ORGANIC REACTIONS

Volume 113

Organic Reactions

FORMER MEMBERS OF THE BOARD
OF EDITORS AND DIRECTORS

Jeffrey Aubé
John E. Baldwin
Dale L. Boger
Jin K. Cha
André B. Charette
Engelbert Ciganek
Dennis Curran
Samuel Danishefsky
Huw M. L. Davies
Scott E. Denmark
Victor Farina
Paul Feldman
John Fried
Jacquelyn Gervay-Hague
Stephen Hanessian
Louis Hegedus
Paul J. Hergenrother
Donna M. Huryn
Jeffrey S. Johnson
Laura Kiessling
Marisa C. Kozlowski
Steven V. Ley
James A. Marshall
Michael J. Martinelli
Stuart W. McCombie
Scott J. Miller
Larry E. Overman
Albert Padwa
T. V. RajanBabu
James H. Rigby
William R. Roush
Tomislav Rovis
Scott D. Rychnovsky
Martin Semmelhack
Charles Sih
Amos B. Smith, III
Barry M. Trost
Peter Wipf

FORMER MEMBERS OF THE BOARD
NOW DECEASED

Roger Adams
Homer Adkins
Werner E. Bachmann
Peter Beak
Robert Bittman
A. H. Blatt
Virgil Boekelheide
George A. Boswell, Jr.
Theodore L. Cairns
Arthur C. Cope
Donald J. Cram
David Y. Curtin
William G. Dauben
Louis F. Fieser
Heinz W. Gschwend
Richard F. Heck
Ralph F. Hirschmann
Herbert O. House
John R. Johnson
Robert M. Joyce
Robert C. Kelly
Andrew S. Kende
Willy Leimgruber
Frank C. McGrew
Blaine C. McKusick
Jerrold Meinwald
Carl Niemann
Leo A. Paquette
Gary H. Posner
Hans J. Reich
Harold R. Snyder
Milán Uskokovic
Boris Weinstein
James D. White

Organic Reactions

VOLUME 113

WILEY

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress Cataloging-in-Publication Data:

ISBN: 978-1-119-98227-2

Printed in the United States of America

INTRODUCTION TO THE SERIES BY ROGER ADAMS, 1942

In the course of nearly every program of research in organic chemistry, the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses*, they have not been subjected to careful testing in two or more laboratories. Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required. Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy, the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

INTRODUCTION TO THE SERIES
BY SCOTT E. DENMARK, 2008

In the intervening years since "The Chief" wrote this introduction to the second of his publishing creations, much in the world of chemistry has changed. In particular, the last decade has witnessed a revolution in the generation, dissemination, and availability of the chemical literature with the advent of electronic publication and abstracting services. Although the exponential growth in the chemical literature was one of the motivations for the creation of *Organic Reactions*, Adams could never have anticipated the impact of electronic access to the literature. Yet, as often happens with visionary advances, the value of this critical resource is now even greater than at its inception.

From 1942 to the 1980's the challenge that *Organic Reactions* successfully addressed was the difficulty in compiling an authoritative summary of a preparatively useful organic reaction from the primary literature. Practitioners interested in executing such a reaction (or simply learning about the features, advantages, and limitations of this process) would have a valuable resource to guide their experimentation. As abstracting services, in particular *Chemical Abstracts* and later *Beilstein*, entered the electronic age, the challenge for the practitioner was no longer to locate all of the literature on the subject. However, *Organic Reactions* chapters are much more than a surfeit of primary references; they constitute a distillation of this avalanche of information into the knowledge needed to correctly implement a reaction. It is in this capacity, namely to provide focused, scholarly, and comprehensive overviews of a given transformation, that *Organic Reactions* takes on even greater significance for the practice of chemical experimentation in the 21st century.

Adams' description of the content of the intended chapters is still remarkably relevant today. The development of new chemical reactions over the past decades has greatly accelerated and has embraced more sophisticated reagents derived from elements representing all reaches of the Periodic Table. Accordingly, the successful implementation of these transformations requires more stringent adherence to important experimental details and conditions. The suitability of a given reaction for an unknown application is best judged from the informed vantage point provided by precedent and guidelines offered by a knowledgeable author.

As Adams clearly understood, the ultimate success of the enterprise depends on the willingness of organic chemists to devote their time and efforts to the preparation of chapters. The fact that, at the dawn of the 21st century, the series continues to thrive is fitting testimony to those chemists whose contributions serve as the foundation of this edifice. Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

PREFACE TO VOLUME 113

They say opposites attract, but like meets like, too.

Ruth Downie, 2015
A Year of Ravens

The construction of functional molecules in a predictable manner is predicated on the ability to design and implement a specific synthetic strategy. Consequently, translating a retrosynthetic analysis into practice requires the identification of successful tactics and thus constitutes the most time-consuming and tedious aspect of such an endeavor. One of the overarching strengths of the *Organic Reactions* series is the collation of reaction conditions in curated tables that enable the reader to a priori select the appropriate tactics to expedite the implementation of a proposed synthetic sequence. The two chapters in this particular volume focus on transition-metal-catalyzed alkyl-alkyl cross-coupling reactions that form challenging carbon-carbon bonds and on the hydrozirconation of alkynes to generate reactive carbon nucleophiles for electrophilic functionalization and cross-coupling reactions. Hence, the two chapters provide important reactions that align with the notion that "*opposites attract, but like meets like, too*" since they both feature cross- and homo-coupling reactions. In contrast to conventional cross-coupling reactions that primarily proceed through a heterolytic-type process, homolytic processes now permit both cross- and homo-coupling reactions. Although the homolytic pathway has often been derided because of the challenges associated with controlling chemo-, regio-, and stereoselectivity, the ability to promote selective cross-coupling reactions through radical intermediates has significantly broadened the scope of these types of transformations.

The first chapter by Takanori Iwasaki and Nobuaki Kambe provides a definitive treatise on transition-metal-catalyzed alkyl-alkyl cross-coupling reactions, the development of which has proven particularly challenging. The coupling of unsaturated partners (i.e., forming bonds between sp and sp^2 components) has been extensively studied and was the subject of the 2010 Nobel Prize in Chemistry. Ironically, the reactions between sp^3-hybridized carbon atoms predate the former and can be traced to the seminal studies of Kharash in the 1940s. Independent studies by several groups in the 1970s illuminated the problems associated with controlling efficiency and selectivity in alkyl-alkyl coupling, stemming from undesirable side reactions. Hence, progress was limited until the 1990s when alkyl halides were identified as promising coupling partners, thereby inspiring the remarkable progress in the 2000s that led to the development of a series of important reactions, including enantioselective variants.

The Mechanism and Stereochemistry section defines the two catalytic cycles that have been used to rationalize these reactions. For instance, Type A proceeds by a more conventional process, triggered by oxidative addition with the alkyl halide,

which is supported by the isolation of the oxidative addition adduct and kinetic studies. In contrast, Type B is initiated by a transmetallation or complexation of the organometallic reagent, which differs significantly based on the metal complex and the type of ligand. For example, the Kumada–Tamao–Corriu cross-coupling reaction catalyzed by nickel or palladium utilizes 1,3-butadiene as a ligand that dimerizes to form a high-oxidation state bis-π-allyl metal complex that reacts directly with the Grignard reagent. This section also addresses the stereochemical aspects of the reaction in the context of the electrophile (alkyl halide or pseudohalide) and nucleophile (organometallic reagent). In the former case, the process can be either stereospecific or stereoselective, which is relevant to developing the enantioselective variations. The catalyst impacts the stereochemical outcome for the alkyl electrophiles, which is ascribed to the switch from a heterolytic to a homolytic pathway (vide supra). Hence, tailoring the metal complex has far-reaching implications that expand the scope and permit the construction of challenging carbon-carbon bonds in a predictable manner. In contrast, the stereochemistry of the alkylmetal reagents is rarely examined because of problems with their stereochemical lability, albeit a few seminal studies are described to provide insight into the current challenges. The section on the relative reactivity of various electrophiles and nucleophiles offers further insight into designing optimal combinations for a specific coupling reaction.

The Scope and Limitations section commences with a chart summarizing the current scope and limitations for the metal catalysts and coupling partners to define the remaining knowledge gaps in this area. This section is organized by the type of metal catalyst (e.g., Cu, Ni, Pd, Ag, Fe, and Co), which is important given the differences in the reaction mechanisms. The sections are further subdivided into the kind of organometallic reagent (Mg, Li, Mn, Zn, Sm, and B), the degree of alkyl substitution and the nature of the leaving group, e.g., the copper-catalyzed cross-coupling of primary alkyl halides and pseudohalides with an array of alkyl Grignard reagents (primary, secondary, and tertiary). The nickel and palladium sections also include the merits of different ligands (e.g., phosphine, nitrogen-based, *N*-heterocyclic carbene, and π-carbon ligands) that have been employed. The section on asymmetric variants of the alkyl-alkyl cross-coupling reaction is important and timely because it clearly illustrates that this process is very much in its infancy and has immense synthetic possibilities. Notably, the enantioconvergent reactions generally require a nickel complex with chiral diamine and triamine ligands to access the requisite alkyl radical intermediate for the enantioconvergent process (e.g., Suzuki-Miyaura, Negishi, and Kumada-Tamao-Corriu cross-coupling reactions).

The Applications to Synthesis section highlights several adaptations of the reaction in natural-product synthesis that involve forming racemic and achiral carbon-carbon bonds. The Comparison with Other Methods section critically assesses homocoupling reactions of alkyl halides and alkylmetal reagents, including reductive cross-electrophile coupling, cross-coupling of alkyl transition-metal reagents, and cross-coupling reactions with unsaturated partners followed by reduction. The Tabular Survey is organized by the type of substitution of the electrophile and alkylmetal reagent (e.g., primary alkyl halides with primary alkylmetals) and then further subdivided by the kind of organometallic reagent (e.g., Mg, Zn, B, etc.), to permit the identification of a specific reaction combination of interest. This outstanding

chapter on an important class of cross-coupling reactions complements the extensive studies with unsaturated variants. Hence, the chapter should interest anyone wishing to develop new variants or employ this type of transformation in target-directed synthesis.

The second chapter by John A. Milligan, Courtney V. Hammill, Desirae L. Crocker, and Peter Wipf describes the hydrozirconation of alkynes, which has been the subject of intensive investigation. Although hydrometallation can be accomplished with early- and late-transition metals, the former permits the stoichiometric conversion of unactivated alkenes and alkynes into various organic compounds by functionalizing the isolable σ-bonded organometallic intermediate. The chapter primarily focuses on the synthetic utility of zirconocene hydrochloride ($Cp_2Zr(H)Cl$, Schwartz Reagent), which can be accessed directly or prepared in situ from either zirconocene dichloride or dihydride. The reagent was first prepared and utilized for hydrozirconation alkenes and alkynes in the late 1960s and early 1970s by Wailes and coworkers. This chapter delineates the evolution of the hydrozirconation reaction with this reagent and the reactions of the zirconium-carbon σ-bond with a range of electrophiles, which has proven to be a versatile and general methodology.

The Mechanism and Stereochemistry section outlines the challenges with the hydrozirconation of alkenes and alkynes, which are formally equilibrium processes initiated by forming a transient π-complex en route to the thermodynamically more favorable σ-complex. Hydrozirconation is analogous to hydroboration since it proceeds through a four-centered, concerted asynchronous transition state. Although zirconocene hydrochloride is commonly employed, these species can also be accessed from β-hydride elimination, albeit the mechanistic details of this process have not been reported. This section highlights the limitations of the current theoretical studies that focus entirely on ethylene and acetylene, which suggest the chlorine and hydrogen ligands are at opposing ends during the addition and that the hydrozirconation process is fully reversible at room temperature. The authors outline important stereochemical aspects through key experimental observations and the impact of solvent on kinetic and thermodynamic control. In addition, the implication of steric and electronic factors in both the reagent and the substrate on regio- and stereoselectivity provides the reader with a comprehensive summary of the factors that control reactivity and selectivity in this process.

The Scope and Limitations section begins with an overview of the functional-group tolerance of the hydrozirconation reaction, which is highly selective for alkynes in the presence of an array of reactive functionalities. Chemoselectivity is further addressed with bimetallic zirconocenes that permit the selective functionalization of the zirconium-carbon bond. The alkenyl zirconocene intermediate is versatile as exemplified by its ability to undergo protonation, deuteration, halogenation, oxidation, and hydrogenation reactions, including insertion reactions with carbon monoxide and isonitriles. Notably, the alkenylzirconocene intermediates undergo homocoupling in the presence of either copper(II) halides or oxovanadium reagents to afford 1,4-butadienes (vide supra). Alternatively, simple halide displacement reactions afford organophosphorus, organosulfur, and organoselenium compounds, as well as amines and enamines. The copper-catalyzed displacement of *O*-benzoylhydroxylamine with an alkenylzirconocene is particularly pertinent since

it provides an attractive method for the regio- and stereodefined construction of acyclic enamines. Furthermore, the ability to transmetallate zirconium with several main-group elements and transition metals (e.g., Al, B, Cu, Ni, Pd, etc.) followed by the stereospecific alkylation with various carbon electrophiles highlights the synthetic utility of this transformation for the stereoselective construction of cyclic and acyclic olefins. The authors also discuss cationic zirconocenes that promote additions to aldehydes and the ring opening of epoxides facilitated by the enhanced Lewis acidity of the alkenylzirconocene intermediate. This section is completed with miscellaneous reactions, limitations, and side reactions to provide the reader with further insight into the remaining challenges associated with these transformations.

The Applications to Synthesis section delineates several examples of preparing complex natural products, illustrating the versatility of the process for the total synthesis of important bioactive agents. The Comparison with Other Methods section primarily focuses on hydroboration, hydrostannylation, and other hydrometallations of alkynes but it also covers haloalkene insertion reactions to afford the regioisomeric 1,1-alkenylzirconocene intermediate. The Tabular Survey follows the same organization as Scope and Limitations, wherein the specific type of functionalization is listed separately to permit the reader to identify the appropriate reaction of interest. This is an outstanding chapter on an important transformation that will be a valuable and practical resource to the synthetic community, particularly given that zirconocene hydrochloride is commercially available.

I would be remiss if I did not acknowledge the entire *Organic Reactions* Editorial Board for their collective efforts in steering this volume through the many stages of the editorial process. I want to thank Dr. John Montgomery, Dr. Kevin H. Shaughnessy (Chapter 1), and Dr. Steven M. Weinreb (Chapter 2) who served as the Responsible Editors to marshal the chapters through the various phases of development. I am also deeply indebted to Dr. Danielle Soenen for her continued and heroic efforts as the Editorial Coordinator; her knowledge of *Organic Reactions* is critical to maintaining consistency in the series. Dr. Dena Lindsay (Secretary to the Editorial Board) is thanked for coordinating the contributions of the authors, editors, and publisher. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the efforts of Dr. Steven M. Weinreb (Executive Editor), Dr. Engelbert Ciganek (Editorial Advisor), Dr. Landy Blasdel (Processing Editor), and Dr. Tina Grant (Processing Editor). I would also like to acknowledge Dr. Barry B. Snider (Secretary) for keeping everyone on task and Dr. Jeffery Press (Treasurer) for ensuring we remain fiscally solvent!

I am also indebted to past and present members of the Board of Editors and Board of Directors for ensuring the enduring quality of *Organic Reactions*. The unique format of the chapters, in conjunction with the curated tables of examples, makes this series of reviews both unique and exceptionally valuable to the practicing synthetic organic chemist.

P. Andrew Evans
Kingston
Ontario, Canada

CONTENTS

ORGANIC REACTIONS

CHAPTER 1

TRANSITION-METAL-CATALYZED ALKYL–ALKYL CROSS-COUPLING REACTIONS

TAKANORI IWASAKI

Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

NOBUAKI KAMBE

Research Center for Environmental Preservation, Osaka University, 2-4 Yamadaoka, Suita, Osaka 565-0871, Japan

Edited by JOHN MONTGOMERY AND KEVIN SHAUGHNESSY

CONTENTS

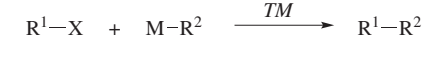
kambe@chem.eng.osaka-u.ac.jp
How to cite: Iwasaki, T.; Kambe, N. Transition-Metal-Catalyzed Alkyl–Alkyl Cross-Coupling Reactions. *Org. React*. **2023**, *113*, 1–456.

Doi:10.1002/0471264180.or113.01

INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions are fundamentally important and particularly useful transformations for organic synthesis. Indeed, they are now widely employed in constructing carbon frameworks in an array of organic

compounds. The simplest variant for cross-coupling is the reaction between organohalides and organometallic reagents, which results in two different carbon centers being connected by a single bond (Scheme 1). The significance of this transformation in the chemical, material, and biological sciences, as well as industrial chemistry has prompted the development of various adaptations, which resulted in the Nobel Prize in Chemistry in 2010 for "palladium-catalyzed cross-coupling in organic synthesis".



R = alkynyl, aryl, alkenyl, alkyl
X = halogen, pseudohalogen
M = MgX, Li, ZnX, AlX_2, SnX_3, BX_2, SiX_3, etc.
TM = transition-metal catalyst

Scheme 1

Cross-coupling of unsaturated carbon moieties (i.e., forming bonds at sp- and sp^2-hybridized carbon centers) has been the subject of extensive study since the early 1970s and has been applied to the synthesis of organic molecules that contain conjugated π-electron systems. Cross-coupling reactions between sp^3-hybridized carbon moieties have a long history, dating back to the 1940s[1] and the pioneering studies of the early 1970s;[2–4] however, limited attention has been paid to alkyl–alkyl cross-coupling reactions until recently, which is due, in part, to the difficulties associated with undesirable side-reactions that result in low selectivity and efficiency. Nevertheless, in the late 1990s, alkyl halides were recognized as promising coupling partners in cross-coupling reactions,[5] which led to remarkable progress in the 2000s in this undeveloped field. Various practical methods for alkyl–alkyl cross-coupling, including asymmetric versions, have now been established by using combinations of suitable ligands and transition-metal catalysts. These reactions promise to provide not only straightforward and powerful tools for constructing carbon chains in organic synthesis but also novel methods for creating asymmetric carbon centers.

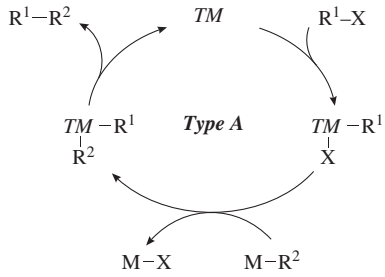
This chapter describes transition-metal-catalyzed cross-coupling reactions between sp^3-carbons, specifically the reactions of alkyl halides or pseudohalides with alkylmetal reagents. With regard to the scope of the halides that can be used in these reactions: except for a few cases, coupling reactions of allylic (pseudo)halides are not covered here because they are reactive toward nucleophiles and can undergo nucleophilic substitution in the absence of a catalyst; their chemistry with transition metals is discussed in published chapters dealing with allylic substitutions via allylmetal intermediates.[6–8] Coupling reactions using allylic and benzylic organometallic reagents are included here, but the alkylations of metal enolates and related stabilized carbanions are excluded. The Scope and Limitations section is divided into subsections according to transition-metal catalysts followed by reagents or ligand systems. Independent subsections are allocated to reagents, reactivities, and asymmetric cross-coupling reactions.

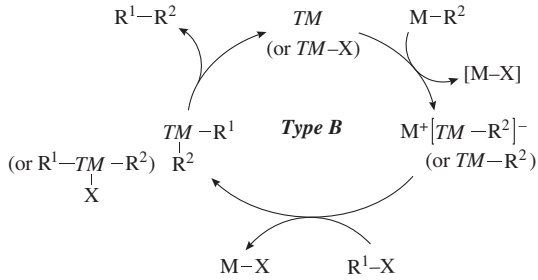
Some excellent reviews are available on coupling reactions employing alkyl halides[9–14] or alkylmetal reagents[15] and both,[14,16–21] including asymmetric variants.[22–26]

MECHANISM AND STEREOCHEMISTRY

General Catalytic Cycles

Catalytic pathways of cross-coupling reactions can be classified into two types, as shown in Scheme 2. In Type A, a low-valent metal species (*TM*) first reacts with an organo (pseudo)halide (R^1–X) and then reacts further with an organometallic compound (R^2–M), giving rise to the coupled product (R^1–R^2). This is a common pathway for the cross-coupling of aryl and vinyl halides, as well as for alkyl halides, and has stimulated numerous synthetic applications using palladium and nickel catalysts. In the Type B pathway, the metal catalyst reacts with these two reagents in the reverse order, i.e., first with an organometallic compound and then with an alkyl halide. Copper-catalyzed cross-coupling is a typical example of this type of mechanism. Reactions of alkyl halides using various transition metals such as rhodium, cobalt, iron, vanadium, as well as nickel and palladium often proceed via





R = organic group
X = (pseudo)halogen
M = typical metal
TM = transition-metal catalyst

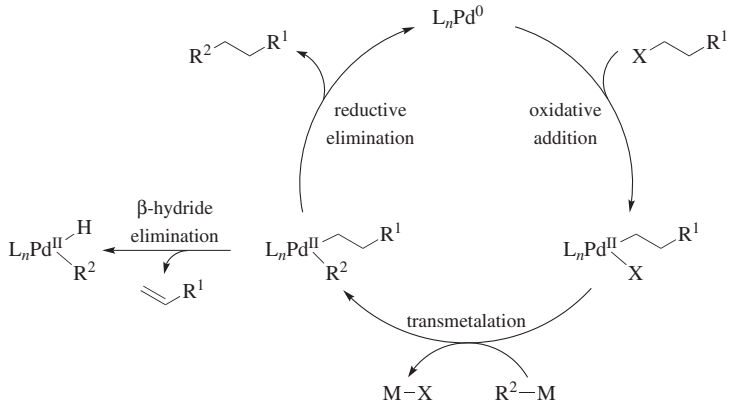
Scheme 2

this pathway. In both pathways, the formation of a carbon–carbon bond proceeds via reductive elimination of a diorganometal intermediate (*TM*R^1R^2 or *TM*R^1R^2X), although a one-step mechanism without the formation of a *TM*R^1R^2 (*TM*R^1R^2X) intermediate cannot be ruled out. The mechanistic details and active catalytic species vary according to the catalytic system. Single-electron-transfer (SET) processes appear to be involved in some cases, especially in the Type B pathway.

Transition metals with low oxidation states undergo oxidative addition to organic halides. This process generally proceeds via the conventional concerted mechanism with the contribution of π-bond orbitals when aryl or vinyl halides are employed. In the case of alkyl halides, this concerted mechanism is less favorable, and S_N2 or SET mechanisms are frequently operative. Strongly electron-donating ligands such as trialkylphosphines and *N*-heterocyclic carbenes (NHCs) are commonly employed as ligands. Chelating amine and π-carbon ligands are also an attractive choice for alkyl–alkyl cross-coupling.

Catalytic Cycles Triggered by Oxidative Addition (Type A)

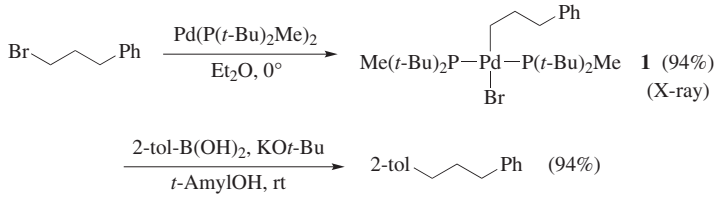
The palladium-catalyzed Suzuki–Miyaura coupling of alkyl halides using bulky trialkylphosphines proceeds via the Type A pathway, which is triggered by the oxidative addition of Pd(0) into the alkyl halides and thus involves successive steps of oxidative addition, transmetalation, and reductive elimination (Scheme 3). The oxidative addition step proceeds through an S_N2-type mechanism characterized by an inversion of the stereochemistry at the reacting carbon center (see below).[27] Bulky trialkylphosphines play an important role in both the oxidative addition and the reductive elimination steps. The high electron-donating ability of the trialkylphosphines accelerates the oxidative addition step, and their large cone angle facilitates the loss of ligands to create an open coordination site to accept substrates. Bulky ligands on the metal also suppress β-hydride elimination and promote the final reductive elimination step in the catalytic cycle.[28] Pd–NHC complexes catalyze alkyl–alkyl cross-coupling, which probably proceeds via a pathway similar to that



Scheme 3

shown in Scheme 3.[29] Monoligated complexes (PdL) are proposed to be the active catalytic species when bulky trialkylphosphines or NHCs are employed.[30]

The alkylpalladium intermediate **1**, generated by an oxidative addition process, has been successfully isolated in 94% yield, and its structure was determined by X-ray analysis.[31] In this complex, the bulky trialkylphosphine ($P(t\text{-}Bu)_2Me$) efficiently suppresses the non-productive β-hydride elimination process. In addition, when this alkylpalladium complex **1** is treated with a boronic acid and a base, the complex undergoes transmetalation and subsequent reductive elimination to give the coupled product in 94% yield (Scheme 4).[31]



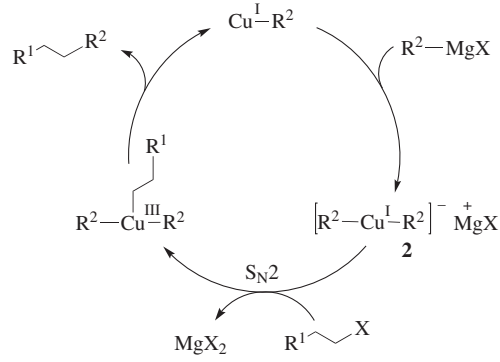
Scheme 4

Kinetic studies on the oxidative addition step in the catalytic cycle show that the activation parameters for the oxidative addition of $Pd(P(t\text{-}Bu)_2Me)_2$ into $n\text{-}C_9H_{19}Br$ are $\Delta G^{\ddagger} = 87.1$ kJ/mol at 20° (81.6 kJ/mol at 0°), $\Delta H^{\ddagger} = 10$ kJ/mol, and $\Delta S^{\ddagger} = -2.6 \times 10^2$ J/mol•K. The large negative $\Delta S^{\ddagger}$ values are consistent with the reaction following an associative S_N2-type pathway. The use of excess $P(t\text{-}Bu)_2Me$ in this reaction does not affect the rate of the reaction, suggesting that the active species for oxidative addition into the alkyl bromide is a bisphosphine complex PdL_2, and not PdL or PdL_3. The $\Delta G^{\ddagger}$ for the oxidative addition into $n\text{-}C_9H_{19}Br$ using PdL_2 with PCy_3, $P(t\text{-}Bu)_2Et$, and $P(t\text{-}Bu)_3$ is estimated to be 83.7 (at 0°), 106 (at 60°), and >119 (at 60°) kJ/mol, respectively. The activation barrier decreases with increasing solvent polarity, consistent with an S_N2-type nucleophilic attack of Pd(0) on the R–X moiety to form an ion pair.[32]

Catalytic Cycles Triggered by Transmetalation or Complexation (Type B)

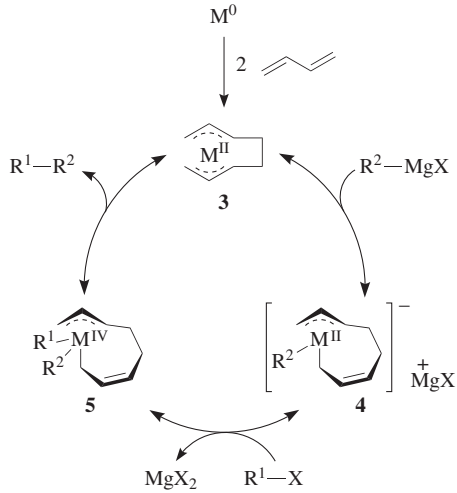
As previously described, some transition metals used as catalysts for cross-coupling reactions of alkyl halides proceed via the mechanism triggered by transmetalation or complexation with the organometallic reagent (Type B pathway). A typical example is the copper-catalyzed alkyl–alkyl cross-coupling reaction, in which cuprates **2** play an important role as the active catalytic species in the reaction with alkyl halides, which proceeds through an S_N2-type mechanism (Scheme 5).[33,34]

Another example of the Type B pathway that occurs via an S_N2-type substitution is the Kumada–Tamao–Corriu alkyl–alkyl coupling reaction, catalyzed by nickel or palladium in the presence of 1,3-butadiene as a ligand precursor (Scheme 6).[35,36] At the outset of the reaction, Ni or Pd salts are reduced to the zero-valent species,



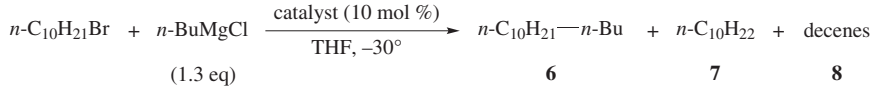
Scheme 5

which react with two molecules of 1,3-butadiene to give bis(π-allyl)metal intermediate **3**. Because the oxidation state of the metal center of complex **3** is +2, it does not undergo oxidative addition with an alkyl halide but instead reacts with a Grignard reagent to form an anionic complex, so-called ate complex **4**.[37,38] The ate complex **4** reacts with an alkyl halide via an S_N2 process at the metal center to form dialkyl M(IV) intermediate **5**, which then undergoes reductive elimination to give the coupled product (Scheme 6).[35,36] Theoretical calculations on nickel catalytic systems support this pathway and suggest that the anionic Ni center in the ate complex **4** nucleophilically attacks the carbon of the alkyl halide with the aid of a Mg cation, which coordinates to the halogen atom of the alkyl halide to activate the C–X bond. The transition state of the subsequent reductive elimination of Ni(IV) has a much lower energy barrier than that of the oxidative addition (rate determining step), as well as that of β-hydride elimination from the Ni(IV) intermediate (side reactions).[39–41]



Scheme 6

This proposed mechanism and the intermediates are supported experimentally using a simple bis(π-allyl)nickel complex and its derivatives. When nickel complexes containing none, one, or two π-allyl ligands are tested in the cross-coupling of *n*-decyl bromide with *n*-BuMgCl, only the bis(π-allyl)nickel complex **10** provides the coupled product **6** in a high yield, whereas $NiCl_2$ and the monoallyl nickel species **9** give complex mixtures (Scheme 7).[42]



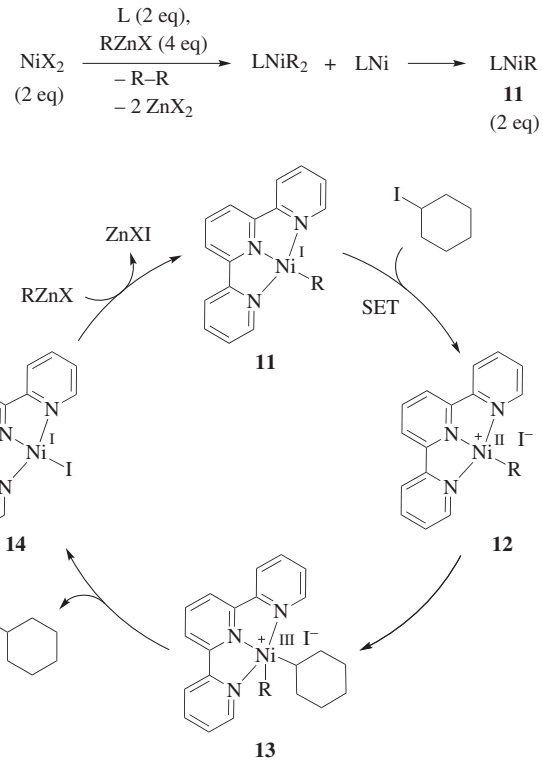
	Yield (%)		
Catalyst	**6**	**7**	**8**
$NiCl_2$	5	33	18
$[(C_3H_5)NiCl]_2$ (**9**)	7	33	24
$(C_3H_5)_2Ni$ (**10**)	94	4	2

Scheme 7

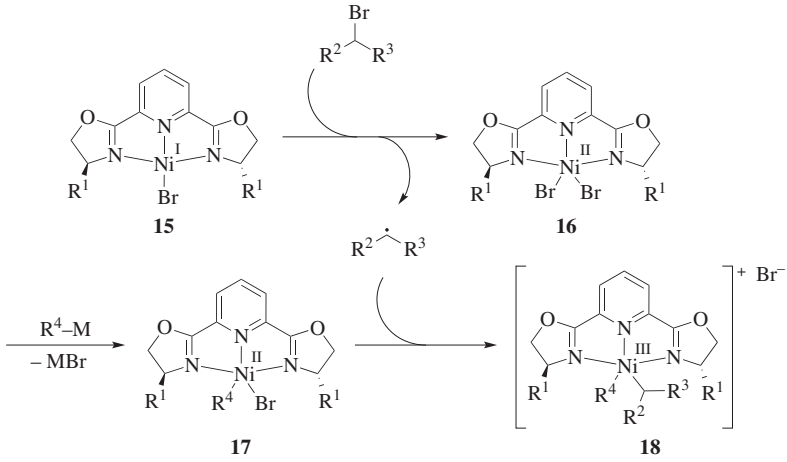
A similar cross-coupling using a Co/LiI/1,3-diene system is also proposed to proceed via an S_N2-type mechanism.[43] In the Ni-, Pd-, and Co-catalytic systems where 1,3-butadiene is used as an additive, the coordinational flexibility of the π-carbon ligand(s) in the allylmetal intermediates via a σ–π interconversion appears to be important for achieving catalysis. These reactions proceed with net inversion of the configuration at the reacting carbon of the alkyl halide (see below), and no evidence of radical intermediates is observed, thus supporting an ionic mechanism. A related Cu-catalyzed coupling reaction using internal alkyne or 1,3-diene additives also follows a similar pathway (vide infra).[44]

Since sp^3-carbon radicals are usually more stable than sp^2-carbon radicals, the reaction of transition-metal catalysts with alkyl halides occasionally generates alkyl radicals as intermediates, resulting in coupling reactions that proceed via alternative mechanisms to the above-mentioned ionic examples.[45] A typical example is the case of the Ni–pincer-ligand system shown in Scheme 8,[46] which is categorized as a Type B process (Scheme 2). Theoretical calculations[46,47] suggest that this reaction is triggered by an SET between the alkyl halide and alkylnickel(I) intermediate **11**, generated by the partial reduction of the nickel precursor and comproportionation. In the Ni(I) intermediate **11**, the radical spin density is localized mainly on the ligand (L) rather than on the central metal (Ni).[46] Complex **11** undergoes SET to the alkyl halide to form Ni(II) intermediate **12** and the corresponding alkyl radical. Recombination of the Ni(II) intermediate **12** with the alkyl radical affords dialkylnickel(III) species **13**, which undergoes reductive elimination to yield the cross-coupling product and Ni(I) halide **14**. Finally, alkylnickel(I) species **11** is regenerated in a transmetalation reaction with the organozinc reagent to close the catalytic cycle.

An alternate pathway involving two nickel complexes in the oxidative addition process was proposed in a related nickel-catalyzed system (Scheme 9).[48,49] In this oxidative addition process, Ni(I) intermediate **15** reacts with an alkyl bromide to



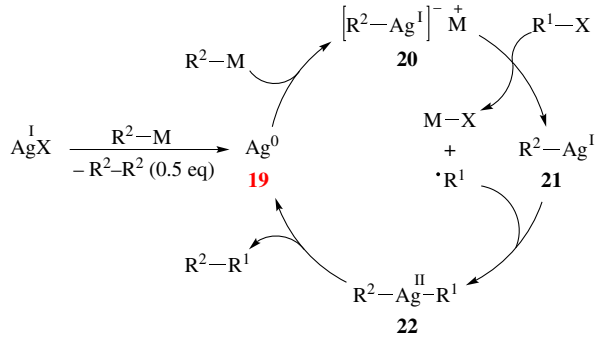
Scheme 8



Scheme 9

generate the alkyl radical and Ni(II) complex **16**. The alkyl radical recombines with another monoorgano–Ni(II) complex **17**, generated by the transmetalation of complex **16** with an organometallic reagent. The resulting Ni(III) complex **18** undergoes reductive elimination to give coupled product and complex **15**.

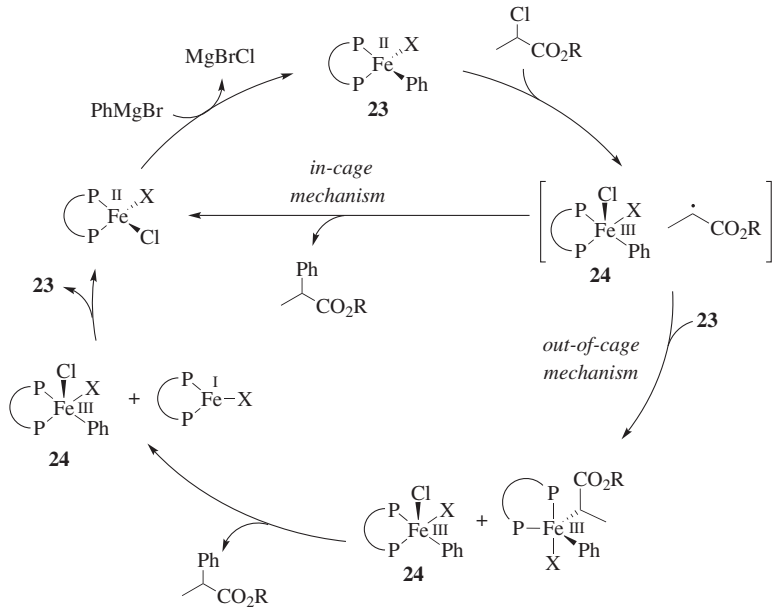
A similar Ag(0)/Ag(II) catalytic mechanism involving radical intermediates is proposed for the cross-coupling of alkyl halides with alkyl-, benzyl-, and allylmetal reagents (Scheme 10).[50] Silver(0) **19** generated by the reduction of a silver(I) salt, reacts with one equivalent of the organometallic reagent to generate the anionic complex **20**. The SET from this anionic alkylsilver species **20** to an alkyl halide gives an alkyl radical and a neutral alkylsilver(I) **21**. The subsequent combination of these two species results in the formation of a dialkylsilver(II) complex **22**, which undergoes reductive elimination to afford the coupled product along with the regeneration of silver(0). Likewise, the cobalt- and copper-catalyzed cross-coupling of alkyl halides with allylic or benzylic organometallic reagents are proposed to follow a similar mechanism.[12,51–56]



Scheme 10

Iron catalysts can also be used in alkyl–alkyl cross-coupling reactions, and a unique catalytic cycle involving carbon radical intermediates is proposed for systems that include a bidentate phosphine ligand.[57–62] The organoiron(II) complex **23**, generated by transmetalation, abstracts a halogen atom from an alkyl halide to form the corresponding alkyl radical and a Fe(III) complex **24**. Based on mechanistic studies using alkyl halides and aryl Grignard reagents, it is proposed that the alkyl radicals combine with the Fe(III) complexes **24** in a solvent cage (in-cage mechanism),[63] or react with Fe(II) intermediates **23** outside the solvent cage (out-of-cage mechanism) (Scheme 11).[64] Both of these mechanisms can operate, and the ligand used as well as the stability of the alkyl radical arising from the alkyl halide may determine the main reaction pathway.

Another possible pathway was proposed based on DFT calculations, in which an Fe(I) chloride complex abstracts a halogen atom from an alkyl halide, and the resulting alkyl radical combines with the organoiron(II) intermediate **23** that is generated



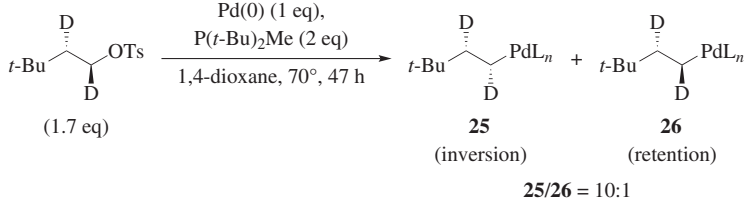
Scheme 11

via transmetalation.[65] However, mechanistic details concerning this reaction remain unclear because of the difficulties associated with experimental analysis.

As mentioned above, the critical step in the reaction is cleavage of the C–X bond triggered by SET to generate the corresponding alkyl radical. New approaches for generating alkyl radicals from non-halogenated substrates have been demonstrated. For instance, the combination of an iridium photoredox catalyst with a nickel catalyst generates alkyl radicals from carboxylic acids or amines by photo-irradiation. The resulting alkyl radicals add to the nickel catalyst, giving rise to coupled products with aryl halides.[66] Similarly, the coupling reaction of alkyl borates with aryl halides by dual photoredox–nickel catalysis is reported.[67] Another approach for generating alkyl radicals from easily accessible alkane carboxylic acids via *N*-hydroxyphthalimide derivatives is employed in cross-coupling reactions with alkylzinc reagents catalyzed by Ni.[68] Although the scope of these processes has not been well studied, these methods might be useful in alkyl–alkyl cross-coupling reactions.

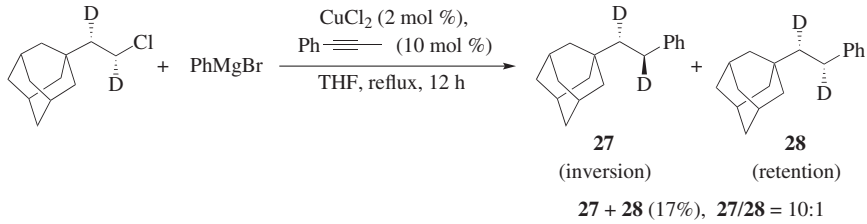
Stereochemistry of Alkyl Electrophiles

In the case of Pd catalysts, the oxidative addition process occurs via an ionic mechanism with inversion of configuration at the carbon bearing the (pseudo)halide group, as demonstrated with intermediate **25** in Scheme 12.[27] The addition of Ph-9-BBN to palladium intermediate **25**, followed by reductive elimination with retention of stereochemistry, affords the corresponding cross-coupled product with net inversion of the configuration relative to the original alkyl tosylate.

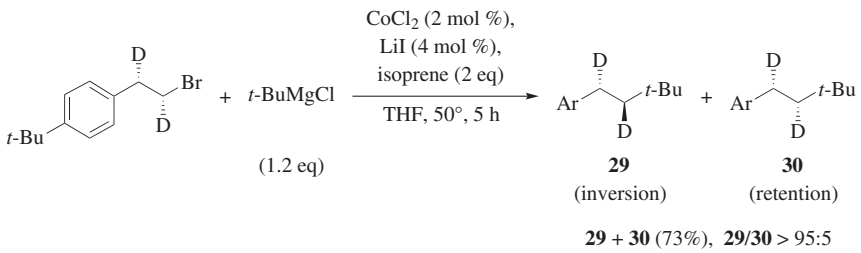


Scheme 12

When a deuterated alkyl chloride or bromide is used in copper- or cobalt-catalyzed coupling reactions using unsaturated hydrocarbon additives, a similar inversion of configuration at the site of the reactive alkyl halide is observed (Schemes 13[44] and 14[43]).



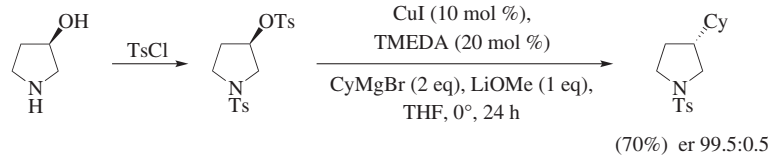
Scheme 13



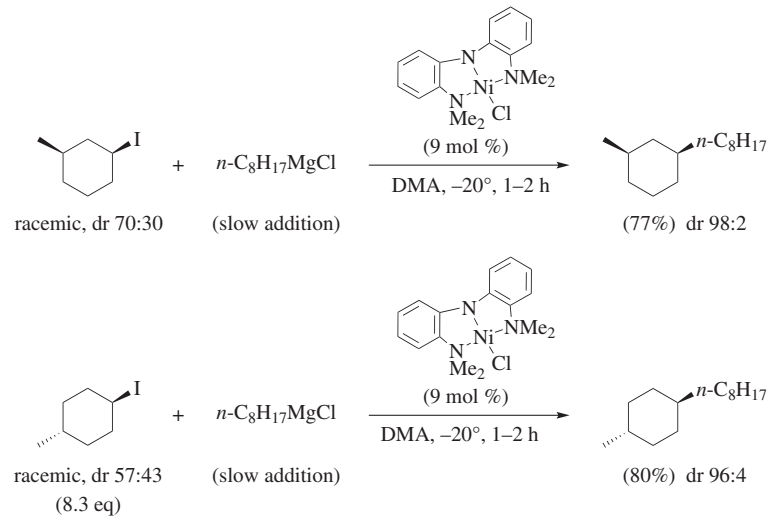
Scheme 14

Stereospecific alkyl–alkyl coupling is useful for constructing chiral carbon frameworks. For example, stereogenic tertiary carbon centers can be created by the tosylation of commercially available chiral secondary alcohols, followed by a copper-catalyzed cross-coupling reaction with a Grignard reagent, with stereo-inversion, without a loss of stereochemical purity (Scheme 15).[69]

In sharp contrast to the aforementioned catalytic systems that proceed via ionic mechanisms, Ni/amine ligand systems catalyze the cross-coupling via radical intermediates as discussed in Schemes 8 and 9, resulting in the loss of the stereochemical integrity at the carbon bearing a halogen atom. For example, 3- or 4-substituted cyclohexyl iodides predominantly afford the more stable diastereomeric products with the two alkyl groups on the ring in equatorial positions (Scheme 16).[70]

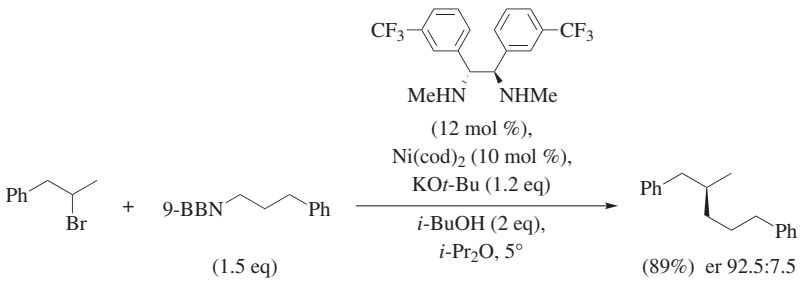


Scheme 15



Scheme 16

A very interesting enantioselective cross-coupling reaction using Ni/chiral diamines or pincer ligand systems, which proceeds via the Type B pathway with radical intermediates, is shown in Scheme 17.[71] In this reaction, racemic secondary alkyl halides are converted into the corresponding radical intermediates to thereby permit a dynamic kinetic asymmetric transformation (DYKAT) process. The recombination of alkyl radical intermediates with a chiral catalyst regenerates a



Scheme 17

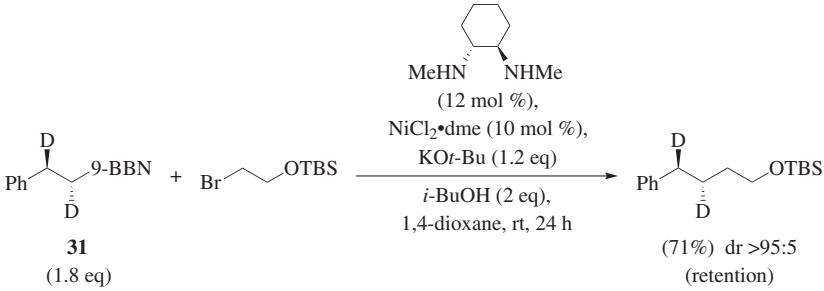
stereogenic center with good enantioselectivity. Hence, the racemic alkyl halides undergo an enantioconvergent process to favor only one enantiomer of the product.

As described above, the stereospecific transformation of alkyl halides with net inversion of their configuration can be attained by employing Pd catalysts or by reactions involving ate complexes of Co, Ni, and Cu. In these cases, an S_N2 substitution and reductive elimination sequence is involved. In contrast, the configuration of the alkyl halides is lost when Ni, Co, Fe, Ag, or Cu catalytic systems are used that involve radical intermediates formed by an SET process. Therefore, the appropriate chiral ligand enables a stereoconvergent cross-coupling, which affords the formation of a single or highly enriched enantiomer from the racemic alkyl electrophile starting materials.

Stereochemistry of Alkylmetal Reagents

The stereochemistry of the alkylmetal reagents used in cross-coupling reactions is rarely discussed because of the lack of accessibility and stereochemical instability, and detailed information is unknown in many cases. Therefore, stereospecific and stereoselective cross-coupling reactions have not been extensively investigated. A few important aspects regarding the stereochemistry of such reactions are discussed below.

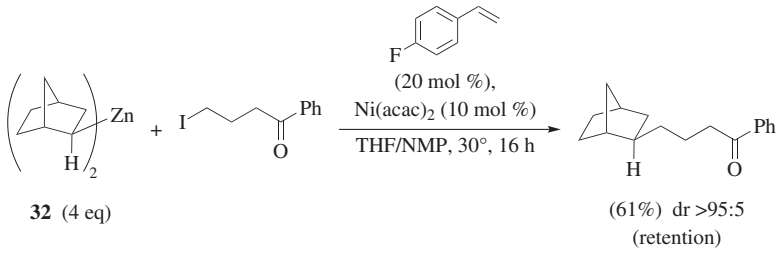
In the Ni/diamine ligand system, the alkyl–alkyl coupling of alkyl bromides with a diastereomerically pure deuterated alkylborane **31** provides the coupled product as a single stereoisomer with retention of configuration at the carbon bearing the boryl group (Scheme 18).[72,73] Similar experiments using deuterated alkylboranes imply that the transmetalation of Pd–phosphine complexes with alkylboranes also proceeds with complete stereo-retention.[74,75]



Scheme 18

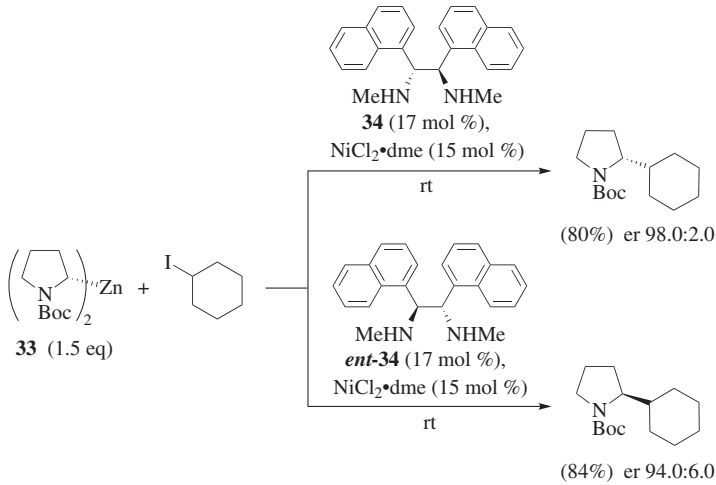
Similarly, the nickel-catalyzed Negishi alkyl–alkyl coupling of di-*exo*-norbornylzinc (**32**) with alkyl iodides provides >95% *exo* selectivity (Scheme 19).[76]

When enantiomerically enriched secondary alkylzinc reagent **33** is coupled with cyclohexyl iodide using chiral nickel catalysts, the reaction proceeds with high enantioselectively, reflecting the configuration of the chiral diamine ligands **34** and ***ent*-34** (Scheme 20).[77] Although it is not clear how the stereo-inversion of the alkyl



Scheme 19

group from the alkylzinc reagent **33** occurs, the possibility of a nickel-mediated β-hydride elimination/reinsertion mechanism was ruled out by a deuterium labeling experiment.



Scheme 20

The stereochemistry of a cross-coupling reaction using chiral secondary alkyl Grignard reagent **35** (ca. 95:5 er) and vinyl bromide has been examined at −78° in THF.[78] The results indicate that the configuration of the alkyl group is retained when $NiCl_2$(dppf) and $PdCl_2$(dppf) are employed as catalysts (Scheme 21).[78] However, a significant loss of enantiopurity is observed when $Fe(acac)_3$ and $Co(acac)_2$ are used as catalysts, which is presumably due to the involvement of an alkyl radical intermediate generated from Grignard reagent **35** (Scheme 21).[79] In a related reaction, the CuCN-mediated conjugate addition of chiral Grignard reagent **35** to an enone at –78 °C results in complete loss of optical purity.[80]

Altogether these results indicate that transmetalation of Ni or Pd with alkylboranes, as well as alkylmagnesium and alkylzinc reagents, proceeds with retention of configuration to give alkylnickel or -palladium intermediates that are configurationally stable, at least at low temperatures. However, in the cases of Co, Cu, and Fe