Science of Synthesis

Knowledge Updates 2016/2

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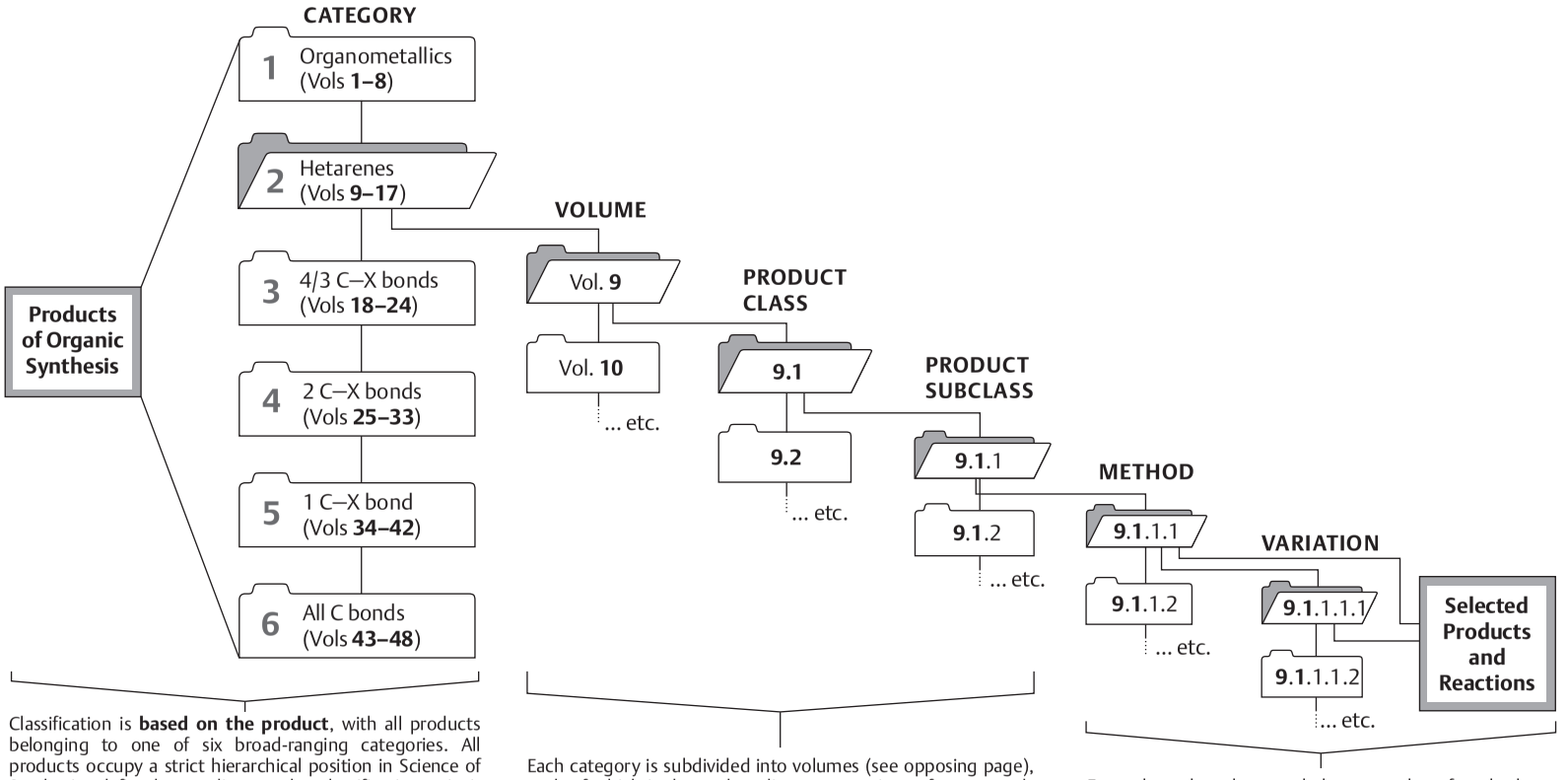
Organizational Structure of Science of Synthesis*

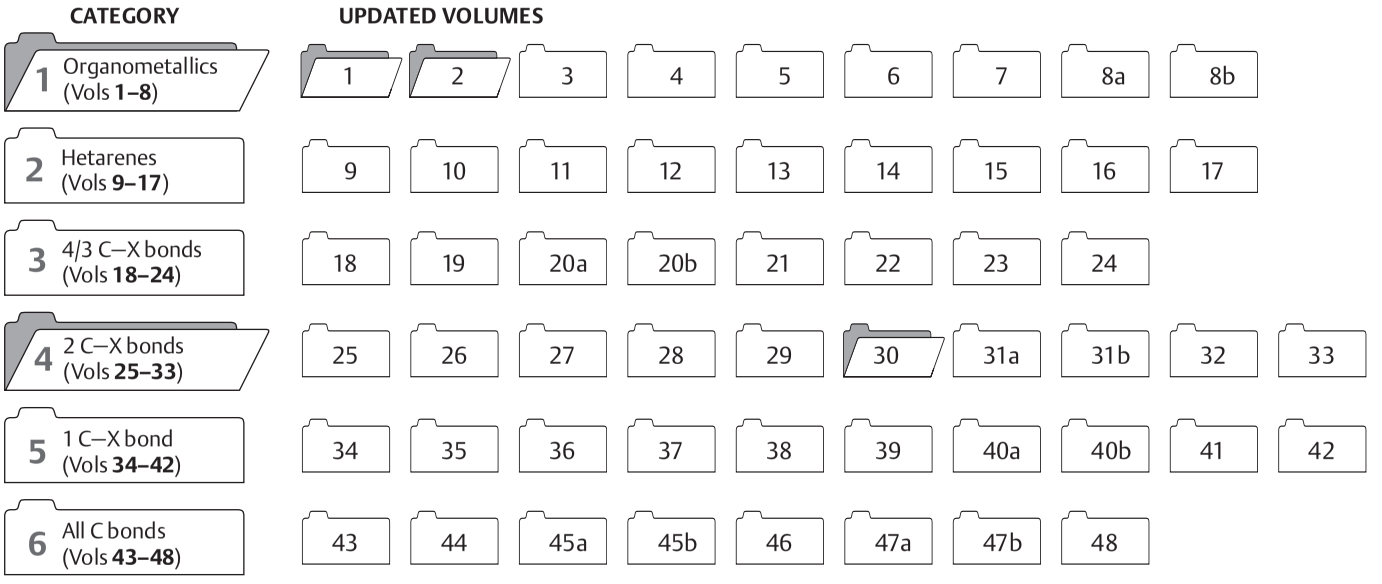
* A complete description of the full classification principles can be found in the **Science of Synthesis Guidebook.**



Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products in Categories 3–6 are organized according to oxidation state, with products containing the greatest number of carbon–heteroatom (C—X) or C—C π-bonds to a single carbon occupying the highest positions (e.g., carboxylates, enolates, and alcoholates are covered in Categories 3, 4, and 5, respectively).

Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., "Thiophenes" is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., "Thiophene 1,1-Dioxides" is Product Subclass 3 of Product Class 10 of Volume 9). Consequently, the relationship between heading name and heading number varies below product class level within individual volumes.

For each product class or subclass, a number of methods are described for synthesizing the general product type. Often there are variations on a method given. Both methods and variations contain experimental procedures with relevant background information and literature references. **Selected products and reactions** display the scope and limitations of the methods.



1 Compounds with Transition Metal—Carbon π-Bonds and Compounds of Groups 10–8 (Ni, Pd, Pt, Co, Rh, Ir, Fe, Ru, Os)
2 Compounds of Groups 7–3 (Mn···, Cr···, V···, Ti···, Sc···, La···, Ac···)
30 Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues

* Detailed listings of product classes and subclasses, methods, and variations can be found in the **Table of Contents** sections of every volume.

Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

Science of Synthesis presents the important synthetic methods for all classes of compounds and includes:

- Methods critically evaluated by leading scientists
- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope

Science of Synthesis

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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

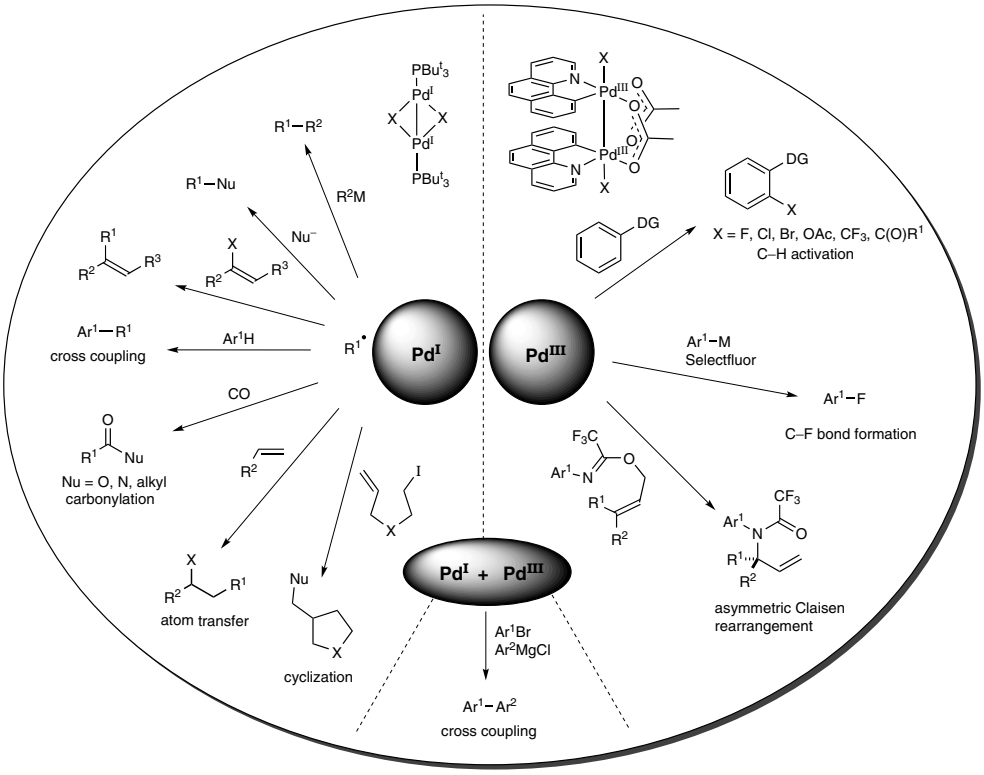
The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

The Editorial Board July 2010

Abstracts

Palladium(0) and palladium(II) species are frequently used as catalysts and are considered to be active intermediates in traditional palladium-catalyzed coupling reactions, participating in oxidative addition and reductive elimination via two-electron-transfer processes. Meanwhile, the catalytic modes involving palladium(I) and palladium(III) have been gradually developed. Single-electron-transfer pathways are thought to be involved via related catalytic cycles. Various palladium(I) and palladium(III) complexes have been synthesized and characterized. The palladium(I) precatalysts in Suzuki coupling and Buchwald–Hartwig amination exhibit higher reactivity than traditional palladium(0) and palladium(II) catalysts. Palladium-catalyzed single-electron-transfer conditions allow alkyl halides to participate in a series of cross-coupling, carbonylation, atom-transfer, and cyclization reactions, in which the palladium(I) species and various alkyl radicals are thought to be key intermediates. Palladium(III) species have been proposed as active intermediates in various directed C—H activation reactions. Moreover, it has been proved that palladium(III) intermediates can catalyze C—F bond formation and asymmetric Claisen rearrangement reactions. Beyond these systems, it is thought that palladium(I) and palladium(III) species might take part in the same system. In summary, radical-type palladium-catalyzed systems possess new properties which help to realize various otherwise difficult transformations.



Keywords: bond construction · palladium(I) catalysis · palladium(III) catalysis · radical processes

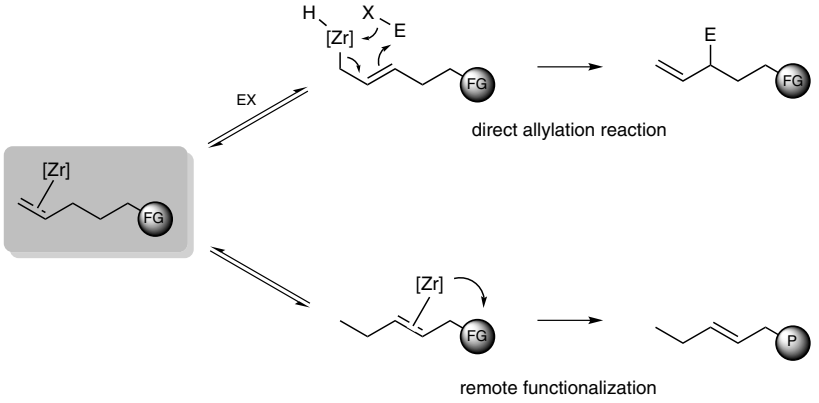
New p 113

2.11.15 C(sp^3)—H Functionalization by Allylic C—H Activation of Zirconocene Complexes

A. Vasseur and J. Bruffaerts

Zirconocene-assisted allylic C(sp^3)—H activation allows the remote functionalization of alkenes through multipositional migration of the olefinic double bond as a communicative process between two distant sites. The transformation involves the successive formation of zirconacyclopropane species along an alkyl chain. This C—H activation promoted migration proceeds rapidly under mild conditions. Moreover, it occurs in a unidirectional manner if associated with thermodynamically favored termination steps such as elimination, selective carbon–carbon bond activation, or ring expansion. The remotely formed zirconocene species can subsequently react with a variety of electrophilic carbon, oxygen, or nitrogen reagents to give a wide range of added-value products from simple substrates. Transmetalation processes further increase the synthetic potential by allowing the remote formation of a new carbon–carbon bond. The global transformation is not

only stereo- and regioselective, but also enables the relay of stereochemical information. Alternatively, a ziconacyclopropane/crotylzirconocene hydride equilibrium can be promoted under particular reaction conditions, leading to direct regio- and stereoselective allylation reactions with acid chloride, aldehyde, diketone and imine derivatives.



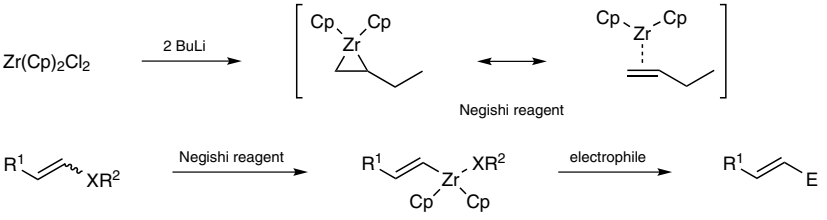
Keywords: zirconocenes · allylic C—H activation · alkenes · conjugated dienes · trienes · homoallylic alcohols · homoallylic amines · alkenylcyclopropanes · cyclopropanols · diastereoselectivity · quaternary stereocenters

New p 147

2.11.16 **Synthesis and Reactivity of Heteroatom-Substituted Vinylzirconocene Derivatives and Hetarylzirconocenes**

J. Bruffaerts and A. Vasseur

Reactive and stereodefined vinylzirconocene derivatives are efficiently prepared from a variety of different heterosubstituted alkenes in the presence of a stoichiometric amount of the Negishi reagent. This chapter describes the synthesis of these compounds along with their applications in the synthesis of various substituted alkenes.



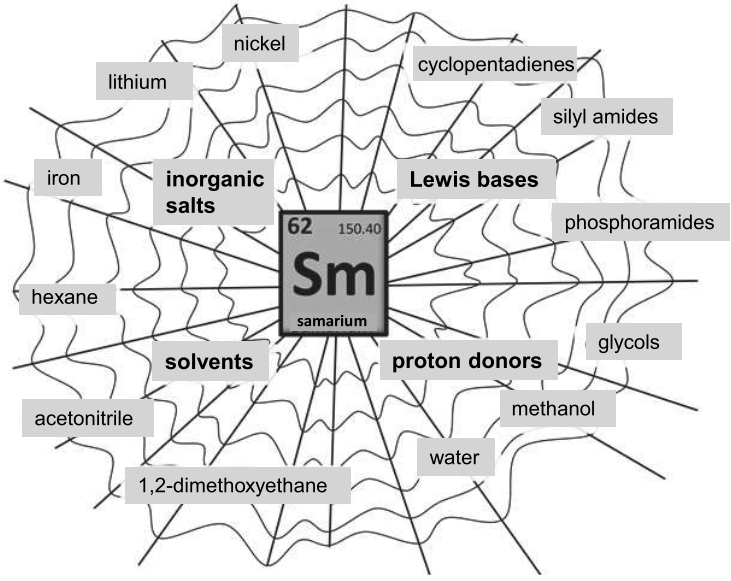
Keywords: organometallic compounds · zirconocenes · alkenes · vinyl compounds · stereoselective synthesis · elimination

New p 177

2.12.17 **The Role of Solvents and Additives in Reactions of Samarium(II) Iodide and Related Reductants**

T. V. Chciuk and R. A. Flowers, II

The use of additives with samarium(II) iodide (SmI_2) greatly impacts the rate, diastereoselectivity, and chemoselectivity of its reactions. Additives that are commonly utilized with samarium(II) iodide and other samarium(II)-based reductants can be classified into three major groups: (1) Lewis bases such as hexamethylphosphoric triamide (HMPA) and other electron-donor ligands and chelating ethers; (2) proton donors, such as water, alcohols, and glycols; and (3) inorganic additives such as nickel(II) iodide, iron(III) chloride, and lithium chloride. In addition, the solvent milieu can also play an important role in the reactivity of samarium(II) reductants, predominantly through changes in the coordination sphere of the metal. The main focus of this chapter is on the use of additives and solvent milieu to provide selective and efficient reactions, with at least one example being given for each subclass of samarium(II)-promoted reaction.



Keywords: cross-coupling reactions · electron transfer · hexamethylphosphoric triamide · inorganic additives · intramolecular cyclization · Lewis bases · proton donors · reductive coupling · ring expansion · samarium(II) iodide · solvent effects

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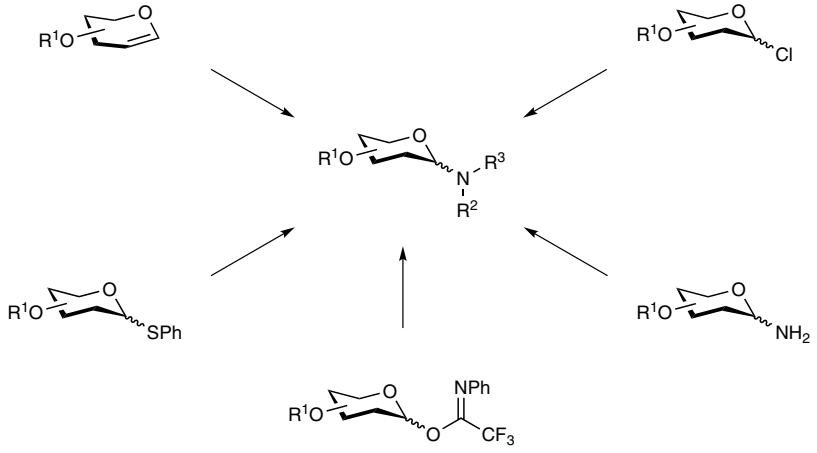
30.1.3 Carbohydrate Derivatives (Including Nucleosides)

T. Nokami

O,*N*-Acetals are found in various types of organic molecules and are core motifs in carbohydrates, including nucleosides. This chapter summarizes the synthetic methods to prepare N-linked glycopeptides, ribonucleosides, 2-deoxyribonucleosides, and others. Glycosylation between the anomeric carbon and the nitrogen atom of a nucleophile is a conventional method for the synthesis of these molecules, but stereoselectivity highly depends on the structures of the substrates. Glycosylamines are also important precursors for the stereoselective synthesis of N-linked glycopeptides and ribonucleosides.



Keywords: aminoglycosides · carbohydrates · glycopeptides · glycosylation · nucleosides

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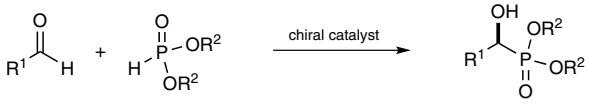
30.2.3 *O*,*P*-Acetals

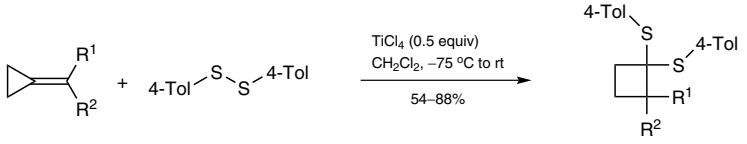
K. Murai and H. Fujioka

This chapter is an update to the earlier *Science of Synthesis* contribution (Section 30.2) describing methods for the synthesis of *O*,*P*-acetals. It focuses on the literature published in the period 2006–2015. Key methods covered include the addition of phosphorus compounds to carbonyl groups (including enantioselective variations), kinetic resolution of α-hydroxyphosphonates, oxidation of α,β-unsaturated phosphorus compounds, addition of phosphorus compounds to *O*,*O*-acetals, reduction of acylphosphonates and related compounds, and aldol-type reactions of keto phosphonates.



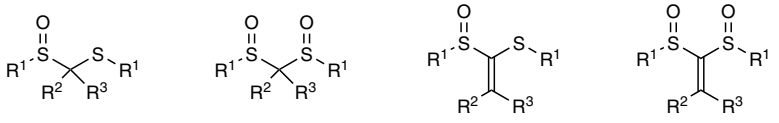
Keywords: *O*,*P*-acetals · asymmetric synthesis · diastereoselectivity · enantioselectivity · kinetic resolution · hydrogenation · organocatalysis · oxidation · epoxidation · reduction · phosphorus compounds · Pudovik reaction

This chapter is an update to the earlier *Science of Synthesis* contribution (Section 30.3.1) describing methods for the preparation of acyclic *S*,*S*-acetals. It focuses on the literature published in the period 2006–2014, presenting complementary information with respect to new developments and transformations. It also contains an important extension of the coverage of the previous contribution. Key methods covered include the thioacetalization of carbonyl compounds using a variety of catalysts, conversion of *O*,*O*-acetals, addition of thiols to C—C multiple bonds, addition of disulfides to methylenecyclopropanes, and ring opening of 1,2-cyclopropanated 3-oxo sugars with thiols.



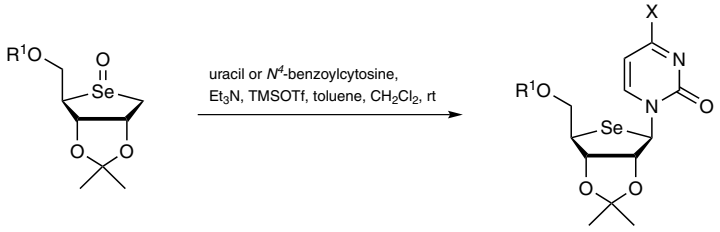
Keywords: acetals · carbonyl compounds · chemoselectivity · Lewis acid catalysts · *S*,*S*-acetals · supported catalysis · surfactants · thiols · ring opening

This chapter is an update to the earlier *Science of Synthesis* contribution (Section 30.3.6) published in 2007. *S*,*S*-Acetal *S*-oxides and *S*,*S*′-dioxides are synthesized by the reaction of sulfanyl- or sulfinyl-stabilized carbanions with electrophiles or by the (asymmetric) oxidation of *S*,*S*-acetals. Reaction of a carbanion with an aldehyde or ketone followed by dehydration provides ketene *S*,*S*-acetal oxides. Recent advances in synthetic application have been seen in conjugate additions of nucleophiles or radicals to ketene *S*,*S*-acetal oxides and in reactions utilizing reactive sulfonium intermediates generated by treatment with acid anhydrides (Pummerer conditions).



Keywords: sulfur-stabilized carbanions · asymmetric oxidation · condensation · ketene dithioacetals · conjugate addition · cyclopropanation · cross-coupling reaction · hydrolysis · Pummerer conditions · benzo[*b*]chalcogenophenes

This chapter is an update to the earlier *Science of Synthesis* contribution (Section 30.5) concerning the synthesis and reactions of selenium- and tellurium-containing acetals. Recent interest has changed to the new field of *Se*,*N*- and *Te*,*N*-acetals including 4′-selenonucleosides, which may be used as unique building blocks for new DNA and RNA analogues. The published methods for *Se*,*N*- and *Te*,*N*-acetals could open up new applications in this field.



Keywords: *Se*,*Se*-acetals · *Se*,*Te*-acetals · *Se*,*N*-acetals · 4′-selenonucleosides · seleno-Pummerer reactions

This chapter is an update to the earlier *Science of Synthesis* contribution (Section 30.7) describing methods for the synthesis of *N*,*P*- and *P*,*P*-acetals. It focuses on the literature published in the period 2007–2014. As well as covering the synthesis of the title compounds, their applications in organic synthesis are also briefly reviewed.

Keywords: α-aminophosphonates · hydrophosphorylation · imines · Pudovik addition · Kabachnik–Fields three-component condensation · Horner–Wadsworth–Emmons alkenation · *gem*-bisphosphonates · phospha-Claisen condensation · Michaelis–Becker substitution · Michaelis–Arbuzov rearrangement

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Volume 30: Acetals: O/N, S/S, S/N, and N/N and Higher Heteroatom Analogues

1.2.7 Radical-Based Palladium-Catalyzed Bond Constructions

Y. Li, W. Xie, and X. Jiang

General Introduction

During the evolution of organic chemistry, palladium catalysts have played an important and irreplaceable role in studies on carbon–carbon[1–7] and carbon–heteroatom[8–10] bond formation. Beyond the methodological studies, palladium-catalyzed reactions have also been widely applied in the preparation of natural products,[11] pharmaceuticals, agrochemicals, and materials, even on large scale.[12] Palladium(0) and palladium(II) species are frequently used as the catalysts and considered as active intermediates, participating in oxidative addition and reductive elimination steps in two-electron-transfer processes.[1–15] Throughout the development of palladium chemistry, an increasing number of single-electron-transfer procedures have been proposed and carefully studied, which mainly involve palladium(I)[16] and palladium(III)[17] species. The focus of this chapter is on radical-based palladium-catalyzed bond constructions in organic synthesis.

1.2.7.1 Method 1: Reactions Involving Palladium(I) Species

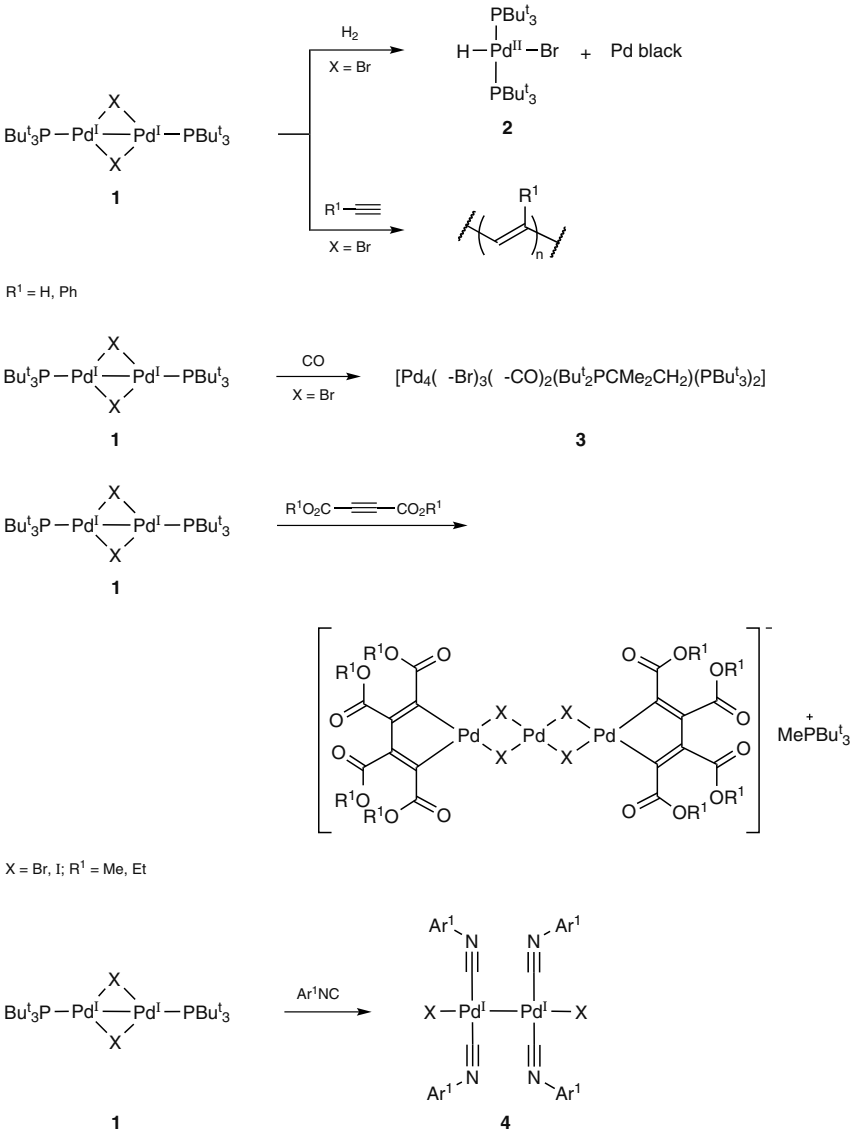
1.2.7.1.1 Variation 1: Synthesis of Organometallic Palladium(I) Complexes

Various palladium(I) complexes have been successfully synthesized, most of which exist as dimers. In previously reported reactions starting from palladium(I) complexes, the palladium species tended to undergo a single-electron oxidation to generate the corresponding palladium(II) complexes in monomeric or dimeric form. Besides the common ligand-exchange reactions, palladium(I) complexes have been transformed with hydrogen, carbon monoxide,[18,19] oxygen,[20] and even ammonia gas,[21] which has helped to further the understanding of palladium chemistry.

The complexes **1** ($\{PdX[P(t\text{-}Bu)_3]\}_2$; X = Br, I) are palladium(I) dimers of great significance that have been successfully isolated and transformed (Scheme 1).[18,19] When the dimer **1** (X = Br) is stirred under a hydrogen or carbon monoxide atmosphere, the new palladium hydride species **2** and CO-bridged palladium complex **3**, respectively, can be isolated and characterized. In addition, dimer **1** (X = Br) also reacts with terminal alkynes to produce polyethylene derivatives. When dimer **1** (X = I) is reacted with 1,2-disubstituted alkynes (diethyl or dimethyl but-2-ynedioate), a new trinuclear palladium species is formed.[19] Furthermore, an isonitrile also reacts efficiently with dimers **1** to generate new palladium(I) dimers **4**, which have four isonitrile units coordinated.

for references see p 111

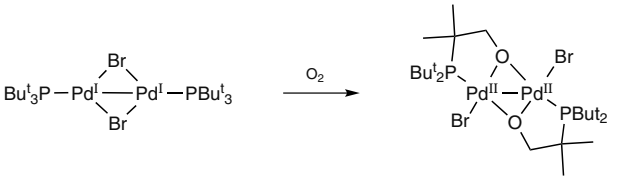
Scheme 1 Typical Reactions of Palladium(I) Dimers[18,19]



X	Yield (%)	Ref
Br	74	[19]
I	58	[19]

The palladium(I) dimer **1** (X = Br) can be reacted with aerial oxygen to produce the Pd–O–Pd bridge complex **5** through dual intramolecular C—H activation (Scheme 2).[20] It has been proposed, but not yet clearly confirmed, that the mechanism might include three steps: (1) coordination between the palladium(I) dimer and molecular oxygen with cleavage of the O=O bond; (2) intramolecular activation of two C—H bonds; and (3) the formation of new C—O bonds. In addition, it is not yet clear whether the two oxygen atoms originate from the same molecule of oxygen.

Scheme 2 Reaction of a Palladium(I) Dimer with Oxygen[20]

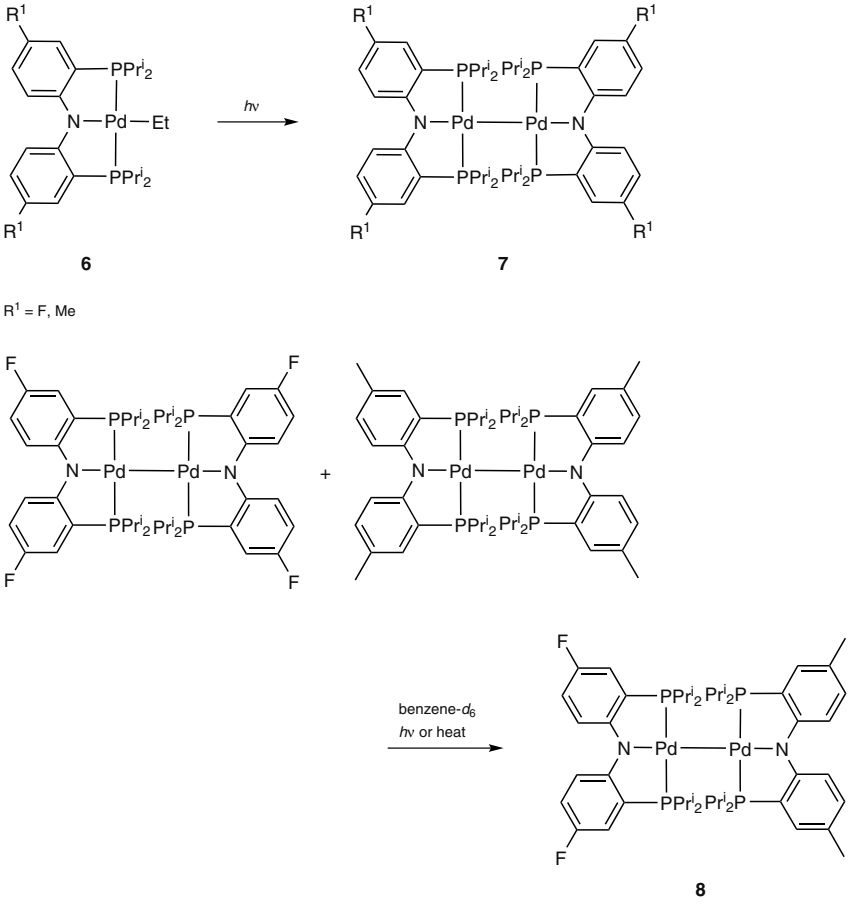


5

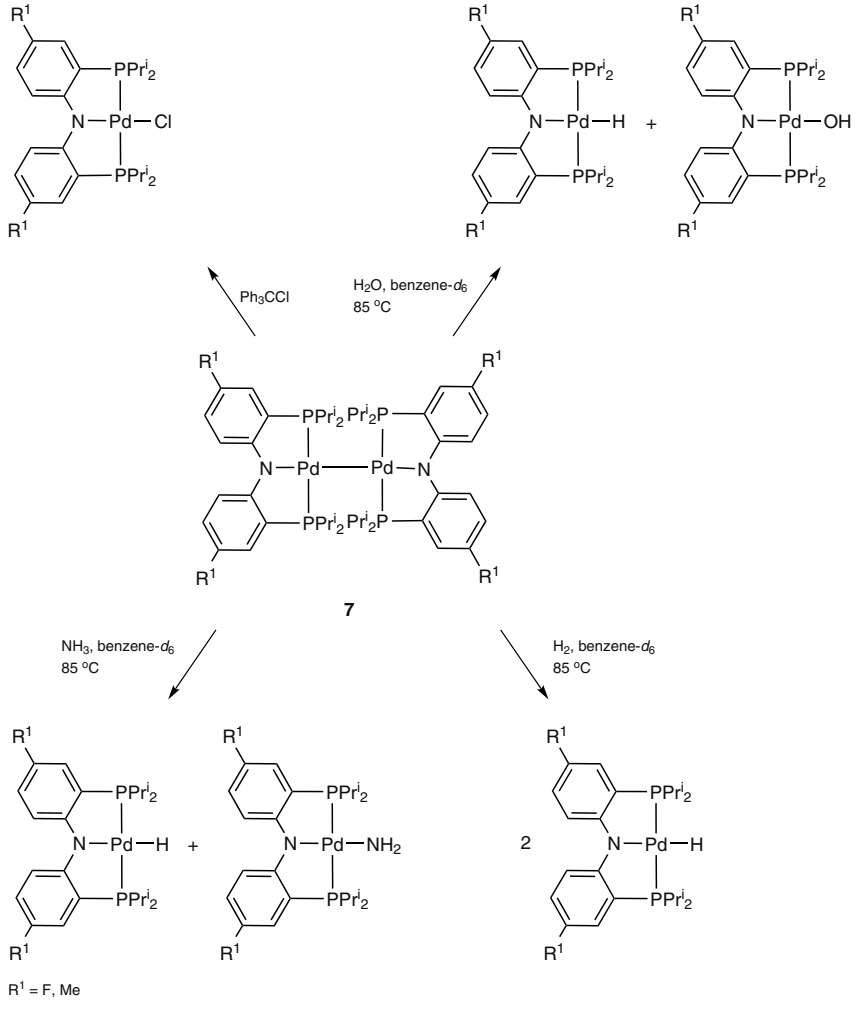
The photochemical homolysis of Pd—C bonds has been observed with the PNP-ligated palladium–alkyl complexes **6**, which form the (PNP)Pd—Pd(PNP) dimers **7** with a single Pd—Pd bond (Scheme 3).[21] X-ray diffraction reveals that each palladium center is four-coordinate with a distorted square-planar environment. In addition, electron paramagnetic resonance (EPR) experiments have helped to reveal that the PNP–palladium monomer is reversibly produced in solvent. In fact, thermolysis or photolysis of a 1:1 mixture of **7** (R^1 = F) and **7** (R^1 = Me) in benzene-d_6 results in the formation of a ca. 1:1:2 mixture of complexes **7** (R^1 = F), **7** (R^1 = Me), and **8**. More importantly, the palladium(I) dimers **7** react efficiently with dihydrogen, water, or ammonia via binuclear oxidative addition (Scheme 4).[21] The reaction with ammonia represents a new mode of activation.

for references see p 111

Scheme 3 Synthesis of (PNP)Pd—Pd(PNP) Dimers[21]



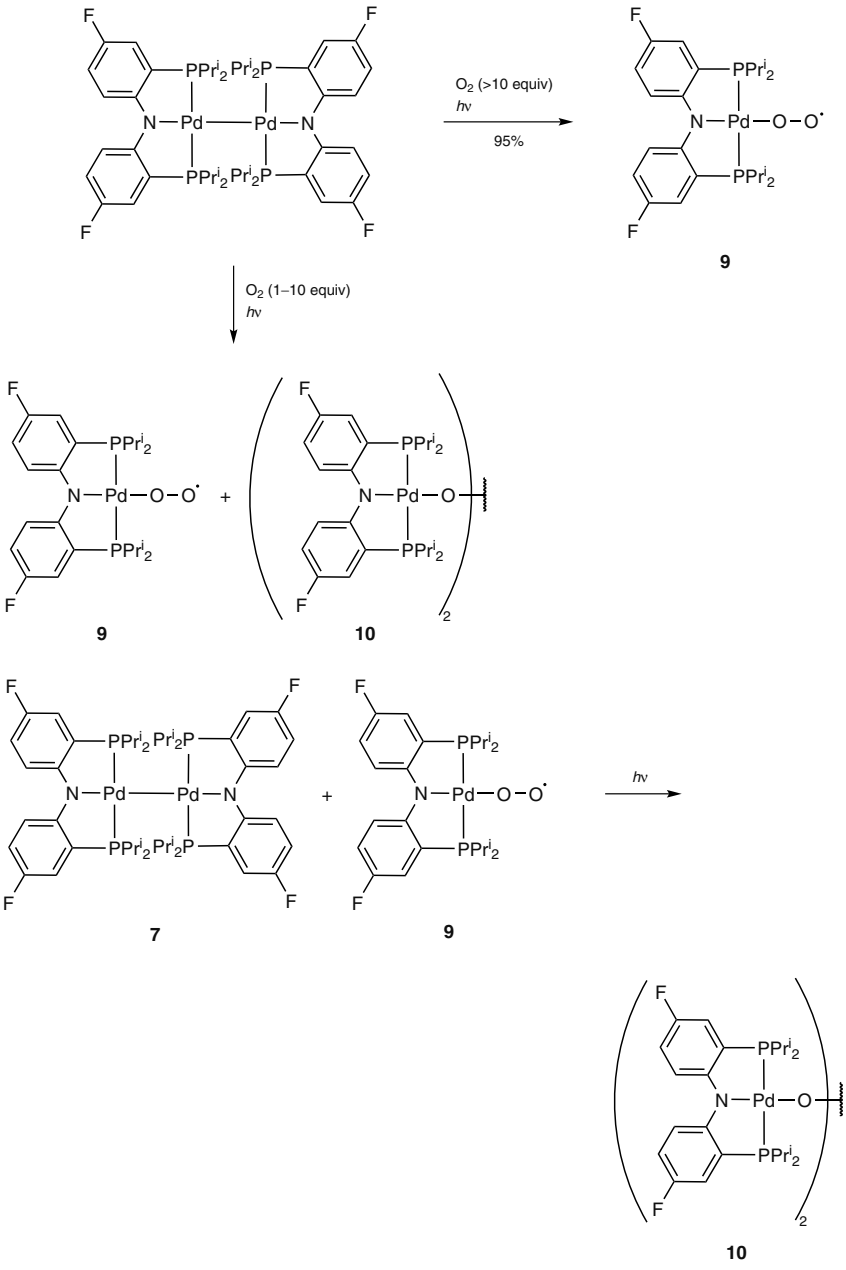
Scheme 4 Oxidative Addition to Palladium(I) Dimers[21]

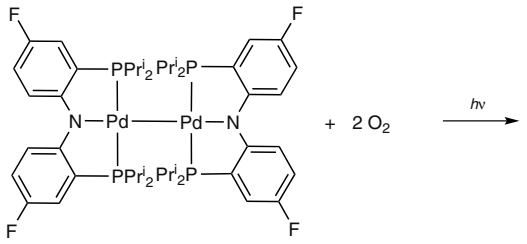


When the palladium(I) dimer **7** (R^1 = F) reacts with oxygen (1 atm, >10 equivalents) under irradiation by sunlight, it affords the palladium superoxide complex **9** in 95% yield within 1 minute (Scheme 5).[22] The mixture undergoes a rapid color change from the green of complex **7** (R^1 = F) to the orange of complex **9**. When the oxygen amount is less than 10 equivalents, the formation of complex **10** can be observed. By combining complex **7** (R^1 = F) and **9** in a ca. 1:2 ratio, it is possible to generate the complex **10** in relatively pure form. When the solution of complex **9** was concentrated, and the residue was redissolved and then irradiated, complex **10** was again detected, which further confirms the equilibrium between complexes **9** and **10**. In summary, the reaction between oxygen and dimer **7** (R^1 = F) is irreversible, but an equilibrium exists between oxygen, complex **9**, and complex **10** (Scheme 5).

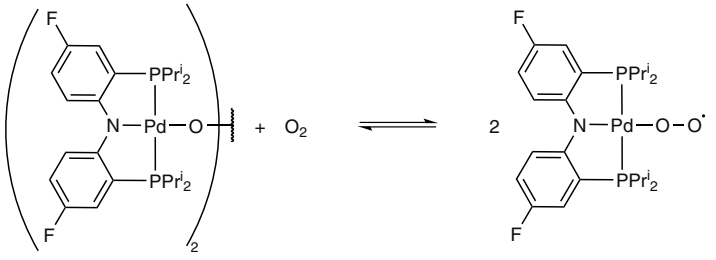
for references see p 111

Scheme 5 Oxidation of a Palladium(I) Dimer with Oxygen[22]





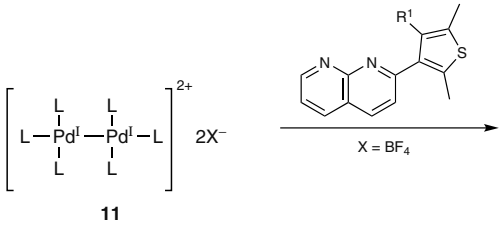
7



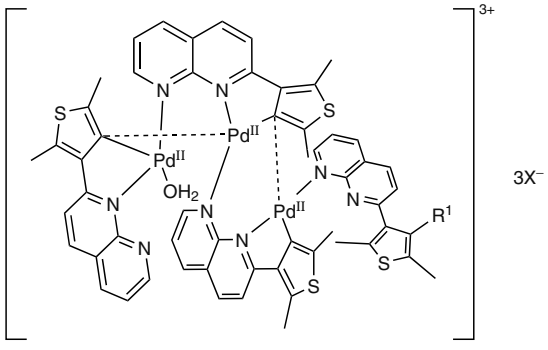
10 **9**

When the solvated complexes $[Pd_2(NCMe)_6]X_2$ **11** [X = BF_4, $NH_2\{B(C_6F_5)_3\}_2$] react with 2-substituted 1,8-naphthyridines, various di- or trinuclear palladium(II) cyclometalated complexes are obtained through C—H/Br activation under mild conditions (Scheme 6).[23]

Scheme 6 Formation of C—H Activated Complexes[23]

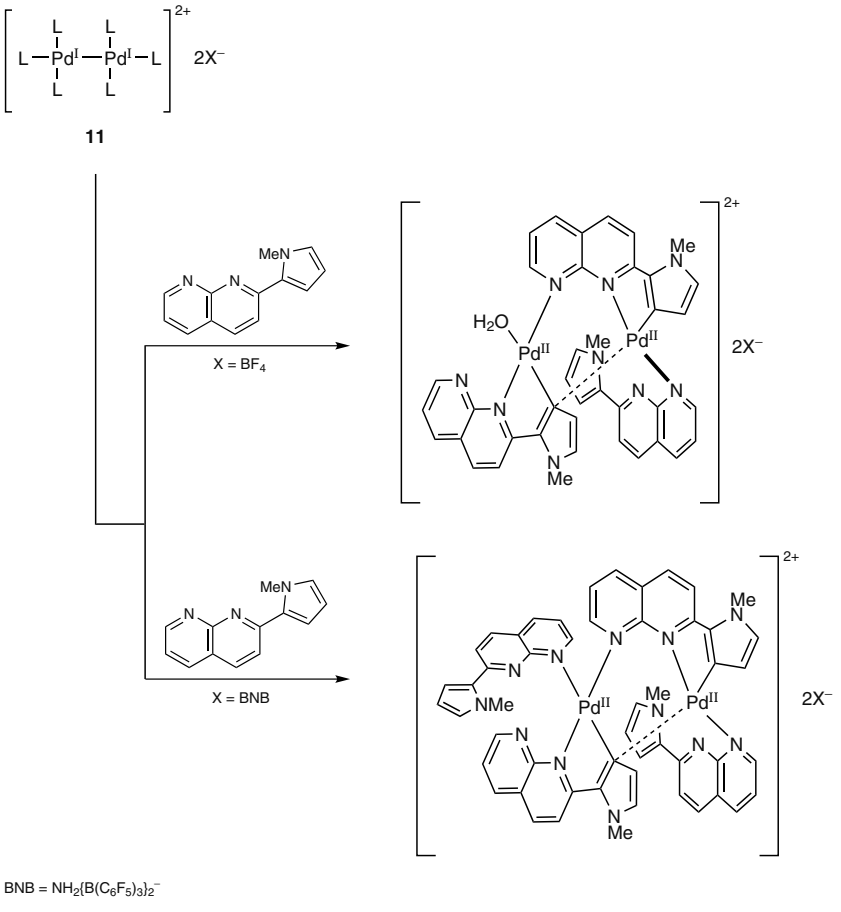


11



L = NCMe; R^1 = H, Br

for references see p 111

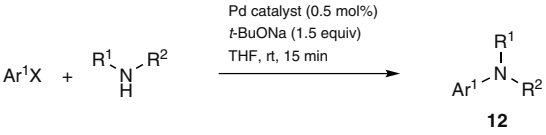


1.2.7.1.2 Variation 2: Reactions Involving Palladium(I) Precatalysts

Most commonly, palladium complexes have been introduced into reaction systems as palladium(0) or palladium(II) species. Since the investigation of palladium(I) catalysts, it has been shown that palladium(I) generally exhibits more efficiency in C—C and C—N bond-forming transformations, which is attributed to the easy generation of active palladium(0) species from the palladium(I) dimer complexes.[24–27] Suzuki couplings, Buchwald–Hartwig aminations, carbonylation couplings, and α-arylation of carbonyl compounds can all be achieved using palladium(I) precatalysts under mild conditions (room temperature) in shortened time (minutes). However, the development of other common cross coupling, oxidative coupling, reductive coupling, and C—H activation reactions is still to be achieved.

The seminal report of a reaction involving a palladium(I) precatalyst is that from Hartwig's group in 2002.[24] Air-stable palladium(I) dimers have been utilized to catalyze the coupling between various aryl bromides/chlorides and amines to give arylamines **12** (Scheme 7). The reactions are complete within minutes at room temperature, with excellent yields. The aryl halides can have an electron-withdrawing or electron-donating substituent; *ortho*-substitution is also tolerated. The amines can be secondary aliphatic ones, or primary or secondary aryl ones. Furthermore, the coupling between aryl bromides and phenylboronic acid has been presented, resulting in biaryls **13** (Scheme 8).

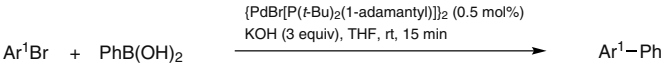
Scheme 7 Cross Coupling between Aryl Halides and Amines Using Palladium(I) Dimer Catalysts[24]



12

Ar^1	X	R^1	R^2	Catalyst	Yield (%)	Ref
4-Tol	Cl	$(CH_2)_2O(CH_2)_2$		$\{PdBr[P(t\text{-}Bu)_2(1\text{-adamantyl})]\}_2$	92	[24]
4-NCC_6H_4	Cl	Bu	Bu	$\{PdBr[P(t\text{-}Bu)_2(1\text{-adamantyl})]\}_2$	93	[24]
4-$O_2NC_6H_4$	Cl	Bu	Bu	$\{PdBr[P(t\text{-}Bu)_3]\}_2$	97	[24]
4-*t*-$BuO_2CC_6H_4$	Cl	Bu	Bu	$\{PdBr[P(t\text{-}Bu)_3]\}_2$	>99	[24]
4-*t*-BuC_6H_4	Br	Bu	Bu	$\{PdBr[P(t\text{-}Bu)_3]\}_2$	96	[24]
4-*t*-BuC_6H_4	Br	Me	Ph	$\{PdBr[P(t\text{-}Bu)_2(1\text{-adamantyl})]\}_2$	98	[24]
4-*t*-BuC_6H_4	Br	Ph	Ph	$\{PdBr[P(t\text{-}Bu)_3]\}_2$	96	[24]

Scheme 8 Suzuki Coupling Catalyzed by a Palladium(I) Dimer[24]



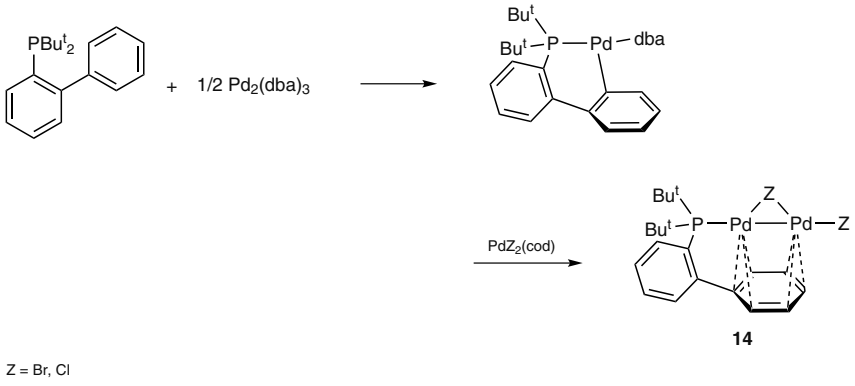
13

Ar^1	Yield (%)	Ref
4-Tol	95	[24]
2-NCC_6H_4	92	[24]
2-$F_3CC_6H_4$	90	[24]
2-$MeOC_6H_4$	96	[24]

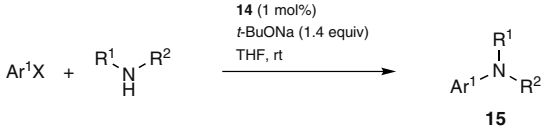
In 2004, new palladium(I)–palladium(I) dinuclear complexes **14** with one bridging halide were synthesized, in which only one phosphine is retained in the dinuclear core.[25] An unprecedented μ^2-η^3:η^3 coordination mode between a phenyl ring of the biphenyl-2-yldi-*tert*-butylphosphine ligand and the palladium(I) unit was present in the complexes (Scheme 9). Furthermore, the catalytic ability in the amination of aryl halides was concisely investigated (Scheme 10); both complexes efficiently catalyze the coupling between an aryl bromide/chloride and primary or secondary arylamines to give diarylamines **15**.

for references see p 111

Scheme 9 Synthesis of a Palladium(I)–Palladium(I) Dinuclear Complex[25]



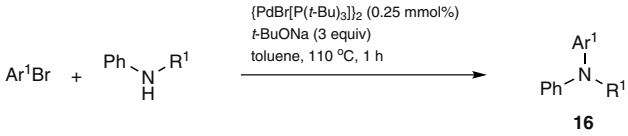
Scheme 10 Application of a Palladium(I)–Palladium(I) Dinuclear Complex in Cross Coupling between Aryl Halides and Amines[25]



Ar^1	X	R^1	R^2	Catalyst	Time (h)	Yield (%)	Ref
4-*t*-BuC$_6$H$_4$	Br	Ph	Ph	**14** (Z = Br)	19	86	[25]
4-*t*-BuC$_6$H$_4$	Br	Ph	Ph	**14** (Z = Cl)	19	76	[25]
4-Tol	Cl	4-Tol	H	**14** (Z = Br)	3	78	[25]
4-Tol	Cl	4-Tol	H	**14** (Z = Cl)	3	81	[25]

The palladium(I)-catalyzed amination of aryl bromides has been investigated with a focus on the use of secondary alkyl(aryl)amines and aryl bromides bearing electron-donating and electron-withdrawing groups (Scheme 11).[26] The reactions using the palladium(I) dimer were conducted in parallel with the use of palladium(II) acetate/tri-*tert*-butylphosphine; generally, the reactions with the palladium(I) dimer as catalyst afford better yields of amines **16**.

Scheme 11 Cross Coupling between Aryl Halides and Aryl(alkyl)amines[26]



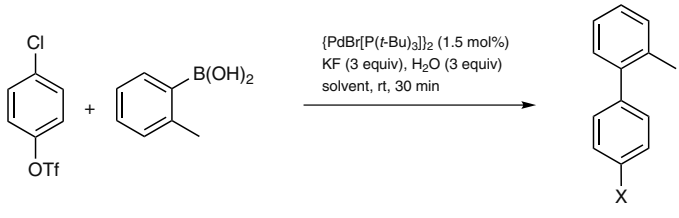
Ar^1	R^1	Yield[a] (%)	Ref
Ph	Cy	93 (86)	[26]
3-MeOC$_6$H$_4$	Cy	94 (89)	[26]
4-FC$_6$H$_4$	Cy	77 (71)	[26]

Ar^1	R^1	Yield[a] (%)	Ref
2-Tol	Cy	60 (52)	[26]
Ph	*t*-Bu	92 (87)	[26]
3-$MeOC_6H_4$	*t*-Bu	91 (90)	[26]
4-FC_6H_4	*t*-Bu	87 (87)	[26]
2-Tol	*t*-Bu	61 (12)	[26]

[a] Yields using $Pd(OAc_2)$ (1 mol%) and *t*-Bu_3P (1 mol%) are given in parentheses.

Control of the chemoselectivity of a palladium(I)-catalyzed Suzuki coupling has been realized by adjusting solvent polarity (Scheme 12).[27] Thus, reaction of 4-chlorophenyl trifluoromethanesulfonate in a polar solvent (acetonitrile) produces the C—OTf insertion product **17** (X = Cl) selectively; in contrast, use of the less-polar solvent tetrahydrofuran provides the C—Cl insertion product **17** (X = OTf). In addition, regioselective coupling has also been achieved with hetaryl halides **18** (Table 1). In mechanistic studies, ^{31}P NMR analysis and DFT calculations have been used to show that a Pd(I)L monomer is the real catalyst, and not the dimer. Detailed computational studies suggest that the active catalyst is generated through a reduction instead of homocleavage or direct disproportionation of the precatalyst. Meanwhile, ^{31}P NMR spectroscopy has confirmed that the combination of an arylboronic acid, potassium fluoride, and water triggers the generation of bis(tri-*tert*-butylphosphine)palladium(0) (Scheme 13). At the same time, a black precipitate forms, which is most likely palladium black. This phenomenon is assigned to the deactivation of catalyst and the incomplete conversion of aryl chlorides in palladium(I)-dimer-catalyzed Suzuki couplings.

Scheme 12 Suzuki Coupling of 4-Chlorophenyl Trifluoromethanesulfonate Using a Palladium(I) Catalyst in Different Solvents[27]

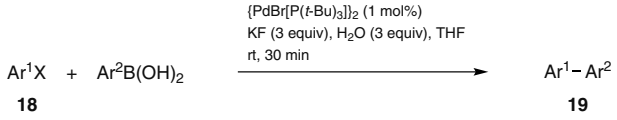


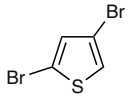
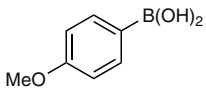
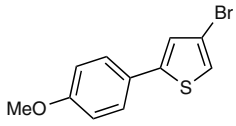
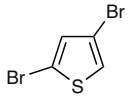
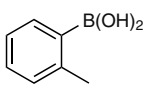
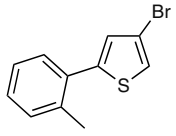
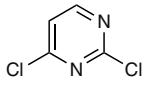
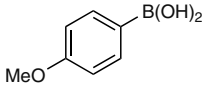
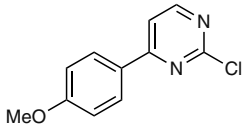
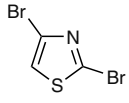
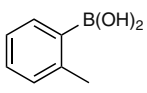
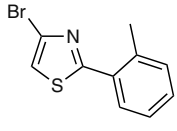
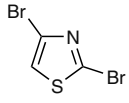
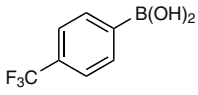
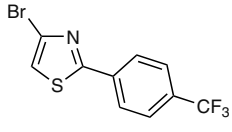
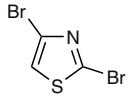
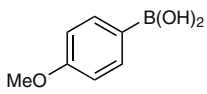
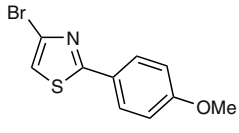
17

Solvent	X	Yield (%)	Ref
THF	OTf	76	[27]
MeCN	Cl	78	[27]

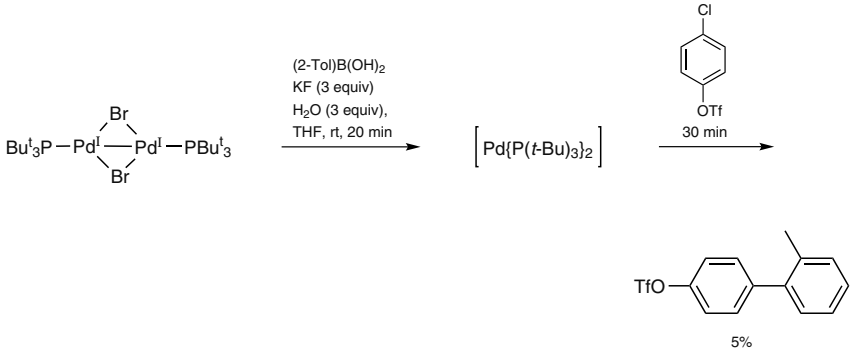
for references see p 111

Table 1 Selective Couplings of Dihalogenated Heterocycles[27]



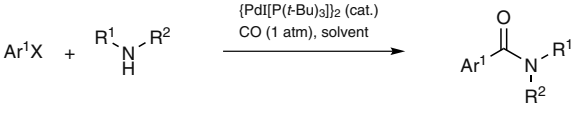
Starting Materials		Product	Yield (%)	Ref
Hetarene	Boronic Acid			
			90	[27]
			92	[27]
			82	[27]
			91	[27]
			87	[27]
			94	[27]

Scheme 13 Reactivity of 4-Chlorophenyl Trifluoromethanesulfonate with Bis(tri-*tert*-butylphosphine)palladium(0)[27]

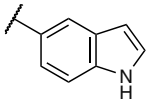


The palladium(I)-catalyzed carbonylative coupling of aryl halides and amines has been achieved under an atmospheric pressure of carbon monoxide (Scheme 14).[28] The reactions yield the desired products **20** in moderate to good yields within 10 minutes. Aryl iodides are better substrates than aryl bromides, and can be transformed with a lower catalyst loading and at a lower temperature. In light of the high efficiency, this system has been successfully applied in synthesizing radiolabeled amides **21** using ^{11}CO gas (Scheme 15).

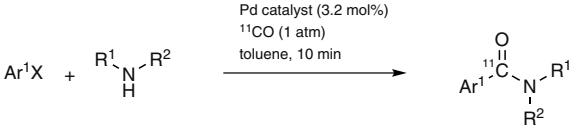
Scheme 14 Palladium(I)-Catalyzed Carbonylative Coupling of Aryl Halides and Amines[28]



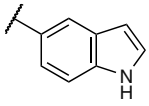
20

Ar^1	X	R^1	R^2	Solvent	Catalyst (%)	Temp (°C)	Yield (%)	Ref
Ph	Br	H	Bn	mesitylene	10	150	46	[28]
4-$MeOC_6H_4$	Br	H	Bn	mesitylene	10	150	46	[28]
2-$MeOC_6H_4$	Br	H	Bn	mesitylene	10	150	46	[28]
	I		$(CH_2)_5$	toluene	2.2	100	82	[28]

Scheme 15 Palladium(I)-Catalyzed Carbonylative Coupling of Aryl Halides and Amines Using ^{11}CO[28]



21

Ar^1	X	R^1	R^2	Catalyst	Trapped Radioactivity (%)	^{11}C Amide RCP[a] (%)	^{11}C Amide RCY[b] (%)	Ref
Ph	Br	H	Bn	$\{PdI[P(t\text{-}Bu)_3]\}_2$	87	81	70	[28]
Ph	Br	H	Bn	$\{PdI[P(t\text{-}Bu)_3]\}_2$	72	68	47	[28]
	I		$(CH_2)_5$	$\{PdI[P(t\text{-}Bu)_3]\}_2$	78	88	69	[28]

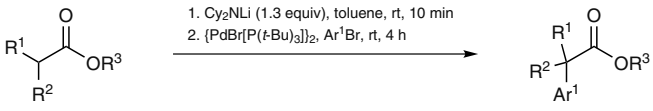
[a] RCP = radiochemical purity.
[b] RCY = radiochemical yield.

The cross coupling between aryl bromides and esters can also be catalyzed by $\{PdBr[P(t\text{-}Bu)_3]\}_2$ in a process promoted by lithium dicyclohexylamide (Scheme 16).[29] The catalyst loading is 0.05–0.5 mol%. The aryl bromides can be substituted by electron-withdrawing or electron-donating groups. In addition, pyridyl and thienyl bromides are also compatible. However, the choice of esters is limited to *tert*-butyl propanoate, methyl

for references see p 111

2-methylpropanoate, and *tert*-butyl acetate. It is worth noting that reactions with all three esters can be conducted on a 10-gram scale.

Scheme 16 α-Arylation of Esters Catalyzed by Palladium(I)[29]



22

R^1	R^2	R^3	Ar^1	$[PdBr[P(t\text{-}Bu)_3]]_2$ (mol%)	Yield (%)	Ref
H	H	*t*-Bu	4-*t*-BuC_6H_4	0.20	83	[29]
H	H	*t*-Bu	4-F_3C-C_6H_4	0.40	73	[29]
H	H	*t*-Bu	4-F-C_6H_4	0.40	82	[29]
Me	H	*t*-Bu	4-*t*-BuC_6H_4	0.04	87[a]	[29]
Me	H	*t*-Bu	4-F-C_6H_4	0.20	88	[29]
Me	H	*t*-Bu	2,4,6-$Me_3C_6H_2$	0.05	72	[29]
Me	Me	Me	4-*t*-BuC_6H_4	0.05	72	[29]
Me	Me	Me	4-F_3C-C_6H_4	0.50	60	[29]
Me	Me	Me	2-pyridyl	0.50	71	[29]
Me	Me	Me	3-thienyl	0.50	75	[29]

[a] Reaction was performed on a 40-mmol scale.

Arylamines 12**; General Procedure:**[24]
In a drybox, the Pd catalyst (0.005 M in THF), *t*-BuONa (144.0 mg, 1.50 mmol), an aryl halide (1.00 mmol), and an amine [1.05 mmol in THF (1 mL)] were added to a vial containing a stirrer bar. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The mixture was then stirred at rt for 15 min. After this time, H_2O (1 mL) was added into the vial, and the mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by column chromatography.

Biaryls 13**; General Procedure:**[24]
In a drybox, $\{PdBr[P(t\text{-}Bu)_3]\}_2$ (0.005 M in THF), KOH (168.0 mg, 3.0 mmol), $PhB(OH)_2$ (1.08 mmol), and an aryl bromide [1.00 mmol in THF (1.5 mL)] were added to a vial containing a stirrer bar. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. The mixture was then stirred at rt for 15 min. After this time, H_2O (1 mL) was added into the vial, and the mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by column chromatography.

Arylamines 15**; General Procedure:**[25]
To an argon-filled Schlenk tube containing a mixture of the catalyst **14** (0.01 mmol), *t*-BuONa (1.4 mmol), an aryl halide (1.0 mmol), and an amine (1.2 mmol) was added THF (1 mL). The resulting mixture was stirred at rt until the aryl halide was consumed, and then it was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by column chromatography (silica gel, hexane/EtOAc).

Alkyldiarylamines 16**; General Procedure:**[26]
To an argon-flushed, three-necked flask, containing $Pd(OAc)_2$ (12.8 mg, 0.057 mmol) or $\{PdBr[P(t\text{-}Bu)_3]\}_2$ (22.0 mg, 0.0285 mmol), *t*-BuONa (1.64 g, 17.1 mmol), an aniline (5.7 mmol), and an aryl bromide (6.9 mmol), was added dry, degassed toluene (20 mL). After stirring at rt for 15 min, $t\text{-}Bu_3P$ [only in the cases where $Pd(OAc)_2$ was used; 11.5 mg, 0.057 mmol] dissolved in toluene was added. Then, the mixture was heated to 108–110 °C and kept at the same temperature for 1 h. After cooling to rt, the reaction was quenched with H_2O (10 mL), and then the organic layer was washed with H_2O and concentrated. The crude product was purified by chromatography (silica gel).

2′-Methyl-[1,1′-biphenyl]-4-yl Trifluoromethanesulfonate (17**, X = OTf) or 4′-Chloro-2-methyl-1,1′-biphenyl (**17**, X = Cl); General Procedure:**[27]
A N_2-filled dry reaction vessel was charged with 4-chlorophenyl trifluoromethanesulfonate (276.0 mg, 1.1 mmol), 2-tolylboronic acid (146 mg, 1.1 mmol), and KF (186 mg, 3.2 mmol). After the vessel was transferred to a drybox, THF or MeCN (2 mL; previously deoxygenated for 30 min) and H_2O (3.0 equiv) were added and the mixture was stirred for 5 min. Then, $\{PdBr[P(t\text{-}Bu)_3]\}_2$ (12.4 mg, 0.016 mmol) was added and the mixture was stirred at rt for 30 min. The resulting mixture was subsequently diluted with Et_2O and filtered through silica using Et_2O as the eluant. The filtrate was concentrated in vacuo and purified by column chromatography.

Hetarenes 19**; General Procedure:**[27]
In a glovebox, to a N_2-filled dry reaction vessel containing the heterocyclic substrate (0.5 mmol) was added recrystallized, deoxygenated, and dried boronic acid (0.5 mmol), KF (87.0 mg, 1.5 mmol), and deoxygenated THF (1 mL). The mixture was stirred for 5 min and then $\{PdBr[P(t\text{-}Bu)_3]\}_2$ (4.1 mg, 0.005 mmol), THF (0.5 mL), and H_2O (3.0 equiv) were added (THF and H_2O were deoxygenated prior to use). After this, the mixture was stirred for an additional 30 min. Then, the mixture was quenched with Et_2O and filtered through silica gel, the filtrate was concentrated, and the residue was purified by column chromatography.

Benzamides 20**; General Procedure:**[28]

CAUTION: *Carbon monoxide is extremely flammable and toxic, and exposure to higher concentrations can quickly lead to a coma.*

To a CO-filled Schlenk tube, containing the catalyst complex (2.2 or 10 mol%), was added the aryl halide (0.45 mmol) and the amine ($BnNH_2$ or piperidine; 4.6 mmol) in the stated solvent. The mixture was stirred in a preheated oil bath for the desired time. Then, the reaction was quenched with 1 M aq HCl (4.5 mL). The rubber septum was removed and the unreacted CO was vented into the fumehood. The crude product mixture was extracted with CH_2Cl_2 (2 × 5 mL), the extracts were filtered and concentrated, and the residue was purified by column chromatography (silica gel).

For the preparation of ^{11}C-radiolabeled benzamides, the procedure was as described above but with the use of ^{11}CO instead of CO.

α-Aryl Esters 22**; General Procedure with *tert*-Butyl Propanoate:**[29]
In a drybox, to a 4-mL, screw-capped vial containing Cy_2NLi (0.243 g, 1.30 mmol) dissolved in toluene (2 mL), was slowly added the ester (1.10 mmol). After stirring at rt for 10 min, the soln was added to another 4-mL, screw-capped vial containing the aryl bromide (1.00 mmol) and catalyst $\{PdBr[P(t\text{-}Bu)_3]\}_2$. The vial was sealed with a cap containing a PTFE septum and removed from the drybox. After stirring at rt for 4 h, the mixture was diluted with Et_2O (30 mL) and then washed with 0.1 M HCl (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL). To the combined organic layers was added sat. aq $NaHCO_3$

for references see p 111

(30 mL), and the aqueous layer was back-extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (30 mL), the aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (silica gel, 2.5% EtOAc in hexanes).

***tert*-Butyl (4-*tert*-Butylphenyl)acetate (22, $R^1 = R^2 = H$; $R^3 = t$-Bu; $Ar^1 = 4$-t-BuC_6H_4); Typical Procedure on a Large Scale:**[29]

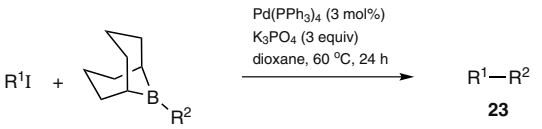
To a N_2-filled, 500-mL, three-necked round-bottomed flask equipped with a rubber septum, a glass stopper, and a stirrer-bar, was added Cy_2NH (10.3 mL, 0.052 mol) dissolved in toluene (300 mL). The mixture was stirred for 10 min at 0 °C, and then a 2.5 M soln of BuLi in hexane (20.7 mL, 0.052 mol) was added slowly to the cooled soln. Then, the mixture was stirred for 30 min at 0 °C. *tert*-Butyl acetate (5.93 mL, 0.044 mol) was added slowly over 20 min. The mixture was stirred for an additional 50 min at 0 °C. To another N_2-filled, pear-shaped, 10-mL flask, containing $\{PdBr[P(t\text{-}Bu)_3]\}_2$ (0.062 g, 0.0790 mmol), were added 1-bromo-4-*tert*-butylbenzene (6.93 mL, 0.040 mol) and toluene (5 mL). The mixture was transferred via cannula to the round-bottomed flask containing the lithium enolate of *tert*-butyl acetate. Toluene (2 × 5 mL) was used to wash the pear-shaped flask, and the wash was transferred to the round-bottomed flask. The mixture was stirred for 4 h at rt, and then concentrated until the reaction volume was reduced to half by rotary evaporation. A sat. aq soln of NH_4Cl (300 mL) was added, and the aqueous phase was washed with Et_2O (5 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated, and purified; yield: 7.90 g (79.5%).

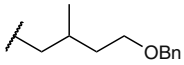
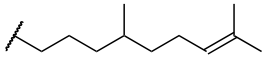
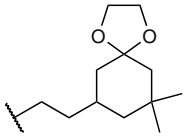
1.2.7.1.3 Variation 3: Cross-Coupling Reactions

Palladium-catalyzed cross-coupling reactions have been studied for about half a century. The typical mechanism involves oxidative addition and reductive elimination via two-electron transfer. Cross-coupling reactions involving alkyl halides, especially those with β-hydrogen atoms, are a challenge because of the slow rate of oxidative addition and the rapid rate of β-hydrogen elimination.[30] At the same time, cross-coupling reactions of the related alkylmetal compounds are also difficult because of the slow rate of transmetalation.[31] Recently, reactions that proceed via single-electron transfer processes have been developed, which have partially solved these problems. Generally, the radical properties of the reaction systems are supported by various radical-trapping experiments.

Cross coupling between 9-alkyl-9-borabicyclo[3.3.1]nonane (9-alkyl-9-BBN) derivatives and alkyl iodides has been achieved in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (Scheme 17).[30] Primary iodides, even including iodomethane, deliver the products **23** in 45–71% yield; neopentyl iodide (1-iodo-2,2-dimethylpropane) also reacts successfully. However, reactions with secondary iodides are not successful. In terms of the boranes, various functionalized compounds are tolerated, including the presence of alkene, ester, and acetal groups.

Scheme 17 Cross-Coupling Reactions of 9-Alkyl-9-borabicyclo[3.3.1]nonane Derivatives with Alkyl Iodides[30]

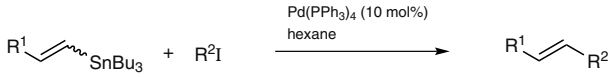


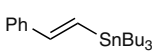
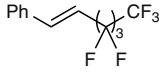
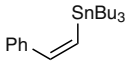
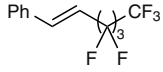
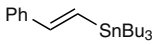
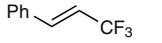
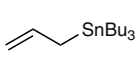
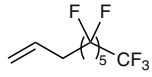
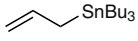
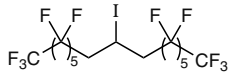
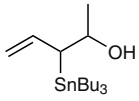
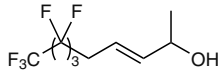
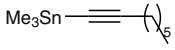
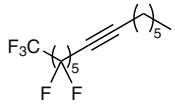
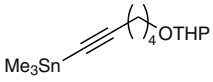
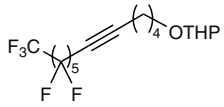
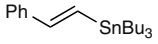
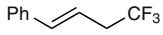
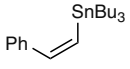
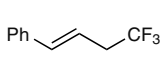
R^1	R^2	Yield (%)	Ref
Me	$(CH_2)_{10}CO_2Me$	71	[30]
$(CH_2)_5Me$	$(CH_2)_7Me$	64	[30]
$(CH_2)_5Me$		58	[30]
$(CH_2)_5Me$	$(CH_2)_{10}CO_2Me$	54	[30]
$(CH_2)_3CN$		61	[30]
$(CH_2)_3CO_2Me$		57	[30]
$(CH_2)_9Me$	(*E*)-CH=CHBu	64	[30]
$(CH_2)_9Me$	Ph	55	[30]

In 1987, reactions of polyfluoroalkyl iodides with organostannanes in a tetrakis(triphenylphosphine)palladium(0)-catalyzed Negishi coupling were reported (Table 2).[32] The stannane can be allyl-, alkenyl-, and alkynyl-substituted. It is worthy to note that even trifluoroiodomethane leads to the desired product, albeit with lower yield (entry 3). Both the *E*- and *Z*-isomers of alkenylstannanes react with an iodide to afford only products with *E* configuration (entries 1, 2, 9, and 10). A possible mechanism is the addition of a polyfluoroalkyl radical to the alkenylstannane, followed by the elimination of tributyliodostannane; the palladium(0) species is thought to act as a radical initiator (Scheme 18).

for references see p 111

Table 2 Cross Coupling of Polyfluoroalkyl Iodides and Organostannanes[32]



Entry	Starting Materials		Equiv of Iodide	Temp	Time (h)	Product	Yield (%)	Ref
	Stannane	Alkyl Iodide						
1		$F_3C(CF_2)_3I$	2	70 °C	4		70	[32]
2		$F_3C(CF_2)_3I$	2	70 °C	4		70	[32]
3		CF_3I	excess	80 °C	3		11[a]	[32]
4		$F_3C(CF_2)_5I$	1.2	rt	1		100	[32]
5		$F_3C(CF_2)_5I$	3	70 °C	3		64	[32]
6		$F_3C(CF_2)_3I$	2	70 °C	4		68	[32]
7		$F_3C(CF_2)_5I$	2	70 °C	6		55	[32]
8		$F_3C(CF_2)_3I$	2	70 °C	6		60	[32]
9		F_3CCH_2I	2	80 °C	4		38[a]	[32]
10		F_3CCH_2I	2	80 °C	4		35[a]	[32]

[a] Benzene was used as solvent.

Scheme 18 Possible Mechanism for the Introduction of a Polyfluoroalkyl Group to (*E*)-Tributyl(styryl)stannane[32]