



Name Reactions for Homologations

Part I

Edited by

Jie Jack Li

Bristol-Myers Squibb Company

Foreword by

E. J. Corey

Harvard University



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Dedicated to

Chris Limberakis, John Montgomery, and Derek A. Pflum

for the good ol'days in Ann Arbor

Foreword

Part of the charm of synthetic organic chemistry derives from the vastness of the intellectual landscape along several dimensions. First, there is the almost infinite variety and number of possible target structures that lurk in the darkness waiting to be made. Then, there is the vast body of organic reactions that serve to transform one substance into another, now so large in number as to be beyond credibility to a non-chemist. There is the staggering range of reagents, reaction conditions, catalysts, elements, and techniques that must be mobilized in order to tame these reactions for synthetic purposes. Finally, it seems that new information is being added to that landscape at a rate that exceeds the ability of a normal person to keep up with it. In such a troubled setting any author, or group of authors, must be regarded as heroic if through their efforts, the task of the synthetic chemist is eased.

These two volumes on methods for the extension of carbon chains by the use of coupling reactions brings to the attention of practicing synthetic chemists and students of chemistry a wide array of tools for the synthesis of new and useful molecules. It is a valuable addition to the literature by any measure and surely will prove its merit in years to come. The new knowledge that arises with its help will be impressive and of great benefit to humankind.

E. J. Corey
October 1, 2008

Preface

This book is the third volume of the series *Comprehensive Name Reactions*, an ambitious project conceived by Prof. E. J. Corey of Harvard University in the summer of 2002. Volume 1, *Name Reactions in Heterocyclic Chemistry*, was published in 2005 and was warmly received by the organic chemistry community. Volume 2, *Name Reactions for Functional Group Transformations* was published in 2007. After publication of the current Volume 3 and 4 on homologations in 2009, we plan to roll out Volume 5, *Name Reactions on Ring Formation* in 2010; and Volume 6, *Name Reactions in Heterocyclic Chemistry-2*, in 2011, respectively.

Continuing the traditions of the first two volumes, each name reaction in Volume 3 is also reviewed in seven sections:

1. *Description;*
2. *Historical Perspective;*
3. *Mechanism;*
4. *Variations and Improvements;*
5. *Synthetic Utility;*
6. *Experimental; and*
7. *References.*

I also introduced a symbol [R] to highlight review articles, book chapters, and books dedicated to the respective name reactions.

I have incurred many debts of gratitude to Prof. E. J. Corey. What he once told me — “*The desire to learn is the greatest gift from God*” — has been a true inspiration. Furthermore, it has been my great privilege and a pleasure to work with a collection of stellar contributing authors from both academia and industry. Some of them are world-renowned scholars in the field; some of them have worked intimately with the name reactions that they have reviewed; some of them even discovered the name reactions that they authored in this series. As a consequence, this book truly represents the state-of-the-art for *Name Reactions for Homologations*.

I welcome your critique.



Jack Li
October 1, 2008

Contributing authors:

Dr. Nadia M. Ahmad
Takeda Cambridge
418 Cambridge Science Park
Cambridge
CB4 0PA
United Kingdom

Dr. Marco A. Biamonte
Medicinal Chemistry
BIOGEN IDEC
5200 Research Place
San Diego, CA 92122

Dr. Victor Cee
Amgen, Inc.
Mailstop 29-1-B
One Amgen Center Drive
Thousand Oaks, CA 91320

Dr. Timothy T. Curran
Chemical Development
Vertex Pharmaceuticals
130 Waverly Street
Cambridge, MA 02139

Dr. Matthew J. Fuchter
Department of Chemistry
Imperial College London
London SW7 2AZ, UK

Dr. Paul Galatsis
Department of Chemistry
Pfizer Global Research & Development
Eastern Point Rd
Groton, CT 06340

Prof. Brian Goess
Department of Chemistry
Plyler Hall
Furman University
Greenville, SC 29613

Dr. David L. Gray
Pfizer Global Research & Development
Eastern Point Rd
Groton, CT 06340

Prof. Gordon W. Gribble
Department of Chemistry
6128 Burke Laboratory
Dartmouth College
Hanover, NH 03755

Dr. Timothy J. Hagen
Medicinal Chemistry
deCODE
2501 Davey
Woodridge, IL 60517

Dr. Xiaojun Han
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Dr. Chris Limberakis
Pfizer Global Research and Development
Eastern Point Road
Groton, CT 06340

Dr. Ivar M. McDonald
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Dr. John Mancuso
Department of Medicinal Chemistry
MethylGene Inc.
7220 Frederick-Banting Rd.
Montreal, PQ H4S 2A1, Canada

Dr. Vincent Mascitti
Pfizer Global Research and Development
Eastern Point Road
Groton, CT 06340

Prof. Richard J. Mullins
Department of Chemistry
Xavier University
3800 Victory Parkway
Cincinnati, OH 45207-4221

Dr. Jeremy M. Richter
Discovery Chemistry
Bristol-Myers Squibb Company
311 Pennington-Rocky Hill Road,
Pennington, NJ 08534

Dr. Frank Rong
ChemPartner
No.2 Building, 998 Halei Road
Zhangjiang Hi-Tech Park, Pudong
Shanghai, China 201203

Prof. Kevin M. Shea
Department of Chemistry
Clark Science Center
Smith College
Northampton, MA 01063

Xiangdong Alan Wang
Discovery Chemistry
Bristol-Myers Squibb Company
5 Research Parkway
Wallingford, CT 06492

Prof. John P. Wolfe
Department of Chemistry
University of Michigan
930 N. University Ave.
Ann Arbor, MI 48109

Dr. Larry Yet
Albany Molecular Research, Inc.
21 Corporate Circle
P.O. Box 15098
Albany, NY 12212-5098

Dr. Ji Zhang
Process Research & Development
Pharmaceutical Research Institute
Bristol-Myers Squibb
Princeton, NJ 08543-4000

Table of Contents

Foreword	vi
Preface	vii
Contributing Authors	viii
Chapter 1. Organometallics	1
Section 1.1 Palladium Chemistry	2
1.1.1 Heck reaction	2
1.1.2 Hiyama cross-coupling reaction	33
1.1.3 Kumada cross-coupling reaction	47
1.1.4 Negishi cross-coupling reaction	70
1.1.5 Sonogashira reaction	100
1.1.6 Stille coupling	133
1.1.7 Suzuki coupling	163
1.1.8 Tsuji–Trost reaction	185
Section 1.2 Organocopper Reagents	212
1.2.1 Castro–Stephens coupling	212
1.2.2 Glaser coupling	236
1.2.3 Ullmann reaction	258
Section 1.3 Other Organometallic Reagents	268
1.3.1 McMurry coupling	268
1.3.2 Nicholas reaction	284
1.3.3 Nozaki–Hiyama–Kishi reaction	299
1.3.4 Tebbe olefination	319
Chapter 2. Carbon-Chain Homologations	335
2.1 Arndt–Eistert homologation	336
2.2 Morita–Baylis–Hillman reaction	350
2.3 Benzoin condensation	381
2.4 Corey–Fuchs reaction	393
2.5 Henry reaction	404
2.6 Horner–Wadsworth–Emmons reaction	420
2.7 Julia–Lythgoe olefination	447
2.8 Knoevenagel condensation	474
2.9 Mukaiyama aldol reaction	502
2.10 Peterson olefination	521
2.11 Sakurai allylation reaction	539

2.12	Stetter reaction	576
2.13	Wittig reaction	588

Chapter 3.	Radical Chemistry	613
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3.1	Barton–McCombie deoxygenation	614
3.2	Barton nitrite photolysis	633
3.3	Sandmeyer reaction	648
3.4	Wohl–Ziegler reaction	661

Appendixes

Appendix 1,	Table of Contents for Volume 1: <i>Name Reactions in Heterocyclic Chemistry</i>	675
Appendix 2,	Table of Contents for Volume 2: <i>Name Reactions for Functional Group Transformations</i>	678
Appendix 3,	Table of Contents for Volume 4: <i>Name Reactions for Homologations-2</i>	680
Appendix 4,	Table of Contents for Volume 5: <i>Name Reactions for Ring Formations</i>	682
Appendix 5,	Table of Contents for Volume 6: <i>Name Reactions in Heterocyclic Chemistry-II</i>	684

Subject index	687
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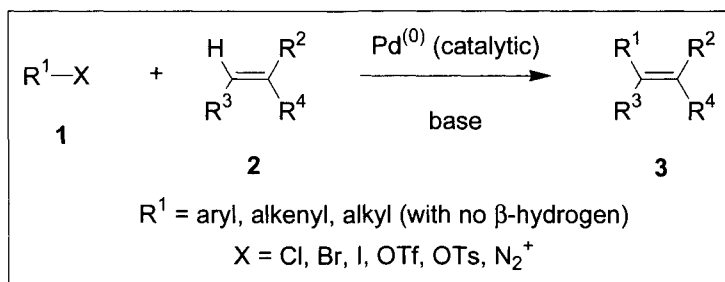
Chapter 1. Organometallics	1
<i>Section 1.1 Palladium Chemistry</i>	2
1.1.1 Heck reaction	2
1.1.2 Hiyama cross-coupling reaction	33
1.1.3 Kumada cross-coupling reaction	47
1.1.4 Negishi cross-coupling reaction	70
1.1.5 Sonogashira reaction	100
1.1.6 Stille coupling	133
1.1.7 Suzuki coupling	163
1.1.8 Tsuji–Trost reaction	185
<i>Section 1.2 Organocopper Reagents</i>	212
1.2.1 Castro–Stephens coupling	212
1.2.2 Glaser coupling	236
1.2.3 Ullmann reaction	258
<i>Section 1.3 Other Organometallic Reagents</i>	268
1.3.1 McMurry coupling	268
1.3.2 Nicholas reaction	284
1.3.3 Nozaki–Hiyama–Kishi reaction	299
1.3.4 Tebbe olefination	319

1.1.1 Heck Reaction

Mathew J. Fuchter

1.1.1.1 Description

The Heck reaction is the palladium-catalyzed alkenylation or arylation of olefins.¹⁻²⁴ It has become one of the most widely used C-C bond forming tools in organic synthesis.

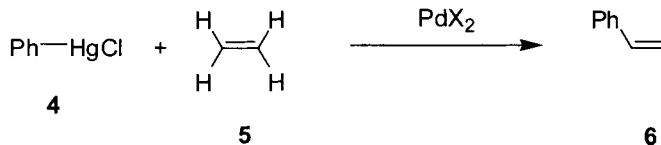


An extensive range of functional groups and substitution patterns on the olefin **2** are tolerated and aryl, alkenyl and some alkyl (lacking β -hydrogen atoms) electrophiles **1** are suitable reaction partners. The active catalyst is generated *in situ* from a variety of available palladium(0) or palladium(II) precatalysts ($\text{Pd}(\text{OAc})_2$, $\text{Pd}_2(\text{dba})_3$, *etc.*). A large number of ligands have been employed including phosphines, palladacycles and carbenes and even “ligand-free” conditions are commonly exploited.¹⁶ By using enantiomerically pure chiral ligands, the reaction can be rendered stereoselective (at centres adjacent to the newly formed olefin). A stoichiometric amount of base is needed, but in practice 3-5 molar equivalents are often used. Tertiary amine bases (for example Et_3N or PMP) or inorganic bases such as K_2CO_3 can be employed. Halide-scavenging additives (such as Ag_3PO_4) can be useful for aryl/alkenyl halide substrates, especially in the case of asymmetric Heck reactions. The reaction tolerates a range of solvents, however polar aprotic solvents such as DMF or NMP are most frequently utilized. The reaction most commonly takes place at elevated temperatures.

1.1.1.2 Historical Perspective

In the early 1970s, T. Mizoroki and R. F. Heck independently discovered that aryl, benzyl and styryl halides react with olefinic compounds and elevated temperature in the presence of a hindered amine base and a catalytic amount

of palladium.^{25,26} This was based on the previous work of Heck when he was at the Hercules Powder Company, Delaware in 1968. He discovered that when palladium(II) chloride (interestingly the use of palladium was inspired by a colleague studying the Wacker reaction) was dissolved in acetonitrile with phenylmercuric chloride (**4**) and ethylene gas (**5**), the presumed transient phenylpalladium chloride rapidly absorbed one equivalent of ethylene to produce styrene (**6**) in high yield.²⁷

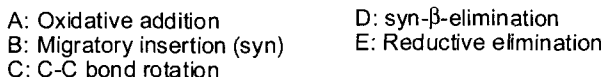


As reports began to appear on the formation of halo(aryl)palladium-phosphine complexes, Heck hypothesized that these intermediates could replace the arylmercurial-palladium combination. Crucially, he also reasoned that the use of a base to quench the hydrogen halide generated would render the reaction catalytic. In the 1970s the use of palladium was considered exotic and the reaction a mere curiosity, which meant its importance was underestimated for decades. In 1982, Heck published a review that contained all known examples in a mere 45 pages.

Today however, the paramount importance of organopalladium chemistry has propelled the Heck reaction into one of the most widely used catalytic C–C bond forming reactions. This was driven by its operational simplicity, unprecedented functional group compatibility and wide applicability. Indeed, from materials science to enantioselective organic synthesis, nearly every sub-discipline of modern organic chemistry has embraced the Heck reaction. It is hard to overstate its importance and in fact, this reaction may also be considered as a forerunner to all other widely used palladium-catalyzed couplings (Stille, Suzuki, Negishi, Hiyama, *etc.*). Perhaps the greatest social impact of the Heck reaction has been its use in the coupling of alkynes to aryl halides; a reaction which was used to couple fluorescent dyes to DNA bases, allowing the automation of DNA sequencing and the elucidation of the human genome.

1.1.1.3 Mechanism

The general mechanism for the Heck reaction has been accepted for many years however numerous recent studies have shown the active catalytic species to vary dramatically depending on the ligands, reaction conditions and substrates.

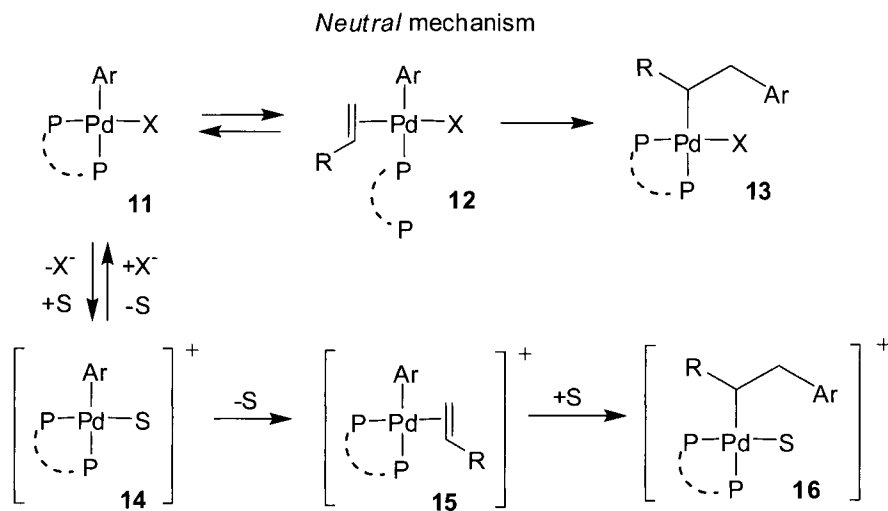


There are several extensive reviews regarding mechanistic studies on the Heck reaction which should be consulted for further detail.^{16,28} In the basic mechanism, aryl (or alkenyl) halides or perfluorosulfonates **1** undergo oxidative addition to a palladium(0) catalyst **7** to afford a σ -arylpalladium(II) complex **8**. All palladium precatalysts are converted to the active palladium(0) catalyst **7** *in situ*, most commonly by phosphine in phosphine assisted catalytic cycles.¹⁶ The order of reactivity for the oxidative addition is $X = I > OTf > Br \gg Cl$.²⁹ Alkene coordination, followed by *syn* addition provides a σ -alkylpalladium(II) complex **9a**. It is widely accepted that this carbopalladation of an alkene is the rate-determining step for Heck reactions.³⁰ Rapid β -hydride elimination releases alkene product **3**. In order to undergo *syn*- β -hydride elimination, the palladium and hydrogen atoms must be co-planar (as in conformer **9b**). Finally, a base is required for the conversion of the hydridopalladium(II) complex **10** to the active palladium(0) catalyst **7**, completing the catalytic cycle. While useful in explaining the discreet mechanistic steps of the Heck reaction, this generalized scheme ignores the precise coordination number, geometry and

formal charge on the palladium and therefore several more detailed mechanistic scenarios have been reported.

Cationic versus “Neutral” Pathways

Historically, the Heck reaction was the functionalization of olefins by aryl iodides, bromides, aryl chlorides, or the corresponding vinyl halides, carried out without ligands in the case of aryl iodides or in the presence of monodentate phosphines (e.g., Ph_3P).² Under these reaction conditions a square planar palladium(II) oxidative addition complex with a weak $\text{Pd}-\text{PR}_3$ bond (or Pd -solvent in the case of iodides) and a strong $\text{Pd}-\text{X}$ bond is generated.⁶ Dissociation of one of these neutral ligands gives a free coordination site to which the alkene can bind. In this context, Heck reported that chelating phosphines “in general do not form useful catalysts”.³¹ Indeed, in the case of reactions employing aryl halide substrates and bidentate ligands, suppression of the reaction is observed due to competitive coordination of the chelating ligand, shifting the equilibrium of **11/12** to the left.⁶

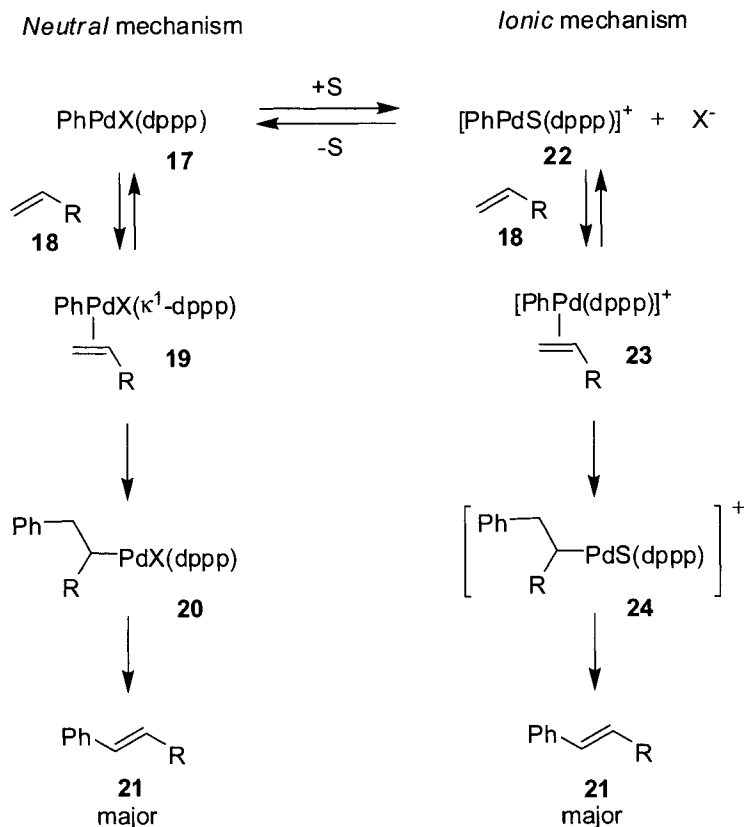


The cationic reaction manifold was first reported independently by Capri³² and Hayashi³³ to describe the Heck reaction of aryl triflates in the presence of palladium-diphosphine catalytic systems. This scenario arises from the lability of the $\text{Pd}-\text{OTf}$ bond present in complex **11** ($\text{X} = \text{OTf}$).⁶ Dissociation of the anionic counterion (^-OTf) affords cationic complex **14** with a vacant coordination site (transiently occupied by a solvent molecule,

S), thus allowing binding of the olefin without decomplexation of either phosphorus atom of the bidentate ligand. The ability to use chelating ligands was crucial to the development of asymmetric Heck reactions employing chiral diphosphines, first pioneered independently by Shibasaki and Overman in 1989.¹⁷ Partial dissociation of the chiral bidentate ligand under “neutral” conditions would diminish the rigidity of the ligand and could lead to erosion of the enantioselectivity. As well as the use of aryl (alkenyl) triflates, aryl (alkenyl) halides can be used in the presence of Ag(I) or Tl(I) additives. These additives mediate halide extraction from complex **11**,¹⁷ facilitating the cationic pathway. Furthermore, the reactivity of complexes **11** and **14** depends on the charge density of the unsaturated system. Competition studies have shown electron-poor olefins (good π -acceptors and poor σ -donors) react faster with neutral complex **11**, whereas electron-rich olefins (poor π -acceptors and good σ -donors) react faster with cationic complex **14**.⁶

Cabri has used the cationic pathway to explain the regioselectivity of the Heck reaction. Moreover, the use of triflates or halide scavenging additives (cationic conditions) in the asymmetric Heck reaction has become widespread. However, recent studies have shown the employment of either “neutral” conditions or cationic conditions may not lead to the expected reaction pathway. In 1992, Overman reported a Pd/BINAP catalyzed Heck cyclization of aryl halides in high enantioselectivity *without halide scavengers* (i.e. “neutral” conditions).³⁴ Since monodentate analogues used to mimic a partially dissociated BINAP gave products of low enantiopurity, it was rationalized that both phosphorus atoms remain coordinated to the palladium in the enantio-discriminating step, despite the “neutral” reaction conditions. Whilst Overman has suggested the reaction proceeds via an associative process involving a pentacoordinated palladium species, theoretical and experimental data has largely dismissed this due to high activation energies of the subsequent migratory insertion.¹⁷

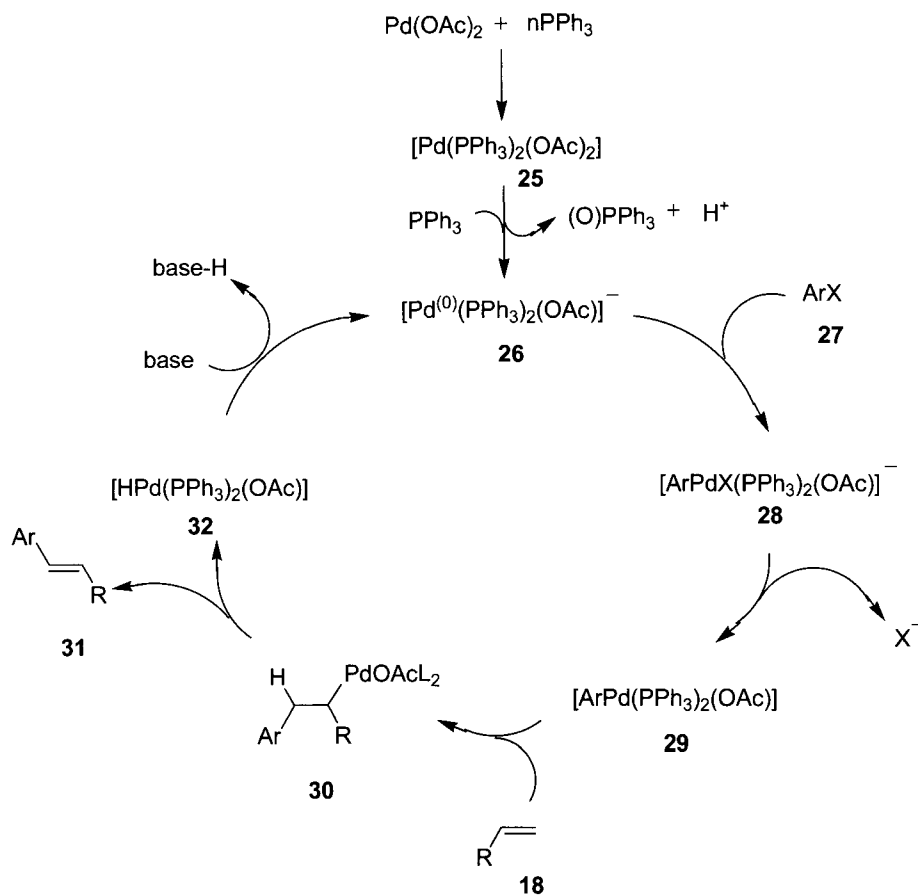
Recent work by Amatore and Jutand on the Heck reaction of aryl palladium complexes ligated by 1,3-bis(diphenylphosphino)propane) (dppp) offers some fascinating new insight into the “neutral” *versus* cationic pathways.³⁰ Based on kinetic studies, they suggest the reactions of electron-rich alkenes (isobutyl vinyl ether) *always* proceed via a cationic mechanism, despite the use of so-called “neutral” conditions. The ability of the base to deliver anions (acetate, carbonate) is often overlooked, and regardless of the medium cationic complex **22** is always the most intrinsically reactive. As such, the regioselectivity of the Heck reaction of electron rich alkenes, as well as asymmetric Heck reactions under “neutral” conditions can be rationalized by considering the rates and equilibria constants of all palladium species under a given set of reaction conditions (concentration, ionic strength of the solvent, additives, counterions, substrates, *etc.*).³⁰



Anionic Pathways

In many palladium-mediated reactions, the exact role of the precatalyst is ignored and simply seen as a means to provide the active palladium(0) catalytic species. However, studies by Amatore and Jutand have shown the counterions of the precatalyst can be non-innocent and dramatically influence the reaction mechanism.³⁵ Pd(OAc)₂ is the most common precatalyst used in the Heck reaction and previous studies have considered the acetate anion as an innocent bystander. Experimental evidence now suggests that the Pd(OAc)₂/phosphine systems initiate a catalytic cycle involving anionic palladium(0) and palladium(II) complexes.³⁵ The active catalyst generated is anionic species **26**, which undergoes oxidative addition to afford a pentacoordinated palladium species **28**, where both the acetate and iodide anions remain ligated to the palladium(II) centre. This short-lived species rapidly loses the halide ion to yield a new palladium(II) complex, *trans*-[ArPd(OAc)(PPh₃)₂] (**29**). The increased reactivity of complex **29** compared to [ArPdI(PPh₃)₂] has been attributed to the bidentate nature of the acetate ligand, which may assist in phosphine release to open a coordination site for

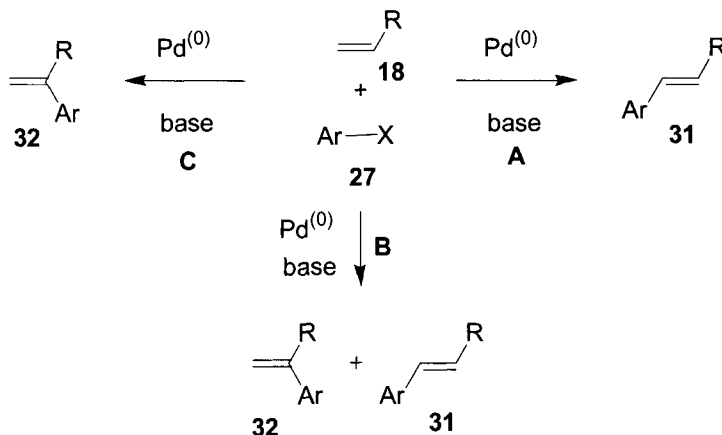
the alkene substrate. Migratory insertion, followed by β -hydride elimination provides olefin **31** and hydridopalladium complex **32**. Base-mediated conversion to palladium(0) species **26** completes the catalytic cycle. This proposed mechanism not only details the crucial role of acetate ions in many Heck reactions, but also provides an explanation of the beneficial effects of additives such as KOAc in certain cases.¹⁷



Related studies on the formation of active catalytic species' derived from $\text{Pd}(\text{OAc})_2$ and bidentate phosphine ligands has also been reported.³⁶ A stable palladium(0) complex is formed in the presence of $\text{Pd}(\text{OAc})_2$, dppp, water and triethylamine. In this case oxidative addition to PhI gives the cationic complex $[\text{PhPd}(\text{dppp})(\text{dppp}(\text{O}))]^+$, in which the oxidized dppp(O) ligand is monodentate. The complex $[\text{PhPd}(\text{OAc})(\text{dppp})]$ is only formed on addition of excess acetate anions. These results suggest that the anionic

pathway could be relevant to systems employing chelating phosphines, in the presence of acetate additives.

Regioselectivity and Stereoselectivity



A: Where R = Aryl, alkyl, CO₂R, CN, etc.

B: Where R = OR, NR₂, etc.

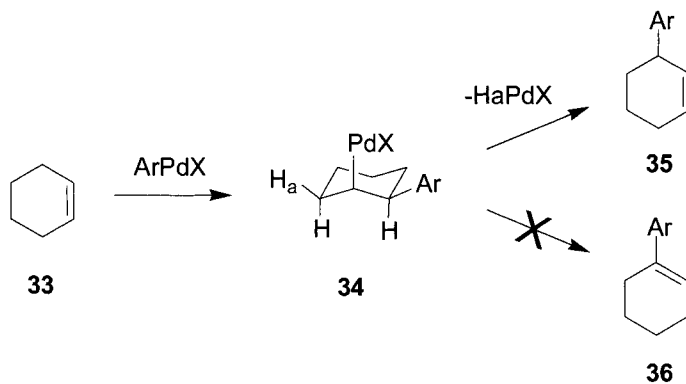
C: Where R = OR, NR₂, etc. and X = OTf

The direction of addition of the organopalladium species to the olefin is almost exclusively sterically controlled, i.e. addition will take place at the least substituted carbon to provide the linear product **31**.² In the case of alkenes containing electron withdrawing double bonds, once again, addition predominantly gives the linear product **31**. For alkenes appended with electron donating groups however, mixtures are often obtained with the sterically favoured isomer predominating. Work by Cabri using aryl triflates or aryl halides with halide scavengers (cationic pathway) has demonstrated, under these conditions, the branched product **32** is obtained in high selectivity for electron-rich olefins.⁶ A recent mechanistic rationale for this effect has been reported.³⁰ While this is a useful guide, it is possible to override this intrinsic regioselectivity bias using other factors such as chelation control. Electron-rich olefins bearing pendant heteroatom functionalized substituents can form linear products exclusively by exploiting neighbouring-group effects.²³

Other selectivity issues can arise during β -hydride elimination. If there is more than one sp³-bonded hydrogen atom beta to the palladium group in the olefin adduct, then a mixture of geometric isomers may result.² Also, if the hydridopalladium(II) species is not scavenged fast enough by the

base, re-addition to the double bond may occur and once again, a mixture of geometric isomers may result.¹⁶ The hydridopalladium(II) species can also be potentially scavenged by the starting olefin; a process which results in isomerization of the starting alkene and therefore leads to the formation of isomeric Heck products.¹⁶ In certain cases it has been demonstrated that the use of low temperatures³⁷ or additives such as silver salts can minimize this type of alkene isomerization.³⁸

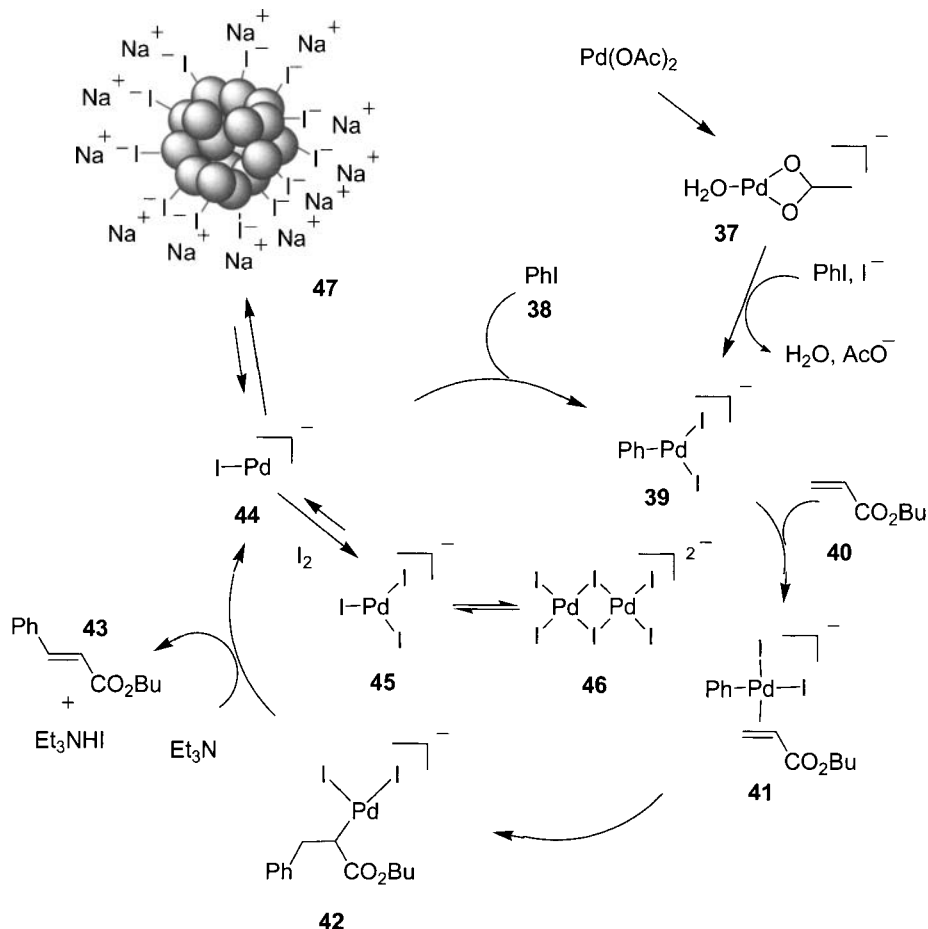
The stereoselectivity of the Heck reaction is governed by *syn*- β -hydride elimination. In the majority of cases, the elimination obeys the Curtin–Hammett kinetic control principle³⁹ and the ratio of *E*- and *Z*-isomers reflects the relative energy of the respective transition states. Unless R (see **18**) is very small (for example CN), the *E*-isomer is predominant and the reaction is highly stereoselective.¹⁶



Selectivity issues noted above are largely irrelevant for intramolecular reactions. In these cases, regiocontrol in the migratory insertion is largely governed by the size of the ring being formed with 5-*exo* and 6-*exo* cyclizations being particularly favoured.¹⁷ The use of cyclic olefin substrates also aids the regioselectivity of the reaction. Stereospecific *syn* addition of an arylpalladium species to a cyclic alkene, such as cyclohexene (**33**) produces σ -alkylpalladium(II) intermediate **34**, bearing a single *syn*- β -hydrogen (H_a). *Syn* elimination of this hydrogen provides product **35** exclusively (providing no isomerization of the product occurs under the reaction conditions, *vide supra*).¹⁷ As a notable alternative, Tietze has used allyl silanes to control β -elimination in acyclic systems.⁴⁰ The additional elements of control in the intramolecular Heck reaction of cyclic substrates is the reason for its huge success in asymmetric, complex molecule synthesis.¹⁷

“Ligand-free” Catalysts

In some of his original work, Heck demonstrated that the reaction of aryl iodides can be carried out using $\text{Pd}(\text{OAc})_2$ in the absence of additional ligands.² It was subsequently shown by Jeffery that this works particularly well in the presence of tetraalkyl ammonium salts.⁷ A detailed mechanism for the “ligand-free” Heck reaction has been reported by de Vries.²⁴



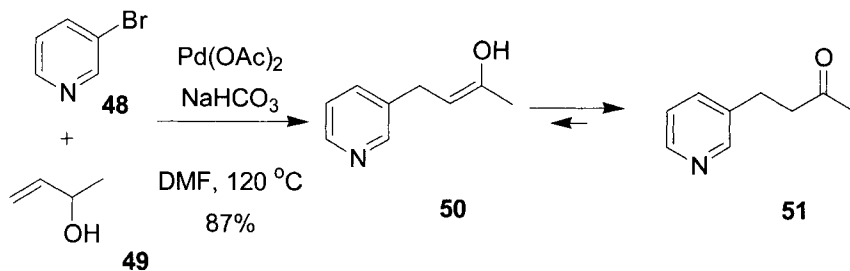
The reaction of iodobenzene (**38**) and olefin **40** was studied under “ligand-free” conditions in the presence of sodium halide additives. As in the generalized mechanism, $\text{Pd}(\text{OAc})_2$ is reduced to transient palladium(0) complex **37**. This undergoes oxidative addition and ligand exchange to form anionic species **39** (potentially containing additional solvent ligands). Olefin complexation, migratory insertion and β -hydride elimination furnish the

product **43** along with highly underligated species **44**. At this stage complex **44** can do one of three things: (a) react with traces of iodine (arising from aerobic oxidation), to give **45** or dimer **46**; (b) form soluble palladium nanoparticles **47**; or (c) react with iodobenzene (**38**). Since oxidative addition is fast for reactive aryl iodides, (c) is the primary pathway observed. Once the substrate is consumed, rapid formation of palladium nanoparticles **47** occurs, which in turn conglomerate to form palladium black.²⁴

For the less-reactive aryl bromides, the situations change. Since oxidative addition of these substrates is slower, formation of palladium nanoparticles is prevalent.²⁴ If these particles grow beyond a certain size, they precipitate as palladium black and the reaction stops. This is the reason aryl iodides were initially reported to be the only substrates to undergo the Heck reaction under “ligand-free” conditions. Therefore, one explanation of the success of Jeffery’s conditions⁷ is that the tetraalkyl ammonium additives stabilize the palladium nanoparticles/colloids, preventing formation of palladium black. Indeed, the pioneering work of Reetz⁷⁰ and Hermann⁷¹ has shown that pre-formed stabilized palladium colloids can be used as active catalysts in the reaction. This unifying mechanism can be extended to other high-temperature Heck reactions (solid-supported palladium, palladacycles) in the absence of strongly coordinating ligands.²⁴ Of perhaps the most experimental significance is that, while most groups have sort stabilizing agents to prevent aggregation of colloidal palladium in these reactions, de Vries has demonstrated that simply maintaining a low substrate/catalyst ratio allows the Heck reaction to compete with colloid formation. Using these conditions he has successfully used aryl bromides under “ligand-free” Heck reactions, in the absence of any additional stabilising agents.²⁴

1.1.1.4 Synthetic Utility

In his initial review on the scope of the reaction, Heck reported the use of a variety of relatively simple aryl, heteroaryl and vinyl halides.² For example, exposure of bromopyridine **48** to alcohol **49** gave ketone **51** in good yield, following tautomerization of the initial Heck adduct **50**.



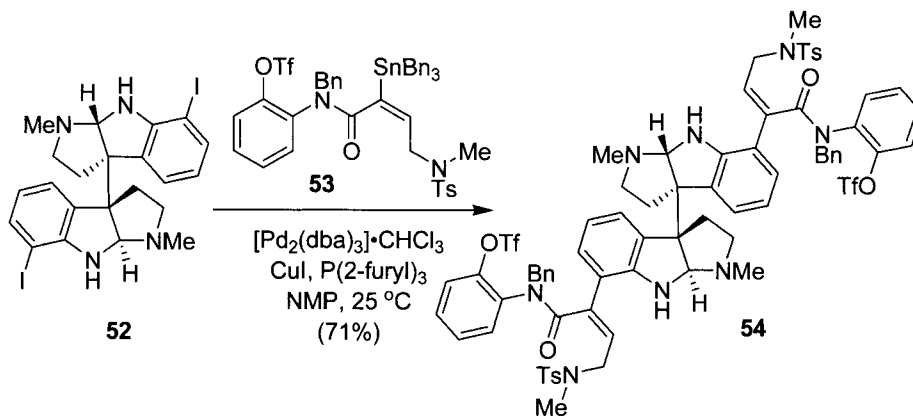
Nowadays however, the Heck reaction is one of the most widely used catalytic C–C bond forming reactions and there are numerous examples in nearly every sub-discipline of modern organic chemistry. The proceeding section will highlight some of the most accomplished uses of this flexible synthetic method.

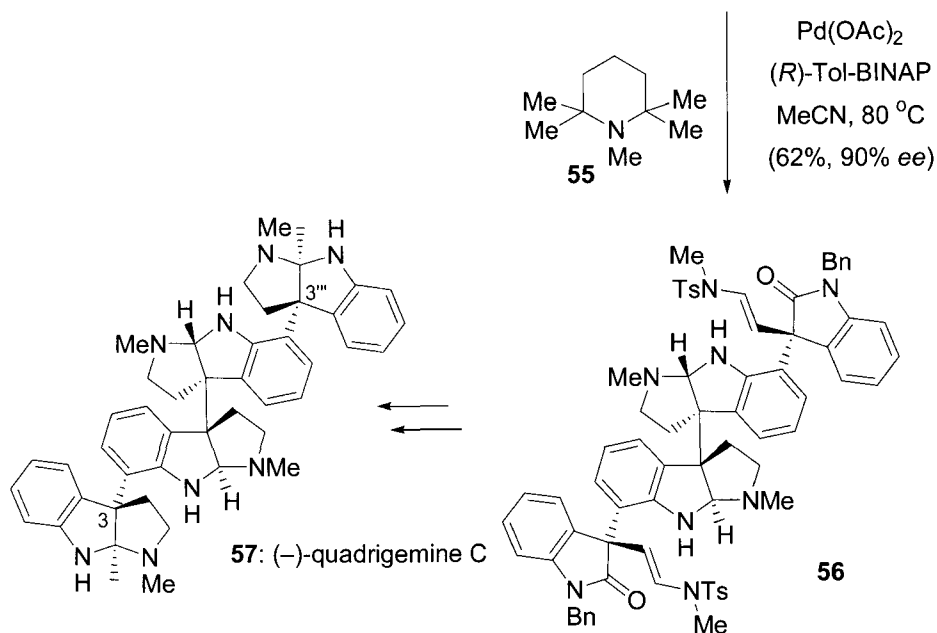
Asymmetric Intramolecular Heck reaction

Perhaps one of the most challenging aspects of complex molecule synthesis is control of the absolute sense of stereochemistry for the preparation of optically-active compounds. In 1989, Shibasaki and Overman independently reported the first examples of asymmetric Heck reactions.¹⁷ These efforts focused on intramolecular cyclization reactions, which display extra elements of regiocontrol. To date, the asymmetric intramolecular Heck has been exploited in the synthesis of terpenoids, alkaloids and polyketides, forging key tertiary and quaternary stereocentres.¹⁷

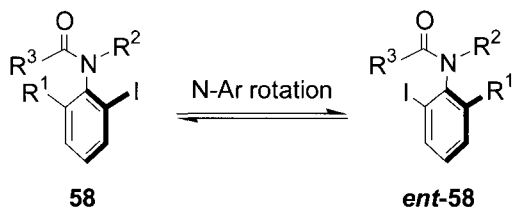
Some of the most spectacular examples have come from the laboratories of Overman at the University of California, Irvine. In his synthesis of (–)-quadrigimine C (**57**), Overman noted that the C3 and C3''' quaternary stereocentres have the same absolute stereochemistry. Therefore, following a Stille reaction to prepare key substrate **54**, a double asymmetric Heck reaction was performed, yielding decacyclic system **56** in good yield and in 90% *ee*.⁴¹ This example truly displays the synthetic power of the Heck reaction in forging quaternary, crowded stereocentres.

Interestingly, the Heck cyclization of anilides, such as **54**, has constituted a frequent strategy in the asymmetric synthesis of alkaloids.¹⁷ While it is often assumed that migratory insertion of the arylpalladium(II) species into the carbon-carbon double bond is the stereocontrolling step, recent studies by Curran have offered an alternative explanation.⁴²



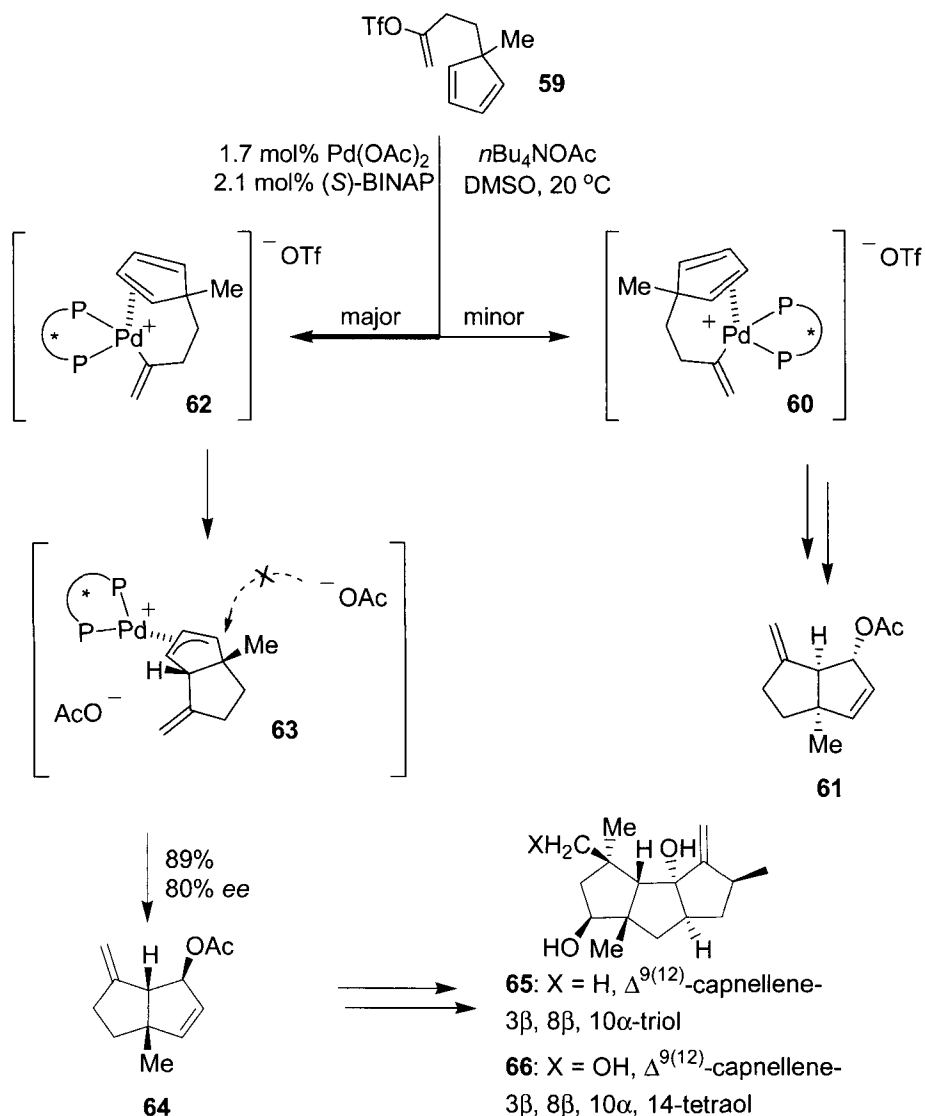


For iodoanilides, such as **58**, hindered rotation around the N–Ar bond renders these molecules axially chiral. Curran showed that low-temperature Heck reactions of chiral anilines **58** with an achiral palladium catalyst occur with efficient transfer of chirality from the chiral axis of the precursor to the stereocentre of the product. Since at high temperature the two axially chiral enantiomers will be rapidly equilibrating, this suggests that the stereocontrolling step in the asymmetric Heck reaction of similar substrates is, in fact, a dynamic kinetic resolution (oxidative addition to the aryl–X bond).

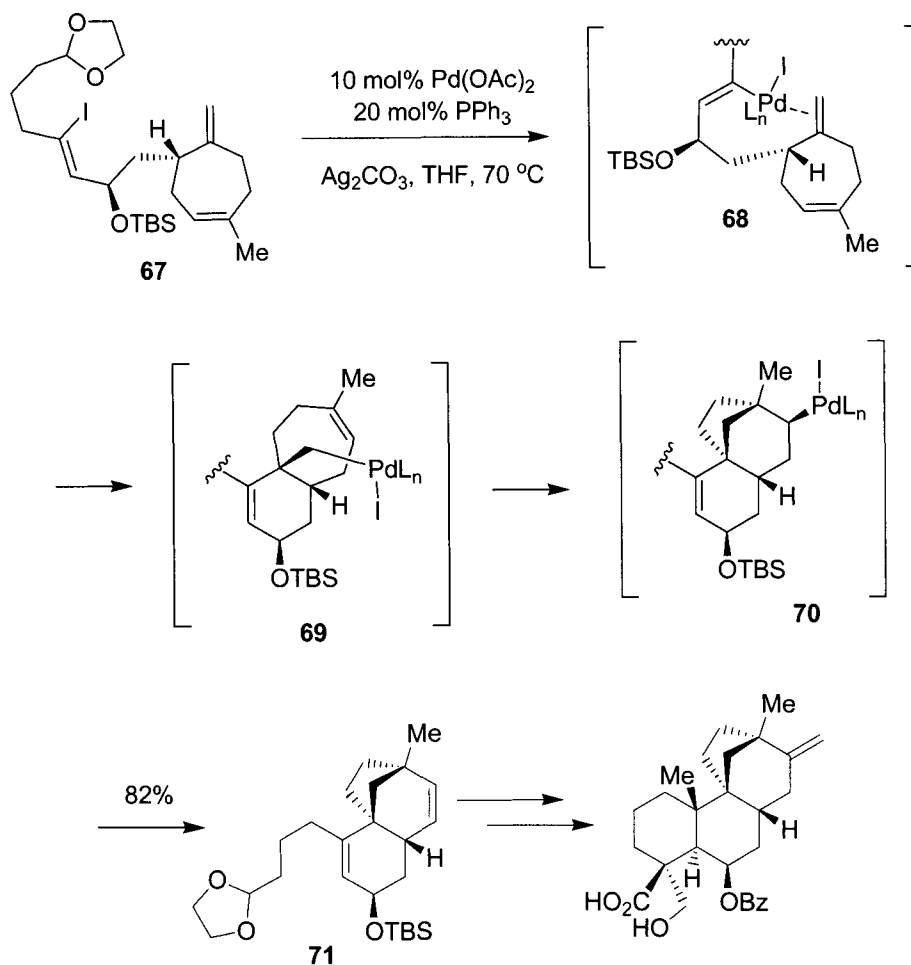


Exposure of prochiral cyclopentadiene **59** to catalytic $\text{Pd}(\text{OAc})_2$, $(S)\text{-BINAP}$ and $n\text{-BuNOAc}$ furnished diquinane **64** in 89% yield and 80% *ee*. The mechanism presumably involves oxidative addition, followed by coordination of either enantiotopic double bond to yield diastereomeric intermediates **60** and **62**. The energetically favoured complex **62** undergoes insertion followed by rapid $\sigma\text{-}\pi$ isomerization to generate the $\pi\text{-allyl}$ palladium species **63**. Trapping of the intermediate with an acetate anion

proceeds with good control of the regioselectivity (attack at the least hindered terminus of the π -allyl complex **63**) and stereoselectivity (attack on the opposite face to palladium) to yield **64**.⁴³



Shibasaki has also reported impressive applications of the asymmetric intramolecular Heck reaction. For example, the Shibasaki group have applied their chemistry to the synthesis of compound **64**, a key intermediate in the total synthesis of two complex triquinane sesquiterpenes **65** and **66**, by making use of a Heck reaction/anion capture cascade sequence.⁴³



72: scopadulcic acid B

One of the most enabling features of the Heck reaction is the ability to facilitate polyene cyclizations in the synthesis of complex multiple ring systems. In the context of natural product synthesis, Overman pioneered this approach towards the synthesis of the scopadulcic acid family of diterpenes.⁴⁴ This inventive strategy formed three out of the four ring systems, including a sterically congested bridged bicycle and two of the three quaternary stereocentres from a simple monocyclic precursor, employing an Heck cyclization cascade. In this case the stereochemistry of the product was under substrate control (i.e. there was no need for chiral ligands). Thus, compound **67** was converted into tricyclic intermediate **71** in one step, using catalytic $\text{Pd}(\text{OAc})_2$, PPh_3 and a silver additive. Oxidative addition of the palladium(0) species into the C–I bond of compound **67** followed by the first