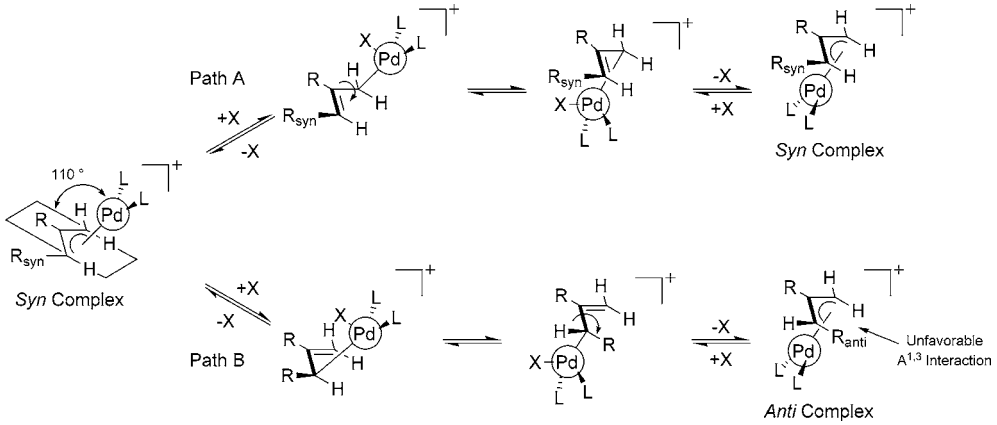



**FIGURE 3.** $\pi-\sigma-\pi$ interconversion.

initial complexation step is reversible, and therefore, palladium can interconvert between the $\pi$ faces of the olefin. Thorough mechanistic work has been done to demonstrate that the ionization of the resulting palladium−olefin complex occurs with inversion of stereochemistry.[3] One can think of this step as an $S_N2$-like displacement of the leaving group by the incoming palladium "nucleophile".[3] Structurally, the $\pi$-allylpalladium intermediate is a square planar 16-electron complex consisting of ligands and a coordinated allyl unit.[4] The substituents on the allyl unit are defined as syn (R syn to the substituent on $C_2$ of the allyl) and anti (R anti to the substituent on $C_2$, Figure 3). X-ray structures indicate that the coordinated allyl deviates from the perpendicular by approximately 20°, placing the allyl termini closer to the palladium center.[5] In consequence, the anti substituents cant toward palladium, putting them closer to the metal center, while the syn substituents cant away.

These $\eta^3$-bound $\pi$-allylpalladium complexes are in equilibrium with the corresponding $\eta^1$ derivatives (Figure 3), a process whose rate is increased in the presence of an external ligand such as a halide.[6] If a $\sigma$ complex forms at a monosubstituted allyl terminus, rotating 180° about the $\sigma$ bond and rehybridization results in a $\pi$-facial exchange of the coordinated allyl (path A). If the $\sigma$ complex forms at a disubstituted allyl terminus, the same process leads to both facial interconversion and exchange of the stereochemistry at that center from syn to anti (path B). Faller et al. found that the rate of $\sigma$ complex formation is influenced by the allyl substitution pattern[7] and steric effects dictate that substitution at the allyl terminus slows their formation.[8] This syn, anti isomerization leads to the question of what the reactive conformation is. While cyclic substrates are locked in an anti, anti conformation, acyclic substrates can freely equilibrate. With bisphosphine ligands, the syn complex is generally lower in energy. The Curtin−Hammet principle dictates that under equilibrating conditions either isomer may be the reactive species. In general, the syn complex is typically thought of as the reactive intermediate when applicable (vide infra).[9,10]

Because nucleophilic attack is the microscopic reverse of ionization, similar principles govern this step of the catalytic cycle. The addition of stabilized nucleophiles ($pK_a < 20$) occurs with inversion of stereochemistry. This step

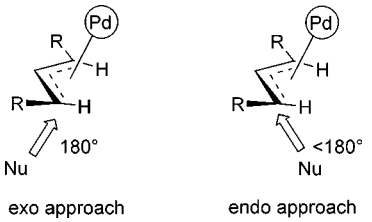



**FIGURE 4.** Exo approach of the nucleophile.

is also considered to be $S_N2$-like with $Pd^{II}$ displaced. To ensure an antiperiplanar trajectory, the nucleophile approaches in an *exo* sense (Figure 4).[2a,11]

In general, $\pi$-allylmetals prefer addition at the less hindered carbon to minimize steric interactions with the nucleophile;[12] however, this preference can be modulated by the sterics and electronics of the complex.[13] Considering sterics, bulky ligands tend to favor addition at the more substituted allyl terminus to minimize interactions between the ligands and the coordinated olefin resulting (path A in Figure 5). Considering electronics, good $\pi$-acid ligands increase the cationic character of the allyl through back-bonding. The increased cationic character is more stable at the substituted allyl terminus and directs nucleophilic addition to that carbon (path C in Figure 5). Furthermore, $Pd^0$ is electron-rich and prefers coordination with more electron-poor olefins, again favoring the addition to the more substituted allyl terminus. In contrast, reactions involving sterically small, $\sigma$-donating ligands and metals in high oxidation states have opposite steric and electronic interactions and as such promote addition at the less substituted terminus.

## Ligand Design for AAA

Because ionization and nucleophilic attack occur in an antiperiplanar fashion, both bond breaking and making events occur outside the coordination sphere of the metal and thus on the opposite face from the chirality control element. Despite this potential difficulty, a wide variety of chiral ligands have been effectively employed.

We have reported the successful application of bidentate DPPBA-based ligands.[1] Many other classes have also shown excellent selectivities in AAA reactions. $C_2$-Symmetric diamine ligands[14] and bisoxazoline ligands[15] have

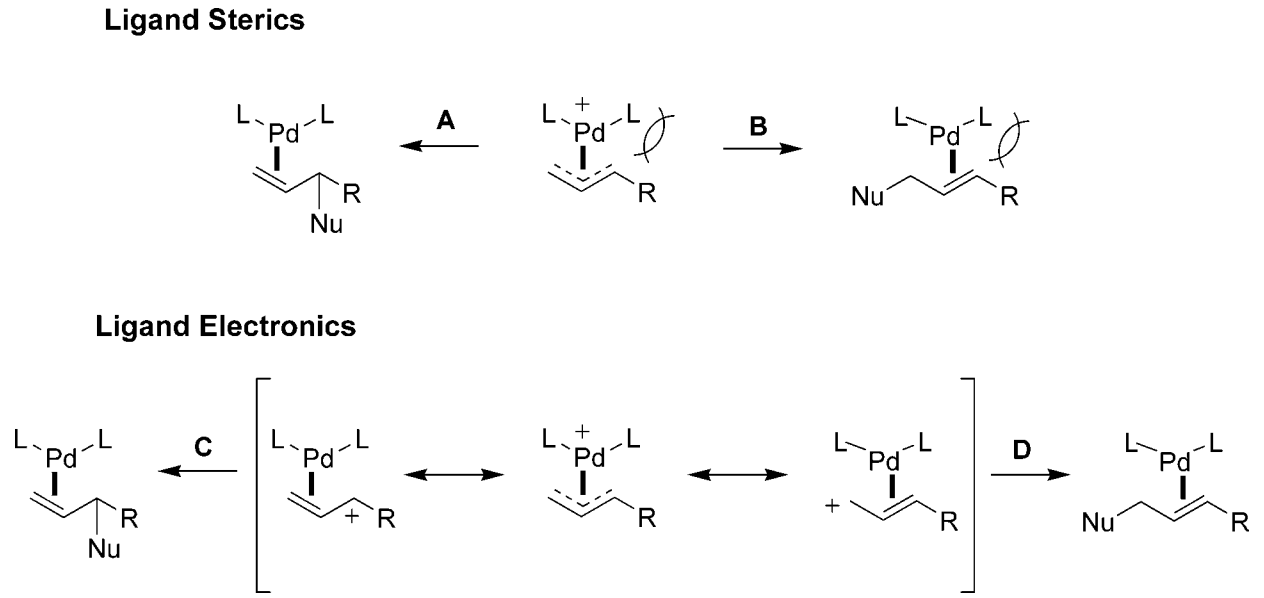



**FIGURE 5.** Sterics and electronics of nucleophilic addition.

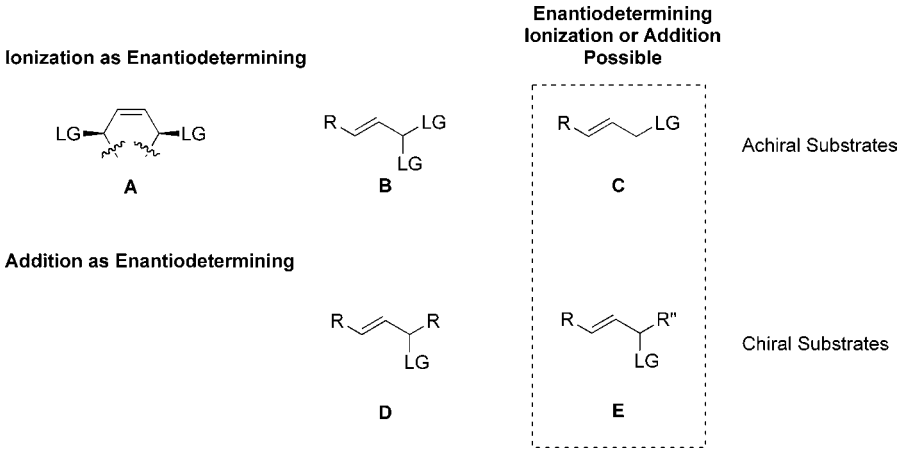



**FIGURE 6.** Classes of electrophiles for Pd AAA.

both shown good enantioinduction. Hayashi et al. have successfully employed ferrocenyl-based ligands employing a chiral arm scaffold to extend the chiral environment to the approaching nucleophile.[16] Although less general in scope, ferrocenyl ligands such as Josiphos also impart excellent selectivity in certain cases.[17] Similarly P,S-[18] and P,N-based[19] ligands use an electronically differentiated bidentate scaffold to induce enantioselectivity with certain substrate classes. Still other ligand classes have been investigated.[20]

## A Working Model for Enantioselective Allylic Alkylation

Given the mechanism of Pd AAA, there are two possible enantiodetermining steps: ionization of the leaving group and nucleophilic addition. If the rate of equilibration of diastereomeric $\pi$-allylpalladium complexes is slower than the rate of nucleophilic addition, ionization is enantiodetermining.[21] On the other hand, if the rate of equilibration is faster than nucleophilic addition, the stereochemical outcome is determined by which $\pi$-allyl reacts with the nucleophile,[21] and the addition is enantiodetermining.

Within both categories, there are subclasses depending upon the structure of the substrate being investigated (Figure 6). Type **A** represents *meso* substrates. The catalyst differentiates two enantiotopic leaving groups in the ionization step. Type **B**, also an achiral compound, represents differentiation of enantiotopic leaving groups on the same carbon center. In type **D**, ionization of a chiral compound results in a pseudo-*meso* $\pi$-allyl intermediate, and thus, differentiation of enantiotopic termini during nucleophilic attack determines the product stereochemistry. Both mechanisms can apply to the simple unsymmetrical $\pi$-allyl intermediates resulting from ionization of **C** and **E**. Generally, these types of substrates fall into the second category, but in some cases, ionization can be enantiodetermining.

Using DPPBA-based ligands in Pd AAA reactions, the Trost group noticed a correlation between ligand and product stereochemistry that evolved into a mnemonic.[22] Considering a Newman projection along the carbons linking the chiral backbone to the amide nitrogens, the disposition of the phosphines are defined as clockwise or counterclockwise (Figure 7). When oriented as depicted, using the (*S*,*S*)-ligand, movement of the catalyst in a

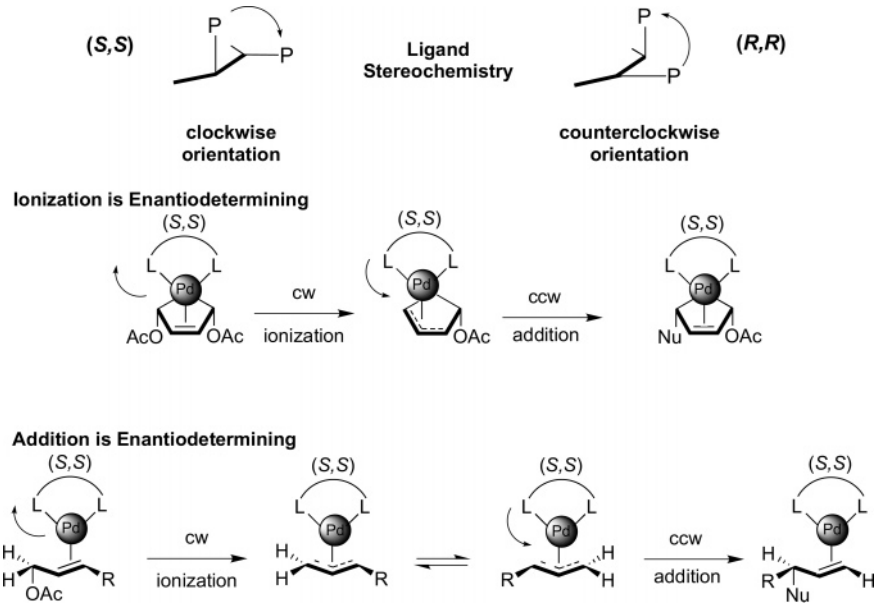



**FIGURE 7.** Mnemonic.

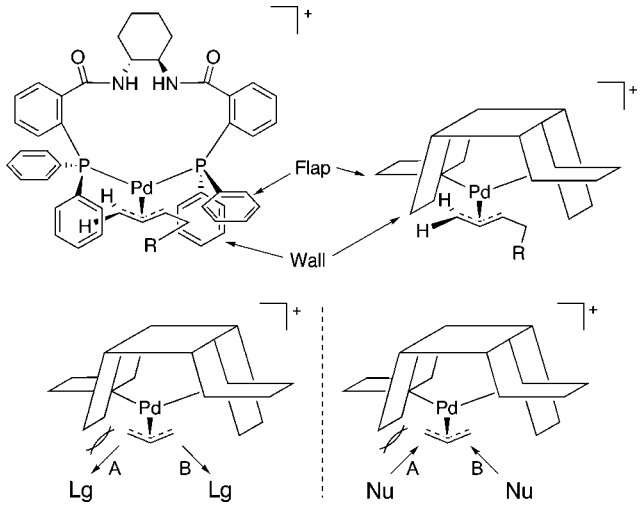



**FIGURE 8.** Cartoon model to describe the Pd−ligand complex.

clockwise motion with respect to the substrate is expected during ionization. Because nucleophilic addition is the microscopic reverse of this process, a counterclockwise motion results. When kinetic capture of the initially formed $\pi$-allyl intermediate is operating, ionization predicts the stereochemistry. When the addition is enantiodetermining, equilibration of the $\pi$-allylpalladium complex followed by addition predicts the stereochemistry. When reactions were designed, there were examples where this simplistic representation led to incorrect predictions. A model that more accurately depicted the palladium−ligand complex was necessary.

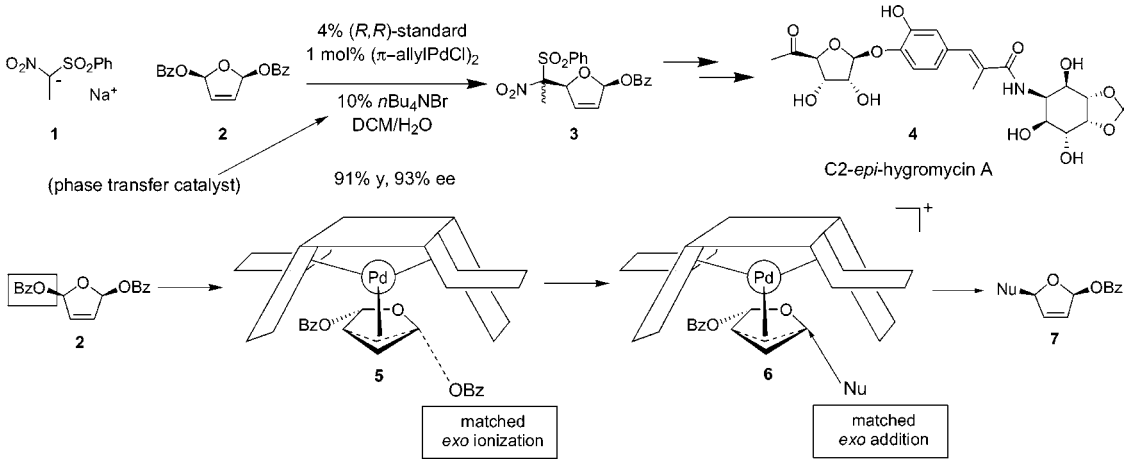
Using a ground-state minimized conformation and assuming a 1:1 Pd/(*R*,*R*)-standard ligand ratio, a simplified cartoon model of the chiral pocket was developed (Figure 8).[2a,c] While the cartoon depicts the ligand in a $C_2$-symmetric fashion in the allyl complex, the existing structural data suggest that it does not coordinate in a $C_2$-symmetric manner.[2c,23] These data demonstrate that $\pi$-allylpalladium complexes of the DPPBA-based ligands are in equilibrium with oligomeric species, with the equilibrium being governed by the catalyst concentration, temperature, and catalyst counterion.[2c] The cartoon thus considers only a time-averaged monomeric species in which the ligand coordinates in a $C_2$-symmetric manner. Characteristic of the bisdiphenylphosphine ligands, the phenyl groups sit in a propeller-like arrangement to minimize interactions with each other. In this conformation, two phenyl "walls" are approximately perpendicular to the plane of the allyl unit and two "flaps" sit parallel to the plane. As illustrated in the model, these ligands create a chiral environment where the back right and front left quadrants are effectively blocked. Because *exo* ionization and nucleophilic addition are preferred by stereoelectronics, attack from the rear quadrants is unfavorable. The two front quadrants are differentiated on the basis of sterics. When leaving groups are ionized to a $\pi$-allylpalladium complex, to minimize contact with the ligand, they prefer to depart from under the front right quadrant (path B) rather than the front left quadrant, which is blocked by the phenyl "wall" (path A). Similarly, nucleophiles prefer to attack the complex from the open front right quadrant rather than from the blocked left quadrant. Ionizations and additions following path B are denoted "matched", whereas those following path A are denoted "mismatched".

Because AAA is an exothermic process, the Hammond postulate indicates that the transition state should resemble the $\pi$-allyl. The cartoon then approximates the transition states for ionization and nucleophilic addition and permits the comparison of transition states, allowing this model to become a qualitative *predictive tool*.

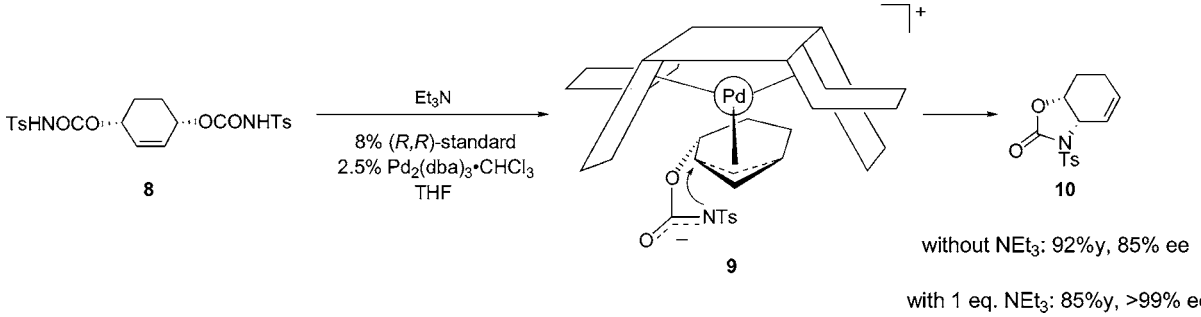
## Using the Working Model To Predict AAAs

**Ionization as Enantiodetermining: Desymmetrization of *meso* Diester (Class A).** Pd AAA reactions of class **A** substrates rely on the differentiation of enantiotopic

**Scheme 1. Furanoside Synthesis**




**Scheme 2. Oxazolidinone Synthesis**




leaving groups during ionization as the enantiodetermining step of the catalytic cycle. Matched *exo* ionization of **2** from under the front right flap of the (*R*,*R*)-standard ligand expels the *pro-R* benzoate.[24] Fast trapping of the resulting $\pi$-allylpalladium complex via a matched nucleophilic addition results in an excellent yield and enantioselectivity for **3** (Scheme 1). Phase-transfer conditions were utilized to increase the solubility of the anionic nucleophile, thus increasing the rate of nucleophilic attack onto the kinetically formed $\pi$-allyl species. The absolute stereochemistry was determined to be (*R*) at the newly formed stereocenter, as the working model predicts.

The importance of fast nucleophilic attack with class **A** substrates is further illustrated with bisisocyanate **8**. When the reaction is performed under similar conditions as for **2**, 85% enantiomeric excess (ee) is obtained. The principal difference is that after matched ionization of the *pro-R* isocyanate, the tethered nucleophile is forced to undergo a mismatched nucleophilic attack (Scheme 2).[25] Furthermore, the tethered isocyanate nucleophile must be deprotonated before it can cyclize. Because only the ionized leaving group can function as a base, the rates of intramolecular nucleophilic attack and recombination of the isocyanate anion become competitive, thereby degrading the ee, which is based on an initial kinetic preference to ionize one of the prochiral isocyanates. Indeed, the addition of exogenous $Et_3N$ to deprotonate the tethered nucleophile increases the rate of cyclization compared to the reverse reaction and the ee to 99%.

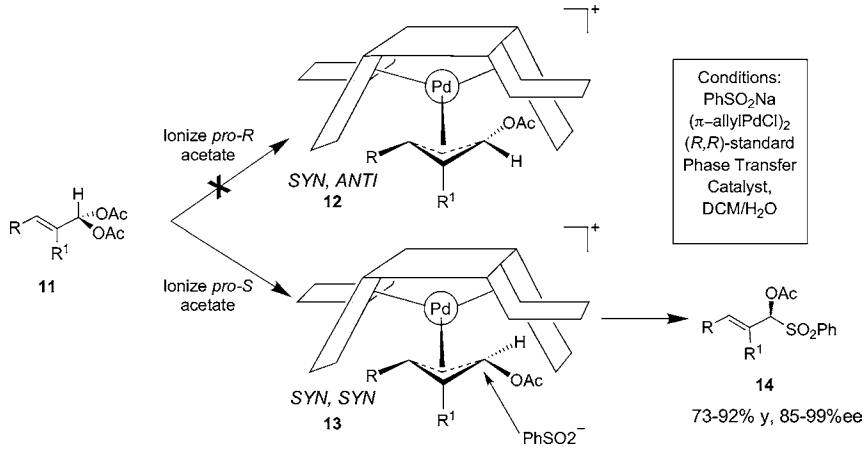
This concept has important ramifications for all desymmetrizations. In the reaction using **2**, better selectivity was seen using benzoate and carbonate leaving groups instead of acetate. Because acetate is a better nucleophile, the rate of the reverse reaction becomes competitive with nucleophilic capture. Both choices of leaving group and pH of the media can have a direct impact on the selectivity of desymmetrization reactions.

**Ionization of Prochiral Leaving Groups (Class B).** The second substrate class that uses ionization as the enantiodiscriminating event involves the desymmetrization of prochiral groups on the same carbon (e.g., **11**). The catalyst must differentiate *both* the prochiral leaving groups and the $\pi$ faces of the olefin.[26] Using the (*R*,*R*)-standard ligand, the $\pi$ faces are differentiated by placing the *gem*-diacetate carbon under the ligand flap. Ionization of the *pro-R* acetate results in the syn,anti complex **12**, whereas ionization of the *pro-S* results in the preferred syn,syn complex **13**. Nucleophilic attack onto this diastereomer gives **14** with (*S*) stereochemistry (Scheme 3).

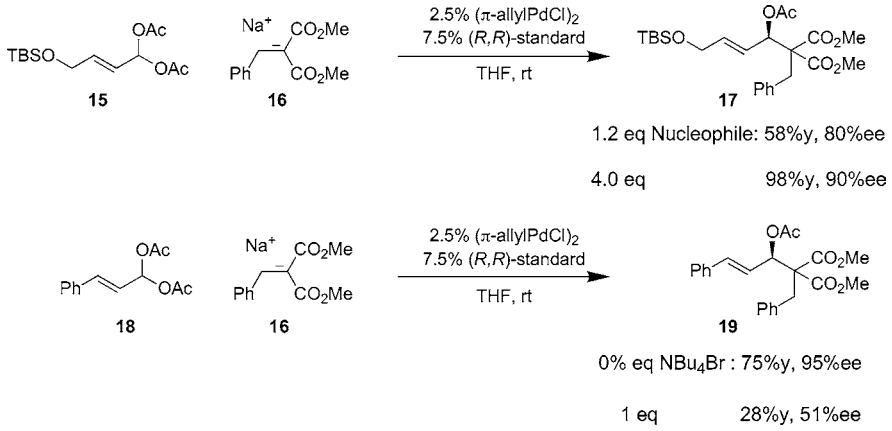
As with previous desymmetrization reactions, increasing the rate of trapping of the initially formed allyl complex leads to higher enantioselectivity. Including a phase-transfer catalyst in the biphasic media significantly increased the rate of trapping and thus the enantioselectivity of **14**. While employing homogeneous conditions with an organic solvent, increasing the equivalents of the nucleophile has the same effect (Scheme 4). Conversely, adding tetrahexylammonium bromide, which increases $\pi-\sigma-\pi$ equilibration, significantly decreases the enantioselectivity.

The inherent difference between class **A** and **B** substrates is the ability of class **B** substrates to undergo $\pi-\sigma-\pi$ interconversion, with the basis for good selectivity relying

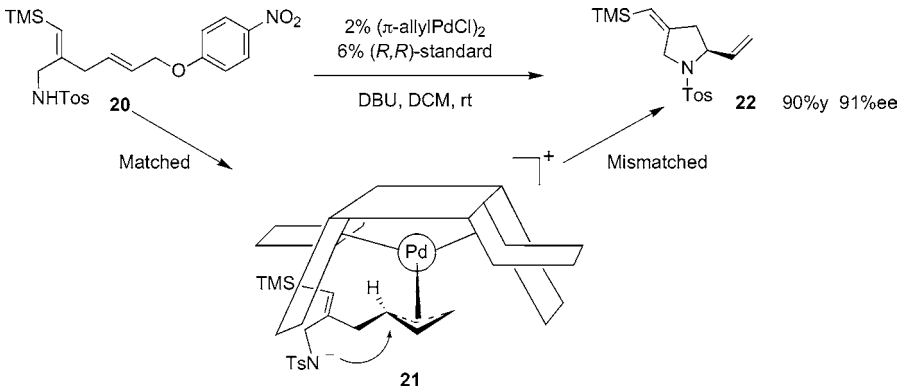
**Scheme 3. *gem*-Diacetate**




**Scheme 4. Mechanistic Studies on *gem*-Diacetate Substrates**




**Scheme 5. Intramolecular Trapping of the Kinetically Formed $\pi$-Allyl Complex**

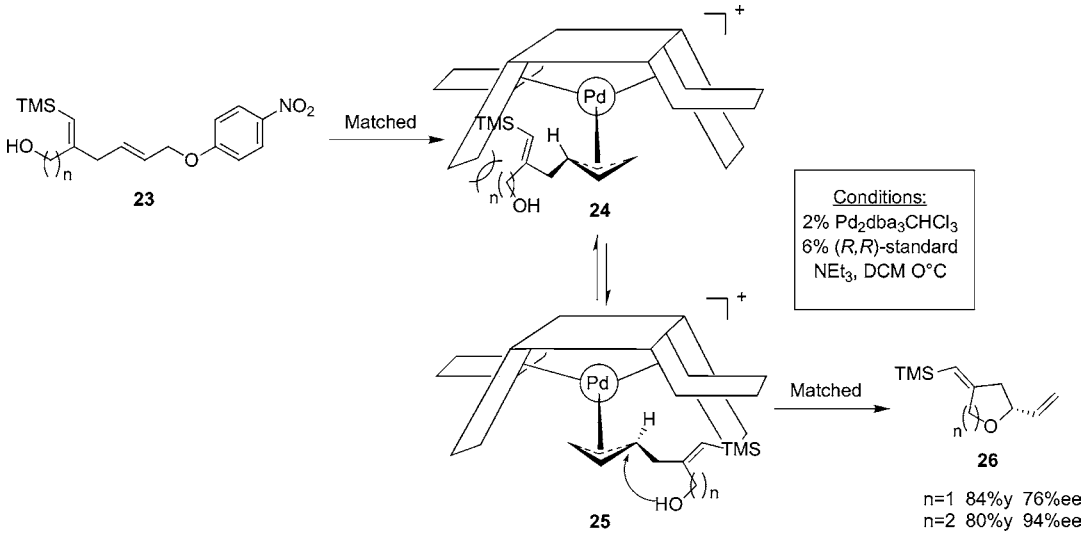



on a preference for direct ionization to the syn,syn complexes followed by rapid capture by the nucleophile.

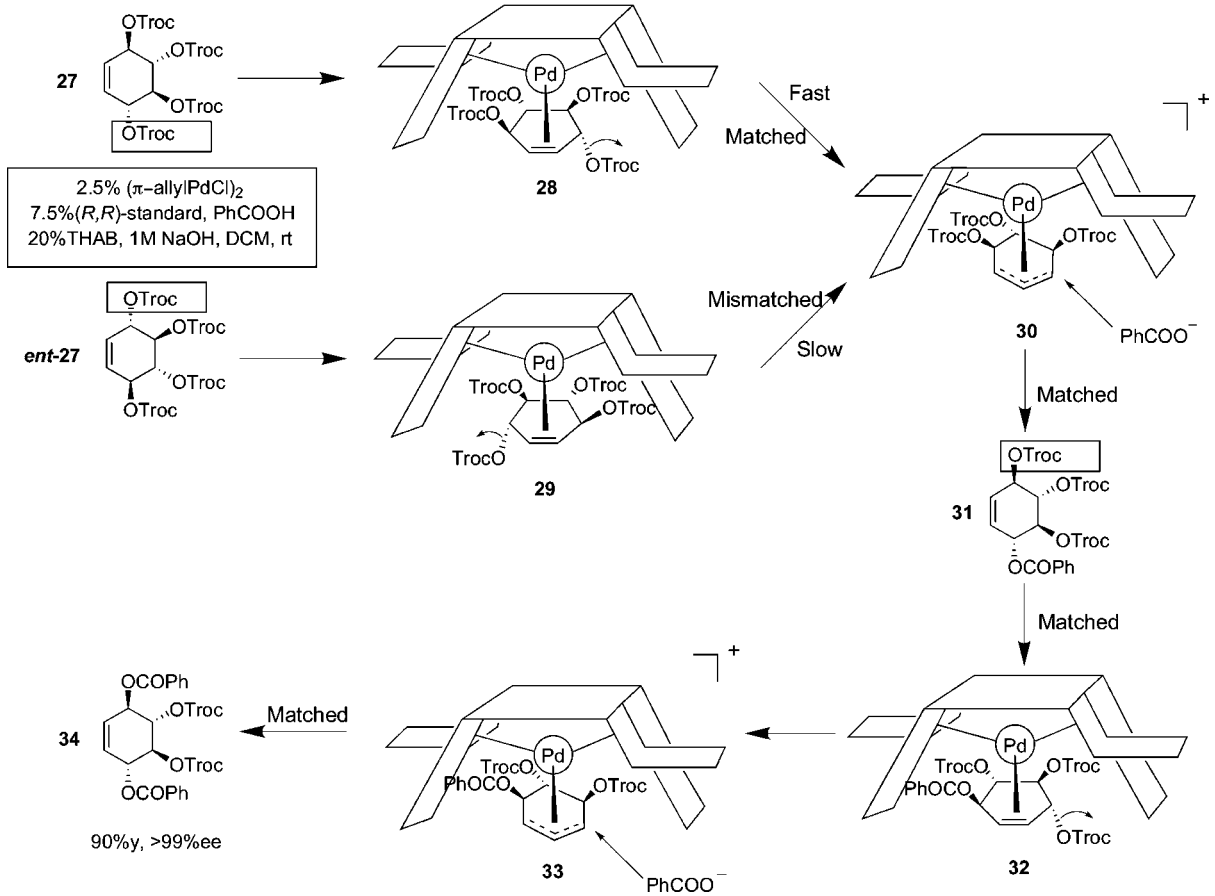
**Ionization to Unsymmetrical $\pi$-Allyl (Class C).** The last substrate class where ionization may represent the enantiodetermining step is a simple unsymmetrical $\pi$-allyl complex, class **C**. Normally these substrates fall into this category; however, when a stabilized nucleophile is tethered to the $\pi$-allylpalladium, the kinetically generated complex can sometimes be trapped before equilibration (Scheme 5).[27] By tethering the nucleophile and using conditions where sulfonamide **20** is fully deprotonated, the rate of mismatched attack is faster than equilibration. Using these guidelines, the working model correctly predicts the observed (*S*) stereochemistry from the (*R*,*R*)-ligand. Again, reaction conditions that favor rapid nucleophilic addition give the highest enantioselectivities. Forming five- and six-membered rings works best, whereas seven-membered rings form with low yield and ee. Furthermore, for the reasons stated above, adding chloride ion dramatically decreases the enantioselectivity.

The nature of the nucleophile is also very important for high selectivity in these reactions.[2a] Using the hard/soft−acid/base theory, "soft" nucleophiles react faster with $\pi$-allylpalladium complexes. With hard nucleophiles, the rate of trapping can become competitive with or slower than allyl interconversion. Alcohols are notoriously poor

**Scheme 6. Intramolecular Attack onto a More Reactive $\pi$-Allyl Complex**




**Scheme 7. Deracemization of Conduritol B Tetracarboxylate**




nucleophiles for Pd AAA.[28] For example, when a simple alcohol substrate such as **23** is cyclized, the resulting stereochemistry switches to (*R*) (Scheme 6) because the rate of addition is slower than equilibration of the $\pi$-allylpalladium complexes. Matched nucleophilic attack then leads to **26**. Supporting this notion is the fact that the slower rate of cyclization to pyrans indeed increases enantioselectivity.

When reactions are designed for class **C** substrates, a careful selection of both the substrate and reaction conditions will be required to bias the system toward the type of enantiodiscrimination desired. For example, using a much more reactive phenoxide as an oxygen nucleophile in a cyclization required employing acetic acid rather than simple base to ensure that the rate of equilibration was faster than nucleophilic attack and thus provide the product in high ee.[29]

**Nucleophilic Addition as Enantiodetermining.** Because $\pi$-allylpalladium complexes have a mechanism by which they can undergo isomerization, chiral racemic substrates (substrate classes **D** and **E**, Figure 6) can

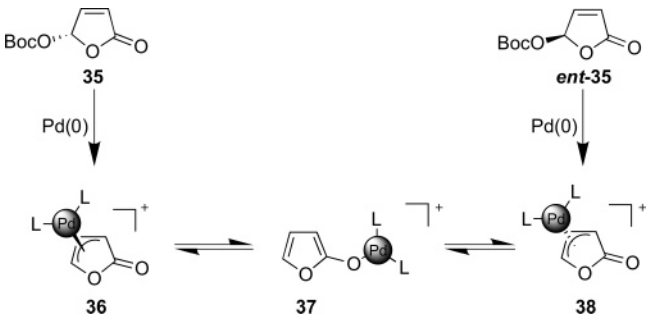



**FIGURE 9.** Racemization of butenolide allyl.

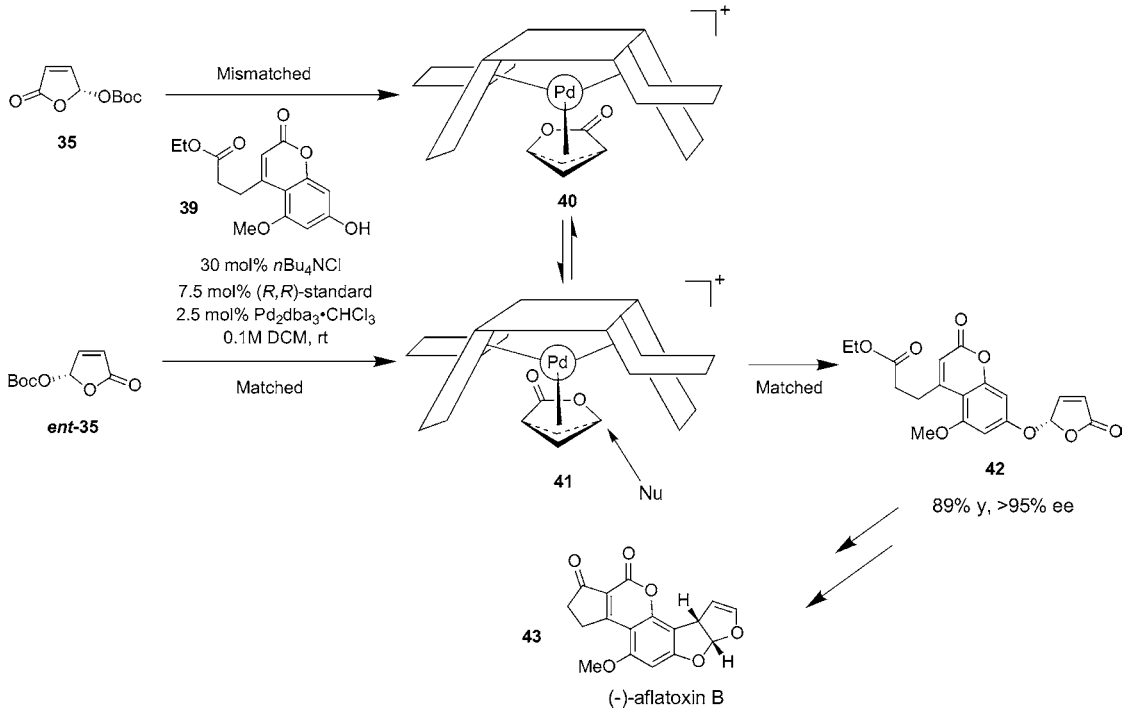
potentially be fully converted into enantiopure materials in this second major mechanistic category. This type of process, wherein both enantiomers of starting material are converted to one enantiomer of product, is denoted a dynamic kinetic asymmetric transformation (DYKAT but is frequently referred to as dynamic kinetic resolution or DKR, which is an inaccurate description of the phenomenon). Unlike a kinetic resolution where the theoretical yield is 50%, a DYKAT allows 100% conversion. The catalyst must effectively become equivalent to a $C_2$-symmetric structure by rapid equilibration between its non-$C_2$-symmetric instantaneous structures and/or between oligomers and monomers. Because nucleophilic addition is enantiodetermining, if it is too fast, such equilibration may become too slow and also lead to lower selectivities.

**Nucleophilic Addition to a Pseudo-*meso* $\pi$-Allyl Complex (Class D).** The simplest type of DYKAT occurs when ionization of the leaving group results in a *meso*-like $\pi$-allylpalladium complex. This concept is illustrated by deracemization of conduritol B tetracarboxylate. With racemic starting material and a chiral ligand, one enantiomer will ionize via a matched pathway, whereas the mismatched enantiomer ionizes at a slower rate. Using racemic conduritol tetracarboxylate, matched ionization of **27** and mismatched ionization of ***ent*-27** leads to the same intermediate (Scheme 7).[30] Conceptually, as long as the matched nucleophilic attack onto the pseudo-*meso* intermediate is faster than the mismatched, high enantioselectivity can be achieved. A matched nucleophilic addition of benzoate will yield monosubstituted adduct **31**. Because **27** is $C_2$-symmetric, **31** also contains a leaving group capable of matched ionization. Ionization followed by matched nucleophilic addition yields disubstituted product **34** in excellent yield and >99% ee.

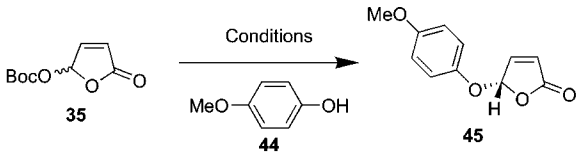
Mechanistically, for the DYKAT to succeed, the difference in energy between the matched and mismatched ionization pathways must not be insurmountable. Interestingly, when racemic conduritol tetraacetate is used, only a kinetic resolution results. However, when we switch to the more easily ionized tetra methyl carbonate derivative, a DYKAT is achieved in that both enantiomers of starting material are ionized, albeit at different rates, and are converted to the same product in 80% yield and 90% enantioselectivity. Moving to trichloroethyl carbonate, a better leaving group, further increases both yield and enantioselectivity.

**Nucleophilic Addition to an Unsymmetrical $\pi$-Allylpalladium Complex (Class E).** When ionization of racemic starting material does not form a pseudo-*meso* $\pi$-allyl intermediate, the resulting complexes are diastereomers. To obtain high enantioselectivity in the product, these diastereomers must interconvert *faster* than nucleophilic attack. If the rate of interconversion is fast, a Curtin−Hammett situation is set up in which the more reactive $\pi$-allylpalladium complex leads selectively to the product. Within this mechanistic class of reactions, cyclic and acyclic substrates are quite different. Acyclic sub-

**Scheme 8. DYKAT with Racemic Butenolide**

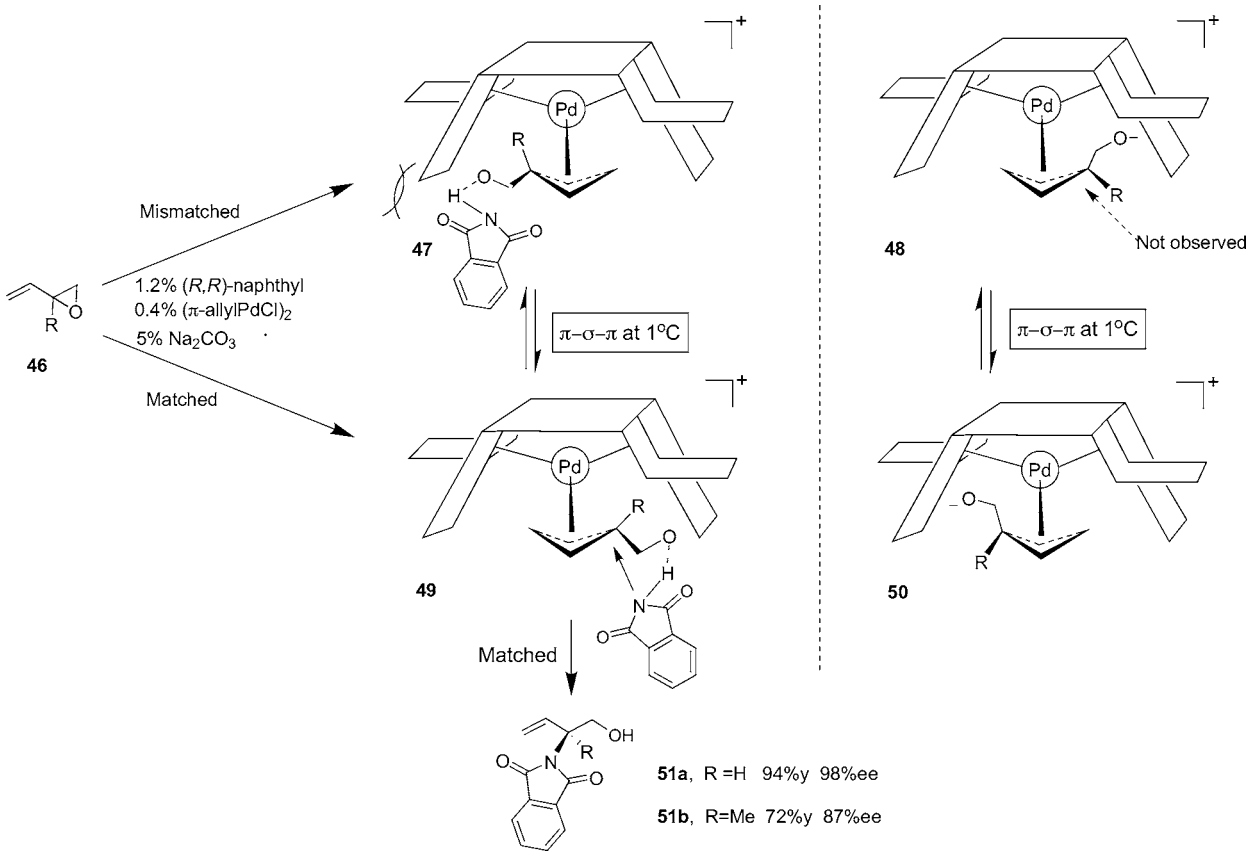


**Scheme 9. Optimizing DYKAT Parameters**




| entry | equiv **44** | mol%Pd | mol% ligand | conditions | y/ee |
|---|---|---|---|---|---|
| 1 | 0.5 | 5 | 15 | 0.1M DCM 10h rt | 45%, 47% |
| 2 | 0.5 | 0.5 | 1.5 | 0.5M DCM 15% $Cs_2CO_3$ rt 16h | 45%, 90% |
| 3 | 1 | 0.5 | 1.5 | 0.2M DCM 15% $Cs_2CO_3$ rt 16h | 80%, 24% |
| 4 | 0.8 | 1 | 3 | 0.1M DCM, 30% TBAC rt 6h | 67%, 82% |
| **5** | **1** | **1** | **3** | **0.1M DCM, 30% TBAC 0°C 6h** | **74%, 84%** |

**Scheme 10. DYKAT with Diene Monoepoxides**

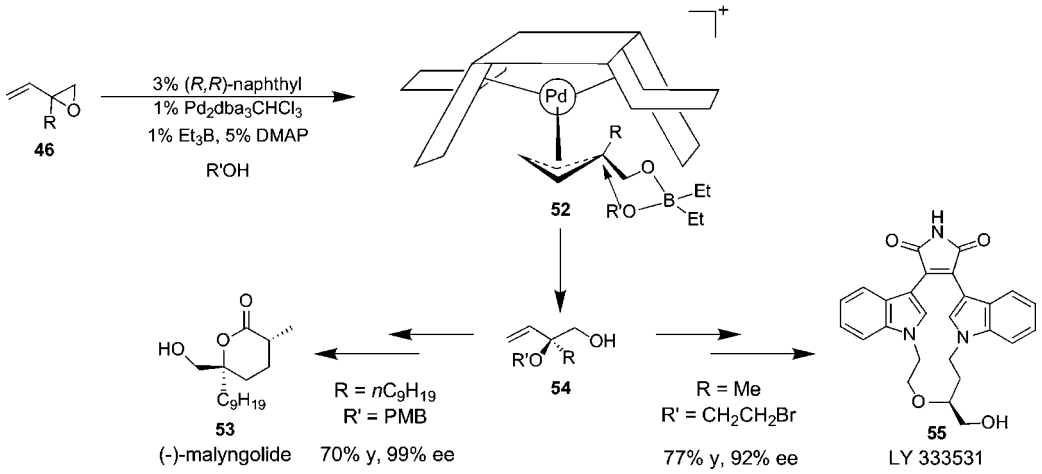



strates readily interconvert by the aforementioned $\pi-\sigma-\pi$ mechanism. Cyclic systems, however, cannot undergo C−C bond rotation about the allyl unit, and therefore, a different mechanism is required. $\gamma$-Acyloxybutenolides offer a unique entry into a DYKAT situation.[31] The initially generated $\eta^3$ diastereomeric complexes are in equilibrium with a $\eta^1$ oxygen-bound palladium complex. Rotation and rehybridization results in a $\pi$-face exchange (Figure 9). The aromaticity of the intermediate furan serves as a driving force for this interconversion.

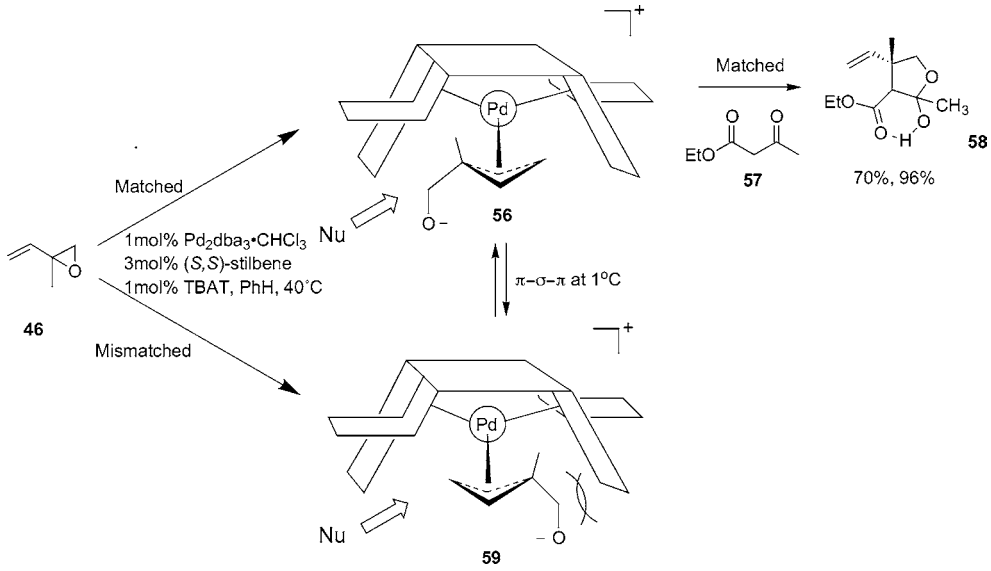
According to the model, **35** undergoes a matched ionization, whereas ***ent*-35** undergoes a slower mismatched ionization (Scheme 8). These diastereomers are in dynamic equilibrium via the mechanism outlined in Figure 9. The regioselectivity of addition is controlled by the stereoelectronics of the butenolide substrate, wherein addition to the oxygen-stabilized terminus is favored. Therefore, the predicted matched nucleophilic addition gives the (*S*) stereochemistry, and this is what is observed experimentally (Scheme 8).

Reaction conditions were very important for obtaining good selectivity in this transformation. Using *p*-methoxyphenol as a nucleophile, the effect of various parameters was investigated (Scheme 9). Using 0.5 equiv of phenol, a kinetic resolution was observed. Using 1 equiv of phenol to effect a DYKAT, the rate of nucleophilic addition could be slowed by removing $Cs_2CO_3$ and lowering the reaction temperature and concentration. Furthermore, the rate of $\pi-\sigma-\pi$ interconversion was increased by the addition of tetrabutylammonium chloride, affording **45** with 84% ee

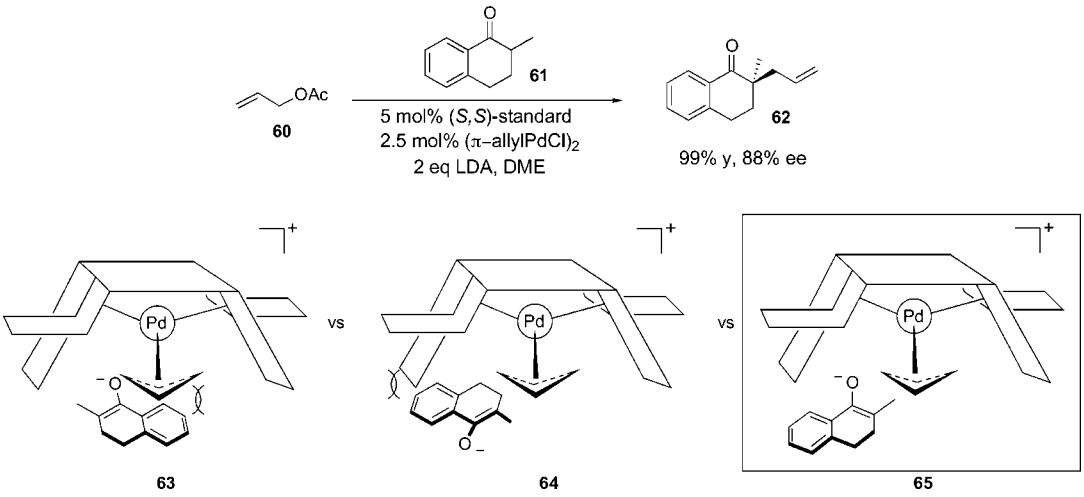
**Scheme 11. DYKAT with Oxygen Nucleophiles**




**Scheme 12. Carbon Nucleophiles in DYKAT**



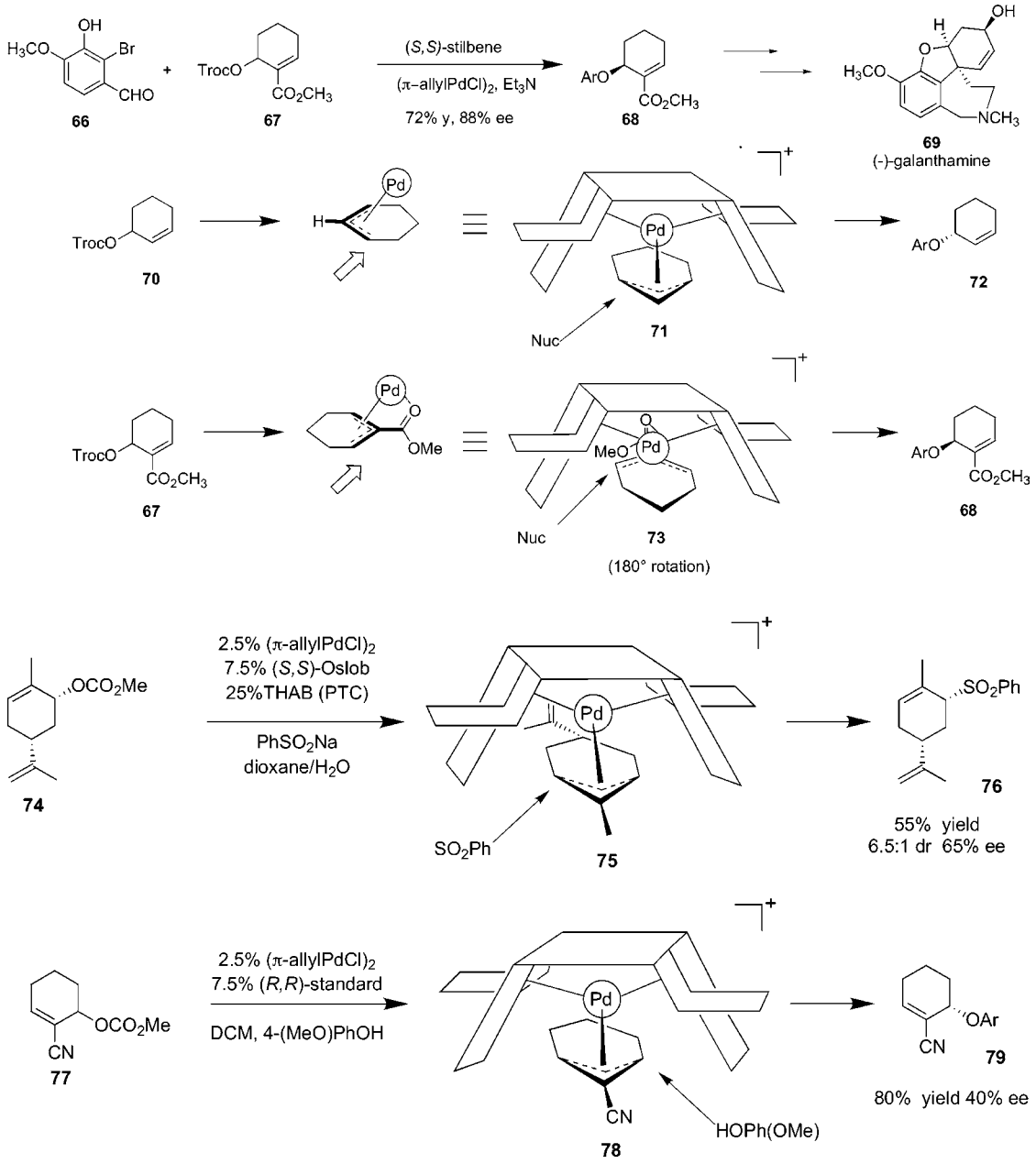

**Scheme 13. Chirality at the Nucleophile**




at full conversion (entry 5). The enantioselectivity was further improved by increasing the steric bulk of the nucleophile (see Scheme 8).

Acyclic $\pi$-allyl complexes can also participate in DYKAT reactions. An example of this class of substrates is the DYKAT of butadiene monoepoxide. Using phthalimide as the nucleophile,[32] with the (*R*,*R*)-ligand, (*S*)-**46** will ionize via a matched pathway to afford **49**, while (*R*)-**46** undergoes a mismatched ionization to give **47** (Scheme 10, R = H). The intermediates **47** and **49** can readily interconvert

**Scheme 14. Studies with 2-Substituted $\pi$-Allyl Complexes**



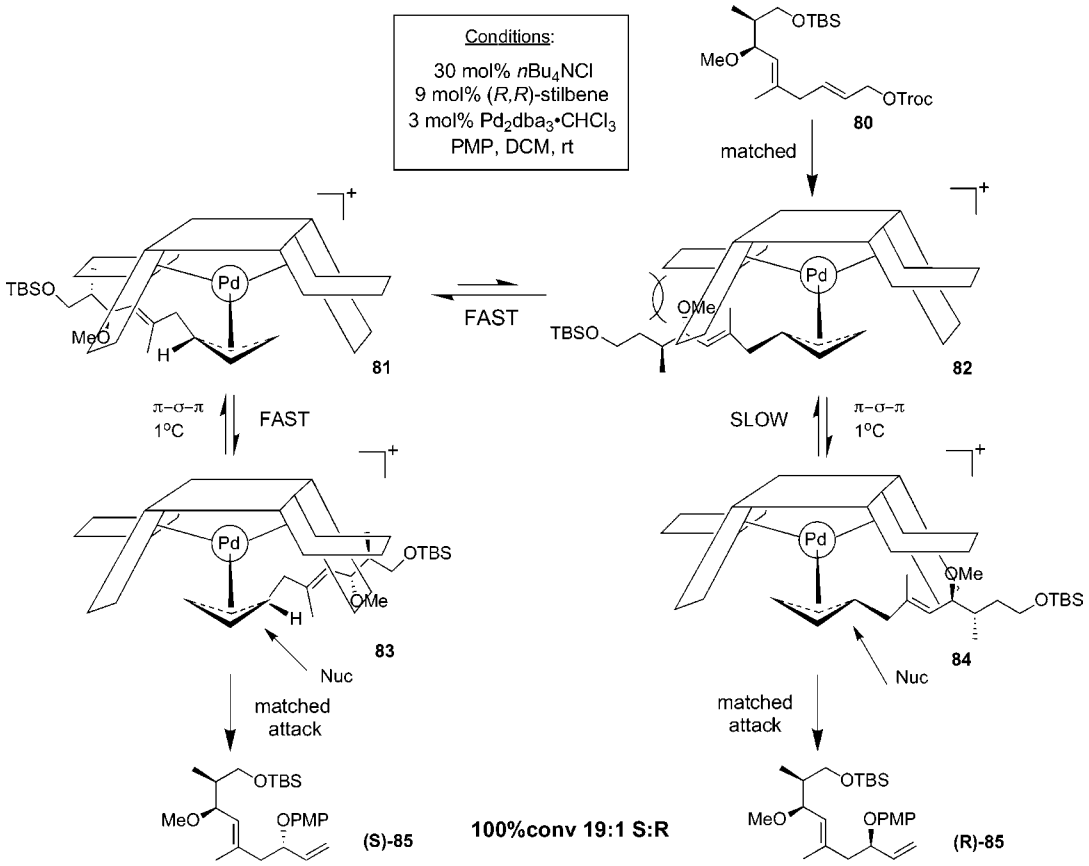

by a $\pi-\sigma-\pi$ mechanism about the monosubstituted allyl terminus. Phthalimide is directed to react at the more substituted carbon by hydrogen bonding. Nucleophilic approach via **49** is favored and yields **51a** in 98% ee.

Using isoprene monoepoxide, a chiral *tertiary* stereocenter would be formed. While a challenging proposal, the experimental results show that the DYKAT can be quite successful. When the reaction is run at 55 °C, up to 87% ee is achieved and the sense of chirality matches that of **51a**.

The DYKAT of diene monoepoxides was also investigated using nonstabilized alcohols, which are usually poor substrates. Tethering the alcohol to the ionized alkoxide using triethylborane as a cocatalyst (Scheme 11) increased the reactivity to viable levels.[33] The arguments for selectivity parallel those for the phthalimide system.

Finally, carbon nucleophiles were investigated. Using racemic standard ligand, 1,2-addition product *rac*-**58** is obtained in 64% yield (Scheme 12).[34] In contrast, using the (*S*,*S*)-standard ligand, the regioselectivity decreases to 2:1, although the enantioselectivity remains high (93%). The increased regioselectivity with the racemic ligand is attributed to a kinetic discrimination in the initial ionization with racemic epoxide and racemic ligand. Both enantiomers of **46** can ionize via matched pathways forming enantiomers of **56**. This intermediate favors a 1,2-addition pathway. With enantiopure ligand and racemic epoxide, complexes **56** and **59** are both formed. While **56** favors the formation of the 1,2-addition product, **59** favors the formation of the 1,4-addition product via a matched addition. Adding tetrabutylammonium triphenyldifluorosilicate to increase the rate of $\pi-\sigma-\pi$ interconversion

**Scheme 15. Synthesis of Callipeltoside A**




consequently increased the amount of the 1,2-addition product, and a 56% yield of **58** was obtained in 93% ee. Switching to the more flexible (*S*,*S*)-stilbene ligand gives improved yield and selectivity, 70% yield and 96% ee.

**Chirality at the Nucleophile.** A second method for the enantioselective formation of chiral quaternary centers is to form a new stereocenter at a prochiral carbon of the incoming nucleophile. This proposal is challenging because the nucleophile approaches the complex on the opposite face of the chiral environment. For a successful reaction, the chiral ligands must influence the trajectory of the approach and impart a facial bias to the incoming nucleophile. This concept was proven possible because various enolates are allylated with good enantioselectivities.[35] Considering allylation of tetralone **61**, there are several approaches to the complex to consider (Scheme 13).[36] Assuming that the preferred transition state will place the sterically bulky aryl ring under the flap rather than under the allyl eliminates **63**. Minimizing steric interactions between the substrate and ligand differentiates **64** from **65**. When the nucleophile approaches as in **64**, there is a steric interaction of both ring systems with the back ligand wall. In **65**, these steric interactions are minimized. This analysis predicts the (*S*) stereochemistry as is determined experimentally.

## Exceptions to the Model

The model described shows excellent fidelity for predicting stereochemical outcomes of palladium-catalyzed reactions; however, two substrates contained structural features that had unexpected effects. These substrates comprise the only known examples where the principles presented thus far are not sufficient to predict the outcome of the reaction.

The first example arose in a synthesis of (−)-galanthamine.[37] The reaction of **67** with a phenol lead to the (*S*) product (Scheme 14). This result is unexpected given that **70** follows the conventions outlined above and matched nucleophilic attack leads to substituted product **72** with (*R*) stereochemistry. Both substrates fall into the category of a DYKAT, where nucleophilic attack is enantiodetermining. Why then should substitution change the outcome of the reaction? The answer can be understood by realizing that coordination of the ester to palladium changes the cant of the $\pi$-allyl species. Normally, the 2 position of the $\pi$-allyl cants away from the palladium metal, but upon coordination, the 2 position then cants toward palladium. Because the stereoelectronics of an antiperiplanar addition must be preserved, the nucleophile approaches from the right rear quadrant of the $\pi$-allylpalladium complex. This analysis predicts the (*S*) stereochemistry as observed. Further corroboration of this model is derived from the fact that methyl-substituted **74** follows the model, indicating that the steric influence of a 2-substitutent does not perturb selectivity.[38] Furthermore, **77**, which has similar electronic influences on the allyl but is geometrically constrained from coordinating to palladium, also follows the model.[39]

The only other known exception to the mnemonic occurred in a total synthesis of callipeltoside A (Scheme 15).[40] Allyl carbonate **80** initially ionizes to give syn complex **82**. In this complex, the bulky side chain experiences a steric interaction with the left wall. Fast $\pi-\sigma-\pi$ isomerization about the secondary carbon forms anti complex **81** and relieves the steric interaction. Without chiral ligands, the syn complex is more stable (vide infra). However, thermodynamic stability of the intermediates is reversed for this substrate in the presence of chiral ligands. Observed product (*S*)-**85** is therefore a result of a matched nucleophilic addition onto anti complex **83**. Notably, the steric interaction of the side chain with the wall also slows the rate of $\pi-\sigma-\pi$ interconversion about the monosubstituted terminus of **82** relative to isomerization about the disubstituted terminus. Rotation during rehybridization of palladium to the monosubstituted $\sigma$ complex effectively moves the side chain closer to the left wall, whereas moving to the opposite terminus pulls the side chain slightly away from the left wall.

## Summary and Outlook

The working model presented is a powerful tool for predicting the stereochemical outcome of DPPBA-based Pd AAA reactions. When ionization is enantiodiscriminating, conditions that favor fast nucleophilic attack are best. Here, basic reaction media, soft nucleophiles, and good leaving groups are important. When the addition is enantiodiscriminating, conditions that favor slow nucleophilic attack and promote equilibration of the intermediates are best. Here, equilibration promoters such as chloride, low reaction pH, and poorer nucleophiles are important. In both classes, steric interactions of both the substrate and nucleophile with the chiral catalyst need to be considered. When regiochemistry is an issue, equilibration of intermediates is also essential. Additionally, if the mechanism of enantiodiscrimination is not initially known, test reactions on opposite extremes can be used to shed light on the situation.

Pd AAA is still an active area of research. This powerful method is currently used to construct a diverse array of structurally and biologically interesting natural products. Furthermore, the concepts outlined are inherent to designing AAAs for many metals and ligand systems.

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