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# Stereoselective Carbonyl Allylation by Umpolung of Allylpalladium(II) Complexes

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**Keywords:** Allyl ligands / Umpolung / Allylation / Palladium / Chiral monoligands

The nucleophilic palladium-mediated allylation of a carbonyl group requires the inversion of the reactivity (umpolung) of the $\eta^3$-allylpalladium moiety. If the reaction is performed with a metal more electropositive than palladium, the stereochemical outcome is influenced by the solvent and by the reagent used for the umpolung. The stereoselectivity is also determined by the rate of $\eta^3$–$\eta^1$–$\eta^3$ equilibration of the $\eta^3$-allylpalladium system relative to that of the transmetallation and addition to the aldehyde. When the umpolung is carried out with $\eta^1$- or bis(allylpalladium) complexes, the stereoselectivity mainly depends on the nature of the substituents on the allyl fragment. Asymmetric addition has been achieved by using chiral ligands that promote palladium-mediated reactions with "hard" nucleophiles. Utilization of selected chiral monophosphanes/phosphoramidite as ligands induces enantioselectivity that depends on the nature of the aldehyde as well as of the umpolung agent. Modest enantiomeric excesses have been obtained by using preformed bis(allylpalladium) systems with one chiral allylic fragment.

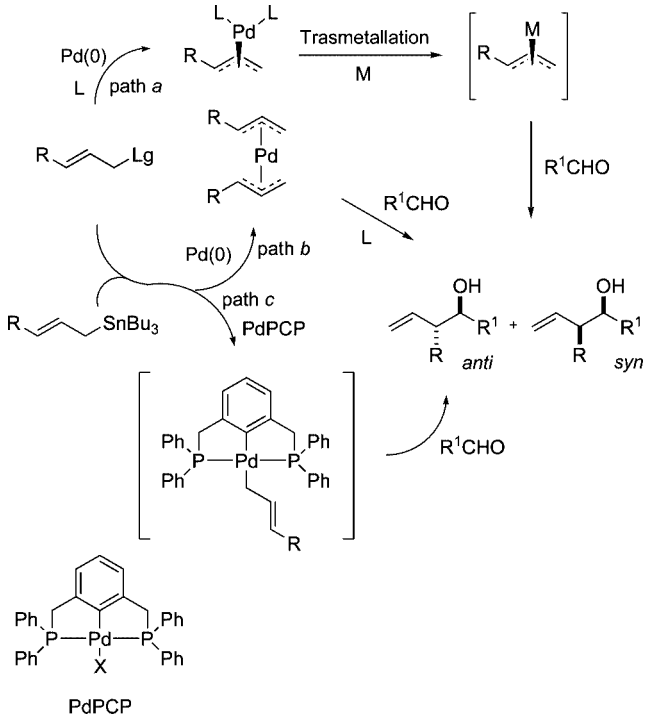


## 1. Introduction

The reaction of electrophilic palladium intermediates is a well-established tool of the synthetic chemist.[1] On the other hand, the transformation of organopalladium compounds into nucleophilic reactants is a relatively new method with exciting potential applications.

In consideration of practical feasibility, versatility, and tolerance of a wide range of functional groups, transformations based on the umpolung of $\eta^3$-allylpalladium(II) complexes are also extremely attractive for preparative and, potentially, industrial applications. The focus of this review is on the stereochemical aspects of the various transformations involving the palladium-catalyzed addition of allylic reagents to carbonyl electrophiles by umpolung.

Two approaches to the diastereoselective allylation of carbonyl compounds can be outlined. 1) The palladium catalyst is involved exclusively in the formation of the organometallic complex and does not take part in the addition process (path *a*, Scheme 1).[2] 2) The palladium catalyst is involved directly in the allylation step, either as a bis-allylpalladium species (path *b*, Scheme 1) or as an pincer $\eta^1$-allylpalladium complex (path *c*, Scheme 1).




Scheme 1.

## 2. Palladium as a Tool for the Formation of the Allyl Complex

As shown in path *a* of Scheme 1, $Pd^0$ complexes are well-known promoters of the $\eta^3$-allylpalladium system that can

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subsequently be converted into an allylmetal (allyl-M) species by transmetallation. If M is more electropositive than palladium, the aldehyde should preferentially undergo nucleophilic attack by allyl-M. Among the different metals capable of promoting such an umpolung, tin, indium, and zinc stand out for the synthetically useful levels of stereoselectivity gained in the overall process.

As the allylating agent is an organo-tin, -indium or -zinc species, the stereochemical outcome is dictated by the typical behavior of these organometallic reagents as they are generated from the corresponding organic halides.[3] However, it should be highlighted that the stereochemical outcome of the addition process can be influenced by the stereochemistry of the $\eta^3$-allylpalladium(II) complex involved in the first step of the reaction. In fact, the *syn* or *anti* stereochemistry around the C–C double bond in the starting material is retained in the $\eta^3$-allylpalladium complex with a high degree of integrity unless the rate of $\eta^3$–$\eta^1$–$\eta^3$ isomerization competes with the transmetallation process.

### 2.1 Stereoselectivity in the Addition of Tin Reagents

The stereoselectivity of the addition to carbonyl compounds by allylstannanes is determined by the stereochemistry of the starting allylic substrate, the nature of the leaving group, the steric and electronic effects of the substituents on the $\eta^3$-allylpalladium(II) intermediate, and by the solvent used.[4] Three different kinds of transition state (TS) were proposed by Masuyama and co-workers to account for the observed stereochemical results, namely two acyclic TSs (antiperiplanar and synclinal) and a classic six-membered Zimmermann–Traxler-like cyclic TS (Figure 1). The preference for one of these TSs depends mainly on the reaction conditions and on the nature of the leaving group.

Note that a cyclic TS results in stereospecific reactions. In contrast, if an open acyclic TS is involved, the stereochemical information encoded in the reactants does not necessarily determine the stereochemistry of the products.

Thus, the presence of three different TSs was invoked to rationalize the stereoselectivity observed in the addition of

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*After his graduation in chemistry, Giovanni Vidari worked with P. A. Grieco at the Indiana University in Pittsburgh (USA). He began his independent research career in the Department of Chemistry at the University of Pavia (Italy), now as full Professor of Organic Chemistry. His interests verge on natural products, enantioselective total synthesis, and biomimetic cyclizations. He has authored more than 130 research publications.*

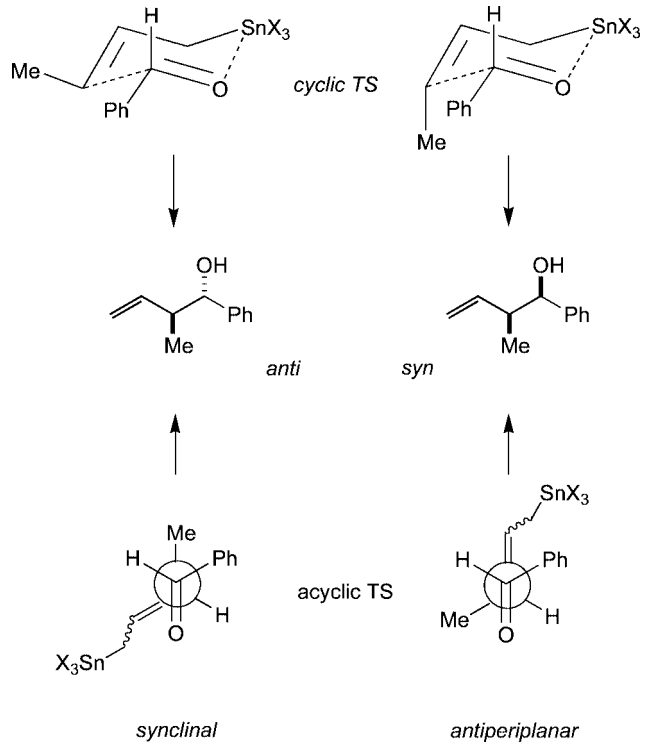


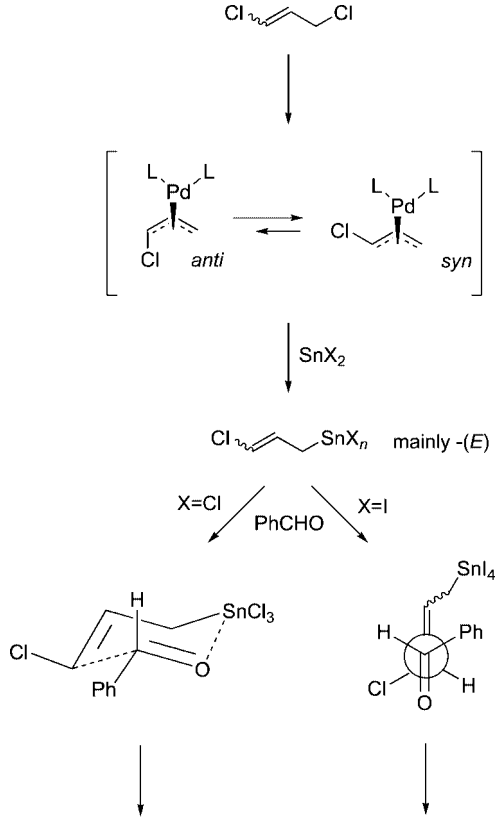

Figure 1. Acyclic transition states in wet DMSO.

allylic alcohol derived complexes to benzaldehyde.[5] In this case, the stereoselectivity changes according to the solvent used and the stereochemistry of the allylic reagent.

For instance, addition of reagents generated from (*E*)-but-2-en-1-ol to benzaldehyde occurred with *anti* selectivity in 1,3-dimethylimidazolidinone (DMI), THF, dilute DMSO/water, and THF/$H_2O$, in agreement with a classic six-membered cyclic TS (Scheme 2). The s*yn* selectivity obtained by starting from (*Z*)-but-2-en-1-ol could be explained by an analogous mechanism (Figure 1).

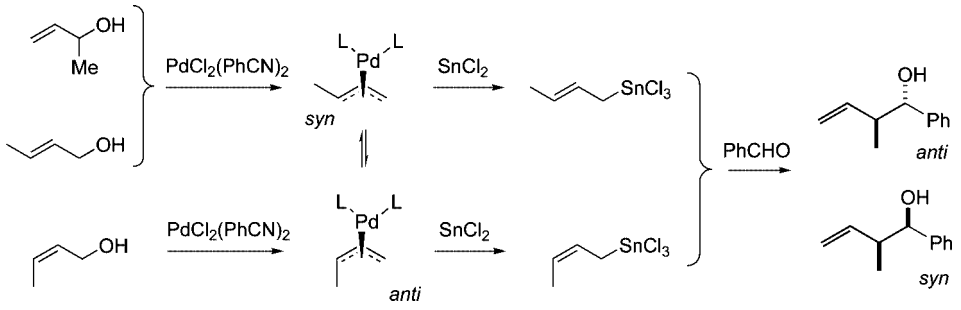
In contrast, starting from either (*E*)- or (*Z*)-but-2-en-1-ol in concentrated DMSO/water mixtures, acyclic transition states accounted for the observed preferential *syn* selectivity. This different stereochemical outcome was explained by assuming that a strong coordination of DMSO to $Sn^{IV}$ likely prevented the formation of a cyclic TS, whereas a larger amount of water in the reaction medium possibly promoted the formation of a cyclic intermediate as the coordination of DMSO to tin would be disfavored. The interconversion between the more stable *syn* and *anti* forms of the $\eta^3$-allylpalladium(II) complex can explain the low selectivity of the reactions of the (*Z*)-alkenols.[6]

The two cyclic TSs and the antiperiplanar acyclic TS are also operative in the diastereoselective synthesis of 2-chlorobut-3-en-1-ols starting from mixtures of (*E*)- and (*Z*)-1,3-dichloropropene (Scheme 3).




Scheme 3.

However, Masuyama et al.[7] observed *anti* selectivity in palladium-catalyzed allylations with $SnCl_2$ in dry DMI, whereas *syn*-2-chlorobut-3-en-1-ols were obtained in the presence of tetrabutylammonium iodide (TBAI) or $SnI_2$ using DMI/water as the solvent. Although the latter reaction also proceeded without palladium catalysis, the presence of $[PdCl_2(PhCN)_2]$ enhanced the yields and *syn* selectivity (Scheme 3).




Scheme 2. L is a palladium ligand such as PhCN or the solvent.

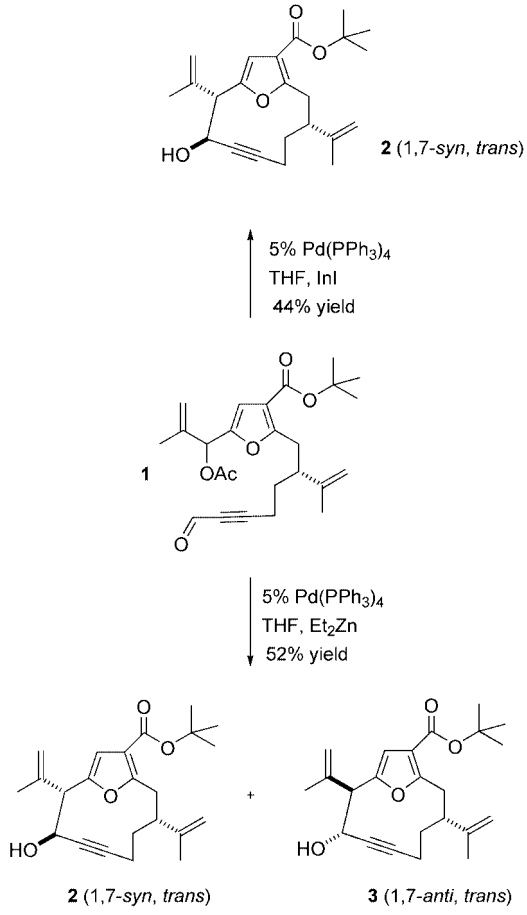
  

As with alkenols (Scheme 2), the s*yn* and *anti* isomers of the $\eta^3$-chloroallylpalladium complex are supposed to be interchanging, the more stable *syn* complex being favored at equilibrium.

In the presence of $SnCl_2$, these reactions are thought to proceed through the usual six-membered TS, with the allylic trichlorotin group coordinated to the aldehyde carbonyl group, leading to *anti* selectivity. In the presence of iodides, a tetraiodotin species is probably formed which is devoid of Lewis acidity and thus undergoes allylation through an acyclic TS leading to *syn* products.

Palladium-catalyzed allylation of aldehydes by allylic esters in the presence of $SnCl_2$ have also been investigated.[6] The acetates yielded puzzling stereochemical results. A better defined stereoselectivity was found with carbonates, which reacted with aldehydes in the presence of [$PdCl_2$-$(PhCN)_2$] and DMI.

The observed modest stereoselectivity depended upon the (*E*)/(*Z*) stereochemistry of the two allylic substrates, which was reflected in the geometry of the intermediate $\eta^3$-allylpalladium(II) complexes.[6] The *anti* adduct was derived from the thermodynamically more stable *syn*-$\eta^3$-allyl complex, whereas the *syn* adduct was derived from the corresponding *anti*-$\eta^3$-allylpalladium(II) complex. Either complex can add to the aldehyde through a cyclic TS. However, the presence of a coordinating solvent such as DMI might shift the TS from a cyclic to an acyclic one, thus promoting the formation of the *syn* product.



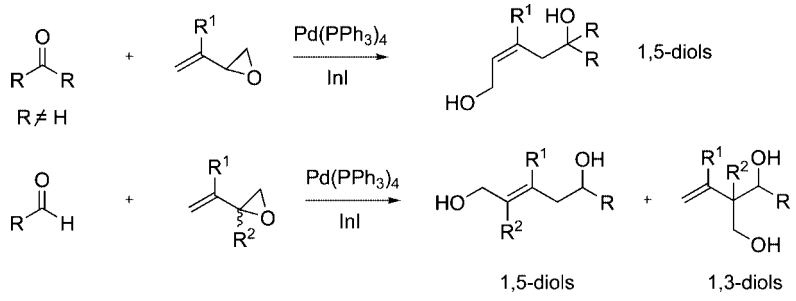

Scheme 4.

### 2.3 Stereoselectivity in the Addition of Indium Reagents

Umpolung using allylindium reagents has given the highest diastereoselectivities to date and, although still at an early development stage, it has been successfully applied to chemical syntheses.[8] As an example, the cyclization of allyl acetate **1** (Scheme 4) afforded an 8:2 mixture of two branched products **2** (1,7-*syn*,*trans*) and **3** (1,7-*anti*,*trans*) when $Et_2Zn$ was used as the umpolung reagent. However, when InI was used for the umpolung, only the *syn*,*trans* isomer was obtained.[9] Palladium-catalyzed allylation reactions in the presence of InI or indium metal are considered to proceed through a reductive transmetallation of an $\eta^3$-allylpalladium(II) complex intermediate to the corresponding allylindium(III) species, which subsequently reacts with the electrophile.[10]

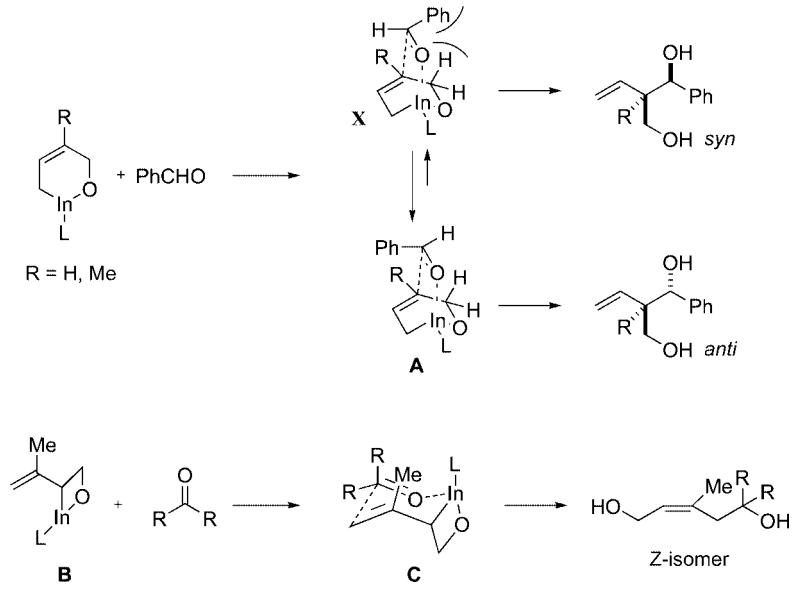
The umpolung of vinyloxiranes has also been reported (Scheme 5).[11] The regioselectivity of the coupling with carbonyl compounds depended on the nature of the substrates. Coupling with ketones afforded 3-ene-1,5-diols almost exclusively. When aldehydes were employed instead, 2-methyl-2-vinyloxiranes gave 1,3-diols exclusively, whereas 2-(prop-1-en-2-yl)oxiranes afforded the corresponding 1,5-diols preferentially.

Two kinds of cyclic TSs were assumed to be involved in the reaction mechanism. 1,3-Diols were likely formed via six-membered boat-like TS **α** (Scheme 6). Steric interaction between the phenyl group of the benzaldehyde and the pseudoaxial hydrogen atom on the ring preferentially led to




Scheme 5.

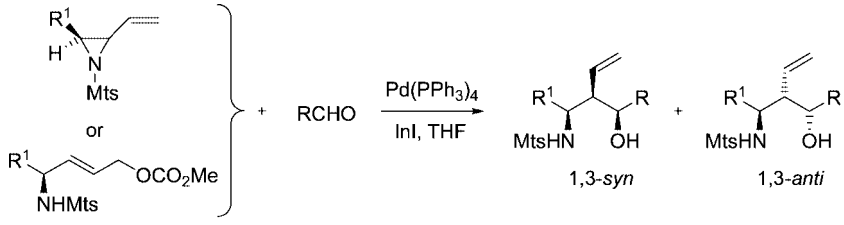
  




Scheme 6.

the *anti*-1,3-diol. The selectivity was higher for R = $CH_3$, probably as a result of a more planar ring conformation.

When ketones were used as the electrophiles, the steric hindrance was probably great enough to prevent any reactions on the six-membered allylindium species. Therefore 1,5-diols could be derived from four-membered indium complex B. Preference for the (*Z*)-olefin can be explained in terms of bicyclic TS **X**, as shown in Scheme 6.




| R | $R^1$ | Yield (%) | *syn*:*anti* |
|---|---|---|---|
| Ph | *i*Pr | 88 | 90:10 |
| *i*Pr | *i*Pr | 88 | 93:7 |
| Et | *i*Pr | 80 | 51:14 |
| $CH_2OTBS$ | Ph | 58 | 88:12 |

Scheme 7. Mts is an abbreviation for the 2,4,6-trimethylbenzenesulfonyl protecting group.

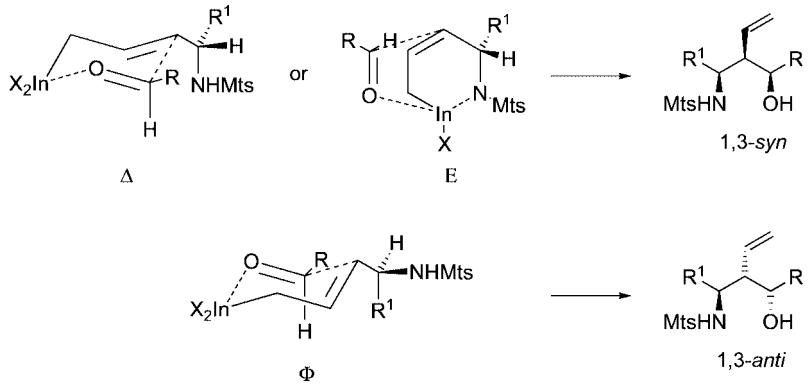



Figure 2. Plausible transition states accounting for 1,3-*syn* and 1,3-*anti* selectivity.

The addition of chiral 2-vinylaziridines to aldehydes led to β-amino acid precursors with good diastereoselectivity when the reaction was carried out in the presence of indium and $[Pd(PPh_3)_4]$.[12]

Similar results, albeit in lower yields, were obtained by employing 4-aminoallyl carbonates. The stereoselectivity was influenced only by the substituent at C-3 of the 2-vinylaziridine as these reactions proceeded through a common $\eta^3$-allylpalladium complex (Scheme 7).

Two possible six-membered TSs were proposed by the authors to rationalize the preferred formation of *syn*,*syn* 1,3-amino alcohols. In TS **Δ**, the indium atom is intermolecularly coordinated to the carbonyl group (Figure 2) in such a way that bulky $R^1$ groups are accommodated in the *anti* orientation, according to the Felkin–Anh model. Conversely, if intramolecular six-membered TS **E** is involved, allylation of the aldehyde preferentially occurs with $R^1$ group being external to the ring. Note, both TSs lead to the same diastereomer. When $R^1$ is a smaller substituent, TS **Φ** can play a major role with the cumbersome protected amino group placed in an *anti* position, thus leading to a larger amount of the *anti* 1,3-amino-alcohol.

### 2.4 Stereoselectivity in the Addition of Zinc Reagents

Tamaru and co-workers disclosed the first stereoselective allylation reactions of $\eta^3$-allylpalladium complexes and diethylzinc. The stereochemical aspects of this reaction have been reviewed by the same author.[13]

The diastereoselectivity observed was rationalized by assuming a six-membered TS analogous to that proposed for the corresponding tin and indium reagents; interestingly, no exception has been raised against this rule. Tamaru proposed two sets of equilibrating TSs to rationalize all the allylation reactions performed with mono- and disubstituted allylic substrates, having substituents at the α, α,β and α,γ positions with respect to the leaving group, respectively (Figure 3 and Figure 4). Moreover, the stereochemistry was dramatically affected by the electronic nature of the C-2 substituents.

Reactions with 2-cyclohexenyl substrates deserve further comment, foreboding the development of asymmetric versions of umpolung-mediated allylation reactions (vide infra).[14] The experimental results indicated that the allylzinc intermediates were generated in a stereocontrolled fashion, were configurationally stable, and delivered solely *syn* adducts. This stereochemical outcome could be explained by the sequential formation of an $\eta^3$-allylpalladium species (**Γ** in Scheme 8), the palladium on the side opposite the leaving group, followed by Pd–Zn exchange with retention of configuration. The resulting complex (**H** in Scheme 8) can then add to aldehydes so that the configuration at the ensuing carbinol carbon atom is dictated by the minimization of steric interactions in the chair-like six-membered TS (**I** in Scheme 8).

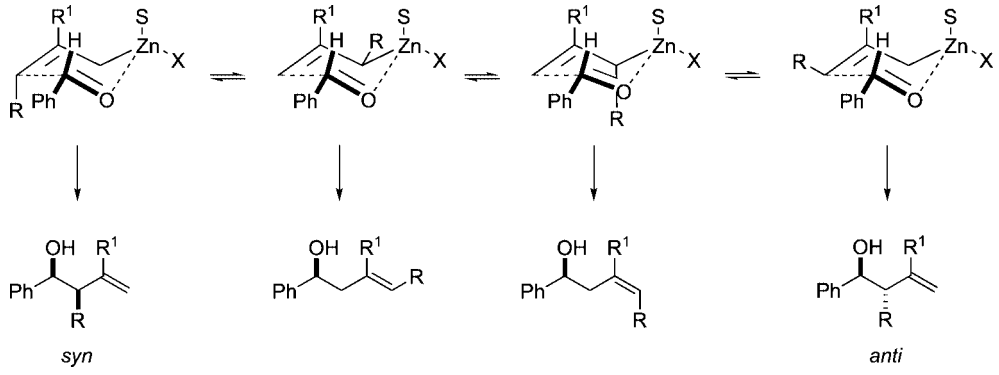



Figure 3. Available TSs for α-mono- ($R^1$ = H) and α,β-disubstituted allylic moieties.

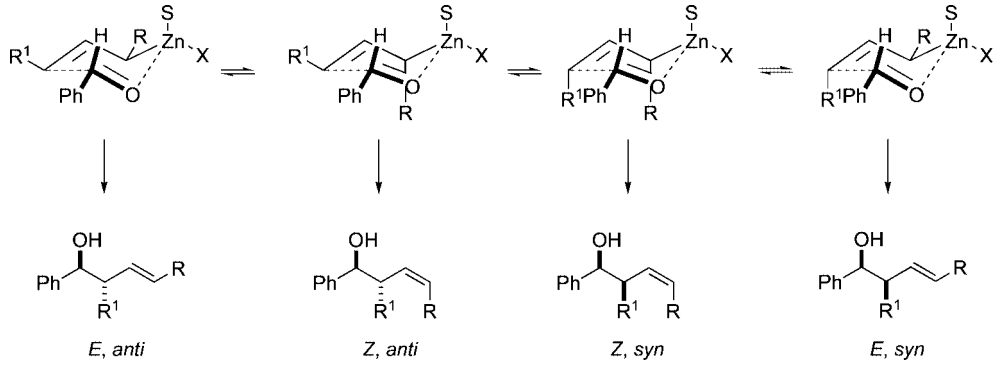
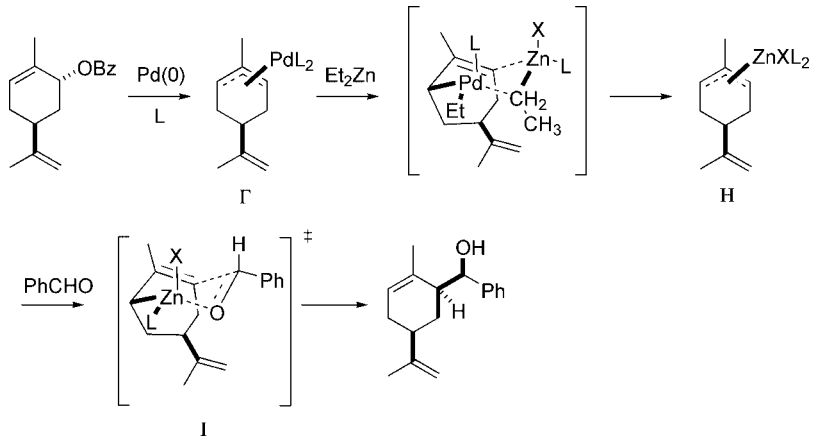



Figure 4. Available TSs for α,γ-disubstituted allylic fragments.



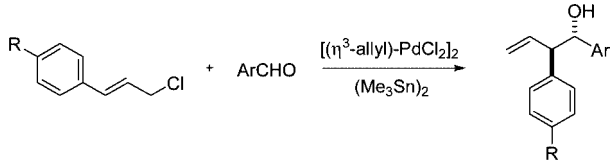

Scheme 8.

## 3. Nucleophilic Addition Promoted by Allylpalladium Species

### 3.1 Bis(allylpalladium) Complexes

Although the addition of a nucleophilic allylpalladium complex to aldehydes was originally reported by Yamamoto and co-workers in 1996,[15] the regio- and stereoselectivity of the reaction was only recently rationalized by Wallner and Szabó through the use of DFT calculations.[16]

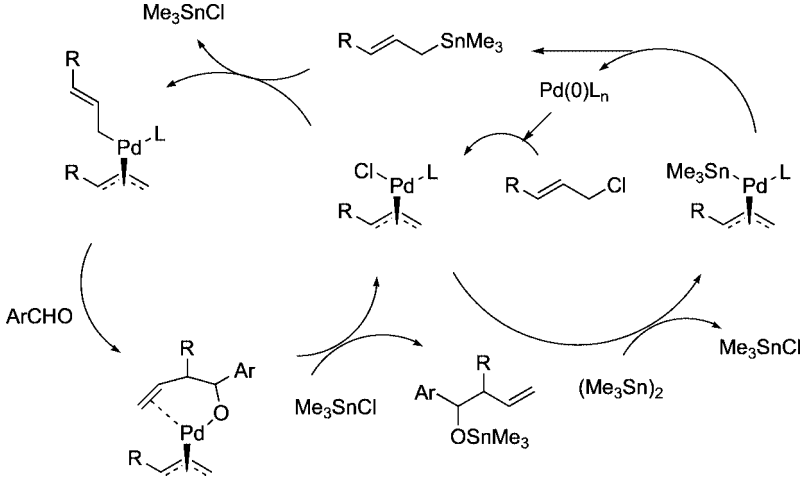
The intermediate $\eta^3$-allylpalladium complex is generated by the reaction of an allyl acetate (or chloride) with $(Me_3Sn)_2$ in the presence of $[(\eta^3\text{-allyl})PdCl_2]_2$ (Scheme 9). The bis-allylic system thus generated can then transfer a nucleophilic allyl fragment to the aldehyde. The reaction of bis(allylpalladium) reagents generally yields branched homoallylic alcohols with prevalent *anti* diastereoselectivity (Scheme 10). As expected, reactions with more reactive allyl substrates (e.g., with a 4-methoxyphenyl substituent at C-3) and electrophiles display lower stereoselectivity.




| R | Ar | Yield | *anti*/*syn* |
|---|---|---|---|
| H | $C_6H_5$ | 80 | 14:1 |
| F | 4-$NO_2C_6H_4$ | 78 | 10:1 |
| OMe | 4-$NO_2C_6H_4$ | 85 | 5:1 |
| OMe | 4-$MeC_6H_4$ | 57 | 18:1 |
| OMe | $C_6H_5$ | 60 | 19:1 |

Scheme 10.

The reaction is believed to proceed through either six-membered TS ϑ or **K**, both featuring a chair-like conformation, delivering the *anti* or *syn* adduct, respectively (Figure 5).




Scheme 9.

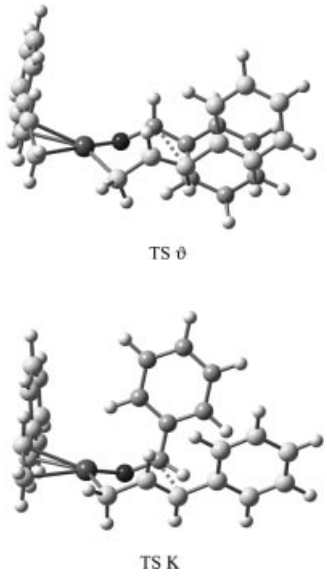



Figure 5. Cyclic six-membered calculated TS structures accounting for the observed stereoselectivity.

The stereochemical outcome of the reaction is therefore dictated by the characteristics of the substituents on the $\eta^1$-allyl moiety and on the aromatic aldehyde. More importantly, the relative stabilities of the two TSs is determined by the sterically demanding substituent on the $\eta^3$-allyl fragment. In TS ϑ, which would deliver the *anti* product, both the *trans*-phenyl groups occupy equatorial positions, whereas in TS **K**, which provides the *syn* product, the phenyl group in the $\eta^1$-allyl moiety is equatorially oriented and the phenyl group of the benzaldehyde is axial. The latter substituent thus displays a destabilizing steric interaction with the $\eta^3$-allyl complex, leading to a much higher activation energy barrier than that for the pathway along TS ϑ.

### 3.2 $\eta^1$-Allylpalladium Complexes

By using appropriate ligands on palladium, $\eta^1$-allylpalladium complexes are more stable than the corresponding $\eta^3$ complexes and in some cases can react as electrophiles.[17] Szabò recently reported the use of "pincer" complexes as strongly coordinating ligands capable of transferring electronic density onto the palladium atom, thus making the allylic fragment nucleophilic.[18]

In fact, tridentate coordination forces the allylic fragment to adopt an $\eta^1$ coordination. On the other hand, the aryl group of the pincer ligand induces a high electronic density on the metal by virtue of its strong σ coordination.

The $\eta^1$-allylpalladium complexes, prepared by reaction of stannanes **4a**,**b** and a palladium pincer complex PdPCP (Figure 6), led to high diastereoselectivity in the addition to aldehydes regardless of the catalyst employed (Scheme 11). The diastereomeric ratio depended on the nature of the allylstannane reagent and on the reaction conditions (Scheme 12).

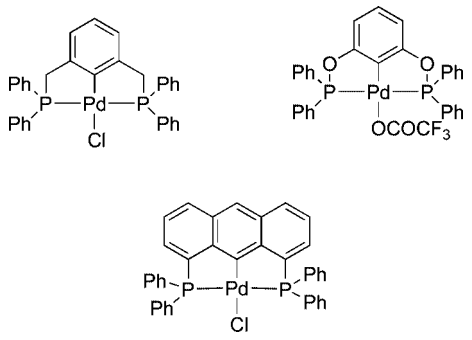
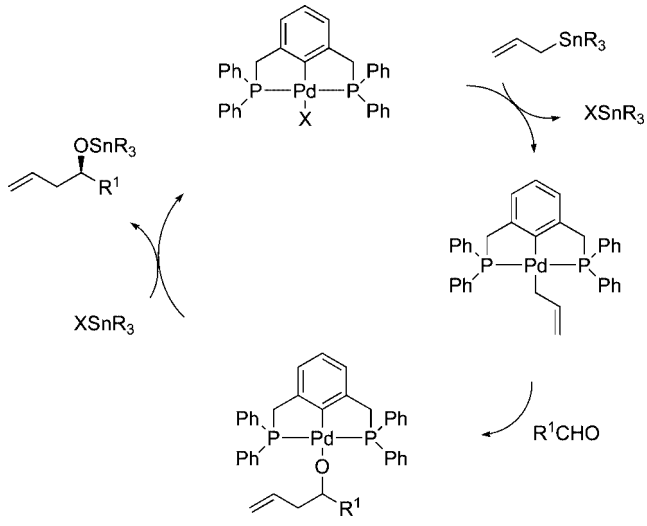
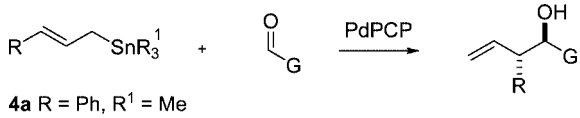


Figure 6. Pincer palladium complexes (PdPCP) employed in Szabó's studies.



Scheme 11.



**4a** R = Ph, $R^1$ = Me

**4b** R = Me, $R^1$ = Bu

| Allylstannane | G | Yield (%) | *anti*/*syn* |
|---|---|---|---|
| **4a** | $C_6H_5$ | 61 | 10:1 |
| **4a** | 4-$NO_2C_6H_4$ | 95 | 10:1 |
| **4a** | Cyclohexyl | 49 | 14:1 |
| **4b** | 4-$NO_2C_6H_4$ | 65 | 1:1 |
| **4b** | $C_6H_5$ | 57 | 1:1 |

Scheme 12.

The high stereoselectivity observed with cinnamylstannane was rationalized by calculating the TS geometry pertaining to electrophilic attack. DFT analysis clearly showed that the *anti* stereoisomer resulted from electrophilic attack via a six-membered cyclic TS in which the allylic terminal substituent and aldehyde reside on distinct axial and equatorial positions (Figure 7). In the more stable TS the bulky substituents are in a *trans*-diequatorial arrangement over the forming carbon–carbon bond, which leads to the *anti*

diastereomer. The steric effects of the phenyl substituents of the pincer ligand and the substituents of the aldehyde have a relatively weak effect on the product stereochemistry.

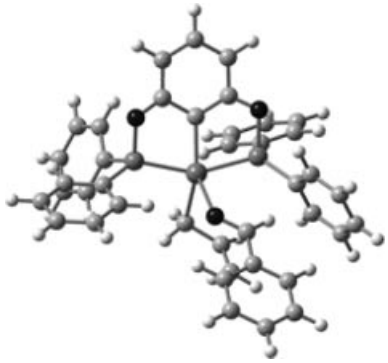


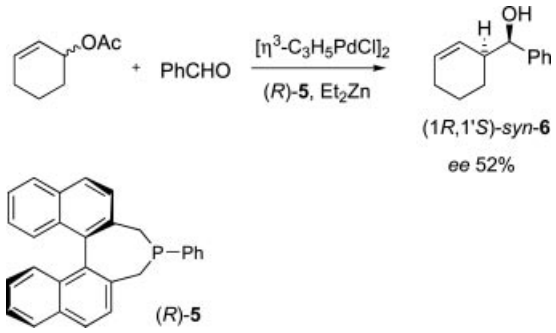
Figure 7. Optimized TS structure occurring in the $\eta^1$-allylpalladium-mediated aldehyde allylation.

## 4. Asymmetric Variants

Only a few examples of catalytic asymmetric carbonyl allylation by umpolung of $\eta^3$-allylpalladium complexes have been reported so far.[19] In the first case a chiral monodentate ligand, such as a monophosphane[20a] or phosphoramidite,[20b] was employed to control the enantioselectivity, in accord with a mechanism proposed by Tamaru to explain the stereoselectivity observed in the addition of cyclohexenyl acetates to benzaldehyde. As the transfer of a "hard" group from zinc to palladium takes place in one of the steps, closer attention to the Pd–Zn exchange mechanism was elicited. Preliminary studies suggested that an alkyl group is transferred from zinc to palladium prior to transmetallation, followed by elimination of diethylpalladium.

It was assumed that the chiral environment established during the alkyl transfer might account for the asymmetric induction on the hypothetical allylzinc intermediate. The enantiodiscriminating event was thus suggested to spawn from the asymmetric induction exerted on the purported transient allylzinc species by the chiral space wherein ethyl transfer occurs. If enantiodiscrimination was indeed occurring in the transfer of a "hard" ethyl group from zinc to palladium in an inner-sphere fashion, a chiral monophosphane would have been the asymmetric inducer of choice.

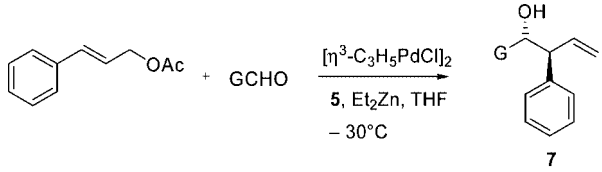
According to this scenario, in the first examples published by us in 2004, allylpalladium complexes generated from cyclohexenyl acetate and cinnamyl acetate were studied.[20a] Diethylzinc and benzaldehyde were used as the umpolung agent and the electrophile, respectively. The reaction indeed occurred diastereo- and enantioselectively when the monophosphane (*R*)-**5** was employed, affording (1*R*,1′*S*)-*syn*-**6** in 52% *ee* as a single diastereomer (Scheme 13).




Scheme 13.

The results observed for different leaving groups on the cyclohexenyl moiety suggested a marked "memory effect"[21] as the better the leaving group could ionize and depart from the allylic unit, the lower the *ee* value. Notably, cyclohexenyl trifluoroacetate afforded the corresponding addition product in the highest yield, but in only 10% *ee*.

Cinnamyl acetate proved to be an even better substrate in that a faster and more stereoselective reaction could be attained. The product from its addition to benzaldehyde, namely (1*R*,2*S*)-*anti*-**7**, was obtained in 70% isolated yield and 70% *ee* (Scheme 14) at –30 °C with 5 equiv. of $Et_2Zn$ (Scheme 14). The allylation of various aldehydes with cinnamyl acetate was then examined, showing excellent diastereo- and enantioselectivity.[22]




| G | Yield (%) | *anti*/*syn* d.r. | *ee* (%) |
|---|---|---|---|
| $C_6H_5$ | 70 | 99:1 | 70 |
| 4-$MeOC_6H_4$ | 80 | 98:2 | 65 |
| 4-$MeC_6H_4$ | 72 | 99:1 | 71 |
| 1-Np | 78 | 99:1 | 80 |
| *tert*-$C_4H_9$ | 57 | 99:1 | 45 |

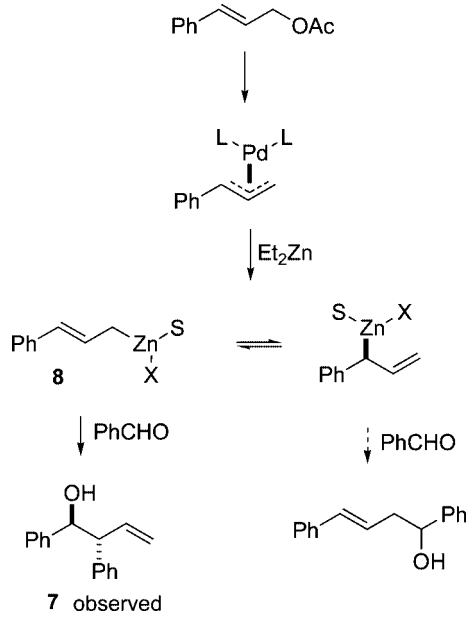
Scheme 14.

The electronic nature of the aromatic aldehydes affected the yield and enantioselectivity of the reaction. Electron-rich aldehydes showed higher yields but lower enantioselectivities, whereas 1-naphthaldehyde and 4-methylbenzaldehyde gave the corresponding homoallylic alcohols in good yields and enantiomeric excesses. In contrast, allylation of aliphatic 2,2-dimethylpropanal gave the corresponding adduct in low yield and enantiomeric excess.

The most interesting facet of the asymmetric modification of the allylation reaction can be found in the regio- and diastereoselectivity of the adduct, the organozinc reactant being attacked at the more substituted allylic terminus with complete *anti* selectivity. Indeed, Tamaru's mechanism predicts that (*E*)-cinnamyl acetate would react with benzal-

dehyde and the umpolung agent to deliver the branched product **7** in a 9:1 *anti*/*syn* diastereomeric ratio (Scheme 15).[13]

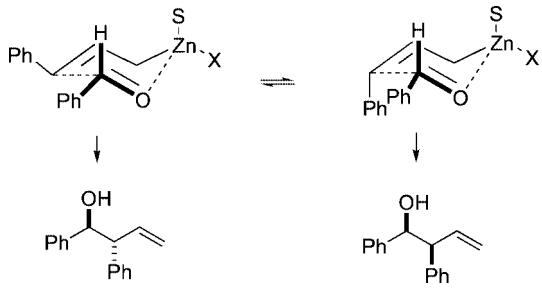



Scheme 15. S and X represent, respectively, the solvent and the counterion, for example, AcO.

The allylation process was thus assumed to proceed through a cyclic TS in which the phenyl substituent on the allyl moiety would occupy an equatorial position (Scheme 16).

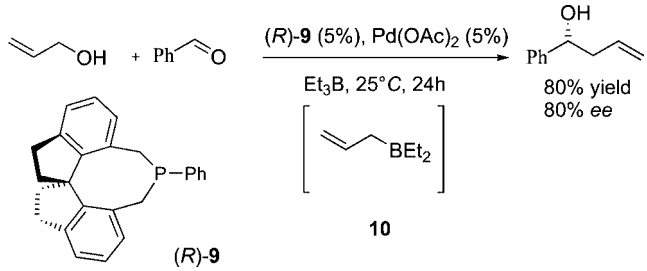
In experiments on asymmetric umpolung performed in our laboratories, cinnamyl acetate afforded the *anti* product in an unprecedented 70% *ee*.[16] The outcome was remarkable as, apparently, on the basis of Tamaru's hypothesis, the *anti* diastereomer would be formed from the achiral organozinc reagent **8**.

Even more astonishing is the result reported by Zhou and co-workers using allyl alcohol (prop-2-en-1-ol) as a substrate.[23] According to Tamaru, allyl alcohol could react




Scheme 16.

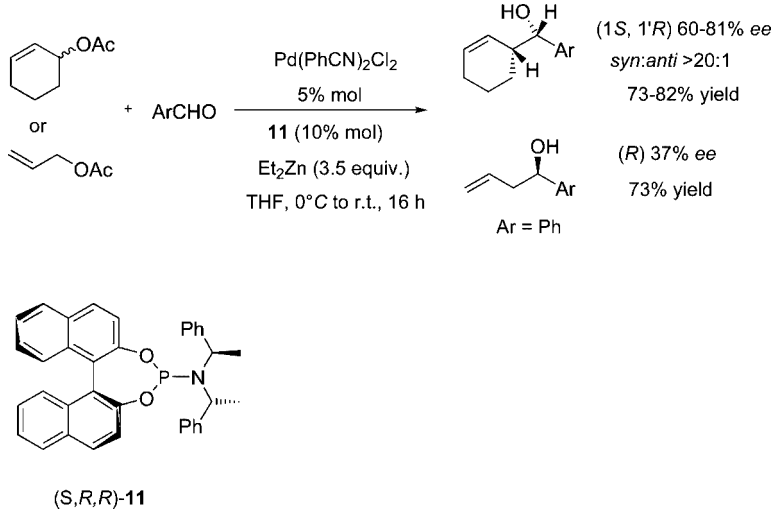
under umpolung conditions if $Et_3B$ is used as the umpolung reagent, thanks to the intermediacy of allylborane **10** (Scheme 17). In the event, allyl and cinnamyl alcohols reacted with PhCHO in the presence of the chiral monophosphane **9**, delivering the corresponding addition products in 80% *ee*.[23]




Scheme 17.

This result is not accounted for by the hitherto discussed TSs in that the $\eta^3$-allylpalladium system would give rise to an achiral allylborane intermediate such as **10**, which would be incapable of generating products with any enantioselectivity. Analogous results were obtained by Feringa and co-workers at the beginning of 2006 using chiral monodentate phosphoramidite ligands like **11** (Scheme 18).[20b]

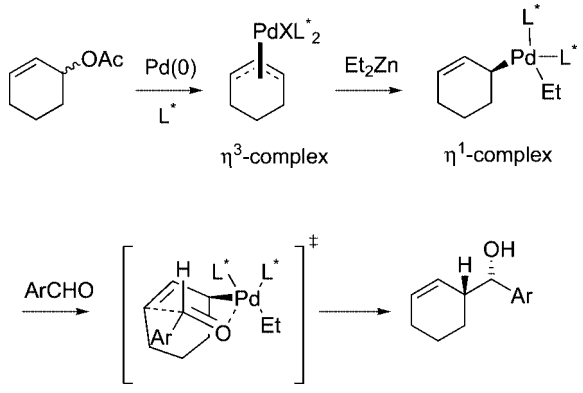
Feringa's protocol worked efficiently for a range of aromatic and heteroaromatic aldehydes; yields and enantioselectivities from moderate to good along with very high




Scheme 18.

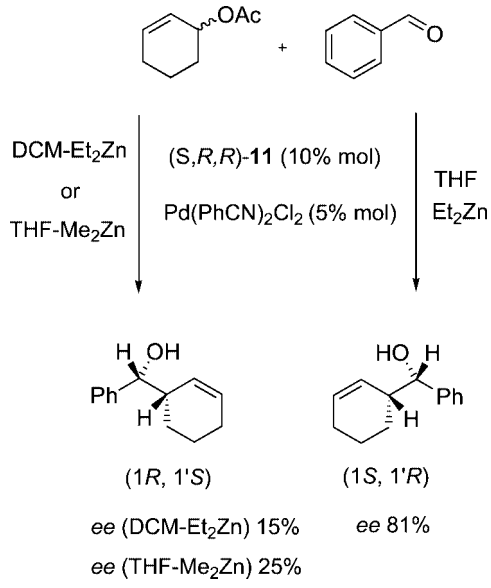
*syn* selectivity were obtained. However, this $Et_2Zn$-mediated protocol is not applicable to aliphatic aldehydes or ketones. The catalyst system is also sensitive to the identity of the allyl fragment, with cyclopentenyl and allyl acetates giving lower enantioselectivities. The mechanism for this kind of allylation reaction, proposed by the same author, involves an $\eta^1$-allylpalladium species which electrophilically allylates benzaldehyde. The required nucleophilic character of the allyl fragment would be achieved by $Et_2Zn$ alkylation of the corresponding $\eta^3$-allylpalladium complex which could proceed enantioselectively (Scheme 19). A Zimmermann–Traxler-like TS would thus explain the observed absolute stereochemistry of the products.




Scheme 19.

Note, during his optimization studies, Feringa noticed inversion of enantioselectivity by changing either the solvent from THF to DCM or the umpolung reagent from $Et_2Zn$ to $Me_2Zn$ while maintaining the same source of chirality and the same palladium catalyst (Scheme 20).[24] This suggests that a more complex scenario, involving either zinc–palladium or boron–palladium aggregates, cannot be ruled out at this stage, requiring additional detailed studies to investigate this further.

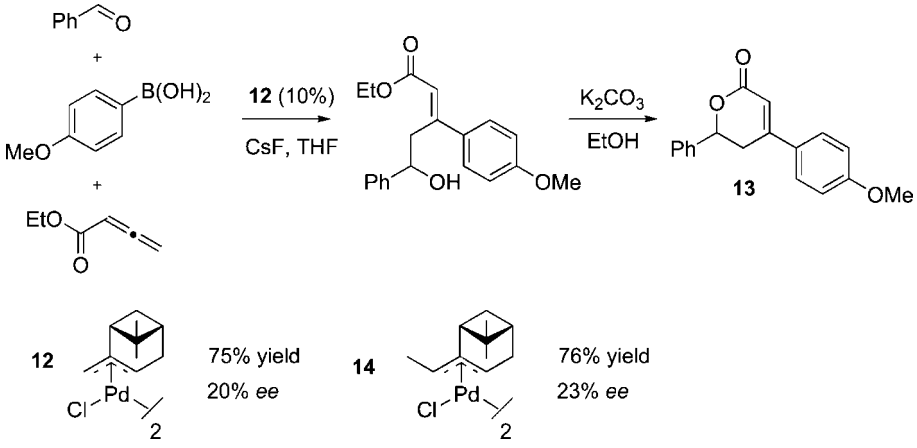
The second, conceptually different example of asymmetric umpolung, involving the mediation of a bis(allylpalladium) complex, was recently reported by Malinakova and co-workers.[25] In this case, the enantioselective allylation




Scheme 20.

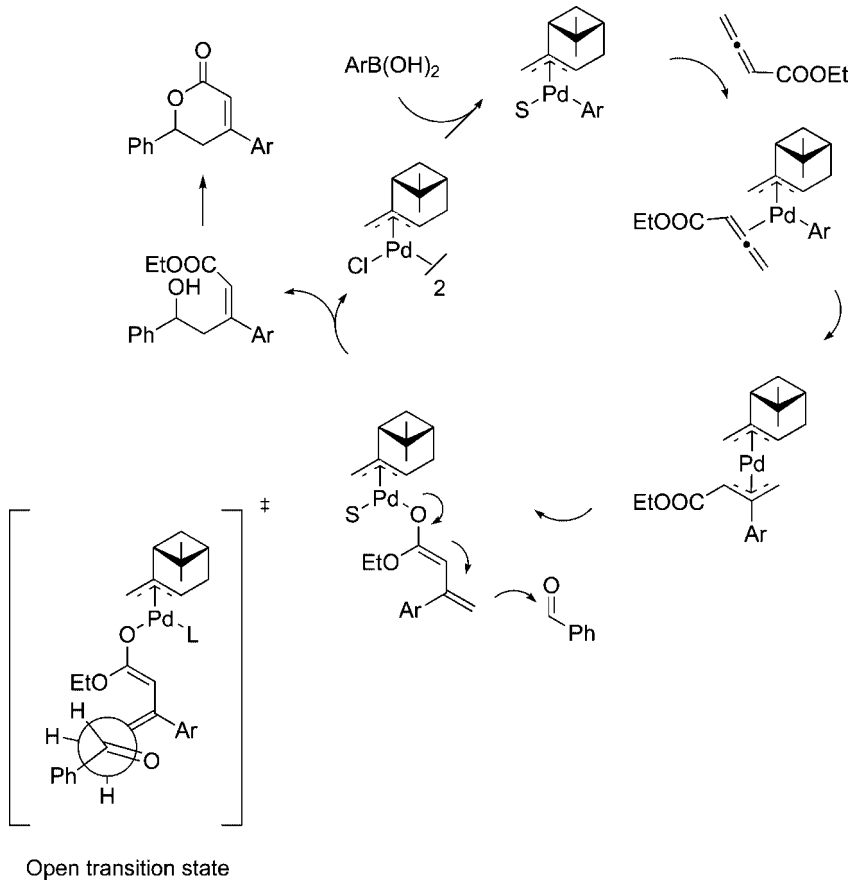
species was prepared by reaction of bis($\eta^3$-allylpalladium) complex **12**, obtained from β-pinene as a chiral ligand, with a (aryl, vinyl, heteroaryl) boronic acid and an allene in the absence of any phosphane ligand. Caesium fluoride and aldehyde were then added to the reaction mixture. The formation of an asymmetric complex, consisting of a transferable allyl fragment and a nontransferable allyl ligand, derived from the β-pinene moiety, underlines the peculiarity of the approach pursued by Malinakova and co-workers. As an example, 4-methoxyphenylboronic acid was treated with ethyl buta-2,3-dienoate and benzaldehyde in the presence of CsF and the chiral complex **12**, delivering lactone **13** in 75% isolated yield, albeit in a modest 20% *ee* (Scheme 21). The same enantioselectivity (23% *ee*) was achieved by employing the methyl-substituted chiral complex **14**.

This methodology is still in its infancy and a convincing explanation of the stereochemical outcome has yet to be advanced. The low efficiency of the asymmetric transfer was rationalized by invoking an open TS lacking the coordination of aldehyde to palladium (Scheme 22).




Scheme 21.




Scheme 22.

## 5. Conclusion and Future Perspectives

Although the palladium-catalyzed diastereoselective allylation of carbonyl compounds by an umpolung approach is a well-established process, the corresponding asymmetric version still remains a promising field of research. Several authors, including us, have demonstrated that good enantioselectivity can be achieved when the $Et_2Zn$-mediated allylation process occurs in the presence of a chiral monophosphane or phosphoramidite ligand. At a first glance, the ligand could intervene in the enantiodifferentiating step that takes place in the inner-sphere of the surmised chiral complex. However, more recent results seem to indicate that chiral nucleophilic $\eta^1$-allyl(alkyl)palladium intermediates, formed by $Et_2Zn$ alkylation of the corresponding $\eta^3$-allylpalladium complexes, are involved in the reaction pathway. Moreover, the possibility that the umpolung reaction proceeds via a more complex zinc–palladium aggregated species should also be considered; additional detailed mechanistic studies are thus required.

With this review we hope to pave the way for further development and successes in the catalytic asymmetric version of umpolung. We foresee that in the next few years a constant growth will take place, taking advantage of novel ligands. In particular, indium salts or organometallic derivatives thereof are expected to exert greater stereochemical control in the addition process. The application of chiral pincer ligands should also allow high enantioselective control to be achieved with either $\eta^1$-allylpalladium or bis(allylpalladium) complexes.

## Acknowledgments

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