Activation and functionalization of benzylic derivatives by palladium catalysts

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Palladium-catalyzed transformations of aryl halides and pseudo-halides involving carbonylation, carbon–carbon and carbon–heteroatom bond-forming reactions, *etc.* are very well documented, and have already been reviewed several times. The metal-catalyzed activation of benzylic derivatives is much less described. However, during the last decades, a number of papers have shown the interest offered by benzylic derivatives (halides, carbonates, acetates, phosphonates) in selective catalytic reactions for organic synthesis, most of them in the presence of palladium catalysts. The purpose of this *tutorial review* is to highlight selected examples of palladium-catalyzed transformations involving reactive benzylic derivatives.

Introduction

Over the past decades, palladium-catalyzed coupling reactions have proven to be one of the most powerful and versatile metal-mediated transformations in organic chemistry.[1] Due to the facile performance of these reactions, they have been for instance extensively used in total synthesis with great success.[2]

Beller and co-workers recently reviewed metal-catalyzed coupling reactions with non-activated alkyl halides. Palladium catalysts are definitely the most represented in such coupling reactions.[3] However, despite the thorough work published and reviewed on the topic of palladium-catalyzed coupling reactions of aryl and/or vinyl halides and their derivatives, no report, to the best of our knowledge, has previously been devoted to the related coupling reactions with benzylic derivatives. Only the corresponding olefination of benzylic dithioacetals using nickel catalysts has been compiled by Luh.[4]

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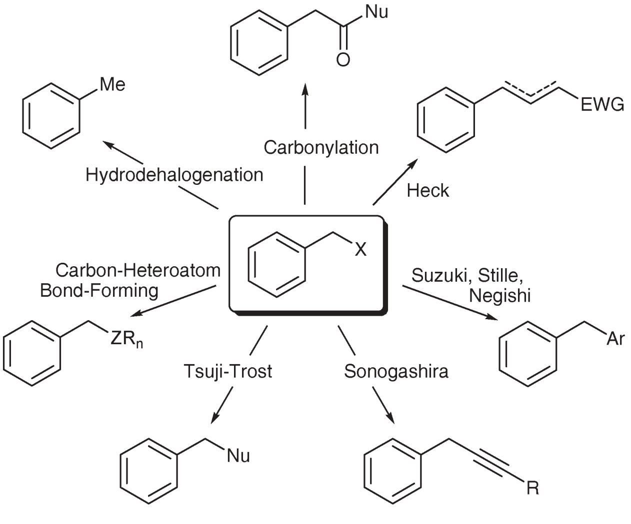
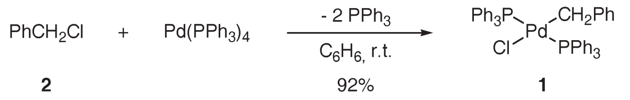
Dr Benoît Liégault obtained his Master degree in 2003 from the Université Pierre et Marie Curie in Paris, under the supervision of Prof. Janine Cossy at the Ecole Supérieure de Physique et de Chimie Industrielles (ESPCI), working on Pd-catalyzed hetero-annulation of ynamides. He then achieved his PhD in 2006 from the Université of Rennes under the supervision of Dr Christian Bruneau, working on hydrogenation of (hetero)aromatic compounds, nitrogen-containing derivatives and their application in organo-catalysis, and Pd-catalyzed annulation reactions. He is currently a postdoctoral fellow in the team of Prof. Keith Fagnou at the University of Ottawa, working on Pd-catalyzed bi-aryl synthesis via direct arylation.

This review focuses on the activation and functionalization of benzylic derivatives by palladium catalysts. Therefore, it describes carbon–carbon and carbon–heteroatom bond forming reactions, hydrodehalogenation reactions, multi-component reactions and carbene insertion (Scheme 1). In the final section, some miscellaneous examples are highlighted.

The very first example of stoichiometric palladium insertion into a benzylic carbon–heteroatom bond was reported by Fitton and co-workers in 1969, who prepared the complex (η^1-benzyl)-chloro-bis(triphenylphosphine)palladium(II) **1** by oxidative addition of benzyl chloride **2** to $Pd(PPh_3)_4$ (Scheme 2).[5]



Scheme 1 Palladium-catalyzed coupling reactions of benzylic derivatives.



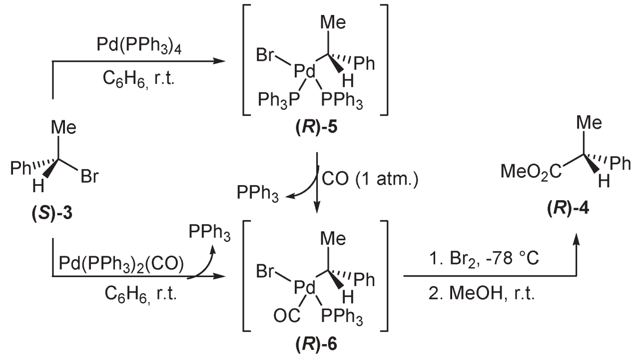
Scheme 2 First example of palladium insertion into a benzylic carbon halogen bond.

Carbon–carbon bond-forming reactions

Carbonylation reactions

Among the palladium-catalyzed carbon–carbon bond-forming reactions with benzylic derivatives, carbonylation reactions have been widely investigated.[6] For example, phenylacetic acid derivatives can be easily prepared from benzylic halides and carbon monoxide.

It is generally accepted that the mechanism proceeds *via* the oxidative addition of the benzylic derivative to a palladium(0) species to generate a benzylpalladium intermediate **A**, which can undergo coordination of carbon monoxide to palladium, and lead to complex **B** (Scheme 3). Depending on the reaction conditions and the nucleophile employed, the latter can then proceed *via* two different pathways, as proposed by Lin and Yamamoto in 1998.[7] On one hand, carbon monoxide insertion into the benzylic carbon–palladium bond leads to the phenylacetyl palladium intermediate **C** (path **a**). Substitution of the halide by the nucleophile gives the intermediate **D**, which liberates the coupling product BnCONu (Bn = Benzyl, NuH = nucleophile) by reductive elimination. On the other hand, benzylpalladium complex **B** can lead to a CO-coordinated cationic species **E** that undergoes nucleophilic attack to generate the benzyl(acyl)palladium intermediate **F** (path **b**). Reductive elimination yields the carbonylation product and regenerates the catalyst.

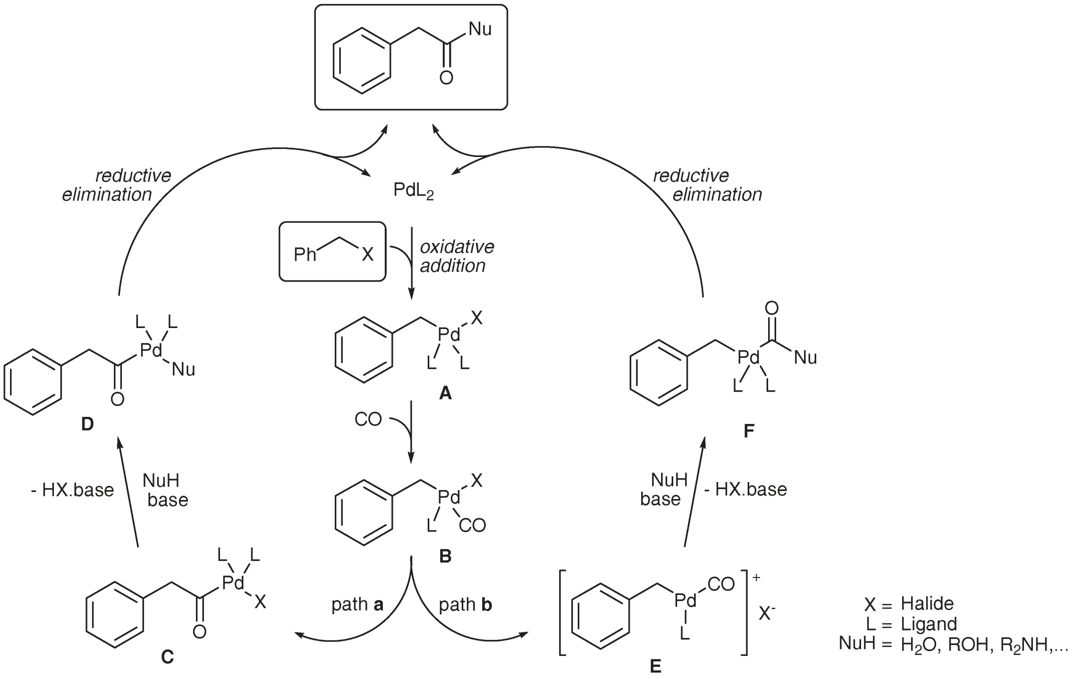


Scheme 4 Evidence for inversion of configuration of the benzylic carbon.

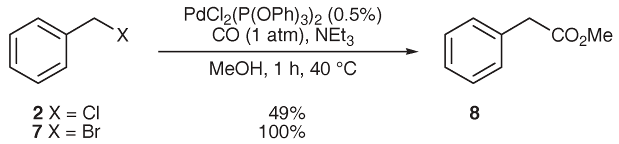
The inversion of configuration of the benzylic carbon during the first step, as Stille and co-workers pointed out in 1976, is noteworthy (Scheme 4).[8] Through this inversion, optically active benzyl bromide **(*S*)-3** is converted into the ester **(*R*)-4**, when employing either Pd(PPh$_3$)$_4$ or Pd(PPh$_3$)$_2$(CO) as precatalysts, *via* intermediates **(*R*)-5** or **(*R*)-6** respectively.

In 2001, Trzeciak and Ziółkowski demonstrated the efficiency of the phosphite P(OPh)$_3$ ligand in the synthesis of ester **8**; the best results were obtained when benzyl bromide **7** was used as the substrate (Scheme 5).[9] Kohlpaintner and Beller also proved that water-soluble phosphines, such as P(m-C$_6$H$_4$SO$_3$Na)$_3$ (TPPTS), were efficient ligands in the synthesis of phenylacetic acid derivatives starting from various substituted benzylic chlorides in water.[10]

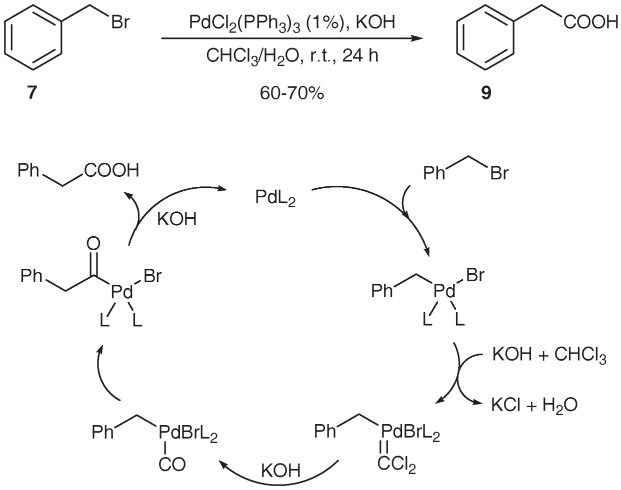
In 1993, Grushin and Alper developed an original method to prepare phenylacetic acid **9** from benzyl bromide **7** in basic biphasic conditions (Scheme 6).[11] The authors proposed that the carbonyl group is generated *in situ* from chloroform and



Scheme 3 Mechanism of the carbonylation reaction of benzylic halides.



Scheme 5 Methoxycarbonylation of benzylic halides catalyzed by $PdCl_2(P(OPh)_3)_2$.

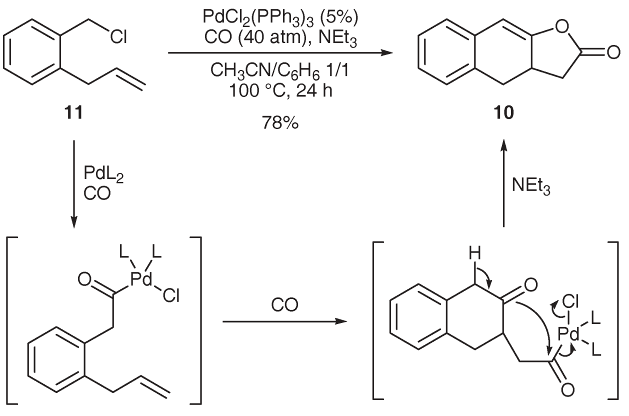


Scheme 6 Carbonylation of benzyl bromide without molecular carbon monoxide.

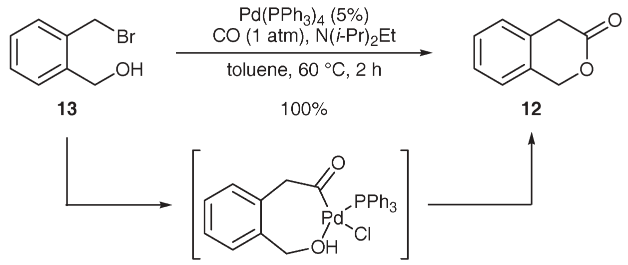
potassium hydroxide, *via* the carbene intermediate CCl_2. The absence of molecular carbon monoxide, the mild conditions, and the good yields render this methodology attractive and environmentally friendly.

Carbonylation reactions on benzylic halides have also been employed in various intramolecular transformations. For instance, Negishi and co-workers reported in 1991 the synthesis of the lactone **10** from *o*-allyl(chloromethyl)benzene **11** in good yield under high CO pressure.[12] Two equivalents of carbon monoxide are necessary in the process, as depicted in Scheme 7.

The synthesis of 3-isochromanone **12**, proposed by Lindsell, Preston and co-workers represents a very efficient application of the intramolecular carbonylation reaction from benzylic halides.[13] Under mild conditions, compound **12** is obtained from 2-hydroxymethyl benzyl bromide **13** with quantitative conversion (Scheme 8).



Scheme 7 Synthesis of lactone **10** by intramolecular carbonylation.



Scheme 8 Synthesis of 3-isochromanone **12** by intramolecular carbonylation.

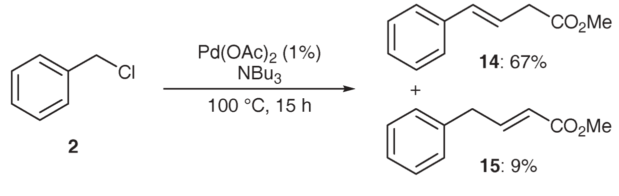
Heck reactions

The formation of two regio-isomers during the Heck reaction of benzylic derivatives with various olefins has limited the investigation of this chemistry to a few significant examples. Indeed, Heck and Nolley reported in 1972 the first palladium-catalyzed coupling reaction between benzyl bromide **2** and methyl acrylate (Scheme 9).[14] In neat conditions, esters **14** and **15** have been obtained in 67% and 9% yields, respectively. The 7.5 : 1 ratio in favor of the isomer **14** can be justified by a higher thermodynamic stability due to the conjugation between the double bond and the aromatic ring. However, selective coupling reactions have been carried out from benzylic trifluoroacetates and olefins in the presence of $Pd(OAc)_2$ associated to a phosphine.[15]

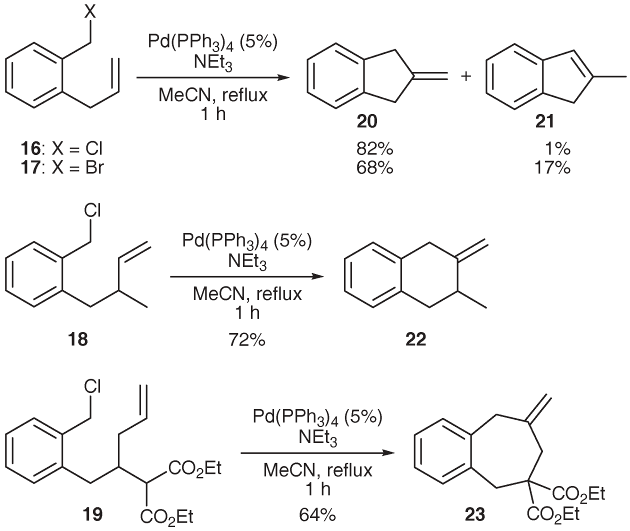
In order to avoid the inconvenience of the formation of two isomers, Heck reactions of benzylic derivatives have been mostly performed intramolecularly. In 1989, Negishi and co-workers described cyclization reactions from unsaturated *o*-substituted benzylic halides **16–19** (Scheme 10).[16] Corresponding 5-, 6- and 7-membered rings **20–23** were obtained with good yields and good to excellent regioselectivities. The authors suggested that the regio-isomerization observed in some cases is catalyzed by HX generated during the process rather than by palladium intermediates.

Two years later, Grigg and co-workers described an original example of an intramolecular pseudo-Heck reaction in the presence of sodium tetraphenylborate.[17] Starting from a 1 : 1 mixture of benzylic halides **24**, the tetrahydroquinoline **25** was produced in 69% yield (Scheme 11). It is worth mentioning that the formation of the quaternary carbon prevents the expected β-H elimination.

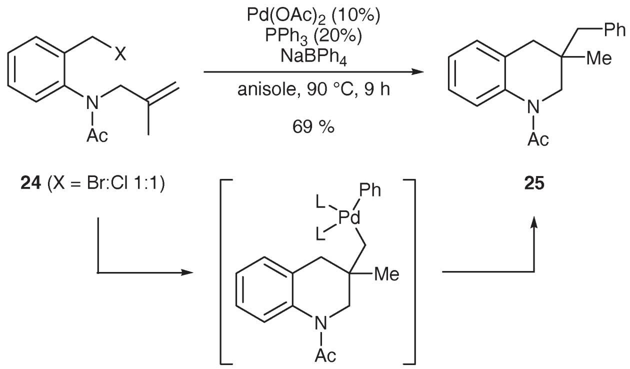
Recently, Pan and co-workers reported the synthesis of cyclopentene derivatives **26** using a palladium-catalyzed cascade cyclization of various substituted benzyl chlorides



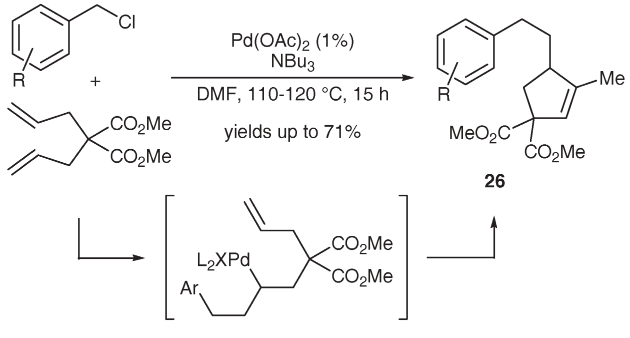
Scheme 9 First Heck reaction with benzyl chloride and methyl acrylate.



Scheme 10 Intramolecular Heck reactions on benzylic halides.



Scheme 11 Synthesis of tetrahydroquinoline **25** from benzylic halides **24**.

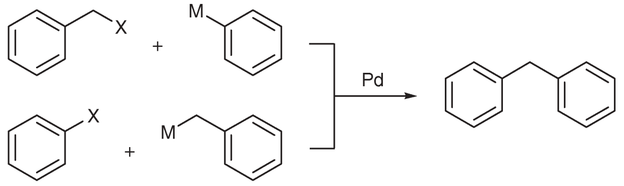


Scheme 12 Cascade cyclization of benzyl chlorides with diethyl diallylmalonate.

and diethyl diallylmalonate (Scheme 12).[18] The authors suggested a mechanism in which the organopalladium intermediate inserts into the second double bond rather than undergoes β-hydride elimination.

Suzuki reactions

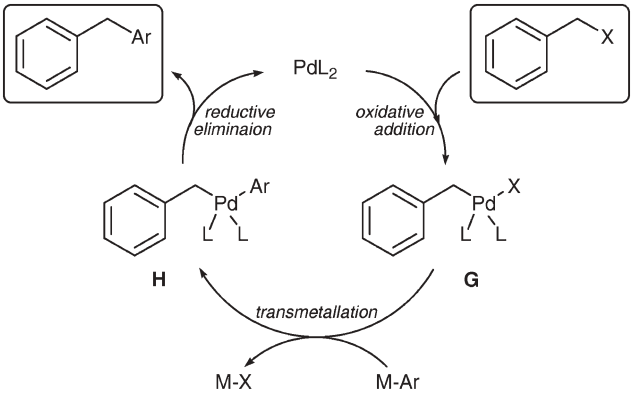
Cross-coupling reactions such as Suzuki, Stille, Negishi and Kumada reactions have been the subject of intense studies, notably in biaryl synthesis.[19] When using benzylic derivatives as substrates, those reactions provide diarylmethane skeletons (Scheme 13), which are commonly found in biologically active compounds or organic materials.



Scheme 13 Alternatives for the palladium-catalyzed cross-coupling construction of diarylmethane derivatives.

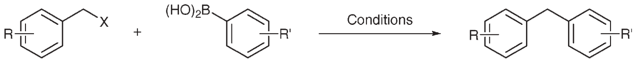
The catalytic cycle producing methylene-linked biaryl systems from benzylic derivatives is similar to the one generally depicted for aryl derivatives (Scheme 14). The first step involves the oxidative addition of the benzylic derivative to a palladium(0) species to generate a benzylpalladium intermediate **G**. The latter then reacts with an organometallic partner *via* transmetallation and leads to intermediate **H**, which gives the desired product and regenerates the active palladium(0) species.

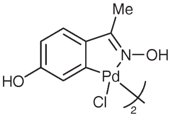
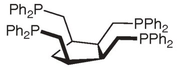
Inspired by the original work reported by Suzuki, Miyaura and co-workers in the early eighties,[20] many research groups have developed new catalytic systems over the past ten years in order to improve reactivity and extend reaction scope (Table 1). In 1999, Chowdhury and Georghiou used tetrakis(triphenylphosphine)palladium(0) as pre-catalyst and performed cross-coupling reactions on a large variety of (bromomethyl)-naphthalene derivatives and naphthylboronic acids (Entry 1).[21] Applying similar reaction conditions, Duchêne and co-workers employed various bromobenzyl bromides, and showed an excellent selectivity in favor of the C(sp^3)–Br, leading to unsymmetrical diarylmethanes (Entry 2).[22] In 2004, the use of palladium(II) chloride in acetone/water (3 : 1) enabled ligand-free cross-coupling reactions with high yields under mild conditions (Entry 3).[23] Also, Nobre and Monteiro were able to decrease the catalyst loading to 0.002% with a $Pd(OAc)_2/PPh_3$ catalytic system (Entry 4).[24] In 2005, Kuwano and Yokogi,[25] as well as McLaughlin,[26] showed that the reaction proceeds using either benzylic acetates, carbonates or phosphates as the



Scheme 14 General catalytic cycle for palladium-catalyzed cross-coupling reactions with benzylic derivatives.

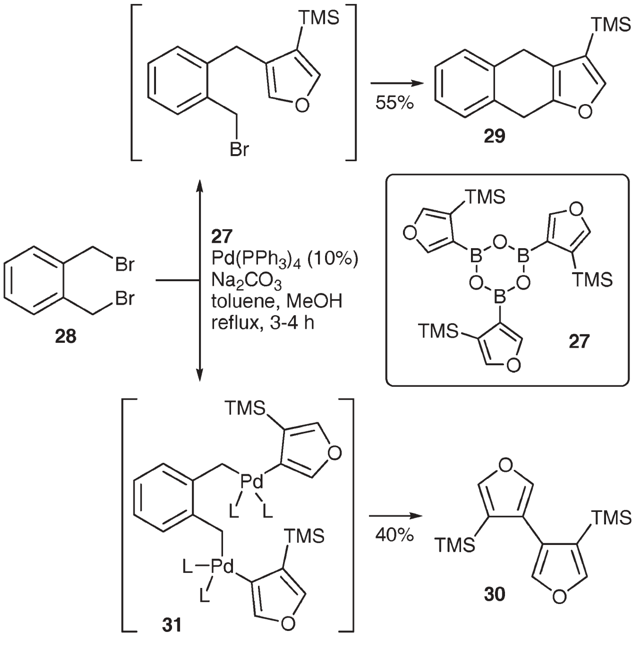
Table 1 Suzuki-Miyaura cross-coupling reactions with various benzylic derivatives



Entry	Catalytic system	X	ArB(OH)$_2$ (eq.)	Conditions[a]	Reference
1	Pd(PPh$_3$)$_4$ (3 mol%)	Br	1.5	Na$_2$CO$_3$, DME, H$_2$O reflux, 16–18 h	Chowdhury and Georghiou[21]
2	Pd(PPh$_3$)$_4$ (3 mol%)	Br	1	Na$_2$CO$_3$, EtOH, toluene r.t.−80 °C, 15–20 h	Duchêne and co-workers[22]
3	PdCl$_2$ (3 mol%)	Br	1	K$_2$CO$_3$, acetone, H$_2$O r.t., 0.5–15 h	Bandgar and co-workers[23]
4	Pd(OAc)$_2$, PPh$_3$ (0.002–1 mol%)	Cl, Br	1.5	K$_3$PO$_4$, toluene 80 °C, 19 h	Nobre and Monteiro[24]
5	[Pd(C$_3$H$_5$)Cl]$_2$, DPEphos (1 mol%)	OAc	1.1	K$_2$CO$_3$, *t*-AmOH 80 °C, 1–4 days	Kuwano and Yokogi[25]
6	Pd(OAc)$_2$, PPh$_3$ (1 mol%)	OP(=O)(OEt)$_2$	1.1	K$_3$PO$_4$, toluene 90 °C, 16 h	McLaughlin[26]
7	 (0.05 mol%)	Cl	1.5	Bu$_4$NBr, KOH, acetone, H$_2$O, r.t., 5 h - 4 days	Botella and Nájera[27]
8	[Pd(C$_3$H$_5$)Cl]$_2$,  (0.0001-0.4 mol%)	Cl, Br	2	K$_2$CO$_3$, xylenes 130 °C, 20 h	Santelli and co-workers[28]

electrophilic coupling partner with organoboron compounds (Entries 5 and 6). Several examples using specific pre-catalytic systems have also been described. Botella and Nájera employed an oxime-derived palladacycle under aerobic conditions,[27] while Santelli and co-workers have used the tetradentate phosphine ligand Tedicyp,[28] leading to diarylmethanes with excellent catalyst turnover numbers (Entries 7 and 8).

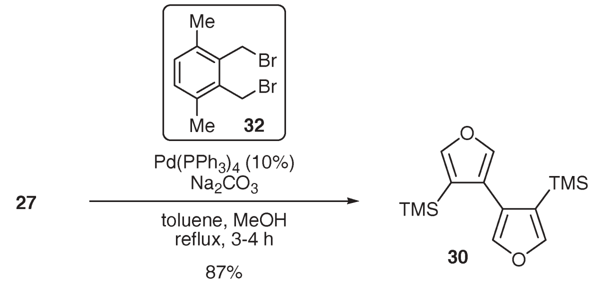
In 1994, Song and Wong used organoboroxines, such as compound **27**, as potent partners in coupling reactions for the synthesis of furan derivatives (Scheme 15).[29] Starting from α,α′-dibromo-*o*-xylene **28**, tricyclic compound **29** and dimeric difuran **30** have been both isolated with significant yields. As compound **29** is formed *via* an expected domino Suzuki-intramolecular Heck reaction, the presence of compound **30** is explained by a mechanism involving a disproportionation reaction of the intermediate **31**. However, organoboroxine **27** can be exclusively converted to difuran **30** by changing the dibromoxylene **28** for its disubstituted analogue **32** (Scheme 16).



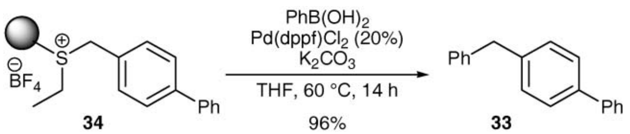
Scheme 15 Use of organoboroxines in Suzuki cross-coupling reactions.

In 2000, Mioskowski and co-workers reported the solid-phase synthesis of various diarylmethanes such as compound **33** through a palladium-catalyzed release of supported benzylsulfonium salts like **34** (Scheme 17).[30] Despite being original and useful, this method requires a high catalyst loading (20 mol% Pd) for moderate to excellent yields.

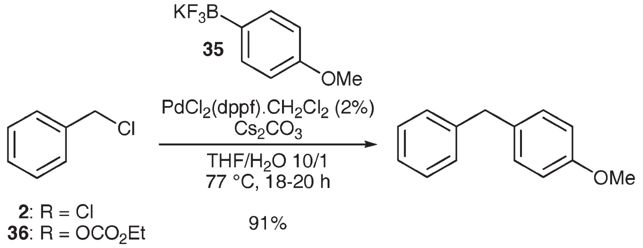
Very recently, Molander and Elia described the palladium-catalyzed synthesis of methylene-linked biaryl systems from benzylic halides and potassium aryltrifluoroborates like compound **35** (Scheme 18).[31] The air and moisture stability, the outstanding nucleophilicity, and the good functional group tolerance of potassium aryltrifluoroborates allowed access to a wide range of diarylmethane derivatives.



Scheme 16 Synthesis of difurans from organoboroxines.



Scheme 17 Solid-phase synthesis of diarylmethanes.



Scheme 18 Use of potassium trifluoroborates in Suzuki coupling reaction.

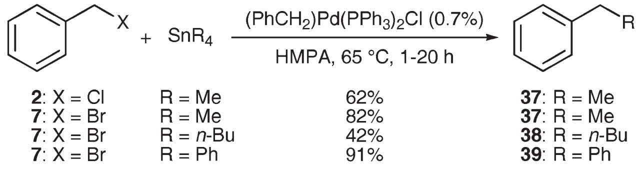
Stille reactions

Stille cross-coupling reactions involving benzylic derivatives are rare. In 1979, Milstein and Stille reported the synthesis of alkylbenzenes **37–38** and diphenylmethane **39** with moderate to very good yields, using benzylchlorobis(triphenylphosphine)palladium as the precatalyst (Scheme 19).[32] Inversion of configuration of the benzylic carbon is detected when α-deuteriobenzyl bromide is used as the substrate.

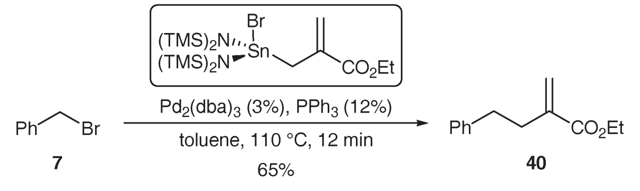
In 1997, Fouquet and co-workers prepared new non-toxic and easily removable monoorganotin reagents from Lappert's stannylene and applied them in cross-coupling reactions with benzyl bromide **7**, leading to allylbenzyl derivatives such as compound **40** (Scheme 20).[33]

More recently, Alami and co-workers described the synthesis of highly substituted enynes **41** *via* a tandem Stille–carbopalladation–Stille sequence (Scheme 21).[34] The mechanism proposed by the authors first involves a Stille coupling step producing the benzylic alkyne intermediate **42**. A regio- and stereoselective benzylpalladation step can then occur to provide vinylpalladium intermediate **43**, which undergoes transmetallation and reductive elimination to generate the resulting enyne **41**.

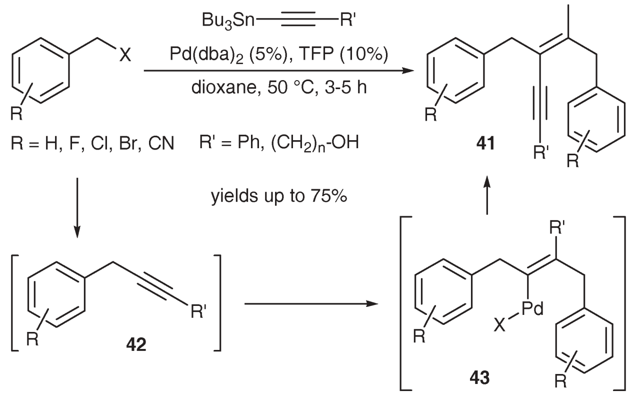
In 2005, Taylor and co-workers prepared and used new air and moisture stable *N*-succinimide palladium(II) complexes in Stille cross-coupling reactions with benzylic halides and aryl or vinylstannanes (Scheme 22).[35] Furthermore, this new type of complex allowed the authors to perform the reactions under mild conditions, avoiding the use of toxic additives such as HMPA (hexamethyl phosphoramide).



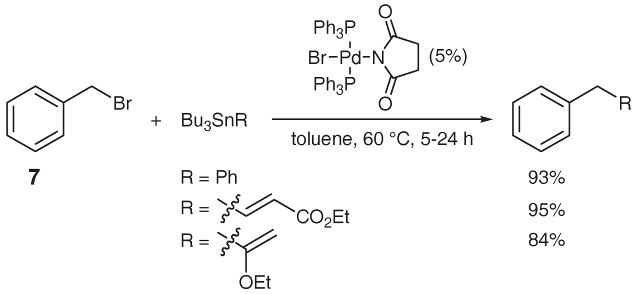
Scheme 19 Stille coupling reactions with benzylic halides.



Scheme 20 Synthesis of allylbenzylic derivatives using Stille coupling reactions with benzyl bromide.



Scheme 21 Palladium-catalyzed reaction of benzylic halides and alkynyl tributyltin reagents (TFP = tri-2-furylphosphine).

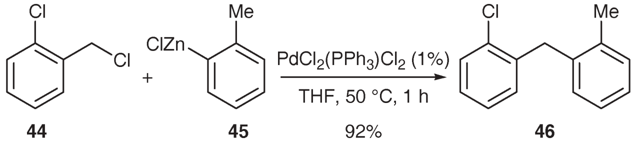


Scheme 22 Stille coupling reactions using new *N*-succinimide palladium(II) complexes.

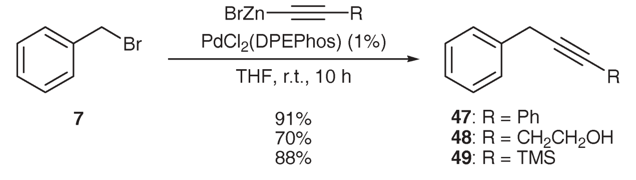
Negishi reactions

Negishi cross-coupling reactions with benzylic halides have only attracted minor attention. In 1998, Brandsma and co-workers reported the coupling of *o*-chlorobenzyl chloride **44** and arylzinc chloride **45** in the presence of 1 mol% of PdCl$_2$(PPh$_3$)$_2$ leading to diarylmethane **46** (Scheme 23).[36]

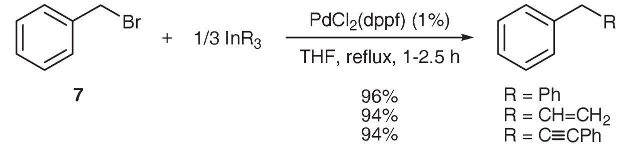
Qian and Negishi recently described the synthesis of benzylic alkynes, such as compounds **47–49**, starting from benzyl bromide **7** and various alkynylzinc derivatives (Scheme 24).[37] The authors showed the high efficiency of PdCl$_2$(DPEPhos) as catalyst precursor.



Scheme 23 Chemoselective Negishi coupling with *o*-chlorobenzyl chloride **44**.



Scheme 24 Negishi coupling with benzyl bromide and alkynylzinc derivatives (DPEPhos = bis(*o*-diphenylphosphinophenyl)ether).



Scheme 25 Palladium-catalyzed cross-coupling between organoindium derivatives and benzyl bromide.

Cross-coupling reactions with other organometallic substrates

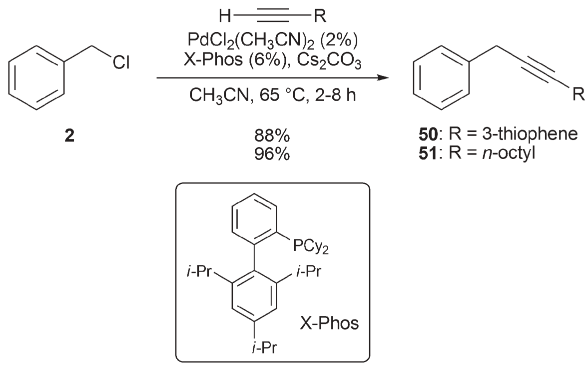
Other than the use of traditional organometallic partners in cross-coupling reactions (B, Sn, Zn,…), some new reagents have recently emerged in the literature and have shown a high efficiency. In 2001, Sarandeses and co-workers employed various triorganoindium derivatives with benzyl bromide **7** in the presence of a catalytic amount of PdCl$_2$(dppf) (Scheme 25).[38] The reaction proceeds under mild conditions (no base), with atom economy, and provides the products in excellent yields. Very recently, organo[2-(hydroxymethyl)phenyl]dimethylsilanes have emerged as a new class of silane coupling reagents for the cross-coupling reaction with allylic and benzylic carbonates.[39]

Sonogashira reactions

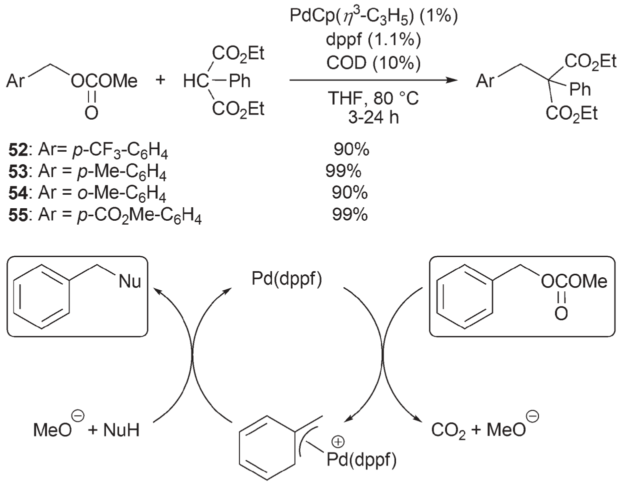
An alternative approach for the synthesis of benzylic alkynes is the use of Sonogashira coupling reactions. One example has been reported so far, by Buchwald and co-workers.[40] Under copper-free conditions, compounds **50** and **51** have been prepared from benzyl chloride **2** and the corresponding terminal alkyne in very good yields, using PdCl$_2$(CH$_3$CN)$_2$ and X-Phos as the catalytic system (Scheme 26).

Tsuji–Trost reactions

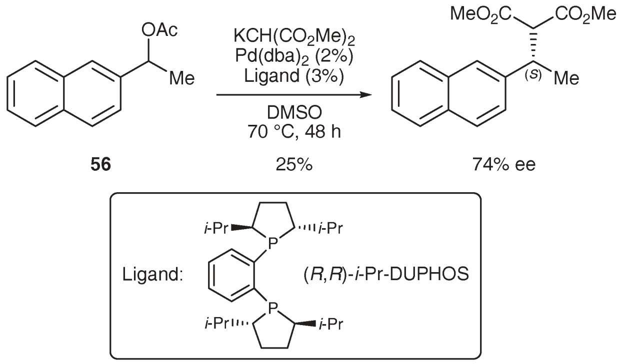
Palladium-catalyzed nucleophilic substitution on benzylic derivatives has been independently studied by the groups of Fiaud and Kuwano.[41,42] The latter used benzylic carbonates like **52–55** and a combination of PdCp(η^3-C$_3$H$_5$) and dppf (1,1′-bis(diphenylphosphino)ferrocene) to react with various nucleophiles (Scheme 27).[42] In addition, the authors employed a catalytic amount of COD (1,5-cyclooctadiene) to stabilize the active palladium(0) species. Moreover, the reaction was conducted without a base. It is suggested that the nucleophile is deprotonated by the methoxide anion generated *in situ* from the carbonate, with concomitant generation of carbon dioxide.



Scheme 26 Copper-free Sonogashira coupling with benzyl chloride.



Scheme 27 Tsuji–Trost reaction on benzylic carbonates.

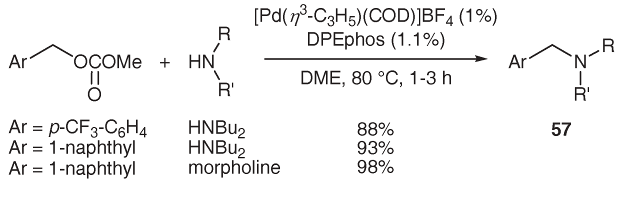


Scheme 28 Enantioselective benzylic alkylation.

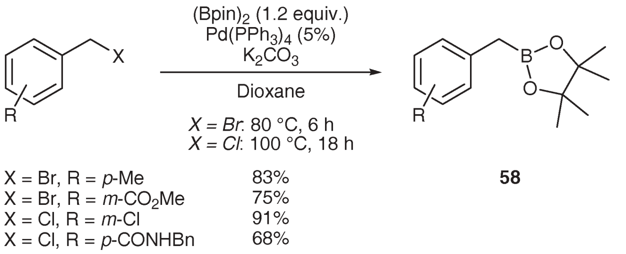
Tsuji–Trost reactions with benzylic derivatives have also been performed in an asymmetric fashion. Fiaud and co-workers employed DUPHOS ligands and obtained good enantioselectivity in the benzylic alkylation of 1-(2-naphthyl) ethyl acetate **56** (Scheme 28).[41] Low isolated yields can be explained by the formation of the vinylnaphthalene by-product coming from undesired base-promoted elimination.

Carbon–heteroatom bond-forming reactions

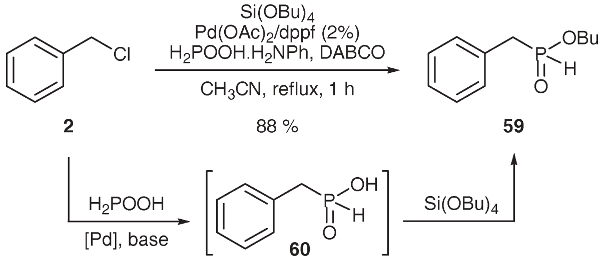
Palladium-catalyzed cross-coupling reactions have also been used to create carbon–heteroatom bonds from benzylic substrates. With [Pd(η^3-C$_3$H$_5$)(COD)]BF$_4$, Kuwano and co-workers prepared various tertiary benzylamines **57** from benzylic carbonates and secondary amines (Scheme 29).[43] Sulfones were also prepared upon activation of benzylic carbonates.[44]



Scheme 29 Palladium-catalyzed synthesis of benzylamines.



Scheme 30 Carbon–boron bond forming reaction under Suzuki coupling conditions.



Scheme 31 Synthesis of benzylphosphinate derivatives by action of $H_2POOH{\cdot}H_2NPh$ and $Si(OBu)_4$ on benzylic chloride.

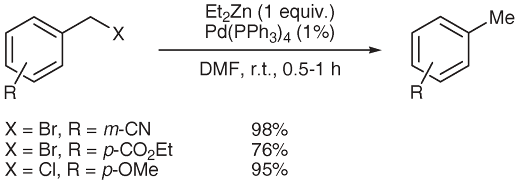
In 2004, Giroux reported the synthesis of pinacol benzylic boronates **58** obtained from various substituted benzylic halides and bis(pinacolato)diboron (Bpin)$_2$, using Suzuki coupling conditions (Scheme 30).[45]

Recently, Montchamp and co-workers showed that benzylphosphinate **59** could be obtained in very good yield from benzyl chloride **2**, *via* the concomitant action of anilinium hypophosphite $H_2POOH{\cdot}H_2NPh$ and silicate $Si(OBu)_4$ in basic conditions (Scheme 31).[46] The authors proposed that the reaction proceeds through the palladium-catalyzed formation of intermediate **60** generated from hypophosphite acid and the base. The latter can then react with the silicate and lead to the desired product.

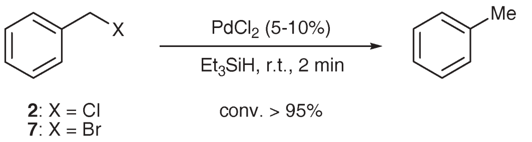
Hydrodehalogenation

Whereas the reduction of benzylic halides often appears as a side-reaction, it has been the central subject of some studies found in the literature. In the mid-90s, Agrios and Srebnik reported that diethylzinc was able to reduce various substituted benzylic halides in the presence of a catalytic amount of Pd(PPh$_3$)$_4$ (Scheme 32).[47]

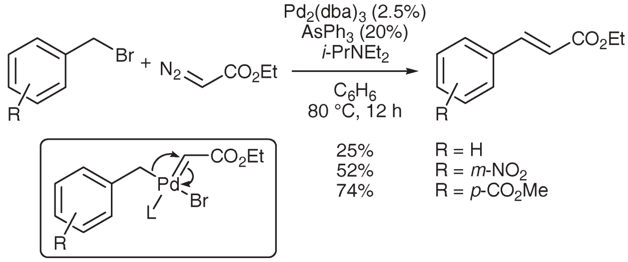
Chatgilialoglu and co-workers also described palladium-catalyzed hydrodehalogenation reactions of benzyl chloride **2** and bromide **7** in nearly quantitative conversions, using triethylsilane as a hydride transfer agent as well as the solvent (Scheme 33).[48]



Scheme 32 Palladium-catalyzed reduction of benzylic halides with diethylzinc.



Scheme 33 Palladium-catalyzed reduction of benzylic halides with triethylsilane.



Scheme 34 Synthesis of cinnamate derivatives by carbene insertion.

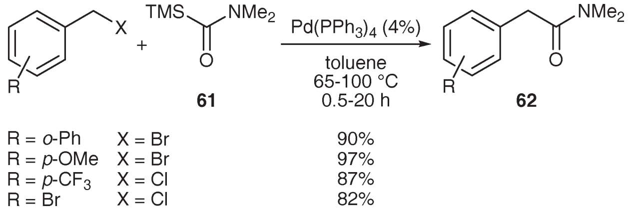
Carbene insertion – homologation

An alternative to the synthesis of cinnamate derivatives has been recently described by Greenman and Van Vranken (Scheme 34).[49] The reaction proceeds *via* migratory-insertion of a carbene–palladium species, generated *in situ* from ethyl diazoacetate. The atypical use of triphenylarsine as the ligand, in order to avoid any side reactions between phosphines and the diazo moiety is noteworthy.

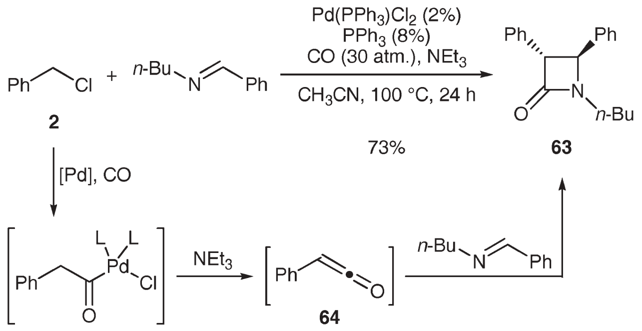
At the same time, Cunico and Pandey used the carbamoylsilane **61** as a carbene precursor to form a wide range of *N*,*N*-dimethylcarbamoyl benzylic compounds **62**, in the presence of a catalytic amount of Pd(PPh$_3$)$_4$ (Scheme 35).[50]

Multicomponent reactions

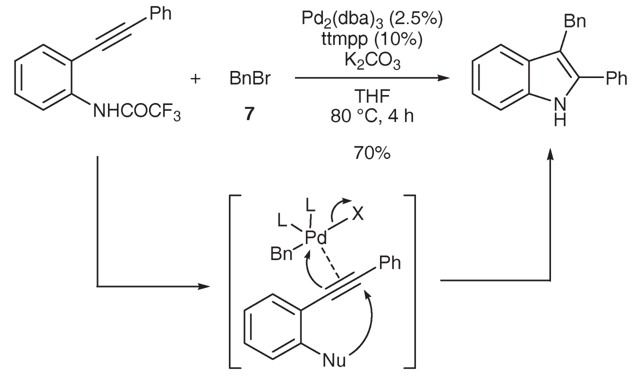
A multicomponent reaction is a reaction where three compounds at least react together to form one single product. As well as many examples described with aryl halides as one of the components, benzylic halides have also been involved with success in this chemistry. In 1999, Shim and co-workers proposed an unprecedented palladium-catalyzed synthesis of β-lactams such as compound **63**. It is assumed that benzyl chloride **2** is first converted into the unstable ketene **64** under carbon monoxide pressure (Scheme 36).[51] The latter undergoes [2 + 2] cycloaddition with *N*-butylbenzaldimine to give the β-lactam **63** with good yield.



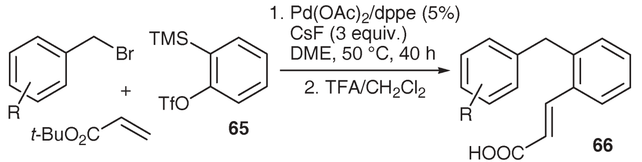
Scheme 35 Palladium-catalyzed synthesis of benzylic amides.



Scheme 36 Palladium-catalyzed synthesis of β-lactams under carbon monoxide pressure.



Scheme 37 Synthesis of indole derivatives from benzyl bromide and propargylic alkynes (ttmpp = tris(2,4,6-trimethoxyphenyl)phosphine).



R = H	65%
R = *o*-NO$_2$	58%
R = *m*-Cl	91%
R = *m*-OMe	62%
R = *p*-CN	89%

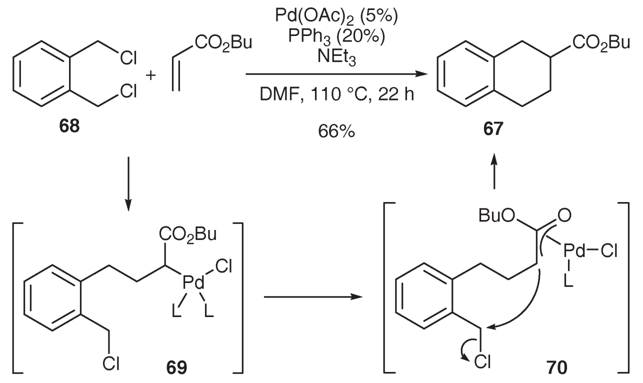
Scheme 38 Three-component coupling of various benzylic bromides.

In 2000, Cacchi and co-workers reported the synthesis of indole derivatives, from benzyl bromide **7** and propargylic alkynes (Scheme 37).[52] The reaction first proceeds by the oxidative addition of benzyl bromide **7**, producing a palladium(II) intermediate complex which activates the triple bond. The latter then undergoes intramolecular aminopalladation, and leads to the indole upon reductive elimination.

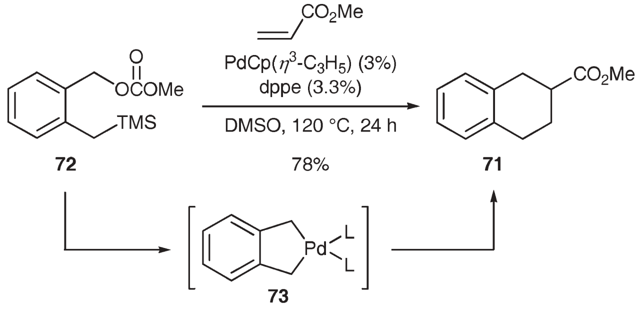
Substituted benzylic bromides, benzyne precursor 2-(trimethylsilyl)phenyl triflate **65**, and electron-poor alkenes have recently been used by Greaney and co-workers to generate various diarylmethane derivatives **66** (Scheme 38).[53]

Miscellaneous transformations

Very recently, Bruneau and co-workers described the palladium-catalyzed synthesis of functional tetralins such as compound **67**, obtained from α,α′-dichloro-*o*-xylene **68** and butyl acrylate (Scheme 39).[54] The mechanism proposed by the authors first proceeds like a Heck reaction to produce intermediate **69**. Then, instead of the expected β-hydride elimination, the latter could be converted into palladium enolate **70**, which undergoes electrophilic attack on the second electrophile (CH$_2$-Cl) and leads to tetralin **67**.



Scheme 39 Palladium-catalyzed synthesis of tetralins from α,α′-dichloro-*o*-xylene **68**.



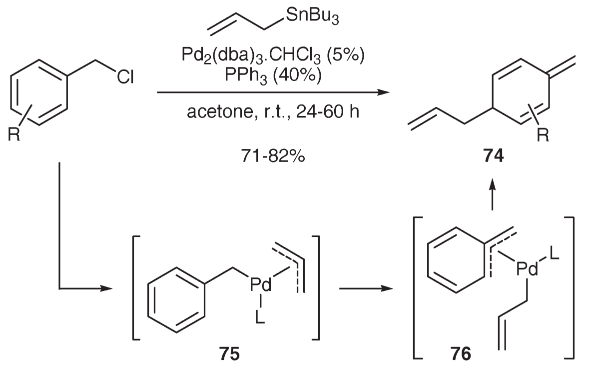
Scheme 40 Palladium-catalyzed synthesis of tetralins from *o*-[(trimethylsilyl)-methyl]benzyl carbonate **72**.

The same type of tetralin derivatives have also been obtained by Kuwano and Shige from [4 + 2] cycloaddition of formal *o*-xylylene and various olefins.[55] The authors suggested that tetralin **71** could be formed from *o*-[(trimethylsilyl)methyl]benzyl carbonate **72** *via* intermediate **73** in the presence of PdCp(η^3-C$_3$H$_5$) and dppe as catalyst precursor (Scheme 40).

In 2001, Yamamoto and co-workers reported an original and unpredicted dearomatization reaction under Stille coupling conditions.[56] In the presence of allyltributyl stannane and a catalytic amount of palladium, various benzylic chlorides have been converted in high yields into allylative dearomatization products **74** (Scheme 41). DFT studies on the mechanism of the reaction later revealed that the kinetically favored formation of product **74** probably goes through isomerization of Pd(η^1-benzyl)(η^3-allyl)(L) **75** into Pd(η^3-benzyl)(η^1-allyl)(L) **76**.[57]

Conclusion

In this review we have outlined the progress made in three decades in the area of direct palladium-catalyzed activation and functionalization of benzylic substrates with a special



Scheme 41 Palladium-catalyzed allylative dearomatization of benzylic chlorides under Stille coupling conditions.

focus on the recent transformations. They mainly involve carbon–carbon bond forming reactions, including all types of well-known reactions usually carried out from aryl halides and pseudo-halides, such as Heck, Suzuki, Stille, Negishi, Sonogashira coupling reactions, as well as carbonylation reactions. Carbon–heteroatom bond forming reactions have also been performed but to a less extent. The future of this chemistry probably lies in the combination of the above reactions with other catalytic reactions in tandem and multi-component intra- and intermolecular transformations. Developments of asymmetric versions of some of the above palladium-catalyzed transformations from benzylic substrates should also provide useful synthetic applications.

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