DOI: 10.1002/ejoc.200800541

Palladium-Catalyzed Asymmetric Conjugate Addition of Aryl–Metal Species

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Keywords: Michael additions / Asymmetric catalysis / Palladium / Arylboronic acids / Enones

The objective of this review is to summarize developments in the recently discovered area of palladium-catalyzed asymmetric Michael additions of organometallic reagents to activated electron-deficient olefins in its practical and theoretical aspects. The methodology has been rapidly developed in the last five years as a useful alternative approach to complement the already existing copper- and rhodium-catalyzed variants, especially in the area of asymmetric aryl transfer to typical Michael acceptors. Although very difficult to control because of numerous side reactions, this palladium catalysis is very promising for applications both in academia and in industry.

Introduction

Transition-metal-catalyzed Michael addition of organometallic species has over the last two decades become an important synthetic tool for constructing homochiral carbon skeletons.[1] To date, catalysis in these reactions has been dominated by copper(I) phosphoramidites[2] and diphosphanerhodium(I)[3] complexes. Each of these strategies has yielded spectacular success, and each has unique advantages and disadvantages. In the copper-catalyzed reactions, the organic groups introduced are mostly limited to simple alkyl groups (Me, Et, *i*Bu) transferred from corresponding dialkylzinc and trialkylaluminium derivatives, and the reaction is carried out at low temperatures, sometimes far below 0 °C. Several otherwise successful attempts to employ diarylzinc compounds unfortunately suffered from difficulties associated with preparation of high-purity diarylzincs, which are necessary to achieve high enantioselectivities. Organolithium and organomagnesium reagents could be perfect starting materials for the copper-catalyzed reactions. However they need temperatures below –70 °C to overcome their high inherent reactivities and their associated fast uncatalyzed background reactions. Other highly attractive organometallic precursors (boron, silicon, tin, etc.) cannot to be conveniently transmetallated with copper by an inexpensive, simple procedure for further conjugate addition reaction. The rhodium-catalyzed reaction is a very robust and flexible approach for introducing aryl and alkenyl groups from a whole range of organometallic species with high yields, excellent enantioselectivities, and minimal side reactions. However, the price of rhodium has exploded over the last decade, making the method less attractive for large-scale industrial applications.

$PdCl_2$-catalyzed conjugate addition of Ph_4Sn[4] and ArHgX[5] to α,β-enones in an acidic two-phase system in the presence of Bu_4NCl was first reported in 1981 by Cacchi et al. Later, Uemura et al. developed an original protocol for addition of arylantimony[6] and aryltin[7] compounds to enones and enals, and later to nitroalkenes.[8] The use of palladium-based catalytic systems remains comparatively less developed, however, despite the lower costs of available palladium precatalysts.[9] This is partly due to the tendency of palladium catalysts to promote several side reactions such as Heck coupling (by β-hydride elimination pathways) with partial formation of palladium black, oxidative Suzuki-like coupling of organometallic substrates to form bi-

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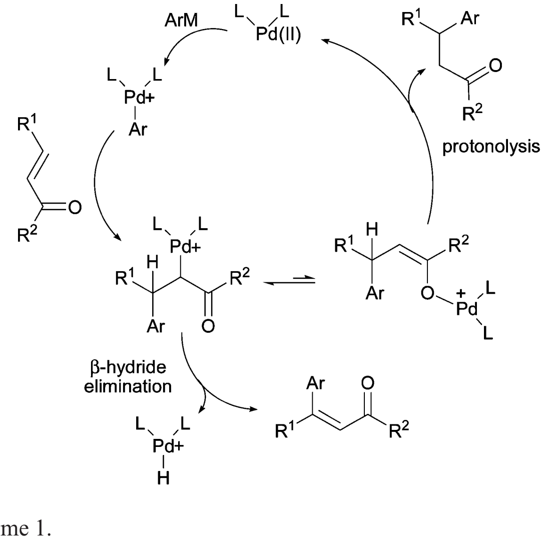
aryls, reduction and oligo-/polymerization of ethylenic Michael acceptors, and even arylation of phosphorus ligands, which sometimes become dominating over the desired pathway under typical reaction conditions. Important advantages of palladium are its high activity in the conjugate addition, with catalyst loading sometimes reduced down to 0.01 mol-%, and its ability to transmetallate many types of organometallic reagents effectively.

The proposed mechanism of the reaction is almost identical to that of the corresponding well established rhodium catalysis (Scheme 1). The only difference is that palladium, unlike rhodium, preferentially binds to carbon and exists in solution in an equilibrium between two forms: the Pd–O enolate and the α-*C*-palladated species,[10] although it reveals a *C*-bound structure in the solid state.[11] The latter form is known to undergo competitive β-hydride elimination easily, leading to Heck products. The use of cationic Pd^{II} complexes is therefore especially advantageous in this case, as they are much more susceptible to hydrolytic Pd–C bond cleavage than neutral palladium complexes, and the fast protonolysis is essential to avoid the competing β-hydride elimination.[11]



Scheme 1.

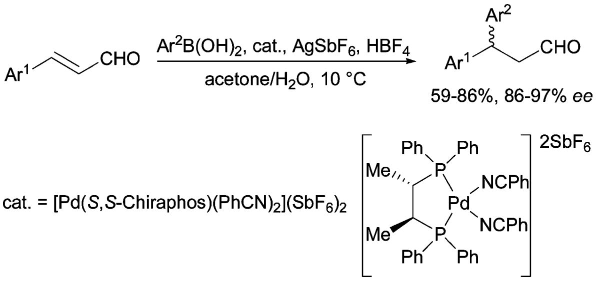
The reactions below are classified according to the type of organometallic substrates used in the reaction.

Arylboronic Reagents

In 1995, Uemura et al. disclosed the $Pd(OAc)_2$-catalyzed (10 mol-%) conjugate additions of sodium tetraphenylborate and arylboronic acids to α,β-unsaturated ketones and aldehydes in the presence of NaOAc (2 equiv.) and $SbCl_3$ (10 mol-%) in acetic acid at 25 °C.[12] The presence of $SbCl_3$ was most important to achieve higher selectivity for the formation of the conjugate addition product and to minimize the formation of Heck products. Recently (2004), Miyaura et al. developed a practical procedure for conjugate additions of arylboronic acids and boroxines $(ArBO)_3$ to enones in the presence of 5–0.5 mol-% of cationic $[Pd(dppe)(PhCN)_2](SbF_6)_2$ {dppe = 1,2-bis(diphenylphosphanyl)ethane} at room temperature.[13] Neutral palladium complexes such as $[PdCl_2(dppe)]$ appeared to be completely inactive, and replacement of dppe with PPh_3, dppp {1,3-bis(diphenylphosphanyl)propane}, (*S*)-Binap [(*S*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl], and some other bisphosphanes also resulted in no catalysis. Variations of complexes with other noncoordinating counteranions (BF_4 etc.) had no significant influence. The presence of benzonitrile was at the time found to be critical: any attempt to remove it from the catalytic complex reduced the yield. Interestingly, this conclusion was reconsidered in later publications, and nitrile-free complexes generated by in situ oxidation of $Pd(dba)_2$ with $Cu(BF_4)_2$ in the presence of phosphorus ligands were found to be much more active catalysts. Addition of bases accelerated the reaction, but also led to strongly increased formation of Heck products. The reaction requires the presence of water, as does the analogous rhodium-catalyzed reaction, and proceeds smoothly in THF/H_2O or $dioxane/H_2O$ mixtures. In contrast with the excellent reactivities of arylboronic acids and boroxines $(ArBO)_3$, all attempts to use arylboronic esters were unsuccessful. The protocol was successfully applied to cyclic enones and acyclic α,β-unsaturated ketones and aldehydes with primary alkyl, secondary alkyl, or phenyl substituents on the β-carbon atom. The reaction with α,β-unsaturated esters was very slow, with Heck products predominating. It should be noted that this reaction, known as oxidative Heck vinylation, has been used as a practical synthetic approach to cinnamates, arylated enones, and stilbenes.[14]

Later, the same group reported that a transmetallation reaction between $[Pd(dppe)(PhCN)_2](BF_4)_2$ and $PhB(OH)_2$ in the presence of PPh_3 allowed the first isolation of the cationic intermediate – $[Pd(Ph)(dppe)(PPh_3)](BF_4)$ – and its characterization by X-ray analysis.[15] A series of transmetallation reactions of *para*-substituted arylboronic acids with $[Pd(dppe)(PhCN)_2](BF_4)_2$ were studied by NMR spectroscopy. From the reaction rates, a Hammett plot with a negative ρ value (–0.54) was obtained, demonstrating that electron-donating substituents slightly accelerate the reaction.

Recently, the methodology was further developed to allow asymmetric formation of 3,3-diarylalkanals (Scheme 2).[16]

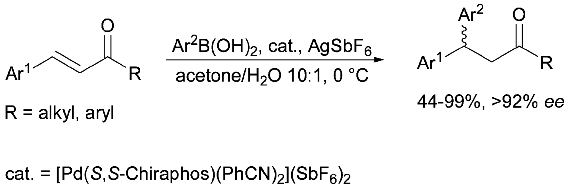


Scheme 2.

The reaction was carried out in $acetone/H_2O$ (10:1) at 10–25 °C in the presence of $[Pd(S,S\text{-chiraphos})(PhCN)_2](SbF_6)_2$ (0.5 mol-%). It was found that addition of $AgSbF_6$

(10 mol-%) and HBF_4 (10 mol-%) had remarkable accelerating effects, allowing the reaction to take place smoothly within 2 hours. The optimized conditions were applied to asymmetric 1,4-addition of various arylboronic acids to β-arylenals, with yields and enantioselectivities in the ranges of 59–86% and 86–97% *ee*. The catalyst showed lower enantioselectivity with aliphatic unsaturated aldehydes. The addition of 3-methoxyphenylboronic acid to *trans*-hexenal and to *trans*-crotonaldehyde resulted in an 84% yield with 70% *ee* and a 99% yield with 67% *ee*, respectively.

A similar procedure was applied to the enantioselective addition of arylboronic acids to β-arylenones to give β-diaryl ketones (Scheme 3).[17]



Scheme 3.

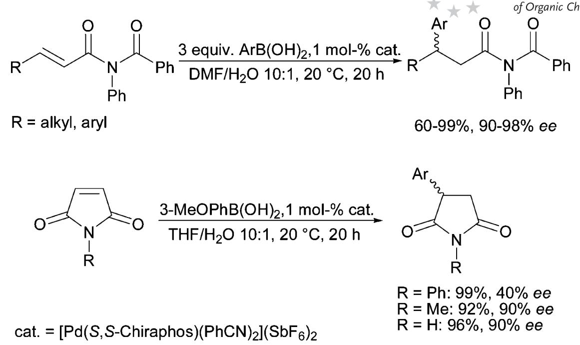
Addition of 5–10 mol-% of silver salts ($AgBF_4$, $AgSbF_6$) had a dramatic effect on the reaction, allowing the catalyst loading to be reduced to 0.05 mol-% without affecting generally high yields and excellent enantioselectivity. Moreover, in some experiments with cyclohexenone the loading could be further reduced even to 0.01 mol-%, with TONs of up to 9900 achieved at >98% yield and >89% *ee*. The role of silver salts was not elucidated experimentally, but the authors attributed it to generation of active nitrile-free Pd^{II} species through ligand exchange and/or to reoxidizing of catalytically dead Pd^0 complexes back to Pd^{II}. Alternatively, they might also activate the enone by complexation with its double bond or carbonyl group. Another important improvement of the method is the finding that only 1.2 equiv. of arylboronic acids can be used, because the unwanted protodeboration reaction was minimal under the reported conditions.

α,β-Unsaturated acid derivatives are known to be problematic substrates for palladium catalysis, favoring Heck-type coupling. However, Miyaura et al. showed that corresponding *N*-benzoyl amides are excellent substrates, affording the desired 1,4-addition products without accompanying Heck products (Scheme 4).[18]

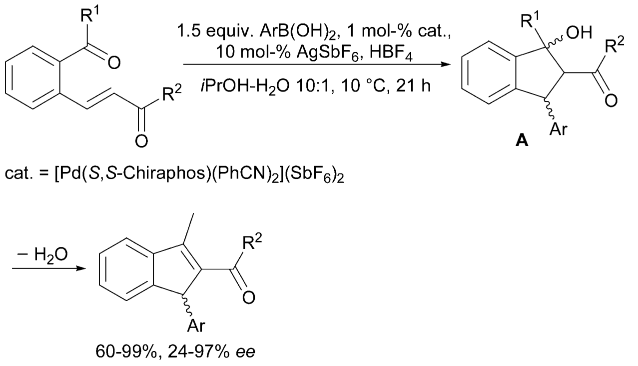
Cyclic maleimides appeared to be suitable substrates as well, though with enantioselectivities strongly dependent on the nature of *N*-substituents.

Recently the reaction was extended to the tandem conjugate addition/aldol cyclization of β-(2-acylaryl)enones to afford optically active 1-aryl-1*H*-indenes (Scheme 5).[19]

The reaction had proceeded by insertion of alkene into the Ar–Pd bond, and the intermediate α-*C*-palladated species were then trapped intramolecularly by the carbonyl group to furnish indanols **A** as inseparable mixtures of two diastereomers. These were dehydrated to form the corresponding indenes with good to excellent yields and *ee* values after two steps.

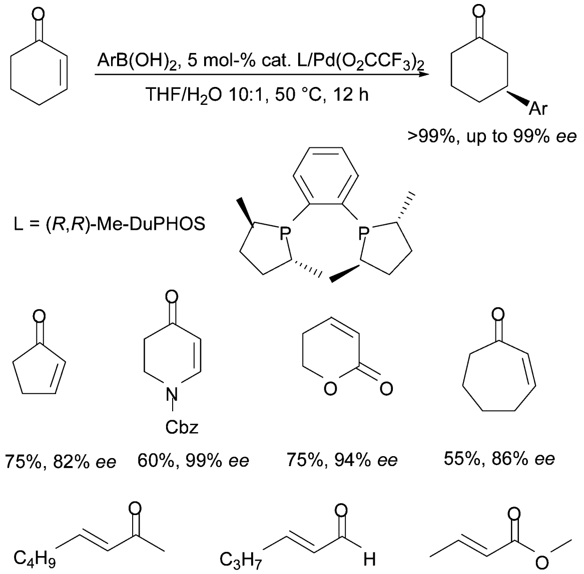


Scheme 4.



Scheme 5.

Minnaard et al. found that catalysts formed in situ from Pd^{II} salts and Me-DuPHOS exhibited excellent activity and enantioselectivity in the Michael addition of arylboronic acids to cyclic enones (Scheme 6).[20,21]

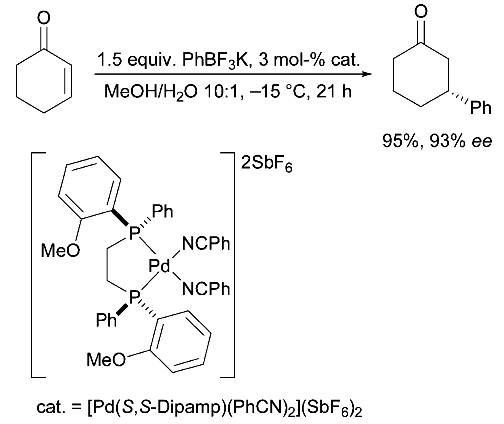


Scheme 6.

The reaction with cyclohexenone did not take place if $Pd(OAc)_2$ was used as precatalyst, requiring additional activation with triflic acid (CF_3SO_3H). Alternatively, $Pd(O_2CCF_3)$ could be used as precatalyst, suggesting that the role of counteranions is crucial for effective catalysis. The catalyst loading was later decreased, and an 85% yield and 98% *ee* were obtained with 1 mol-% of catalyst in 30 h. *ortho*-, *meta*-, and *para*-Tolylboronic acids and *ortho*- and *meta*-anisylboronic acids afforded high yields and excellent *ee* values, whereas *meta*-nitrophenylboronic acid refused to react and *meta*-chlorophenylboronic acid gave incomplete conversion. This was attributed to slower transmetallation of electron-poor arylboronic acids with Pd^{II} complexes. Quite unexpectedly, prop-1-enylboronic acid also did not afford any conversion with cyclohexenone.

The optimized reaction was extended to other α,β-unsaturated compounds and showed the best results for cyclic enones (>55% yields, 82–99% *ee* values). Acyclic enals and enones appeared to be considerably less reactive (<45% yields), with lower enantioselectivities (49–82% *ee* values). An attempted addition to methyl (*E*)-crotonate resulted in the Heck coupling product (73%), together with a 27% yield of almost racemic (8% *ee*) conjugate addition product.

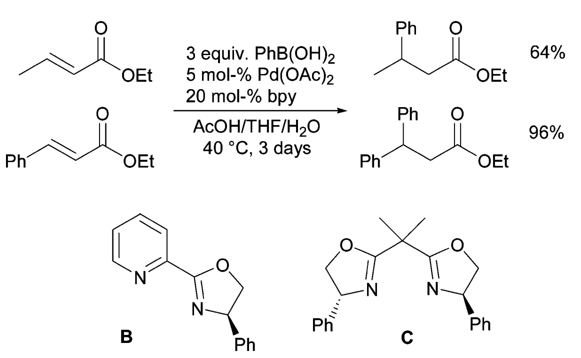
Chiral cationic Pd complexes were successfully used by Miyaura et al. in the conjugate addition of aryltrifluoroborates (Scheme 7).[22,23]



Scheme 7.

The reaction proceeded smoothly in $MeOH/H_2O$ (10:1) at –15 °C over 21 hours, and the palladium catalysts – $[Pd(S,S\text{-Dipamp})(PhCN)_2](SbF_6)_2$ and $[Pd(S,S\text{-Chiraphos})(PhCN)_2](SbF_6)_2$ (3 mol-%) – were generated in situ and did not require additional activation. Other complexes prepared from analogous bisphosphanes bridged by two carbon atoms (Norphos, Me-DuPHOS) showed no catalytic activity even at room temperature. Cyclic enones (cyclopentenone, cyclohexenone, cycloheptenone) afforded higher enantioselectivities (up to 99% *ee*) when the Dipamp-based catalyst was used, whereas the complex with Chiraphos was more efficient with acyclic substrates (generally >90% *ee* values).

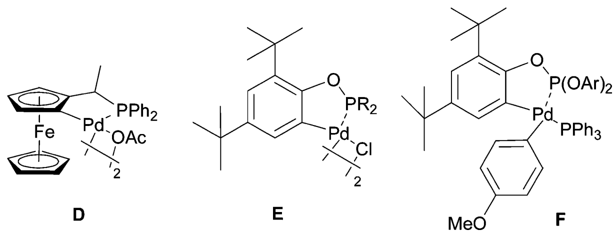
Lu and Lin developed an original catalytic system – $Pd(OAc)_2$/2,2′-bipyridine – for high-yielding conjugate addition of arylboronic acids to a variety of enones, enals, nitroalkenes, and, most surprisingly, cinnamates and acrylates (Scheme 8).[24]



Scheme 8.

Only marginal results were obtained without bpy in the test reaction with cyclohexenone, with side reactions predominating. The addition of 20 mol-% of bpy dramatically improved the yield, and also prevented formation of biaryls and Heck-type coupling products, as well as precipitation of palladium black. Some other ligands such as pyridine, 1,10-phenanthroline, and chiral (*R*)-Pymox-Ph **B** and phenyl-substituted bisoxazoline **C** were also tested, but all afforded the product in poor yields. In a later publication from the same group the reaction was successfully carried out in water as the only solvent in the presence of anionic surfactants.[25]

Recently, Hu et al.[26] and then Bedford et al.[27] demonstrated that several palladacycles of the **D** and **E** types (Scheme 9) are very active catalysts (5–0.1 mol-%) for the conjugate addition of arylboronic acids and arylsiloxanes to chalcones, acyclic and carbo-/heterocyclic enones, and β-nitrostyrenes without formation of Heck coupling byproducts.

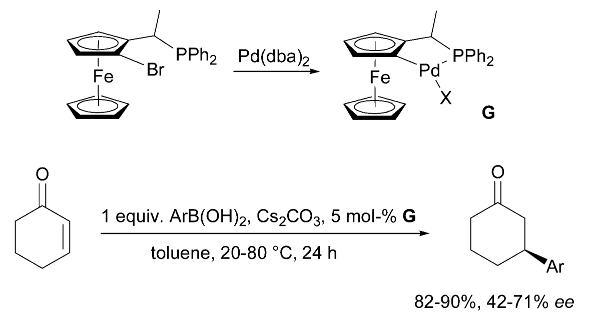


Scheme 9.

Spectroscopic (NMR) evidence has been provided for the formation of the arylated palladacyclic complex **F**, a possible catalytic intermediate for the conjugate addition.[27]

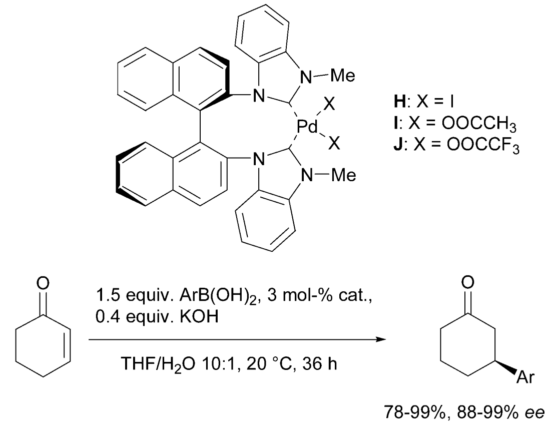
Most recently, Ohta et al. have developed an asymmetric version of the reaction (Scheme 10).[28]

The catalytic palladacyclic complex **G** generated in situ from optically active (*S*,*Rp*)-[1-(2-bromoferrocenyl)ethyl]diphenylphosphane ligand and $Pd(dba)_2$ was applied to the conjugate addition of arylboronic acids to cyclohexenone. The reaction afforded good yields and a promising 71% *ee*.



Scheme 10.

Shi and Zhang reported that asymmetric conjugate addition of arylboronic acids to cyclic enones can be catalyzed by cationic palladium(II) complexes with a chiral bidentate *N*-heterocyclic carbene as a ligand (Scheme 11).[29]



Scheme 11.

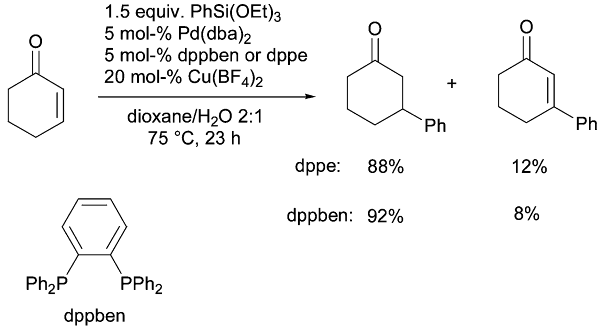
The reaction with cyclohexenone proceeded smoothly in the presence of 0.4 equiv. of KOH and 3 mol-% of diacetate and ditrifluoroacetate complexes **I** and **J**, whereas diiodide **H** showed no activity. The optimized reaction conditions were applied to a number of carbo- and heterocyclic enones with generally high yields and enantioselectivities, except in the case of cyclopentenone, which furnished a 58% yield and a 32% *ee*.

Arylsilicon Reagents

Organosilicon compounds are known to be weak nucleophiles and often need additional activation through coordination with alkoxy, hydroxy, or fluoride anions, which allows the rate-determining Si-Pd transmetallation step to proceed more rapidly. On the other hand, organosilanes are more stable than the corresponding boronic acids and are also compatible with a wide range of functional groups. Last but not least, they are very cheap, easy to handle, and environmentally friendly reagents.

In 2003, Denmark and Amishiro developed a protocol for palladium-catalyzed [5–10 mol-% of $Pd(OAc)_2$] conjugate addition of aryltrialkoxysilanes to cyclic and acyclic enones, enals, and nitroalkenes.[30] The reaction was typically carried out in CH_3CN at 60 °C over 24–48 h and required Bu_4NF (4 equiv.), $SbCl_3$ (4 equiv.), and acetic acid (5 equiv.) as additives for effective catalysis and to minimize the formation of Heck-type products.

Miyaura et al. published a detailed study focused on evaluation of the catalytic activity of cationic Pd-bisphosphane catalytic systems in the conjugate addition reactions of arylsiloxanes (Scheme 12).[31]



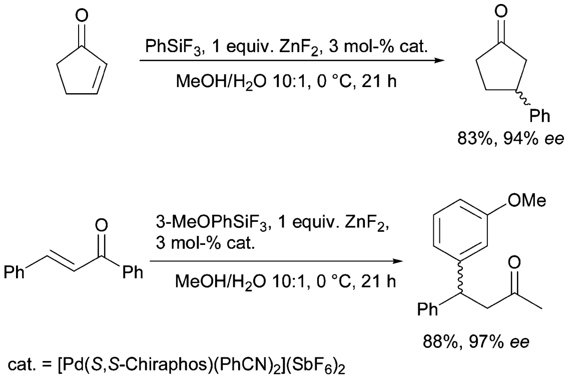
Scheme 12.

The use of cationic nitrile-free Pd catalysts was critical for the reaction, because of the slow transmetallation of arylsiloxanes relative to that of arylboronic acids. $[Pd(dppe)(PhCN)_2](SbF_6)_2$ and $[Pd(dppe)(PhCN)_2](BF_4)_2$ complexes showed no activity, even at 75 °C. The best catalysts for arylsiloxanes were obtained by in situ oxidation of $Pd(dba)_2$ with $Cu(BF_4)_2$ in the presence of 1 equiv. of dppe or dppben, and gave 80% and 77% yields, respectively, with minimal formation of the Heck product. The reaction seems to be almost insensitive to variation of substituents in the arylsiloxanes. Against expectations, addition of CsF and Bu_4NF strongly retarded the catalysis.

Screening of other enones, cyclic and acyclic, revealed that cyclopentenone has a stronger tendency to yield the Heck product (57%), whereas in the case of cycloheptenone the side reaction was negligible (<1%). The preferential formation of Heck products with some cyclic enones can be explained, since the *syn* addition of an Ar–[Pd]$^+$ species to a cyclic enone affords a *C*-bound palladium intermediate that has a β-hydrogen *trans* to the C–Pd bond. The β-hydride elimination to give the Heck product may thus proceed through epimerization of the C–Pd bond *cis* to the β-hydrogen through equilibration between *C*-palladium enolate and *O*-palladium enolate. Several acyclic substrates tested in the reaction gave good yields of the conjugate addition products (72–90%) with >99% selectivity.

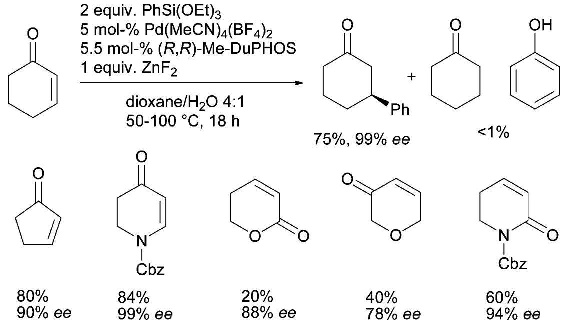
Later on, Miyaura et al., using $ArSiF_3$ reagents, disclosed the first enantioselective version of the conjugate addition (Scheme 13).[22]

The reaction was carried out at 0 °C in $MeOH/H_2O$ (10:1) over 21 h, and addition of ZnF_2 significantly accelerated the catalysis with 3 mol-% of [Pd(*S*,*S*-Dipamp)$(PhCN)_2](SbF_6)_2$ and [Pd(*S*,*S*-Chiraphos)$(PhCN)_2](SbF_6)_2$ complexes. Both catalysts showed excellent activity (73–99%) and enantioselectivity (76–99% *ee* values) for cyclic and acyclic substrates.



Scheme 13.

Conjugate addition of arylsiloxanes to cyclic enones, lactones, and lactams was also studied by Minnaard et al. (Scheme 14).[21,32]



Scheme 14.

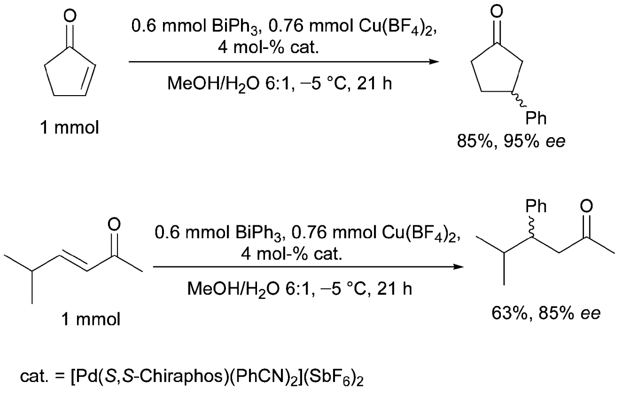
Initially, the conditions developed earlier for the conjugate addition of arylboronic acids – 5 mol-% of Pd(CF_3COO)$_2$ and 5.5 mol-% of (*R*,*R*)-Me-DuPHOS in dioxane/H_2O (10:1) at 100 °C – were applied to the reaction. After 24 h, the reaction had produced a mixture of cyclohexanone and phenol as a result of redox disproportionation of the starting cyclohexenone without any trace of the conjugate addition product. The use of $Pd(CH_3CN)_4(BF_4)_2$ as precatalyst afforded the desired product with 30% yield and 94% *ee*. The corresponding Heck-type product was not found by GC, but considerable amounts of cyclohexanone and phenol were still detectable. Addition of 3 equiv. of Bu_4NF gave no conversion, and CsF and NaF led only to the disproportionation reaction. Fortunately, addition of 2 equiv. of ZnF_2 gave full conversion in 2 h at 100 °C, afording the desired product with 70% yield (97% *ee*) and only a 10% yield of phenol/cyclohexanol. Further optimizations resulted in even better yield (75%) and enantioselectivity (>99% *ee*) virtually without side products, and the catalyst loading was decreased to 2 mol-%. The efficiency of ZnF_2 in relation to the other fluoride sources was attributed to its ability to act as a double activator: F^- increases the reactivity of the organosiloxane while Zn^{2+} coordinates to the oxygen of the carbonyl group, thereby increasing the reactivity of the enone.

Screening of substituted arylsiloxanes was carried out under the optimized conditions. All *para*- and *meta*-substituted derivatives afforded good yields (>60%) and excellent enantioselectivities (>95% *ee* values), and electronic effects seemed to play no significant role. On the other hand, the more sterically hindered *ortho*-MePhSi(OEt)$_3$ gave only 15% conversion even at 100 °C.

The scope of the reaction in terms of substrates was also investigated, and most of the tested carbo- and heterocyclic enones afforded moderate to good yields (20–84%) and good to excellent enantioselectivities (78–99% *ee* values). At the same time, the reactions with cycloheptenone and (*E*)-octen-2-one led to incomplete conversion, the main products being the corresponding saturated ketones.

Triarylbismuth Reagents

The use of arylbismuth compounds in such metal-catalyzed reactions is still rare despite the simplicity of their preparation, isolation, and handling, as well as their high functional group compatibility. In 2004 Miyaura et al. applied triarylbismuth reagents to asymmetric conjugate additions to cyclic and acyclic enones (Scheme 15).[22,33]

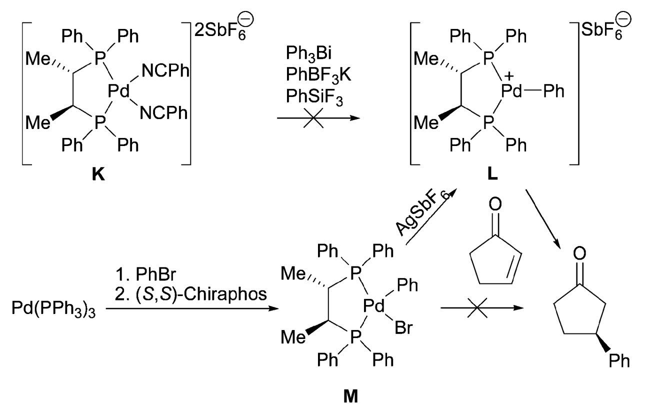


Scheme 15.

The reactions were carried out in aqueous methanol in the presence of 4 mol-% of chiral phosphane/dicationic palladium(II) complexes, and those based on (*S*,*S*)-Chiraphos or (*S*,*S*)-Dipamp showed best activity and highest enantioselectivity (up to 95% *ee*). This is consistent with an earlier observation that bisphosphanes bridged by two carbon atoms are essential to achieve high catalytic efficiency. The reaction suffered from the formation of reasonable amounts of biaryls (18–24%) as a result of Suzuki-like coupling. Pd^0 complexes generated thereby were reoxidized in situ with Cu(BF$_4$)$_2$ to catalytically active Pd^{II} species. Moreover, the role of the copper salt is also believed to be the generation of a highly electrophilic nitrile-free palladium complex by benzonitrile ligand exchange. The efficiency of the aryl transfer is very high, allowing utilization of two to 2.8 of the three phenyl groups on the bismuth atom. Best results, generally with >90% yield and >90% *ee*, were achieved with cyclic enones, whereas acyclic substrates afforded slightly lower yields and enantioselectivities.

In screening of various Ar_3Bi substrates, it was found that the use of two *para*-substituted derivatives (4-MePh and 4-CF_3Ph) unexpectedly resulted in 74% *ee* and 84% *ee* for an unknown reason, whereas other *para*- and *meta*-substituted arylbismuths (3-MeOPh, 3-MePh, 4-FPh, 3-FPh) easily afforded >90% *ee* values.

It should be noted that Bi/Pd transmetallation of Ar_3Bi compounds proceeds at –5 °C and is therefore much easier than transmetallation with $ArB(OH)_2$ (20 °C) and $ArSi(OMe)_3$ (75 °C). Interestingly, the direct transmetallation between $[Pd(S,S\text{-Chiraphos})(PhCN)_2](SbF_6)_2$ complex **K** and Ph_3Bi, $PhBF_3K$, or $PhSiF_3$ failed to give detectable amounts of monocationic arylpalladium(II) intermediate **L** (Scheme 16).[22]



Scheme 16.

The complex **L** was prepared in situ through ion exchange between [Pd(Ph)(Br)(*S*,*S*-Chiraphos)] **M** and $AgSbF_6$ and was found to react with cyclopentenone to give 3-phenylcyclopentanone in 65% yield and with 94% *ee* within 2 h at 0 °C. The reaction between the neutral bromide complex **M** itself and cyclopentenone resulted in no product for periods of up to 48 h at 0 °C, thus indicating high reactivity of the cationic palladium complex **L** towards insertion of alkenes. This result is in agreement with the general tendency of cationic $L_2PdAr(X)$ complexes to bind and insert alkenes much more actively than corresponding neutral complexes do. This property is used in, for example, copolymerization of olefins with carbon monoxide with in situ catalytic systems $[L_2Pd(NCPh)_2]/BAr_3$.[34]

Very recently, Yamamoto, Nishikata, and Miyaura have published a personal account of their longstanding efforts in the field of palladium-catalyzed conjugate addition reactions.[35]

Conclusions

The palladium-catalyzed asymmetric 1,4-conjugate addition of organometallic reagents to α,β-unsaturated ketones and aldehydes provides an important complement to traditional rhodium- and copper-catalyzed reactions. However, the method still has a significant way to go before it can gain practical recognition in academia and in industry.

Acknowledgments

Collaboration and innumerable discussions with fellow scientists at Chiroblock GmbH are gratefully acknowledged.

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[1] a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, *2*, 171–196; b) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, *9*, 1279–1300.

[2] B. Feringa, R. Naasz, R. Imbos, L. Arnold in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, 224–258.

[3] K. Yoshida, T. Hayashi in *Modern Rhodium-Catalyzed Organic Reactions* (Ed.: P. Andrew Evans), Wiley-VCH, Weinheim, **2005**, 55–77.

[4] S. Cacchi, F. La Torre, D. Misiti, *Tetrahedron Lett.* **1979**, *20*, 4591–4594.

[5] S. Cacchi, D. Misiti, G. Palmieri, *Tetrahedron* **1981**, *37*, 2941–2946.

[6] C. S. Cho, S. Motofusa, K. Ohe, S. Uemura, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2341–2348.

[7] T. Ohe, T. Wakita, S. Motofusa, C. S. Cho, K. Ohe, S. Uemura, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2149–2155.

[8] T. Ohe, S. Uemura, *Tetrahedron Lett.* **2002**, *43*, 1269–1271.

[9] Development of Rh and Pd prices in the period January 20, 2003 to June 20, 2008: Rh 380 \$ → 10010 \$ per ounce, Pd 146 \$ → 471 \$ per ounce.

[10] D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817.

[11] A. C. Albéniz, N. M. Catalina, P. Espinet, R. Redón, *Organometallics* **1999**, *18*, 5571–5576.

[12] C. S. Cho, S. Motofusa, K. Ohe, S. Uemura, S. C. Shim, *J. Org. Chem.* **1995**, *60*, 883–888.

[13] T. Nishikata, Y. Yamamoto, N. Miyaura, *Angew. Chem. Int. Ed.* **2003**, *42*, 2768–2770.

[14] M. M. S. Andappan, P. Nilsson, M. Larhed, *Chem. Commun.* **2004**, 218–219, and references therein.

[15] T. Nishikata, Y. Yamamoto, N. Miyaura, *Organometallics* **2004**, *23*, 4317–4324.

[16] T. Nishikata, Y. Yamamoto, N. Miyaura, *Tetrahedron Lett.* **2007**, *48*, 4007–4010.

[17] T. Nishikata, Y. Yamamoto, N. Miyaura, *Adv. Synth. Catal.* **2007**, *349*, 1759–1764.

[18] T. Nishikata, Y. Yamamoto, N. Miyaura, *Chem. Lett.* **2007**, *36*, 1442–1443.

[19] T. Nishikata, Y. Kobayashi, K. Kobayashi, Y. Yamamoto, N. Miyaura, *Synlett* **2007**, *19*, 3055–3057.

[20] F. Gini, B. Hessen, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 5309–5312.

[21] F. Gini, PhD Thesis, University of Groningen, **2007**.

[22] T. Nishikata, Y. Yamamoto, I. D. Gridnev, N. Miyaura, *Organometallics* **2005**, *24*, 5025–5032.

[23] T. Nishikata, Y. Yamamoto, N. Miyaura, *Chem. Lett.* **2005**, *34*, 720–721.

[24] X. Lu, S. Lin, *J. Org. Chem.* **2005**, *70*, 9651–9653.

[25] S. Lin, X. Lu, *Tetrahedron Lett.* **2006**, *47*, 7167–7170.

[26] P. He, Y. Lu, C.-G. Dong, Q.-S. Hu, *Org. Lett.* **2007**, *9*, 343–346.

[27] R. B. Bedford, M. Betham, J. P. H. Charmant, M. F. Haddow, A. Guy Orpen, L. T. Pilarski, *Organometallics* **2007**, *26*, 6346–6353.

[28] Y. Suzuma, T. Yamamoto, T. Ohta, Y. Ito, *Chem. Lett.* **2007**, *36*, 470–471.

[29] T. Zhang, M. Shi, *Chem. Eur. J.* **2008**, *14*, 3759–3764.

[30] S. E. Denmark, N. Amishiro, *J. Org. Chem.* **2003**, *68*, 6997–7003.

[31] T. Nishikata, Y. Yamamoto, N. Miyaura, *Chem. Lett.* **2003**, *32*, 752–753.

[32] F. Gini, B. Hessen, B. L. Feringa, A. J. Minnaard, *Chem. Commun.* **2007**, 710–712.

[33] T. Nishikata, Y. Yamamoto, N. Miyaura, *Chem. Commun.* **2004**, 1822–1823.

[34] S. Mecking, *Coord. Chem. Rev.* **2000**, *203*, 325–351, and references therein.

[35] Y. Yamamoto, T. Nishikata, N. Miyaura, *Pure Appl. Chem.* **2008**, *80*, 807–817.

Received: June 4, 2008