

Multimetallic Catalysts in Organic Synthesis

Edited by

Masakatsu Shibasaki and Yoshinori Yamamoto



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Library of Congress Card No.: Applied for
British Library Cataloging-in-Publication Data
A catalogue record for this book is available from the British Library.

**Bibliographic information published by
Die Deutsche Bibliothek**

Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the internet at <http://dnb.ddb.de>.

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KGaA, Weinheim

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Printed in the Federal Republic of Germany.
Printed on acid-free paper.

Composition Manuela Treindl, Laaber
Printing Strauss GmbH, Mörlenbach
Bookbinding Litges & Dopf Buchbinderei
GmbH, Heppenheim

ISBN 3-527-30828-8

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Preface

Tyrosinase monooxygenases, which catalyze the ortho-hydroxylation of phenols, are dioxygen-activating enzymes. These proteins contain bimetallic centers, but it is not known in detail how the bimetallic centers are involved in enzyme activity, although there might be cooperative effects between the two metal atoms. Chemical transformations induced by bimetallic (or multimetallic) catalyst systems often have higher reaction rates and selectivities than those induced by monometallic and mononuclear complex catalysts, indicating that the development of multimetallic catalysts is one of the most important fields in chemical science for the 21st century.

A few years ago, Dr. Elke Maase suggested that we edit a book about multimetallic catalysts. Although we were very interested, there was some hesitation, since multimetallic catalysts were still very much under development. After several discussions, we decided to edit the book, because we believed that it would be very helpful to chemists who were interested in considering new ideas.

This book is about one of the major developments in current organic chemistry: the use and application of multimetallic catalysts for the synthesis of fine chemicals and structurally more complicated organic building blocks. Multimetallic catalysts have contributed tremendously to organic synthesis over the last few decades, and it seems clear that this trend will continue in future. The aim of this book is to provide readers with an interest in multimetallic chemistry for organic synthesis an insightful, up-to-date survey of this area. We have focused on the most important multimetal catalyzed methods as well as multitransition metal catalyzed reactions with a particular emphasis on the most recent developments. The literature available up to early 2003 was carefully reviewed, and, in some cases, important reactions that were published even in late 2003 were also incorporated. Due to space restrictions, we emphasized the methodology and paid less attention to the total synthesis of natural products compared to the synthesis of structurally less complicated building blocks and fine chemicals. We believe that in most cases the latter examples more clearly illustrate the principles that govern the reactivity of multimetallic catalysts in organic synthesis.

The book consists of three sections. The first describes efficient chemical transformations using two different metals such as the Nozaki-Hiyama-Kishi reaction, where two metals exist independently to effectively promote chemical transformations. The second section discusses asymmetric catalyses promoted by

heterobimetallic (or homobimetallic) catalysts, while the final section describes bimetallic (or multimetallic) catalyst-promoted transformations.

Finally, we sincerely hope that this book will be a valuable source of information for researchers working in academia and industry and that it will stimulate new development in this fascinating and intellectually appealing interdisciplinary area.

Masakatsu Shibasaki
Yoshinori Yamamoto

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1

Organic Synthesis with Bimetallic Systems

Shin Kamijo and Yoshinori Yamamoto

1.1 Introduction

The application of bimetallic systems to organic synthesis has emerged dramatically in recent years, and great progress has been made in research aimed at developing reactions promoted with catalytic amounts of activating reagents. The cross-coupling reaction is a representative example of this type of transformation. In the early stages of the investigations, most studies were focused on transition metal (TM)-catalyzed reactions using main group organometallic compounds (R^2-M). The organometallic compound (R^2-M) was used as a coupling partner of the substrate (R^1-X); the cross-coupling reactions can be regarded as transformations promoted by a bimetallic system (*cat.* TM/*stoichiometric* R^2-M) (Figure 1.1a). Not only cross-coupling reactions (Section 1.2.1), but also reactions of π -allylpalladium complexes (Section 1.2.4) and nickel-catalyzed three-component coupling (TCC) reactions (Section 1.2.5) can be classified as belonging to category **a**. The conjugate addition of organomagnesium and -lithium reagents to Michael acceptors in the presence of catalytic amounts of copper salts also belongs to this category, but such organocopper reactions are not mentioned in this chapter since many excellent reviews and monographs have been published on these topics in recent years [1]. Another characteristic feature of these cross-coupling reactions is that an enhancement of the reaction rate is often observed in the presence of an additional metal salt (MX). The coupling reaction between R^1-X and R^2-M proceeds very smoothly in the presence of catalytic amounts of TM and stoichiometric amounts of MX (Figure 1.1b). Wacker reactions (Section 1.2.2), Heck reactions (Section 1.2.3), most of the reactions involving π -allylpalladium complexes (Section 1.2.4), and Nozaki-Hiyama-Kishi (NHK) reactions (Section 1.2.6) belong to this category **b**. We will discuss the reactions promoted by a combination of catalytic and stoichiometric amounts of metals (categories **a** and **b**) in the first section.

Recent studies have revealed that a wide variety of bimetallic catalytic systems composed of a transition metal and an additional metal salt (*cat.* TM/*cat.* MX) efficiently catalyze organic transformations, such as the cross-coupling reaction

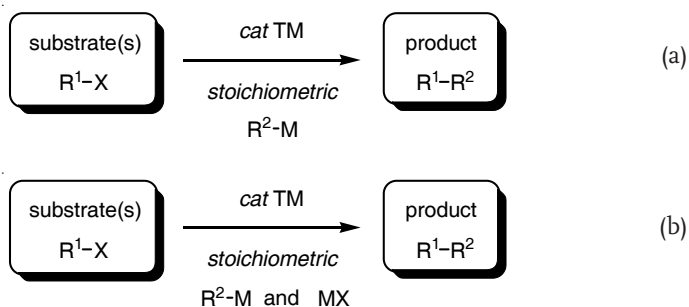


Figure 1.1

between $\text{R}^1\text{-X}$ and $\text{R}^2\text{-M}$ (Figure 1.2c), the Wacker reaction, reactions involving π -allylpalladium complexes, and so forth (category c). The MX catalyst often promotes these reactions by forming a reactive species in situ via transmetalation and halide abstraction. In some cases, the MX catalyst behaves as a Lewis acid and activates the substrates and intermediates through coordination. The reactions belonging to category c are mentioned in Sections 1.3.1 to 1.3.5. The utilization of dinuclear metal catalysts (cat. M–M) is one of the approaches to realize new catalytic transformations, although application of such catalytic systems to organic synthesis is not so popular and relatively few examples have been reported to date. The reactions belonging to this category d are mentioned in Sections 1.3.6.1 and 1.3.6.2 (Figure 1.2d). The unique catalytic properties of M–M catalysts originate from double activation by the two metal centers. Several combinations of two transition metals (cat. $\text{TM}^1/\text{cat. TM}^2$) have been applied in both one-pot and sequential reactions (Figure 1.2e). The overall transformation is achieved through the two successive reactions promoted by each transition metal catalyst. The Pauson–Khand (Section 1.3.4.4) and sequential reactions (Section 1.3.6.3) are classified as belonging to this category e. We will discuss the reactions promoted by a combination of catalytic amounts of two metals (categories c, d, e) in the second part of this chapter. The details of each reaction will be considered in each section.

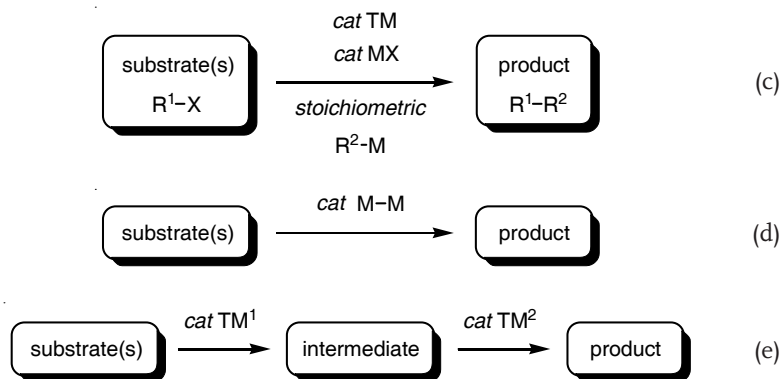


Figure 1.2

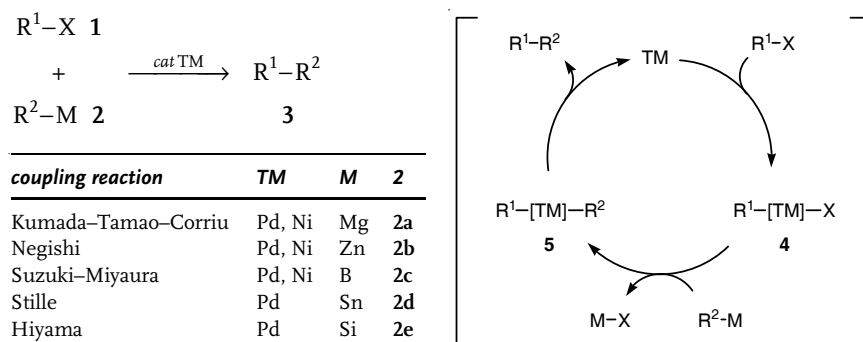
1.2

Reactions Promoted by a Combination of Catalytic and Stoichiometric Amounts of Metals

1.2.1

Transition Metal-Catalyzed Cross-Coupling Reactions

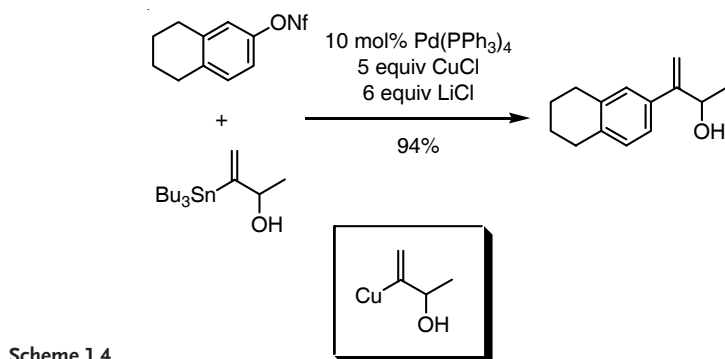
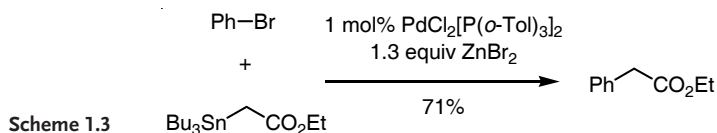
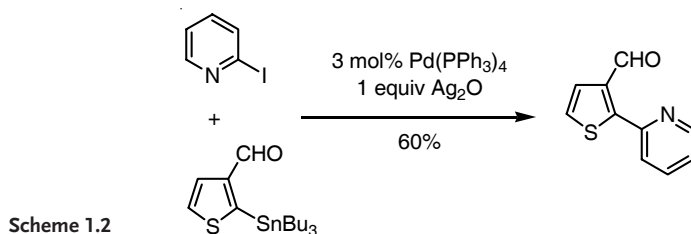
Transition metal-catalyzed cross-coupling reactions have been developed by employing various combinations of catalysts and organometallic compounds [2]. Although the organometallic compounds are exploited as a reagent, the cross-coupling reactions can be regarded as transformations promoted by a bimetallic system. A representative reaction scheme and catalytic cycle are depicted in Scheme 1.1. Generally, the reactions begin with oxidative addition of transition metal catalysts (TM) to aryl and alkenyl halides R^1-X (1) to form the intermediates 4. Transmetalation between 4 and organometallic compounds R^2-M (2) affords the intermediates 5, and reductive elimination of TM catalysts results in the formation of a carbon-carbon bond to furnish the coupling products R^1-R^2 (3). Palladium and nickel catalysts usually show excellent activities in these transformations.

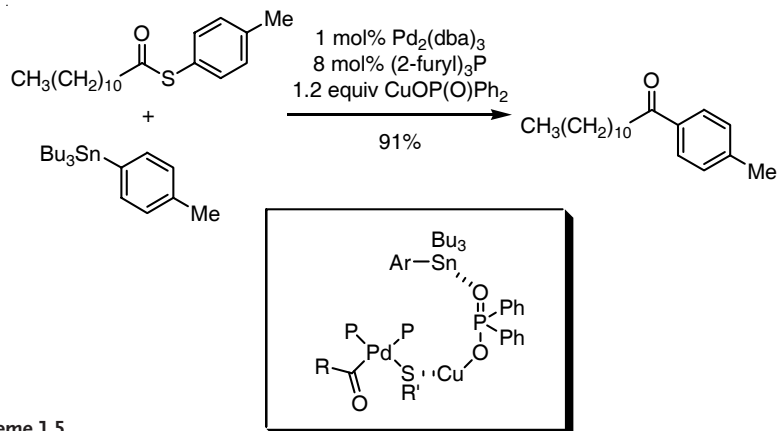


Scheme 1.1

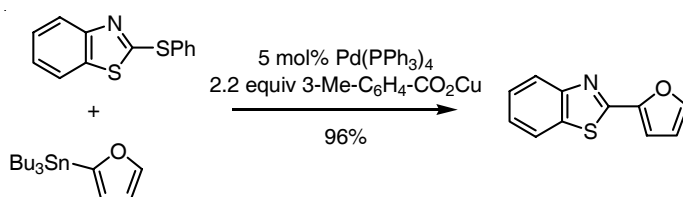
The first successful nickel-catalyzed cross-coupling reaction between halides and Grignard reagents R^2-MgX (2a) was simultaneously achieved by two research groups and is now referred to as the Kumada-Tamao-Corriu reaction. The palladium-catalyzed cross-coupling reaction between halides and organozinc reagents R^2-ZnX (2b) was developed by Negishi and co-workers. Some reactions were also catalyzed by a nickel complex. Organozinc reagents are most conveniently prepared in situ from organolithium, -magnesium, or -aluminum compounds with a ZnX_2 salt. The use of organozinc reagents extended the range of compatibility to functional groups such as ketones, esters, cyano, and amide groups, which react with Grignard reagents. Suzuki and Miyaura et al. investigated the palladium-catalyzed coupling reaction of halides with organoboron compounds $R^2-BR'_2$ (2c). The addition of base is required to activate either the boron reagent or the Pd catalyst in order to promote the coupling reaction. This transformation is widely applied due to its high tolerance of a broad range of functionalities and of water.

Coupling reactions between halides and organotin compounds $R^2-SnR'_3$ (**2d**) in the presence of a palladium catalyst have been extensively studied and are now referred to as the Stille coupling reaction. This transformation proceeds under essentially neutral conditions. The standard catalyst system is a combination of a Pd catalyst with a ligand such as $(2\text{-furyl})_3\text{P}$ or AsPh_3 . Although the Stille coupling reaction is an excellent carbon–carbon bond-forming procedure, unsatisfactory results are sometimes encountered due to substrate instability. Therefore, many additives have been examined for an accelerating effect on the reaction. Gronowitz and co-workers [3] employed Ag_2O as an activator in the reaction between 2-iodopyridine and a stannylthiophene (Scheme 1.2). Migita and co-workers [4] observed an acceleration of the coupling reaction between aryl bromides and α -stannylacetate by utilizing ZnBr_2 as an additive (Scheme 1.3). Corey and co-workers [5] applied CuCl as an activator for coupling reactions between aryl nonaflate and vinylstannanes (Scheme 1.4).



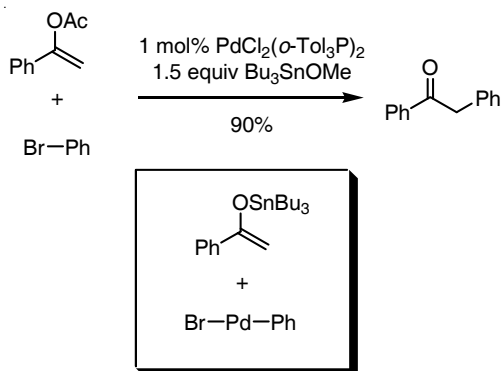


Scheme 1.5

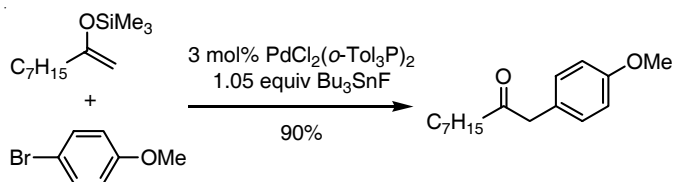


Scheme 1.6

These reaction activators most probably facilitate transmetalation of the organic group from the stannane to the palladium center through the formation of more reactive organometallic species such as vinylcopper, as shown in Scheme 1.4. Liebeskind and co-workers [6] have recently reported the Stille-type coupling reaction between thiol esters and organostannanes (Scheme 1.5). The reaction proceeded in the presence of a combination of Pd₂(dba)₃/(2-furyl)₃P as catalyst and CuOP(O)Ph₂ as an activator. The role of the Cu additive is activation of the acylpalladium thiolate intermediate to facilitate transmetalation of the aryl group from the stannane to the palladium atom. These authors applied a similar Pd–Cu bimetallic catalyst to the coupling reaction between a heteroaromatic thioether and an organostannane (Scheme 1.6) [7]. The same type of reaction was also reported by Guillaumet and co-workers [8]. Migita and co-workers [9] developed a method for the α -arylation of ketones based on a coupling reaction between enol acetates and bromobenzene (Scheme 1.7). The key to realizing this coupling reaction is to perform it in the presence of a combination of PdCl₂(*o*-tolyl)₃P)₂ catalyst and Bu₃SnOMe. The enol acetates are transformed in situ to the corresponding tributyltin enolates, which react with the Pd intermediate to afford the coupling product. A similar coupling reaction utilizing silyl enol ethers and aryl bromides was investigated by Kuwajima et al. (Scheme 1.8) [10]. In this case, the addition of Bu₃SnF in combination with PdCl₂(*o*-tolyl)₃P)₂ is essential for successful reaction.

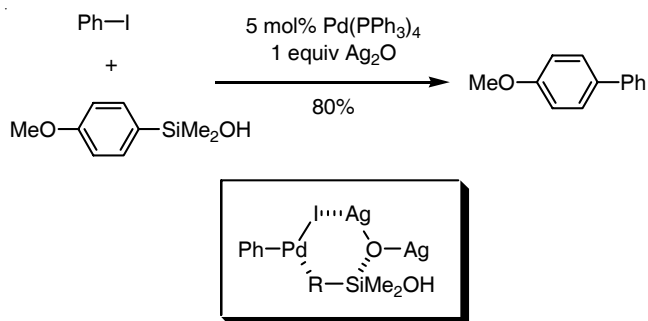


Scheme 1.7



Scheme 1.8

Hiyama and co-workers found that a cross-coupling reaction between halides and organosilanes R²-SiR'₃ (**2e**) could be achieved in the presence of a palladium catalyst combined with a fluoride anion source such as tetrabutylammonium fluoride (TBAF) or tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF). The addition of a fluoride source is essential to facilitate transmetalation of the organic group through the formation of a five-coordinate silicate species. Hiyama and Mori et al. [11] applied silanols as coupling partners with aryl iodides in the cross-coupling reaction (Scheme 1.9). The reaction proceeded particularly well in the presence of Ag₂O as an activator with a catalytic amount of Pd(PPh₃)₄. A fluoride activator such as TBAF, which is often employed for the usual Hiyama coupling reaction using a fluorosilane as a starting material, failed to give the corresponding adduct. The role of the Ag additive can be rationalized in terms of two cooperative



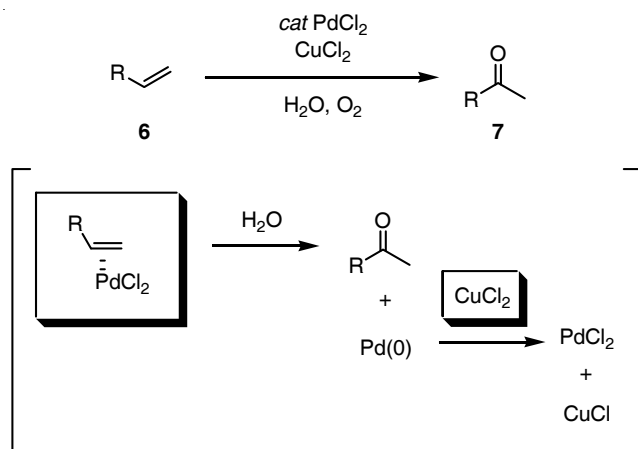
Scheme 1.9

functions, which may be outlined as follows. One is the formation of a penta-coordinate silicate species to facilitate transmetalation of the aryl group from the Si to the Pd atom, and the other is interaction with the iodide on the organopalladium intermediate to make transmetalation feasible. A similar reaction using alkynyl-silanols as coupling partners has been reported by Chang and co-workers [12].

1.2.2

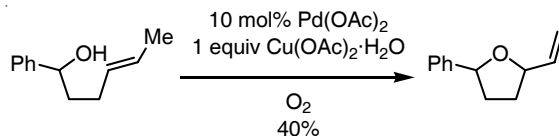
The Wacker Reaction

The synthesis of acetaldehyde **7** ($R = H$) by oxidation of ethylene **6** ($R = H$) in the presence of a catalytic amount of PdCl_2 and a stoichiometric amount of CuCl_2 is known as the Wacker process (Scheme 1.10) [13]. The reaction involves nucleophilic addition of H_2O to ethylene coordinated by PdCl_2 . The Pd catalyst activates the carbon-carbon double bond by π -coordination. The Cu additive serves to oxidize the generated Pd^0 species so as to regenerate the PdCl_2 catalyst. The role of oxygen is assumed to be oxidation of the CuCl produced to regenerate the CuCl_2 additive, although a stoichiometric amount of CuCl_2 is employed in most cases. The reaction has been extended to substituted alkenes.

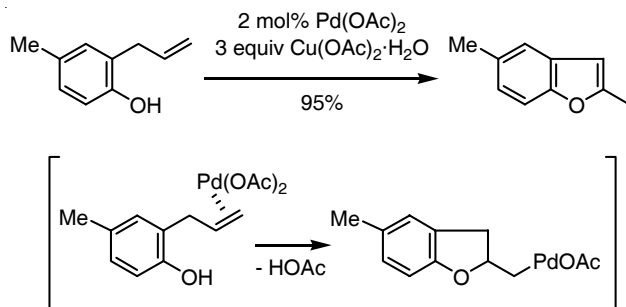


Scheme 1.10

Wacker-type reactions have been successfully applied for the formation of a wide variety of heterocyclic compounds. For example, various kinds of oxygen-containing heterocycles, such as tetrahydrofuran (Scheme 1.11) [14] and benzofuran derivatives (Scheme 1.12) [15], have been synthesized in the presence of a catalytic amount of



Scheme 1.11

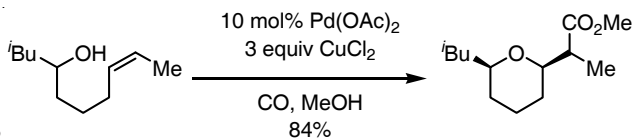


Scheme 1.12

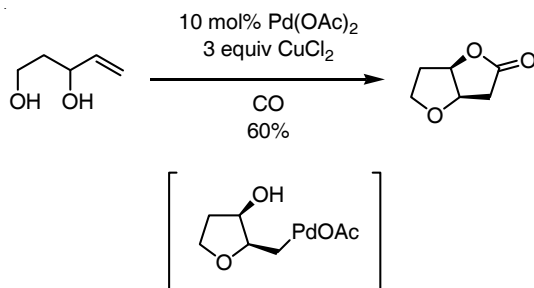
a Pd^{II} species and a stoichiometric amount of Cu oxidant. The reactions involve intramolecular alkoxylation of the alkene to form a σ -alkylpalladium intermediate, followed by β -elimination to furnish the cyclized products.

When the reaction was conducted under CO atmosphere, insertion of CO into the σ -alkylpalladium species took place to afford carbonylated products. Semmelhack et al. investigated the synthesis of pyran derivatives by using a combination of Pd(OAc)₂ and CuCl₂ oxidant under CO gas (Scheme 1.13) [16]. Tamaru and co-workers [17] succeeded in obtaining bicyclic lactone derivatives via the intramolecular alkoxy-carbonylation reaction using a Pd–Cu system (Scheme 1.14). Semmelhack et al. [18] also succeeded in trapping an alkylpalladium intermediate with alkenes and the corresponding carbon chain elongated products were obtained (Scheme 1.15).

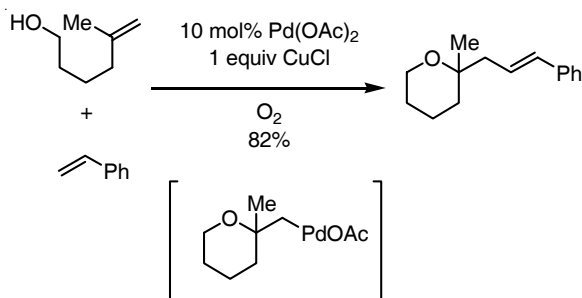
The reaction has also been applied for the synthesis of nitrogen-containing cyclic compounds. Gallagher and co-workers [19] subjected allenyl amides to a CO atmosphere in the presence of PdCl₂ and CuCl₂ and thereby obtained pyrrolidine



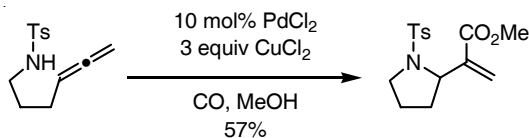
Scheme 1.13



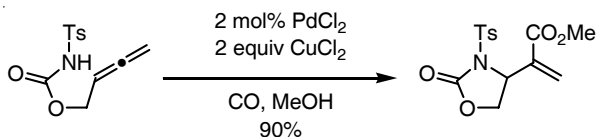
Scheme 1.14



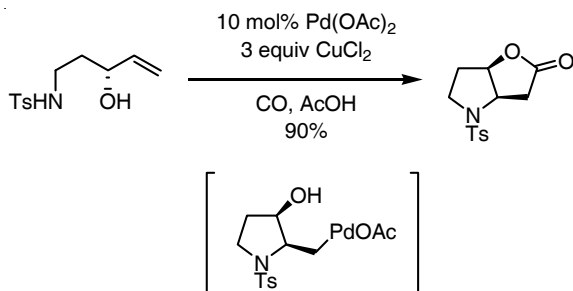
Scheme 1.15



Scheme 1.16



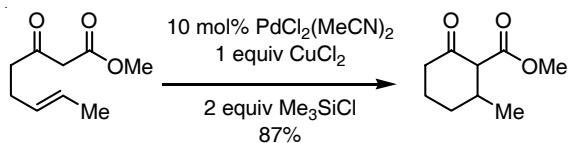
Scheme 1.17



Scheme 1.18

derivatives (Scheme 1.16). A similar cyclization has been reported by Tamaru and co-workers [20] (Scheme 1.17). Tamaru and co-workers [21] also observed the formation of bicyclic compounds through an intramolecular aminocarbonylation reaction using a Pd–Cu system (Scheme 1.18).

Widenhoefer et al. [22] reported a similar type of cyclization reaction using a Pd–Cu bimetallic system. The reaction probably proceeds through addition of the enolate to the alkene activated by coordination of the Pd complex (Scheme 1.19).



Scheme 1.19

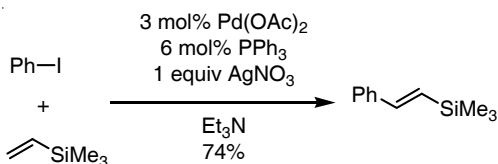
The combination a catalytic amount of $\text{PdCl}_2(\text{MeCN})_2$ and a stoichiometric amount of $\text{Yb}(\text{OTf})_3$ was also found to be effective by Yang and co-workers [23]. The catalytic use of $\text{Yb}(\text{OTf})_3$ proved to be effective for some substrates, although the use of a stoichiometric amount of $\text{Yb}(\text{OTf})_3$ was seemingly required to obtain the desired carbocycles in good yields.

1.2.3

The Heck Reaction

The Pd^0 -catalyzed coupling of an aryl or vinyl halide or triflate with an alkene is known as the Heck reaction [24]. The reaction is normally carried out using a Pd catalyst with phosphine ligands under basic conditions. Investigations aimed at selecting the optimal additive for the Heck reaction revealed that the addition of an Ag salt increased the reaction rate and led to consistently higher reactivities compared to the original catalyst systems.

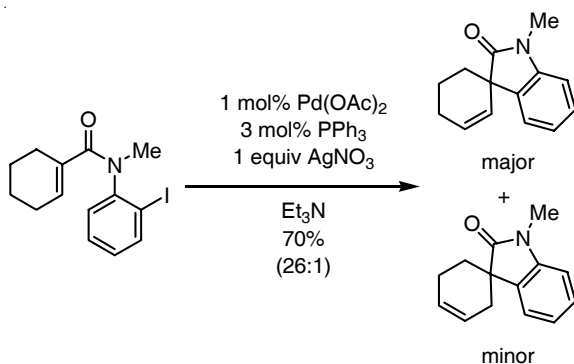
A stoichiometric amount of silver additive was first employed in the coupling reaction between iodobenzenes and vinylsilane by Hallberg and co-workers [25] (Scheme 1.20). When this reaction was carried out in the presence of a combination of a catalytic amount of $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ and a stoichiometric amount of AgNO_3 , styrylsilanes were obtained without the formation of any desilylated styrenes, which are the products under the standard conditions of the Heck reaction. The addition of the Ag salt suppressed cleavage of silyl group during the course of the reaction.



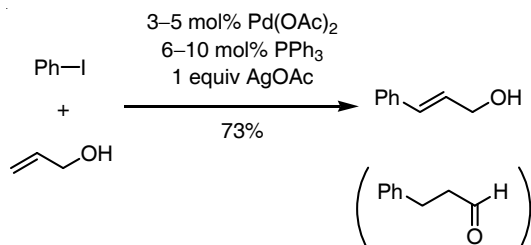
Scheme 1.20

Overman and co-workers [26] found that the addition of a silver salt minimized alkene isomerization in the derived products (Scheme 1.21). Jeffery [27] reported that the addition of an Ag salt to suppress alkene isomerization was especially effective in reactions using allyl alcohols as coupling partners (Scheme 1.22). The formation of aldehydes could be avoided by simply adding a stoichiometric amount of AgOAc to the reaction mixture.

Acceleration of reaction rates and enhancement of enantioselectivity were observed in the presence of a Pd–Ag catalyst system, and extensive investigations on the construction of quaternary carbon centers via the intramolecular Heck reaction were carried out. Overman and co-workers first reported the intramolecular

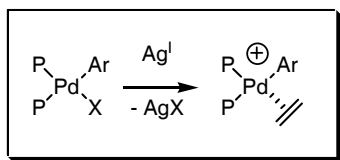


Scheme 1.21

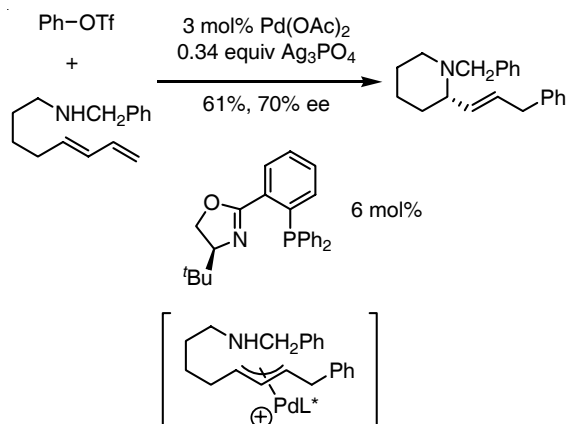


Scheme 1.22

Heck reaction using a combination of a catalytic amount of Pd(OAc)₂/PPh₃ complex and a stoichiometric amount of AgNO₃, as indicated in Scheme 1.21. Shibasaki and co-workers [28] demonstrated for the first time that an enantioselective intramolecular Heck reaction could be achieved by utilizing a catalytic amount of Pd(OAc)₂/*R*-BINAP with a stoichiometric amount of Ag₂CO₃ (Scheme 1.23). The Heck reaction in the presence of an Ag salt is proposed to proceed through a cationic pathway. The role of the Ag salt is to abstract the halide ion from the palladium intermediate to leave a vacant site for coordination of the alkene. Grigg and co-workers [29] reported that the addition of a Tl^I salt instead of an Ag^I salt led to a similar effect.

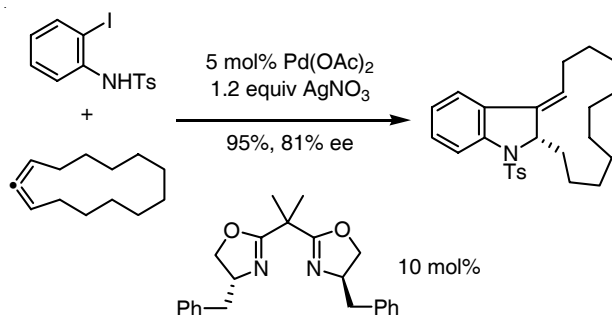


Scheme 1.23



Scheme 1.24

A silver salt is often utilized in enantioselective tandem reactions involving the Heck reaction. For example, Helmchen et al. [30] reported the synthesis of chiral piperidine derivatives through the Heck reaction and subsequent asymmetric allylic amination of the resulting π -allylpalladium intermediate (Scheme 1.24). The addition of a stoichiometric amount of an Ag salt proved essential to achieve high enantioselectivity. Larock and co-workers [31] reported the asymmetric heteroannulation of allenes using functionalized aryl iodides (Scheme 1.25).



Scheme 1.25

1.2.4

Reactions Involving π -Allylpalladium Intermediates

1.2.4.1 Electrophilic Reactions

Poli and co-workers [32] applied a $\text{Pd}_2(\text{dba})_3/\text{PPh}_3$ and $\text{Ti}(\text{O}^i\text{Pr})_4$ bimetallic catalyst system to the allylation of active methylene compounds (Scheme 1.26). They investigated the reactions between allyl acetates and various carbon nucleophiles. The Ti additive coordinates to the nucleophiles and produces titanium enolates after deprotonation. The $\text{p}K_a$ value of the active methylene compound is lowered by the coordination of the Ti additive, making it more reactive. Accordingly, a wide range of nucleophilic agents can be used as reaction partners with π -allylpalladium