1,4-Additions of arylboron, -silicon, and -bismuth compounds to α,β-unsaturated carbonyl compounds catalyzed by dicaticionic palladium(II) complexes*

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Abstract: An enantioselective synthesis of cyclic and acyclic β-aryl ketone and aldehydes via Pd(II)-catalyzed 1,4-addition of Ar·m [m = B(OH)2, BF3K, Si(OMe)3, SiF3, BiAr2] to α,β-unsaturated ketones or aldehydes is described. The catalytic cycle involves transmetallation between Ar·m and Pd complexes as a key process, the mechanism of which is discussed on the basis of characterization of the transmetallation intermediate and electronic effect of the substituents. The enantioselection mechanism and efficiency of a chiraphos ligand for structurally planar α,β-unsaturated ketones are discussed on the basis of the X-ray structure of the catalyst and results of density functional theory (DFT) computational studies on the model of coordination of the substrates to the phenylpalladium(II)/(S,S)-chiraphos intermediate.

Keywords: dicationic Pd catalyst; asymmetric 1,4-addition; arylboron compounds; transmetallation; enantioselection mechanism.

INTRODUCTION

Transmetallation between organometallic reagents and transition metals is a fundamental process involved in metal-catalyzed C–C bond-forming reactions. It is the first step in metal-catalyzed 1,4-addition of organic electrophiles to α,β-unsaturated carbonyl compounds [1] and the second step in the Pd- or Ni-catalyzed cross-coupling reactions of organoboron compounds with carbon nucleophiles [2]. In this field, we recently reported a new catalytic cycle starting from transmetallation to give an arylrhodium(I) or -palladium(II) intermediate for 1,4-addition of organoboronic acids to electron-deficient alkenes [3,4]. Rh(I) complexes are found to be excellent catalysts for the 1,4-addition of aryl or 1-alkenyl boron [4,5], silicon [6], tin [7], titanium [8], zinc [9], zirconium [10], and indium [11] compounds to α,β-unsaturated carbonyl compounds and to other activated or inactivated C–C [12], C–O [13,14], and C–N [15,16] double bonds or triple bonds. Here, we wish to review our efforts on 1,4-addition of ArB(OH)2, [ArBF3]K, ArSiX3 (X = MeO, F) or Ar2Bi to α,β-unsaturated carbonyl compounds in an aqueous medium via transmetallation between R3·m (m = B, Si, Bi) and dicaticionic Pd(II) complexes such as [Pd(dppe)(PhCN)2]2+ (Scheme 1) [3,17]. The enantioselective reactions were
achieved by \([\text{Pd(chiraphos or dipamp)(PhCN)}]^{2+}\) catalysts. 2-Cyclopentenone and acyclic enones possessing an aryl group at the \(\beta\)-carbon which each have a planar conformation, gave high ee with the chiraphos catalyst. On the other hand, the dipamp catalyst resulted in a high order of enantioselection for the skewed conformations of 2-cyclohexenone and 2-cycloheptenone.

\[
\begin{array}{cccc}
\text{1} & \xrightarrow{\text{[Pd}^{2+}\text{]}} & \text{2} & \xrightarrow{\text{R}^{3}\text{m}} & \text{3} \\
\end{array}
\]

\(m = \text{B(OH)}_{2}, \text{BF}_{3} \text{K}, \text{Si(OMe)}_{3}, \text{SiF}_{3}, \text{Bi} \text{Ar}_{2}^{+}\)

\(\text{R}^{1}, \text{R}^{2} = \text{H, alkyl, alkenyl, aryl}\)

\(\text{R}^{3} = \text{aryl}\)

Scheme 1 1,4-Additions of organoboron, -silicon, and -bismuth compounds catalyzed by dicationic Pd complexes.

**CATALYTIC CYCLE**

Boron compounds are attractive reagents in organic syntheses due to their high degree of thermal stability and air stability for isolation or handling and their compatibility with a wide range of functional groups, but transmetallation to transition metals is very slow due to low nucleophilicity of the organic group on those nonmetal elements. However, they transfer the organic groups to Pd(II) or other transition metals by one of the following three processes (Scheme 2) [18]. The addition of a base such as alkoxy, hydroxy, or fluoride anion exerts a remarkable accelerating effect on the cross-coupling reactions of organoboron compounds (eq. 1). Thereby, the coordination of a negatively charged base enhances the nucleophilicity of the organic group so that ligand exchange proceeds smoothly via a \(\text{S}_{\text{E2}}\) (cyclic) transmetallation state. The second process is transmetallation to \([\text{M}]\)-OR complexes (eq. 2). Due to the high basicity of \([\text{M}]\)-OR complexes, transmetallation takes place without any assistance of a base. Thus, cross-coupling reactions often proceed under neutral conditions for organic electrophiles, directly yielding RO–Pd complexes via oxidative addition. Indeed, cross-coupling reactions of boron compounds with allylic acetates, allylic carbonates, 1,3-butadiene monoxide, propargyl carbonates, acetic anhydrides, and phenyl trifluoroacetate have been carried out in the absence of a base. The third process is transmetallation to cationic transition-metal complexes (eq. 3). Cross-coupling reactions of

\[
\begin{align*}
\text{[M]} & \xrightarrow{\text{X}} \text{[M]–[R]} \\
\text{[M]} & \xrightarrow{\text{[M]-OR'}} \text{[M]-[R]} \\
\text{[M]} & \xrightarrow{\text{H}_{2}\text{O}} \text{[M]-[R]} \\
\end{align*}
\]

\(\text{M}=\text{Pd(II), Ni(II), Rh(I); X}=\text{halogen; Y}=\text{HO}^{+}, \text{RO}^{−}, \text{F}^{−}\)

\(\text{M}=\text{Pd(II), Rh(I), Re(I); R}^{=}=\text{H, Me, Ac}\)

\(\text{M}=\text{Pd(II), Pt(II)}\)

Scheme 2 Transmetallation between organoboron compounds and transition-metal complexes.
boron compounds with Ph$_3$BF$_4$ or Ar$_2$BF$_4$, which affords an Ar-[Pd]$^+$ intermediate via oxidative addition, have been carried out in the absence of base.

Another example reported in this category is a stoichiometric reaction between [Pt(S)$_2$(PEt$_3$)$_2$][CF$_3$SO$_3$]$_2$ (S = MeOH or H$_2$O) and [Ph$_3$B]Na, Ph$_3$B or PhB(OH)$_2$ giving [Pt(Ph)(S)(PEt$_3$)$_2$]$^{2+}$.

Transmetallation between [Pd(dppe)(PhCN)$_2$](BF$_4$)$_2$ and PhB(OH)$_2$ provides a monocationic arylpalladium(II) complex [Pd(Ph(dppe)(S))$^+$ (S = H$_2$O, PhCN) which was isolated as a triphenylphosphine complex [3c]. Thus, a catalytic cycle analogous to that of Rh catalysts was proposed (Fig. 1) [3c]. Addition of R$_3$-m to enone in an aqueous solvent gave a 1,4-addition product via a sequence of transmetallation to give 8, insertion of an enone into the Ar–Pd bond, giving a C- or O-bound enolate (9, 10) and, finally, hydrolysis of 10 with water. The cationic Pd(II) catalysts meet the following requirements to develop a catalytic cycle in aqueous media. (i) The transmetallation to Pd(II)-halogen complexes, which is a key process involved in Pd-catalyzed cross-coupling reactions of organoboron compounds, requires the presence of bases, but they smoothly react with dicationic Pd(II) complexes at temperatures lower than 20 °C under neutral conditions. (ii) The presence of a vacancy in the square planar Pd(II) center causes marked rate enhancement toward alkene insertion over those of neutral complexes [19]. (iii) Unlike neutral Pd enolates, the cationic Pd(II) enolates exist in solutions as equilibrating C- and O-bound tautomers and are highly susceptible to hydrolytic cleavage. Thus, they selectively yield 1,4-addition products in the presence of water without formation of Heck coupling products via β-hydride elimination.

Fig. 1 Catalytic cycle of 1,4-addition catalyzed by Pd(2+).

**PALLADIUM(II)-CATALYZED 1,4-ADDITION**

Although the benzonitrile complexes (11–13) are bench-stable catalysts that require no further activation for ArB(OH)$_2$ and [ArBF$_3$]K, the corresponding nitrile-free complex (14) is a more active catalyst effective for transmetallation of ArSiX$_3$ (X = OMe, F) [3]. Chemical oxidation of Pd(dba)$_2$ with Cu(BF$_4$)$_2$ in the presence of dppe is convenient for in situ preparation of 14 (Scheme 3) [3c]. Another method is ligand exchange between a nitrile complex and Cu(BF$_4$)$_2$ or other Lewis acids. Since pre-purified catalysts are generally required for asymmetric reactions, this ligand exchange method would be convenient for in situ generation of nitrile-free chiral catalyst from stable and isolable complexes such as 12 and 13. Since both the transmetallation and insertion steps involve dissociation of one ligand from a square planar four-coordinated complex, these complexes bearing a weakly donating ligand (S = H$_2$O, solvent) will react faster than nitrile complexes. The catalyst efficiency is specific for bis-
phosphines bridged by two carbon atoms since the complexes possessing a dpmm, dppp, dppb, or binap ligand result in almost no product. Thus, Pd complexes of dipamp and chiraphos (12, 13) are catalysts that meet this requirement.

The results of asymmetric 1,4-additions to representative cyclic and acyclic enones are shown in Scheme 4. The reaction of arylboronic acids with enones is carried out in acetone–H$_2$O at 0 °C in the presence of a benzonitrile-chiraphos or -dipamp complex and AgBF$_4$ (1 equiv) (method A) [3g]. Enantioselectivities giving β-arylketones up to 99 % are attained when using the chiraphos complex for 2-cyclopentenone and acyclic (E)-enones, whereas the dipamp complex results in the best selectivities for 2-cyclohexenone and 2-cycloheptenone (89–96 % ee). The presence of AgBF$_4$ is not always required; however, it may serve to increase the yields and catalyst turnover numbers and is absolutely necessary for the slow reaction of 3-methoxyphenylboronic acid. The Pd-chiraphos complex catalyzes the reaction of [ArBF$_3$]K in aqueous MeOH (method B) [3e,f]. The use of nitrile-free catalysts is critical for arylsilicon compounds because of their slow transmetallation. ArSi(OMe)$_3$ is added to enones at 75 °C with a nitrile-free catalyst in situ generated from [Pd(dppe)(PhCN)$_2$](BF$_4$)$_2$ and Cu(BF$_4$)$_2$. Alternatively, the Pd-chiraphos complex catalyzes the addition of PhSiF$_3$ to enones at 0 °C in the presence of ZnF$_2$ (0.5 equiv) (method C) [3b]. The corresponding reaction of Ar$_3$Bi is conducted in the presence of Cu(BF$_4$)$_2$ as well as a Pd(II) catalyst (method D) [3d]. The reaction suffers from decomposition of the catalyst, resulting in the formation of homo-coupling biaryl with precipitation of 11.

Scheme 3 Catalysts for Pd(II)-catalyzed 1,4-addition.

Scheme 4 Asymmetric 1,4-addition catalyzed by Pd(II) complexes.
Pd black. Thus, Cu(II) salt is used to recycle the precipitated Pd(0) species to a cationic Pd(II) complex.

The addition to either cyclic or acyclic enones results in a different order and opposite sense of enantioselection in the presence of chiral phos- and dipamp-based catalysts. The 1,4-addition of Ph-\(m\) (\(m = B, Si, Bi\)) to 2-cyclohexenone with (S,S)-dipamp catalyst provides (\(R\))-3-phenylcyclohexanone with enantioselectivities in a range of 92–93 % ee. The (S,S)-chiraphos catalyst provides \(S\) products for 2-cyclopentenone and 5-methyl-3-hexen-2-one, respectively. A comparison of the structures of these enones suggests that the most important feature for the catalyst substrate recognition is planarity of the substrate. Thus, 2-cyclopentenone and \(\beta\)-arylketones, which each have a planar structure, give high ee with the chiraphos catalyst. On the other hand, the dipamp catalyst results in a high order of enantioselection for the skewed structures of 2-cyclohexenone and 2-cycloheptenone.

1,4-Addition of arylboronic acid to \(trans\)-\(\beta\)-aryl enals proceeds smoothly in acetone/water (10/1) at 10–25 °C in the presence of \([Pd(S,S\text{-chiraphos})(PhCN)_2][SbF_6]_2\) (12) (0.5 mol %), \(AgX\) (\(X = BF_4, SbF_6, 10\) mol %) and aqueous 42 wt % HBF_4 to afford optically active 3,3-diarylalkanals with high enantioselectivities in a range of 86–97 % ee (Scheme 5) [3h]. Both Rh- and Pd-catalyzed 1,4-additions of organoboronic acids to enals in aqueous solvents suffer from slow reaction due to the formation of a stable hydrate (27). The acid catalyst may accelerate this equilibrium via a protonated intermediate (26), which would be much more activated for 1,4-addition than the parent aldehyde (25).

The protocol provides the first catalytic method for enantioselective short-step synthesis of optically active (+)-(\(R\))-CDP 840 (Scheme 6) [3h,20]. 1,4-Addition of arylboronic acid possessing 3-cyclopentyloxy and 4-methoxy groups to \(trans\)-cinnamaldehyde with a Pd/(\(R\),\(R\))-chiraphos catalyst affords (\(R\))-28 in 70 % yield with 94 % ee. The product is finally converted into (+)-(\(R\))-CDP 840 in 43 % total yield and with 94 % ee.

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The first enantioselective synthesis of optically active 1-aryl-1$H$-indenes (35) via tandem 1,4-addition–aldol condensation is shown in Scheme 7. The 1,4-addition of arylboronic acids in the presence of HBF$_4$, as well as a Pd-chiraphos catalyst directly give desired indenes in 60–99 % yields and with 90–97 % ee. The protocol can be useful as a one-pot method for the preparation of a 1,3-diarylindene structure of endothelin receptor antagonists, which was previously accomplished in four steps using analogous 1,4-addition of arylboronic acids [4j].

![Scheme 7 Synthesis of 1-aryl-1$H$-indenes.](image)

The synthesis of 4-aryl-4$H$-chromenes (39), which were recently identified as potent apoptosis inducers, was achieved by Cacchi by Pd(II)-catalyzed 1,4-addition of (2-hydroxyaryl)mercury chlorides to $\beta$-arylenones [21]. 1,4-Addition of arylboronic acids to $\beta$-(2-hydroxyaryl)enones (36) provides 37 and 38 as a mixture of two isomers, which are then led to single isomers, chromenes (39) via acid-catalyzed dehydration (Scheme 8) [3g]. The mode of face selection is the same as that previously reported for 1,4-addition of arylboronic acids to enones. The addition of phenylboronic acid to enone 40 provides a 1,4-addition product which is then subjected to Baeyer–Villiger oxidation to give phenylchromanone (41) with 93 % yield and 93 % ee. Recrystallization from hexane/ether affords pure 41.
(99.6 % ee) in 70 % yield. Thus, the formation of R-product from the (S,S)-chiraphos complex was well established by the specific rotation reported for (R)-4-phenylchroman-2-one [22].

All attempts at 1,4-addition to α,β-unsaturated esters and enamides with Pd catalysts failed due to the formation Heck products by β-elimination from the C-enolate intermediate (9). However, N-benzoyl amides such as 42 exceptionally give 1,4-addition products in high yields and high enantio-selectivities in a range of 90–98 % ee (Scheme 9) [23].

ENANTIOSELECTION MECHANISM

The X-ray structure of [Pd(S,S-chiraphos)(PhCN)2]2(SbF6)2 (12) displays a slightly twisted square planar coordination geometry for the Pd(II) atom ligated with two phosphorous atoms of chiraphos and two nitrogen atoms of benzonitrile (Scheme 10). Two phenyl groups in the upper left and the lower right occupy pseudo-axial positions in the chelate ring, whereas the phenyls of another pair are in pseudo-equatorial positions. There is steric hindrance between the equatorial phenyl groups and two benzonitrile ligands to pressure the left benzonitrile molecule upwards and the right one downwards with respect to the P–Pd–P plane, thus suggesting that space is accessible to a substrate in the upper left and lower right quadrants. The dihedral angle between the P–Pd–P and N–Pd–N planes is 9.1° with clockwise rotation of the N–Pd–N plane.
The solid-state structures of conformationally flexible complexes, in general, cannot be reliably used for the mechanism of enantioselection since the conformations of real intermediates might differ from the solid-state structures of catalyst precursors. Thus, the mode of a substrate coordination to the chiral phosphine–phenyl Pd(II) intermediate is calculated, the reaction stage directly preceding the stereodetermining insertion step by density functional theory (DFT) computations at the B3LYP/SDD level of theory (Fig. 2) [3f].

Two stable adducts between [Pd(S,S-chiraphos)(Ph)]^+ and 2-cyclopentenone located computationally are shown by 44 and 45. Both si- and re-coordination of the substrate are preferred with low energies, but only the precursor of the experimentally observed enantiomer giving an S product has conformational minimum with parallel coordination of the C–C double bond to the Ph–Pd bond (44, 0.1 kcal/mol relative to [Pd(S,S-chiraphos)(Ph)(H2O)]^+). In this model, the two phenyl groups on the Pd and phosphine atom constitute a planar free space for coordination of an enone to the metal center and the upper right area is blocked by one of the equatorial phenyl groups of S,S-chiraphos ligand. It seems that the reason for enantioselection is not the relative stability of the complexes, but rather their capability for the next insertion reaction. If the coordination takes place on the opposite re-face, the next insertion process is retarded because the parallel orientation of C=C and Ph–Pd bonds becomes unstable due to the steric hindrance caused by the upper right axial phenyl. On the basis of DFT calculation of the stereodetermining insertion step, the efficiency of a chiraphos ligand for planar α,β-unsaturated carbonyl compounds such as 2-cyclopentenone and acyclic unsaturated ketones is attributed to a planar free space consisting of a metal-bound, aryl group-derived arylboronic acid and an axial P-bound phenyl group. A large steric interaction between the upper right equatorial phenyl group and the car-

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steric interaction between the metal-bound aryl group and the bonyl group of enones unequivocally determines the enantioselectivity. The model also indicates that does the Rh complex for representative enones.

**REFERENCES AND NOTES**


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