Umpolung of π-Allylpalladium Complexes

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Abstract

It is widely accepted that π-allylpalladium complexes (η^3-allylPdX, X = halides, OAc, OCOOR,…etc) act as an electrophile in nature allowing the attack of various nucleophiles (Nu¯) leading to the formation of the allylated products (allyl-Nu). However, in the presence of a reductant, the electrophilic reactivity of π-allylpalladium complexes is converted to nucleophilic one; referred as umpolung. In this review, the recent progress made in the palladium-catalyzed umpolung of π-allylpalladium complexes is described.

Keywords: Electrophilic π-allylpalladium complex; Reductant; Nucleophilic π-allylpalladium complex; Umpolung; Carbonyl compounds

1. Introduction

It is widely accepted that a mono π-allylpalladium complex acts as an electrophile in nature allowing the attack of various nucleophiles, leading to the formation of allylated products (eq. 1). These reactions are commonly referred as Tsuji-Trost reaction. However, in the presence of a reductant, the electrophilic reactivity of π-allylpalladium complexes is converted to nucleophilic one by transmetalating them into other organometallics or by reducing them with electrochemical means. In situ generation of nucleophilic allylmetal species or allyl anion from electrophilic mono π-allylpalladium complexes leads to the reversal of reactivity. This phenomenon of reversing the reactivity is known as umpolung of π-allylpalladium complexes (eq. 2). In 1999, an excellent review appeared on the above mentioned topic. In this review, the recent progress made after 1999 in the palladium-catalyzed umpolung of π-allylpalladium complexes is described. This review also includes the old examples which were not cited in the previous review. In some cases, to keep the chemistry complete, there may be some minor overlap with the contents in previously published reviews. It should be noted that bis-π-allylpalladium complex acts as a nucleophile in contrast to mono π-allylpalladium complexes,

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however, the present review will focus only on the umpolung of mono \( \pi \)-allylpalladium complexes.

\[
\text{Nu} \xrightarrow{\text{Pd-Ln}} \text{Nu} \quad (1)
\]

\[
\text{Pd-Ln} \xrightarrow{\text{M or MX}_2} \text{M-Ln} \xrightarrow{\text{RCHO}} \text{OH} \quad (2)
\]

2. Umpolung of \( \pi \)-Allylpalladium Complexes

Allylic substrates undergo palladium catalyzed allylation with carbonyl compounds in the presence of various reductants to give the homoallyl alcohols (eq. 3). Nowadays, many reductants are known to affect this conversion, for example, \( \text{Et}_2\text{Zn}, \text{SnCl}_2, \text{InI}, \text{SmI}_2, \text{Et}_3\text{B} \ldots \) etc. There are also few reports on the allylation of carbonyl compounds with allylic acetates via electrochemical reduction. \(^9\)

\[
\text{R-CHO} + \xrightarrow{\text{cat. Pd}} \xrightarrow{\text{reductant}} \text{OH} \quad (3)
\]

Recent research shows that hexamethylditin can also be used for inducing umpolung in the \( \pi \)-allylpalladium complexes \(^{10}\). Palladium-catalyzed allylation of aldehydes with functionalized allyl chlorides and allyl acetates was achieved in the presence of \( \text{Sn(Me}_3)_2 \) (eq. 4). The reaction occurred with very high regioselectivity at the branched allylic terminus. Not only aldehydes but also imines could be allylated under these conditions with high regioselectivity (eq.5).

\[
\text{Ph} \xrightarrow{\text{Cl}} \xrightarrow{\text{CHO}} \xrightarrow{[\eta^1\text{-allylPdCl}_2 (5%)]} \xrightarrow{\text{Sn(Me}_3)_2 (1.2 \text{ equiv})} \text{Ph} \quad (4)
\]

\[
\text{Ph} \xrightarrow{\text{Cl}} \xrightarrow{\text{NHBs}} \xrightarrow{[\eta^1\text{-allylPdCl}_2 (5%)]} \xrightarrow{\text{Sn(Me}_3)_2 (1.2 \text{ equiv})} \text{Ph} \quad (5)
\]

The same research group later reported an efficient procedure for palladium-catalyzed electrophilic substitution of allyl acetates in the presence of \( \text{bis(pinacolato)diboron} \).\(^{11}\) These reactions proceeded with an excellent regioselectivity and with a remarkably high stereoselectivity. The catalytic allylation took place via palladium-catalyzed formation of allyl boronates, from \( \pi \)-allyl palladium complexes and
diboronates, which subsequently reacted with aldehyde (eq. 6) and imine (eq. 7) electrophiles to afford the corresponding homoallylic alcohol and amine, respectively. Various functionalized allyl acetates are known to react with aldehyde or imine electrophiles to give the alkylation products with high regio- and stereoselectivity.

$$\text{Ph-CH}_2\text{CH(OAc)} + \text{CHO} \xrightarrow{\text{Pd}_2\text{(dba)}_3 (6 \text{ mol\%}), DMSO, 86\%} \text{OH} \quad \text{(6)}$$

$$\text{Ph-CH}_2\text{CH(Cl) + Ph-CH=N}(\text{Ph}) \xrightarrow{\text{Pd}_2\text{(dba)}_3 (6 \text{ mol\%}), DMSO, 91\%} \text{NHPh} \quad \text{(7)}$$

B$_2$O$_3$ = benzenesulfonyl

A highly diastereoselective synthesis of (-)-erythrodiene was achieved via an intramolecular palladium catalyzed umpolung reaction as the key step (eq.8).[12] It was found that Pd(OAc)$_2$/Bu$_3$P was a superior catalyst for this reaction, compared to Pd(PPh$_3$)$_4$. In the presence of an excess amount of Et$_2$Zn in Et$_2$O, the organozinc intermediate was quenched with iodine to yield the desired iodo compound in 90% yield with excellent diastereoselectivity. The dehydroiodination from the iodide with KO'Bu yielded natural (-)-erythrodiene.

$$\text{OAc} \quad \text{i) Pd(OAc)$_2$, Bu$_3$P, Et$_2$Zn, Et$_2$O} \quad \text{90\%} \quad -\text{erythrodiene}$$

$$\text{d}r = 95:5$$

The reaction of electron-deficient imines with allylic substrates in the presence of a catalytic amount of palladium(0) complex and indium(I) iodide gave the corresponding alkylation products.[13] High diastereoselectivities are reported for various allylic substrates. It is interesting to note that selective formation of the $\alpha$-adduct was observed in anhydrous THF, on the other hand, the use of H$_2$O/THF resulted in the formation of the $\gamma$-adduct (eq. 9).
Similar to allylic substrates, propargylic substrates also undergo similar type of umpolung reactions. The propargylation of carbonyl compounds are known to proceed smoothly at room temperature by stirring a solution of a propargylic benzoate, carbonyl compounds, diethylzinc and tetrakis- (triphenylphosphine) palladium in THF (eq10)\(^{[14]}\). However diastereoselectivity was poor in those cases. For example, when \(R^1 = \text{Me}\) and \(R^2 = \text{H}\), the corresponding product was obtained in 70% yield as a 1:1 mixture of syn and anti isomers. It was reported that not only benzoates but also other leaving groups such as -OTs, -OCOOME, and -Br could be utilized with similar efficiency. In another report by Mikami et al. it was reported that propargylic phosphonates also undergo similar type of reaction, albeit, with Sml\(_2\) as a reductant (eq 11).\(^{[15]}\)

An intramolecular coupling reaction between propargyl esters and carbonyl functionalities tethered by a carbon chain was mediated by Pd(0)/samarium diiodide leading to the formation of homopropargyl cycloalkanols (eq. 12).\(^{[16]}\) The reaction proceeded through the allenylpalladium complex which was reduced by two equiv. of Sml\(_2\) to the organosamarium intermediate that underwent intramolecular cyclization to afford the cyclic homopropargyl alcohols upon protonation and aqueous workup of an initially formed samarium alkoxide.
The important consequence of the umpolung chemistry is that the chirality can be easily transferred from chiral substrates to the products. For example, when (R)-mesylate was treated with 5 mol % of Pd(PPh₃)₄, 2.4 equiv. of Et₂Zn, and 1 equiv. of cyclohexane carboxaldehyde in THF at 0 °C to room temperature, the corresponding homopropargyl alcohol was obtained with 95% ee (eq. 13). The addition proceeded with excellent anti selectivity in 85% yield. As the chirality is transferred from substrates to products, it was surmised that the reaction proceeded with chiral allenylzinc intermediate.

If allyl alcohols themselves can be directly used as allylating agents, the step to prepare their esters or carbonates is no longer needed and the overall process of the allylation becomes highly efficient and atom economical. It is obvious that an allylic alcohol can be used as an allylating agent only in the presence of activators which can coordinate with a hydroxyl group, thereby increasing the leaving group ability of the hydroxyl group. In most cases, a reductant exhibits the function of activators, thereby making this process feasible. For example, the use of SnCl₂ and Et₃B allows the use of allyl alcohols for the allylation of carbonyl compounds. As can be seen from (eq.14), aromatic aldehydes, for instance, benzaldehyde undergo palladium catalyzed allylation with cinnamyl alcohol in the presence of Et₃B. However, the reaction was not applicable to aliphatic aldehydes; aliphatic aldehydes undergo competitive nucleophilic and electrophilic allylation under similar conditions. The same authors later reported that the nucleophilic allylation of aliphatic aldehydes with allyl alcohols proceeded selectively just by substituting Et₃B to Et₂Zn (eq.15). Next, the authors envisaged that the reaction conditions that were successful for the activation of allyl alcohols should be applicable to the activation of allyl ethers because an ether group is a much better leaving group than a hydroxyl group. Indeed, allyl 2-tetrahydrofuryl ether turned out to readily effect nucleophilic allylation of ω-formylalkanolate formed in situ to furnish 1,4-dihydroxy-6-heptene in excellent yield (eq.16).
Tamaru et al. reported\textsuperscript{[21]} that a catalytic system, \( \text{Pd(OAc)}_2 \) (10 mol %)-\( \text{P(n-Bu)}_3 \) (20 mol %)-\( \text{Et}_3\text{B} \) (360 mol %) using allylic alcohol promotes the allylation of anisidine-imines of aromatic and aliphatic aldehydes to furnish homoallylamines in good to moderate yields (eq.17). In contrast to many precedents indicating that phenyl group generally displays better stereoselectivity than methyl group does, in the present case, methyl group showed higher anti-selectivity than phenyl group (eq 18 vs 19).

In the case of symmetric bis-allyl alcohols one of the allyl alcohol moieties undergoes electrophilic allylation at the \( \alpha \)-position of aldehydes and the other remaining allyl alcohol moiety, on the other hand, selectively reacts as an allylic nucleophile toward the aldehyde (C=O) to give 3-methylenecyclopentanols in good yields (eq. 20).\textsuperscript{[22]} These two processes can be catalytically promoted by \( \text{Pd(OAc)}_2/\text{PPh}_3 \) in combination with triethylborane. The similar reaction was extended to imines; the corresponding bis-benzyl ether undergoes
sequential amphiphilic (nucleophilic and electrophilic) alkylation with aldimines furnishing 3-methylene-2-phenyl-pyrrolidine (eq. 21)[23]

\[
\text{HO} + \text{CHO} \xrightarrow{\text{Pd(OAc)\textsubscript{2}, PPh\textsubscript{3}, Et\textsubscript{3}B, Et\textsubscript{3}N, LiCl, THF, rt}} \text{OH}
\]

70-88%

The first palladium catalyzed enantioselective addition of allyl acetate to aldehydes was reported by Zanoni and co-workers. They reported that a catalytic amount of a Pd complex, derived from \((\eta^3\text{C\textsubscript{3}H\textsubscript{5}PdCl})\textsubscript{2}\) and a chiral monophosphane, effectively catalyzes the allylation of benzaldehyde with cinnamyl acetate in the presence of Et\textsubscript{2}Zn (eq.22).[24] The highest enantioselectivity up to 70% was achieved, however, the substrate scope was not investigated.

\[
\text{OAc} \xrightarrow{\text{Pd(OAc)\textsubscript{2} (10%), nBu\textsubscript{3}P (20%), Et\textsubscript{3}B (480%), 80%}} \text{OH}
\]

70% yield, 70% ee

Recent report from Zhou et al.[25] revealed that allyl alcohols can also be used directly for asymmetric umpolung of π-allyl palladium complexes (eq.23). They prepared a novel chiral monodentate spiro phenylphospholane ligand and tested for the reaction between cinnamyl alcohol and various aromatic as well as aliphatic aldehydes. This ligand has proven to be efficient for Pd-catalyzed enantioselective allylation of aldehydes with allylic alcohols. Aromatic, heteroaromatic, and aliphatic aldehydes gave homoallylic alcohols in good enantioselectivities (up to 83% ee) and with excellent anti diastereoselectivities (up to 99:1 dr).

\[
\text{R}^1\text{-OH} + \text{R}^2\text{-CHO} \xrightarrow{\text{Pd(OAc)\textsubscript{2} (5%), Et\textsubscript{3}B, THF, 25 \degree C}} \text{OH}
\]

dr: up to 99:1

ee: up to 83%
3. Miscellaneous Reactions

The palladium catalyzed addition of the N-acetyl cycloadduct to aliphatic aldehydes in the presence of 1.5 equiv. of InI afforded the cis-1,4 products in good yields and with high regio- and stereoselectivity (eq. 24). In a similar manner, aromatic aldehydes are also known to react with the N-acetyl cycloadduct favouring the cis-1,4-product over trans-1,4-product.

\[
\text{N} \quad \text{O} \\
\text{R} \\
\text{H} \\
\text{O} \\
\text{146} \\
Pd(OAc)_2 (5%), PPh_3 (5%) \\
\text{InI (1.5 eq), THF/H}_2\text{O (3:1)} \\
\text{cis-1,4-product} \\
\text{1.1:1 to 7:1 (dr on C6)} \\
(24)
\]

The formation of allylindium species by transmetallation of π-allylpalladium complexes generated from aryl iodides and allenes, was reported by Grigg et al. The resultant allylindium species subsequently added to carbonyl compounds affording homoallylic alcohols (eq. 25).

\[
\text{Ar-I} + \begin{array}{c}
\text{R} \\
\text{R}^1 \text{H} \\
\text{O} \\
\text{Pd(0), In, DMF} \\
\text{Ar} \\
\text{R} \\
\text{R}^1 \text{OH} \\
\text{up to 75% yield} \\
\text{PhCHO, In}
\end{array} \\
(25)
\]

Grigg and coworkers later reported the use of the above reaction to a palladium catalyzed cyclisation-termolecular queuing cascade. This cascade involves palladium catalyzed cyclisation of an aryl iodide moiety onto proximate alkynes followed by allene insertion. The resulting π-allylpalladium(II) species then undergoes transmetallation with indium metal generating an allylindium species which subsequently adds to an aldehyde component, affording heterocyclic diene (eq. 26).

\[
\text{Pd(0), In, DMF, 52%} \\
\text{I} \\
\text{O} \\
\text{Ph} \\
\text{H} \\
\text{O} \\
\text{XPd} \\
\text{XPd} \\
\text{PhCHO, In} \\
(26)
\]
Treatment of optically active 3-alkyl-2-vinylaziridines and aldehydes with InI in the presence of Pd(PPh$_3$)$_4$ gave chiral allylindiums bearing an amino group at the δ-position, which reacted with several aldehydes in highly regio- and stereoselective manner to afford the amino alcohols possessing three contiguous chiral centers in good yields (eq. 27). Various reducing agents such as Et$_2$Zn, SnCl$_2$, EtI$_2$, InI were tried by the authors. Among them the use of InI proved best. Similar to 2-vinylaziridines, vinyl epoxide could also be used. The reaction was performed in one-pot style, as demonstrated for the reaction between vinyl epoxide and diphenylacetaldehyde. Exposure of the organic substrates to Pd(acac)$_2$/nBu$_3$P at room temperature for 3 h, followed by injection of Et$_3$B and stirring for 3 days at room temperature, furnishes the 2-vinylcyclobutanol derivative in 55% isolated yield (eq. 28).

![](image)

Treatment of 3-alkyl-2-ethynylaziridines with InI in the presence of Pd(PPh$_3$)$_4$ and H$_2$O gave allenylindium reagents which reacted in situ with aldehydes affording 2-ethynyl-1,3-amino alcohols, bearing three contiguous chiral centers in good yields (eq. 29).

![](image)

4. Perspective

In general, mono π-allylpalladium complexes act as an electrophile in nature. However, in the presence of reductant, these mono π-allylpalladium complexes are converted into nucleophilic allylating agents, thereby allylating various carbonyl compounds. Recent progress showed that catalytic asymmetric versions of these processes are also possible as maximum ee up to 83% was achieved for the allylation of aldehydes with allylic substrates. Although the nucleophilic addition of Grignard
reagents and organolithiums to carbonyl compounds is a reliable process, the present reaction also gains much interest to organic chemists. Not only π-allylpalladium complexes but also π-allylnickel complexes undergo transmetalation with indium iodide widening the use of this concept. It is expected that future development in umpolung enatioselective processes.

5. References


