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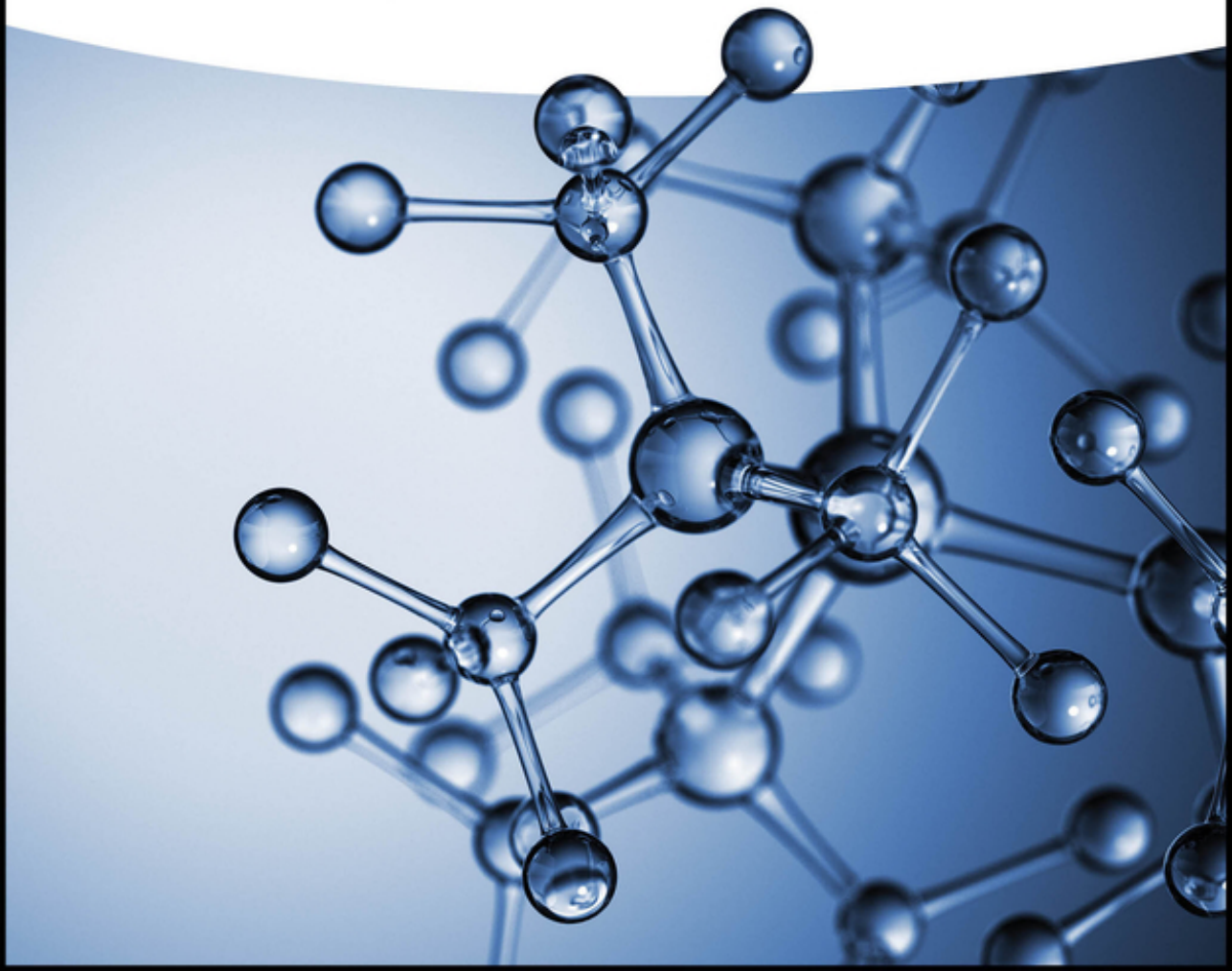
Edited by Xin-Yuan Liu and Guosheng Liu

Catalytic Asymmetric Radical Reactions

Foreword by Professor Mukund P. Sibi



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Foreword

Radical reactions have emerged as a powerful tool with unique advantages in organic synthesis. Their high reactivity, tolerance of many reactive functionalities, and reduced sensitivity to steric crowding make them invaluable in organic synthesis, drug discovery, and materials science. However, harnessing the potential of radical reactions to access chiral molecules through catalytic asymmetric transformations has been a formidable challenge in the twentieth century, mainly due to the difficulty in stereocontrol over the highly reactive radical species. Over the past two decades, the chemistry community has witnessed a surge of innovative research in the development of asymmetric catalytic methods for enantioselective radical reactions. Organic chemists have dedicated their efforts to developing novel strategies, catalysts, and reaction conditions to achieve stereocontrol in reactions with radical intermediates. Despite this flurry of activity, there has been a conspicuous absence of a comprehensive resource that consolidates and presents these advancements in a systematic manner. This edited volume, *Catalytic Asymmetric Radical Reactions*, aims to fill that void.

Catalytic enantioselective radical reactions have evolved significantly since the seminal reports in 1996 using chiral Lewis acid catalysis. Early methods were often plagued by high catalyst loadings, excess of radical initiators and radical precursors, limitations of competent radical traps, and the use of highly toxic radical chain reagents such as tin hydrides. These drawbacks have led to the development of other catalytic methodologies over the past two decades. Synergistic photoredox and other forms of catalysis (using chiral Lewis acids, chiral Brønsted acids, hydrogen-bonding compounds, polarity reversal catalysts, etc.) expanded the scope of radical traps used and introduced alternate ways of quenching – with radicals, nucleophiles, or electrophiles (generated by radical polar crossover reactions of intermediates). The photoredox catalysts used in most of the synergistic catalytic methods are Ir- and Ru-based systems that are expensive and less readily available. These limitations can be overcome by developing green and sustainable organophotoredox systems. Recent advancements in chiral base metal (Fe, Cu, Co, Ni, Mn) catalyzed enantioselective radical reactions should enable the development of methodologies that expand the radical reactions to larger numbers of substrates in green and sustainable ways. An emerging trend in the field of catalytic enantioselective radical transformations is the use of enzymatic catalysis

to control absolute stereochemistry, although it has not been discussed in this book. Remarkable transformations have been demonstrated using this promising greener mode of catalysis. Enzymatic catalysis poses disadvantages including enzyme engineering and reaction scale-up but is optimal in terms of toxicity profile. This methodology has a bright future when used individually or synergistically with other catalytic systems.

This edited volume brings together the collective expertise of researchers in the field, each contributing a chapter on a specific area of catalytic asymmetric radical reactions. The collection begins with an in-depth exploration of transition metal-catalyzed reactions, covering a wide range of metals from iron to precious transition metals. The chapters in this section not only detail the reaction mechanisms but also showcase the reaction scope and the impact of these reactions on the synthesis of chiral molecules. The next section outlines the exploration of chiral Lewis acids and chiral-at-metal-catalyzed asymmetric radical reactions. The contributions in this part shed light on the unique activation modes and stereochemical outcomes enabled by these catalysts. The organocatalysis section rounds off the book, highlighting the power of covalent and noncovalent interactions in asymmetric radical transformations. Chiral amines and phosphoric acids, among other organocatalysts, have proven to be effective in achieving high levels of enantioselectivity, and the chapters here provide a comprehensive overview of these fascinating reactions.

I believe that this edited volume will serve as an essential reference for researchers, students, and industrial chemists alike. It offers a view of the current state of the art in catalytic asymmetric radical reactions, from the fundamental concepts to the most recent breakthroughs. By presenting the strategies and achievements in this field, it will inspire the next generation of chemists to further explore and expand the boundaries of asymmetric radical catalysis. The editor and all the contributors for the volume should be commended for their invaluable expertise and hard work in preparing their chapters. Their dedication has made this edited volume possible. The continued participation of the scientific community should be recognized for their contributions to this exciting area of research. This edited volume will serve as a catalyst for further discovery in the field of catalytic asymmetric radical reactions.

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Preface

Asymmetric synthesis is of great importance in the field of organic chemistry as it allows for the direct synthesis of valuable enantiomerically enriched molecules. Radical species, characterized by unpaired electrons, serve as highly reactive intermediates that are integral to a wide range of chemical transformations, such as organic synthesis, polymerization, and biological processes. In contrast to ionic reactions, radical reactions usually have high reactivity, good functional group tolerance, and less sensitivity to steric crowding. Therefore, the development of catalytic asymmetric radical reactions should be highly appealing but has been less recognized in the history of organic synthesis. The lag might stem from a long-standing misconception that radicals are highly reactive and uncontrollable species, which renders the enantiocontrol challenging. Over the past two decades, however, there has been an extraordinary surge in the development of numerous catalytic asymmetric radical reactions, driven by innovations in chiral Lewis acid catalysis, organocatalysis, transition metal catalysis, and enzymatic catalysis, with the rapid advancement of photo- and electrocatalysis further accelerating progress in the field. Meanwhile, our interest in this field dates back to before 2016, when both the editors of this book published their first publication of the topic independently, drawing on their expertise in transition metal catalysis. Since then, we have devoted sustainable effort to developing chiral copper catalysis for the asymmetric radical transformations of simple chemical feedstocks, including C—H functionalization, difunctionalization of alkenes, and cross-coupling of alkyl halides. Concurrently, a growing array of innovative strategies has emerged in this field, promoting a recognition of the need for a comprehensive summary that encompasses the diverse methodologies developed to date. At this moment, we were honored to receive an invitation from Wiley Publishing to contribute a book dedicated to catalytic asymmetric radical reactions. This opportunity provided the impetus for the creation of the present book.

The content of this book is organized into 3 main parts, encompassing 15 chapters in total. Chapters 1 through 9 provide a comprehensive overview of transition metal-catalyzed asymmetric radical reactions, encompassing both earth-abundant 3d transition metal catalysts – such as iron, cobalt, nickel, copper, and manganese, and precious metal catalysts, including palladium, rhodium, and iridium. Chapter 1 summarizes iron-catalyzed radical asymmetric reactions, utilizing various chiral

ligands to facilitate the construction of chiral C—C and C—X bonds in reactions such as C—H functionalization, alkene difunctionalization, and the cross-coupling of racemic alkyl halides. Chapter 2 presents cobalt-catalyzed radical transformations through strategic ligand design, focusing on three key systems: [Co(Por)]-based metalloradical catalysis enabling stereocontrolled cyclopropanation, aziridination, C—H functionalization, and radical cascade reactions, [Co(salen)]-catalyzed hydrofunctionalization of alkenes involving metal-hydride hydrogen atom transfer (MHAT), and cross-coupling of alkyl halides with organometallic reagents. Chapter 3 highlights the advances in nickel-catalyzed asymmetric radical cross-coupling reactions of racemic alkyl halides and organometallic reagents. In addition, other radical precursors beyond alkyl halides are also discussed to illustrate the broad applicability of asymmetric radical cross-coupling reactions. Chapter 4 summarizes the development of nickel-catalyzed asymmetric radical cross-electrophile coupling reactions under reductive conditions, which circumvent the need for air- or moisture-sensitive organometallic reagents. This chapter mainly introduces the scope of the coupled electrophiles and further highlights their application in alkene difunctionalization. In Chapter 5, copper-catalyzed asymmetric radical cross-coupling of C(sp^3)—H bonds via a radical relay process is presented. The discussion in this chapter emphasizes diverse bond-formation reactions of the resulting radicals, encompassing cyanation, arylation, alkynylation, trifluoromethylation, and amination with various chiral ligands. In Chapter 6, copper-catalyzed enantioconvergent radical cross-coupling reactions of racemic alkyl halides with diverse nucleophiles under thermal conditions are presented. The discussion herein predominantly focuses on the design of chiral ligands for tuning the reducing capability of copper to initiate the radical reaction and creating a chiral environment to achieve the enantiocontrol of radicals. Chapter 7 summarizes manganese-catalyzed asymmetric radical reactions, primarily covering C—H oxidation and related enantioselective desymmetrization. Chapter 8 discusses recent progress in photoredox and earth-abundant metal-catalyzed asymmetric radical reactions, highlighting their ability to generate diverse radical species and enable chiral C—C and C—X bond formations under mild conditions. Chapter 9 highlights the advances in precious transition metal-catalyzed asymmetric radical reactions, involving palladium, rhodium, and iridium catalysis. Since they are reluctant to the single-electron transfer process, a photocatalyst is often incorporated into the reaction system to facilitate the generation of radical species.

Chapters 10 and 11 focus on Lewis acid-catalyzed asymmetric radical reactions. Chapter 10 provides an overview of asymmetric radical reactions catalyzed by classic chiral Lewis acids, such as chiral boranes and metals bearing bidentate, tridentate, or multidentate chiral ligands. Chapter 11 highlights the chiral-at-metal complex-catalyzed asymmetric radical reactions, enabling numerous transformations such as alkylation, alkenylation, amination, addition, deracemization, and rearrangement. Chapter 12 presents asymmetric photochemical reactions within supramolecular assemblies, emphasizing the impact of the chiral host framework and the synergistic effects of non-covalent interactions on photoreaction

stereoselectivity. It also discusses the influence of external environmental factors such as temperature, solvent, and pressure.

Chapters 13 through 15 focus on organocatalyzed asymmetric radical reactions. Chapter 13 summarizes the advances in organocatalysis via covalent bonds for asymmetric radical transformations. The discussion in this chapter is organized based on different modes of organocatalysis, including chiral amine-catalyzed transformations of carbonyl compounds and nitrogen-heterocyclic carbene (NHC) catalysis. Chapter 14 focuses on the role of hydrogen-bonding interactions in asymmetric radical transformations. It is categorized into eight radical transformations including radical cycloaddition, radical cyclization, radical addition, radical coupling, Minisci reactions, asymmetric protonation, radical/polar crossover reactions, and deracemizations. In Chapter 15, advances in the use of covalent interactions involving sulfur-, stannyl-, and boron-centered radicals to achieve high enantioselectivity in radical transformations are presented. The discussion focuses on how such covalent interactions between the substrate and radical species modulate both the reactivity and stereochemical outcome. In addition, the enzymatic catalysis has progressed rapidly to realize asymmetric radical reactions, but this topic is not covered in this book.

We would like to acknowledge the dedicated efforts of many friends and their collaborators who wrote the corresponding chapters and made this book a reality, including Hongli Bao from Fujian Institute of Research on the Structure of Matter, X. Peter Zhang from Boston College, Wangqing Kong from Wuhan University, Lingling Chu from Donghua University, Lei Liu from Shandong University, Wenjing Xiao and Jia-Rong Chen from Central China Normal University, Shouyun Yu from Nanjing University, Lei Gong from Xiamen University, Jiajia Ma from Shanghai Jiaotong University, Cheng Yang from Sichuan University, Danqing Zheng from Nanjing Tech University, Zhiyong Jiang from Henan Normal University, and Yi-Feng Wang from University of Science and Technology of China. We also want to extend our gratitude to our group members Pinhong Chen from Shanghai Institute of Organic Chemistry and Xiao-Yang Dong from Great Bay University, who helped us accomplish Chapters 5 and 6. In particular, Zhong-Liang Li from Great Bay University is acknowledged for his invaluable assistance in organizing and proofreading all the chapters. Professor Mukund Sibi is greatly appreciated for his support of this book and his willingness to contribute a Foreword, which serves as a remarkable introduction to the content of this book. We also appreciate people from Wiley Publishing, Dr. Lifen Yang, Priyadarshini Natarajan, Naveen Kumaran Shanmugam, and Jona Nussbeck, for their kind assistance.

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1

Iron-Catalyzed Radical Asymmetric Reactions

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1.1 Introduction

The remarkable earth's abundance and low toxicity of iron make it an environmentally benign and economically viable alternative to conventional transition-metal catalysts. Over the past several decades, the development of iron-catalyzed reactions has exemplified the ingenuity and innovation within the organic chemistry community, and iron catalysis has become a cornerstone in modern organic synthesis, revolutionizing the way chemists construct complex molecules [1–9]. Harnessing the unique reactivity of iron, researchers have developed a diverse array of transformations that have not only expanded the synthetic toolbox but also addressed sustainability challenges in the field. From unconventional bond formations to intricate cascade reactions, iron catalysis has demonstrated exceptional versatility and efficiency, offering a promising platform for the continued advancement of sustainable synthetic methodologies.

Iron-catalyzed asymmetric reactions have garnered significant attention in the field of organic chemistry, with several excellent reviews documenting the remarkable progress achieved [10–18]. The development of chiral ligands and the elucidation of their role in controlling the enantioselectivity of iron-catalyzed reactions has been a key focus. Chiral porphyrins, chiral bipyridines, chiral salens, chiral bisoxazolines (BOX) and pyridine bisoxazolines (PyBOX), chiral diamines, chiral diphosphines, chiral binaphthyls, and planar-chiral ferrocenyls were among the most studied ligands for iron catalysis. The continuous exploration and refinement of iron-catalyzed asymmetric reactions showcase their potential as powerful tools in asymmetric synthesis. For example, iron-catalyzed enantioselective oxidation, hydride transfer, activation of Lewis basic substrates, carbene transfer, nitrene transfer, and more provide transformative strategies for accessing enantioenriched compounds sustainably.

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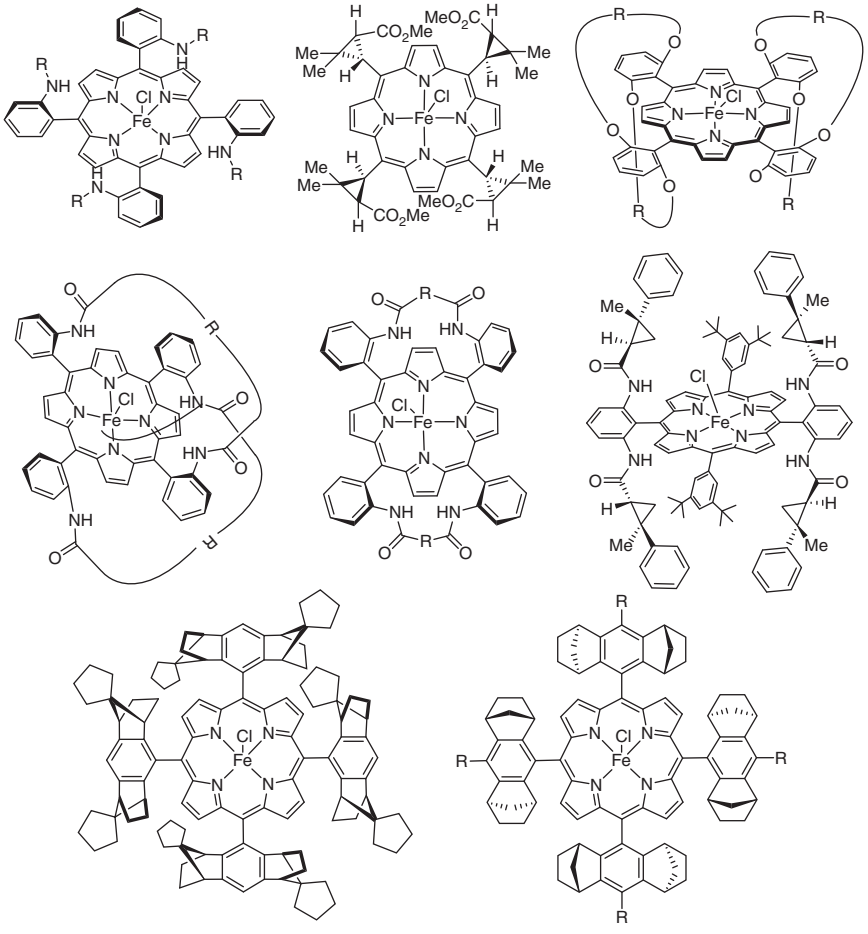
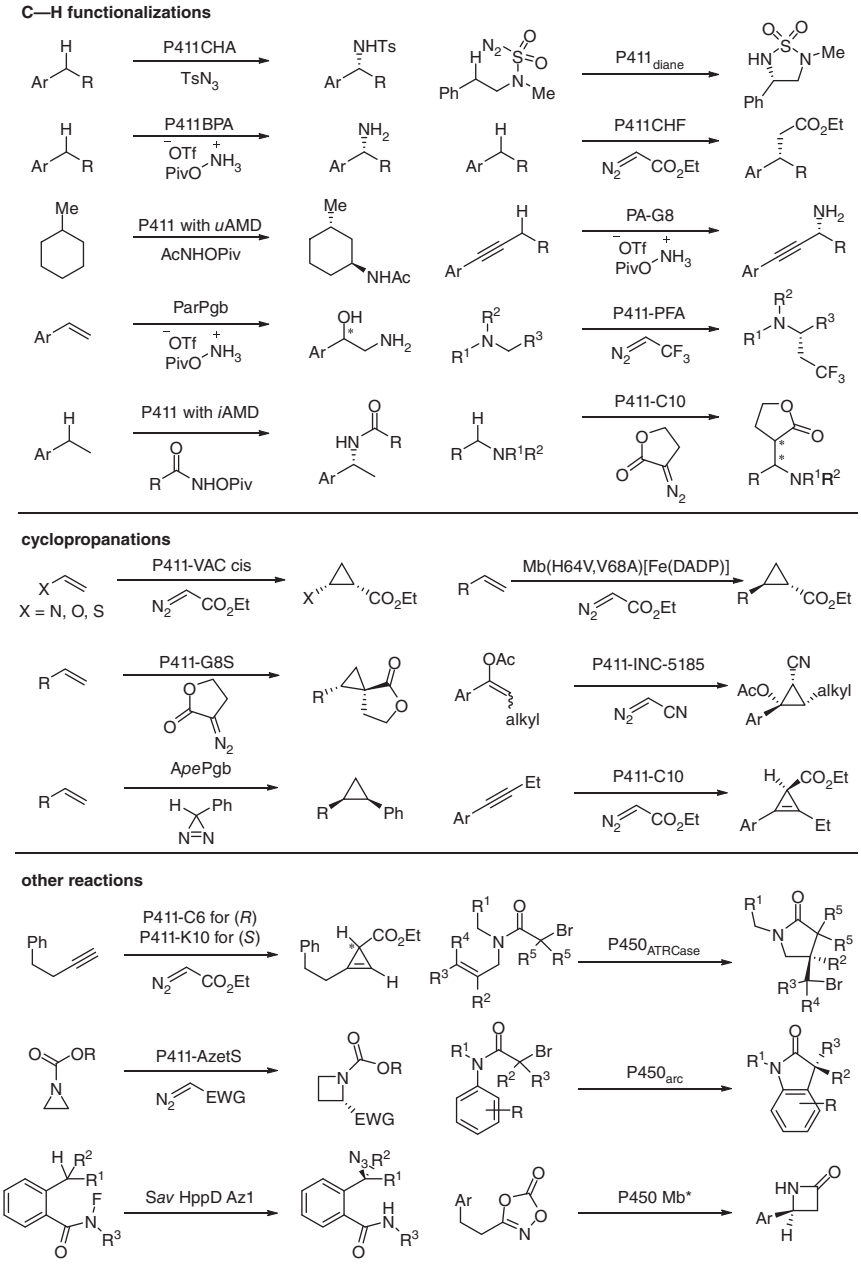
In this chapter, we will introduce the advancements in iron-catalyzed radical asymmetric reactions. In this field, iron-porphyrins play an important role in biomimetic radical asymmetric catalysis. By using metalloporphyrins as the catalysts, researchers have been able to successfully mimic several types of reactions, including epoxidation [19–21], cyclopropanation [22–24], sulfoxidation [25–27], C—H amination/hydroxylation [28, 29], and so on. Several reviews on metalloporphyrin catalysis have been well documented to cover the remarkable achievements [30–39]. On the other hand, the Arnold group elegantly pioneered the use of P411-mutants derived from well-known cytochromes P450 in organic reactions. Their work has led to great successes in radical asymmetric C—H functionalization [40–50], cyclopropanation [51–58], and so on [59–69]. Important reviews on the reactions of P411-mutants and cytochromes P450 have been published [70–76]. Therefore, these are out of the scope of this chapter and will only be briefly depicted (Schemes 1.1 and 1.2).



Scheme 1.1 Selected iron-porphyrins for radical asymmetric catalysis.



Scheme 1.2 Engineered cytochrome P450s for radical asymmetric catalysis.

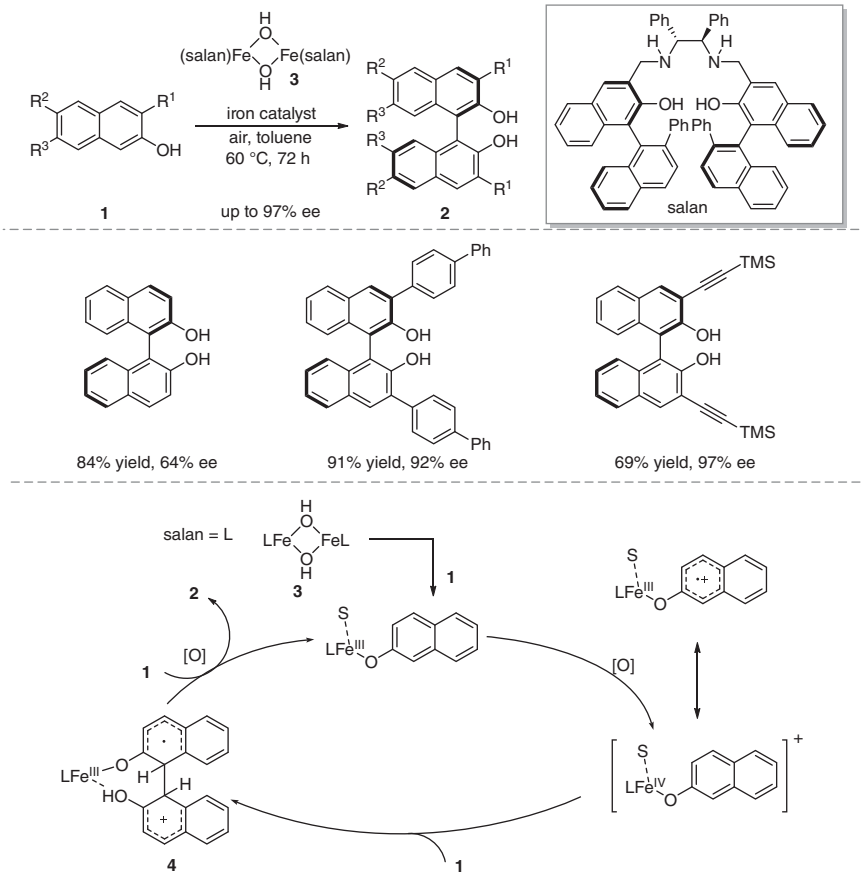
Sibi and coworkers have made substantial contributions to the advancement of radical asymmetric chemistry and a comprehensive survey of the progress achieved in enantioselective radical reactions has recently been updated [77–79]. However, the utilization of iron/chiral ligand complexes in asymmetric radical

reactions is unexpectedly underdeveloped [80–87]. This may stem from two pivotal reasons: (i) the challenge in controlling the enantioselectivity of highly reactive radicals; (ii) iron's capacity to adopt various oxidation states and partake in a diverse range of radical-mediated elementary processes. This chapter aims to elucidate how asymmetry is controlled in iron-catalyzed radical asymmetric catalysis.

1.2 Asymmetric Oxidative Coupling of C—H Bonds

1.2.1 Coupling for Binaphthyl Synthesis

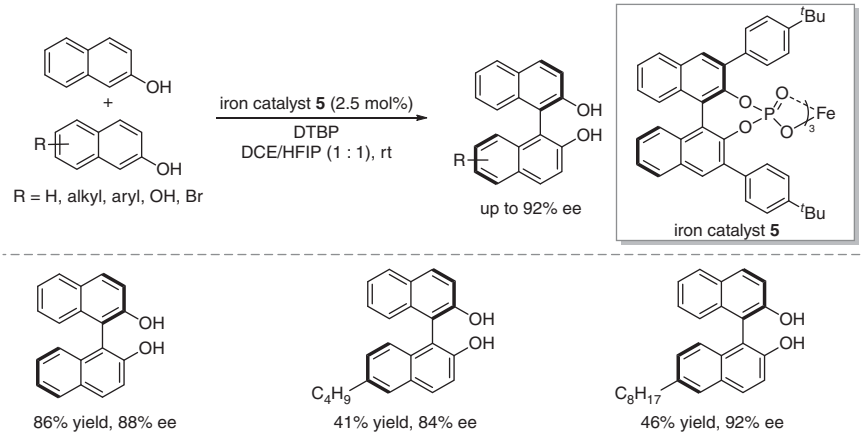
Transition-metal-mediated oxidative C—H/C—H coupling reactions represent one of the most straightforward and powerful tools in modern organic synthetic chemistry [88–90]. In 2010, Katsuki and coworkers pioneered the studies on iron-catalyzed radical asymmetric oxidative C—H/C—H coupling for the synthesis of C_1-symmetric 1,1′-bi-2,2′-naphthols (BINOLs) (Scheme 1.3) [91]. Using the



Scheme 1.3 Iron-catalyzed C—H/C—H cross-coupling of 2-naphthols.

iron(salan) complex as the catalyst, a range of 2-naphthols **1** underwent the aerobic oxidative cross-coupling reactions and many highly enantiopure BINOLs **2** can be obtained with up to 95% enantiomeric excess (ee). The mechanistic studies suggested that the (di-μ-hydroxo)iron^{III}(salan) catalyst **3** first underwent ligand exchange with a 2-naphthol **1** to form the 2-naphtholated iron^{III}(salan) species. The latter was oxidized to form the 2-naphtholated iron^{IV}(salan) species, which then asymmetrically reacted with another molecule of 2-naphthol **1** to give the radical cation species **4** that was associated with the iron^{III}(salan) core. After further oxidation and dissociation, the final chiral BINOL **2** was produced and the iron catalyst was recycled. The oxidation of 2-naphtholated iron^{III}(salan) to 2-naphtholated iron^{IV}(salan) species might be the rate-determining step of this iron-catalyzed oxidative coupling.

In 2016, the Pappo group disclosed that enantioselective oxidative homocoupling and cross-coupling of 2-naphthols can be catalyzed by chiral iron phosphate complexes **5** (Scheme 1.4) [92]. Enantioenriched C_1- and C_2-symmetric BINOLs can be smoothly produced in up to 92% ee. After reaction condition screening, the chiral phosphonic acid (CPA) with 4-^{t}Bu-Ph substituents was found to be the best chiral ligand. Di-*tert*-butyl peroxide (DTBP) was used as the oxidant and 1,2-dichloroethane (DCE)/1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was used as the mixed solvent. Based on kinetic studies, an iron-catalyzed oxidative radical-anion coupling mechanism was proposed. They point out that the use of CPAs as ligands may provide a general platform for the application of chiral iron catalysts in asymmetric synthesis.

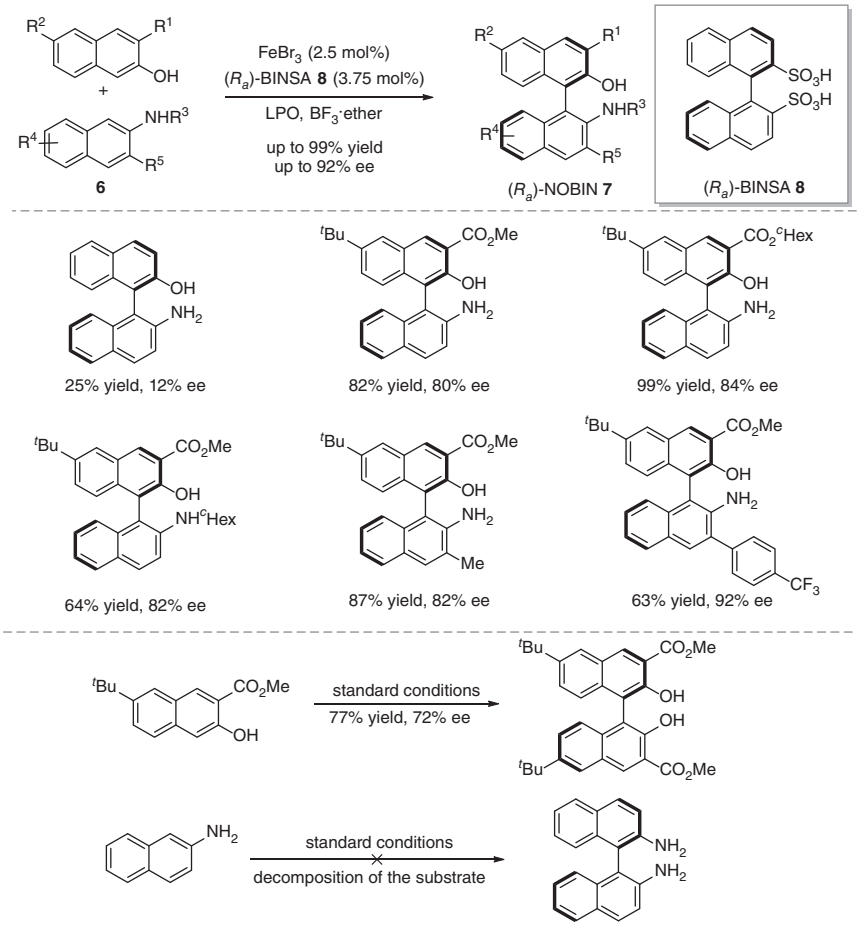


Scheme 1.4 Iron-catalyzed C–H/C–H cross-coupling of 2-naphthols.

Bryliakov and coworkers tested a series of bipyrrolidine-derived iron aminopyridine complexes as the catalysts in the oxidative homocoupling of 2-naphthols [93]. However, when the reaction was carried out in chlorobenzene at 50 °C, only up to 56% ee was obtained. While the Ishihara group reported a chiral diphosphine oxide–iron(II) complexes ((*S*)-xylyl-^{i}PrO-BIPHEP-oxide: Fe(OTf)$_2$) for oxidative

homocoupling of 2-naphthols with *tert*-butyl hydroperoxide (TBHP) as the oxidant. The C_1-symmetric BINOLs were generated in up to 98% yield and 92% ee [94].

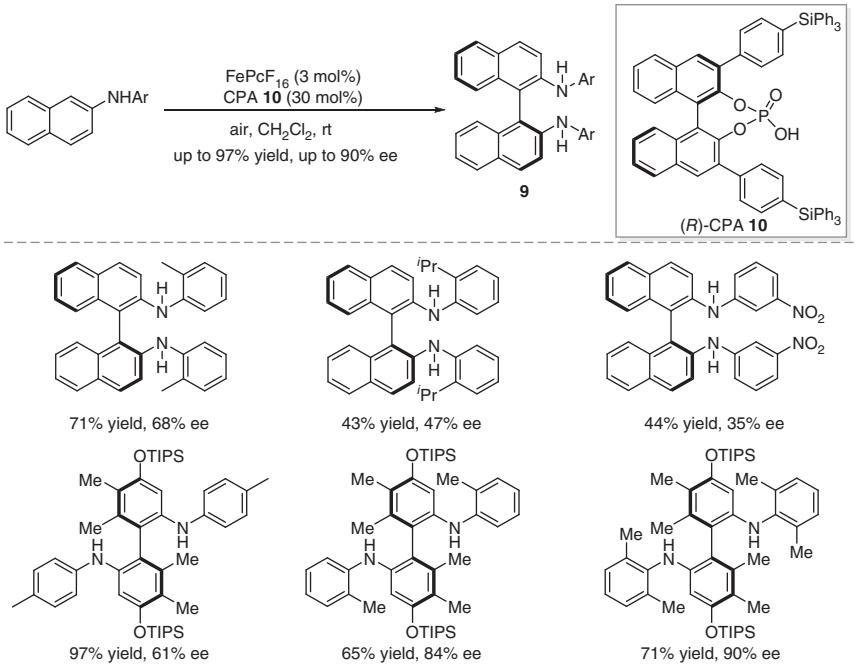
2-Amino-2′-hydroxy-1,1′-binaphthyls (NOBINs), as a kind of biaryl compounds bearing axial chirality, frequently serve as building blocks, ligands, or catalysts in asymmetric transformations [95]. In 2022, Pappo and coworkers developed an interesting asymmetric oxidative C—H/C—H cross-coupling between 2-naphthols and 2-aminonaphthalene derivatives **6** (Scheme 1.5) [96]. This cross-coupling reaction was catalyzed by a novel type of chiral redox disulfonate iron complex $[Fe((R_a)\text{-BINSate})]^+$ (BINSate = 1,1′-binaphthalene-2,2′-disulfonate), which was in situ generated from iron salt and (*Ra*)-BINSA **8**. Under the optimal reaction conditions with lauroyl peroxide (LPO) as the oxidant and boron-trifluoride-etherate $BF_3 \cdot OEt_2$ as the additive, the selective cross-coupling reactions proceeded smoothly, providing the NOBINs **7** in good yields and high enantioselectivities.



Scheme 1.5 Iron-catalyzed C—H/C—H cross-coupling of 2-naphthols and 2-aminonaphthalene derivatives.

Without $BF_3 \cdot OEt_2$, the [Fe((R_a)-BINSate)]$^+$ complex would catalyze the oxidative homocoupling of a 2-naphthol derivative to afford the corresponding BINOL as the product, while the homocoupling of 2-aminonaphthalene led to the complete decomposition of the substrate. These results suggested that a radical–nucleophile coupling mechanism was involved. Moreover, the high-resolution mass spectrometry (HRMS) study and the nonlinear effect experiment suggested the involvement of mono-ligand/mono-iron species during the selectivity-determining step.

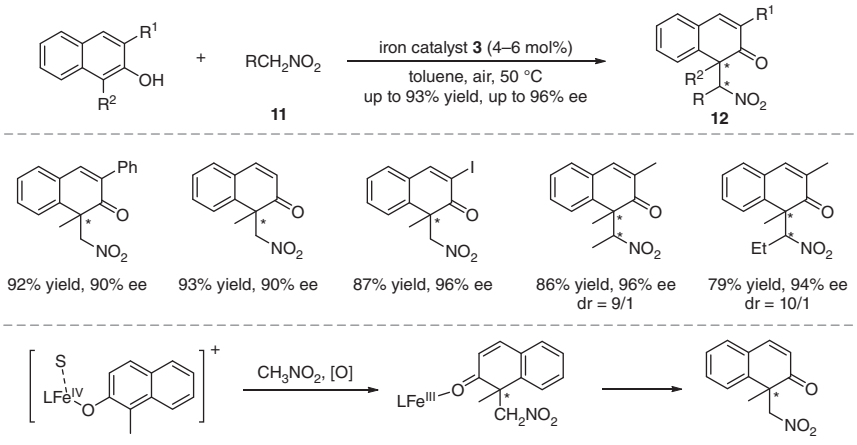
The Knölker group found that the iron/CPA complex enabled the asymmetric C—H/C—H coupling of 2-aminonaphthalene derivatives (Scheme 1.6) [97]. After examination of more than 10 different chiral phosphonic acids, it was found that the use of triphenylsilylated CPA **10** afforded the best result. The coupled 2,2′-bis(arylamino)-1,1′-biaryls **9** can be obtained in up to 97% yield and 90% ee. However, the enantioselectivity was poor for most substrates. Notably, higher yields can be obtained for phenyl naphthyl amines, and heavily electron-rich substituents are required for diphenyl amines to afford better yields and chemoselectivity. A similar mechanism proceeding via a radical cation-chiral phosphate ion pair was proposed.



Scheme 1.6 Iron-catalyzed homocoupling of 2-aminonaphthalene derivatives.

1.2.2 Coupling of Other C—H Bonds

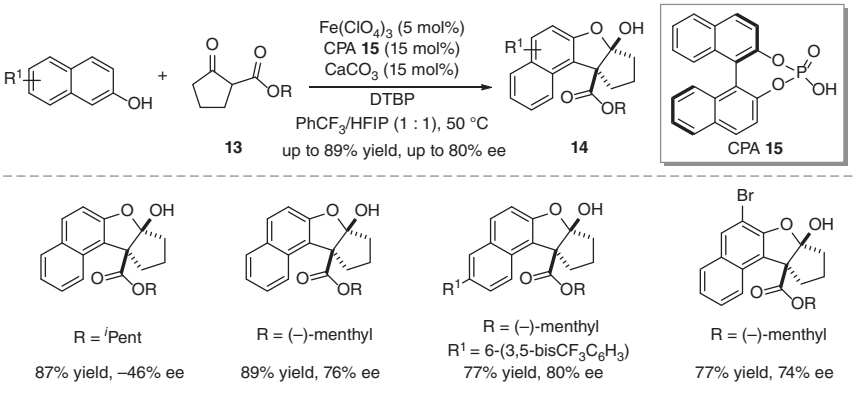
In 2012, the Katsuki group found that if the 1-position of 2-naphthol was blocked by a substituent, these 2-naphthols would react with nitroalkanes **11** to



Scheme 1.7 Iron-catalyzed coupling of 2-naphthols and nitroalkanes.

generate the enantioenriched products with an all-carbon quaternary stereocenter (Scheme 1.7) [98]. In the presence of the previously discussed iron(salan) complex **3** as the catalyst, the reactions simultaneously underwent oxidative dearomatization/asymmetric construction of the all-carbon quaternary stereocenter in an intermolecular manner to produce the products **12** in up to 93% yield and 96% ee. This iron(salan) complex-catalyzed asymmetric aerobic oxidative coupling of 2-naphthols and nitroalkanes was supposed to involve the nucleophilic attack of the nitroalkane to the radical cation species.

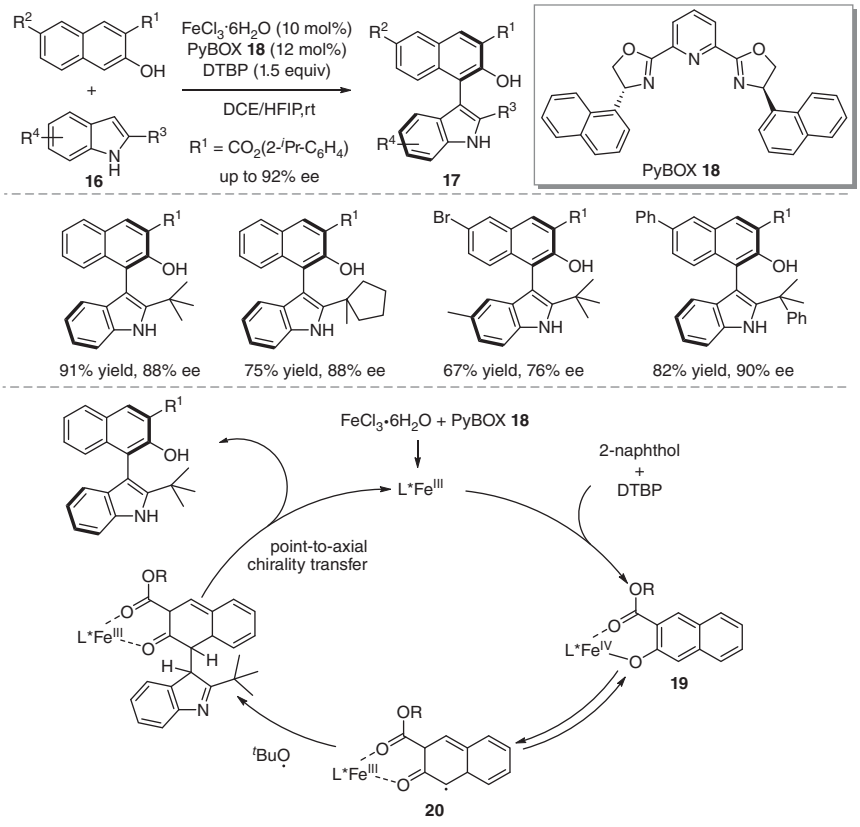
Pappo and coworkers explored the asymmetric cross-dehydrogenative coupling of 2-naphthols with β-ketoester derivatives (Scheme 1.8) [99]. At room temperature, the chiral iron phosphate catalyst derived from iron salt and ligand **15** and DTBP in a mixed solvent of $PhCF_3$/HFIP would only result in the homocoupling of 2-naphthols. Interestingly, the coupling of 2-naphthols with β-ketoester derivatives



Scheme 1.8 Iron-catalyzed cross-coupling of 2-naphthols and β-ketoester derivatives.

13 proceeds smoothly at elevated temperatures, yielding the corresponding polycyclic hemiacetals **14** in good yields. Extensive screening of CPA ligands revealed a correlation between the size of the 3,3′-substituents of the phosphoric acid and the diastereoselectivity of the product. Notably, the use of chiral auxiliary (−)-menthyl was found to be crucial for enantiocontrol. The mechanism studies supported that the coupling took place between two associated ligands via a radical–anion coupling mechanism.

The significance and interest in heterobiaryl compounds with axial chirality have been growing across various fields. However, the enantioselective synthesis of these compounds through direct oxidative methods remains a significant challenge. In 2022, Smith and coworkers developed an iron-catalyzed oxidative cross-coupling of 2-naphthols and NH-free indoles for the synthesis of atropisomeric heterobiaryl compounds (Scheme 1.9) [100]. The chiral PyBOX ligand **18** was found to be the best one, and the cross-coupling product **17** can be obtained with high levels of chemoselectivity and enantioselectivity. The measurement of the oxidation potentials of 2-tert-butylindole and 2-isopropylphenyl 3-hydroxy-2-naphthoate clearly showed that the indole exhibited a lower oxidation potential compared to the

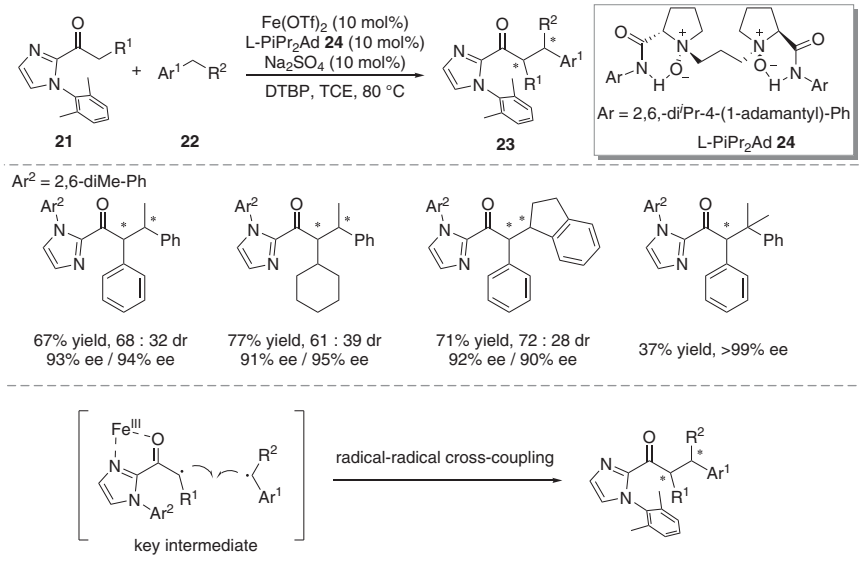


Scheme 1.9 Iron-catalyzed cross-coupling of 2-naphthols and indoles.

naphthol component under standard conditions. Interestingly, the cross-coupling of 2-naphthols and NH-free indoles **16** was found to exclusively produce the cross-coupled products **17** without any competing homocoupling products. These findings suggest that the oxidation of the heterocyclic component does not significantly contribute to the catalytic cycle. Further mechanistic investigations, including radical clock experiment, HRMS, electron paramagnetic resonance (EPR) spectroscopy, and the Hammett plot analysis, supported the radical-involved mechanism.

First, the PyBOX ligand associated with the Fe(III) salt to form an octahedral Fe/PyBOX complex, which underwent ligand exchange with the 2-naphthol to produce a complex with the 2-naphthol binding in a bidentate fashion. Second, the single-electron transfer of the Fe(III) complex by DTBP afforded an Fe(IV) complex **19** and an accompanying *tert*-butoxy radical, and the subsequent reversible single-electron transfer generates the Fe(III)-ligated naphthoxy radical **20**. Then, directly controlled by the chiral ligand, the π-nucleophilic indole could facially attack the Fe(III)-ligated naphthoxy radical via an outer-sphere mechanism in the presence of the *tert*-butoxy radical to afford the coupling product, followed by ligand exchange to enable release of the enantioenriched heterobiaryl and an Fe(III) complex for the next catalytic cycle.

The previous work covers dehydrogenative coupling in which at least one sp^2-hybridized carbon was involved. The cross-dehydrogenative coupling of two inert C(sp^3)—H bonds would generate two adjacent sp^3-hybridized carbons [101, 102]. In 2024, Feng, Liu, and coworkers reported an iron-catalyzed radical asymmetric dehydrogenative coupling of 2-acylimidazoles **21** with benzylic and allylic hydrocarbons as well as nonactivated alkanes **22** (Scheme 1.10) [103]. In this

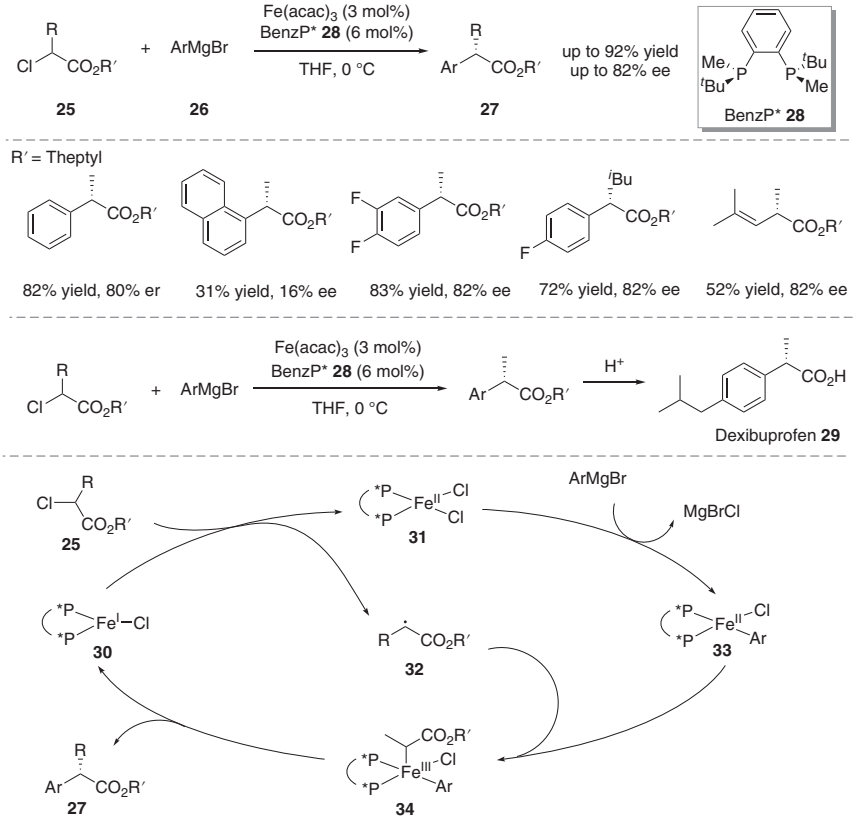


Scheme 1.10 Iron-catalyzed coupling of two inert C(sp^3)—H bonds.

method, the two inert C(sp^3)—H bonds were enantioselectively coupled. The readily available and tunable *N*,*N*′-dioxide ligand L-PiPr$_2$Ad **24** and DTBP exhibited excellent asymmetric induction. Based on the Density functional theory (DFT) calculation and control experiments, a radical-radical cross-coupling mechanism was proposed.

1.3 Asymmetric C—C Coupling of Alkyl Halides

The Kumada reaction is a widely employed method in organic synthesis, which involves the cross-coupling of an organohalide with an organometallic compound. In 2015, the Nakamura group developed the first iron-catalyzed asymmetric Kumada reaction (Scheme 1.11) [104]. The enantioselective cross-coupling of α-haloesters **25** with aryl Grignard reagents **26** was conducted in the presence of Fe(acac)$_3$/chiral biphosphine ligand **28**. Good yields and high ee values of the coupled products **27** were obtained. Deprotection of the coupled products led to carboxylic acids, and further co-crystallization with octylamine constituted a nice approach for the synthesis of enantiopure dexibuprofen **29**. As supported by the control experiments, the reaction involved the abstraction of a halogen

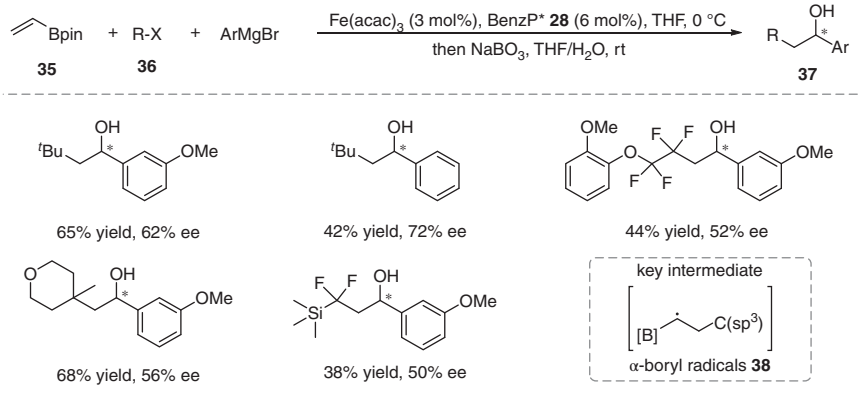


Scheme 1.11 Iron-catalyzed asymmetric Kumada reaction.

from α-haloesters to generate an alkyl radical intermediate and underwent a Fe(III)—Fe(II)—Fe(I) catalytic cycle.

Shortly after that, the authors conducted theoretical calculations to further investigate the mechanism [105]. It was found that Fe^{I}(BenzP*)Cl complex **30** was the active intermediate for the C—Cl bond activation to provide L*$Fe^{II}Cl_2$ **31** and an alkyl radical **32**. The formation of the C—C bond through an inner-sphere mechanism was the selectivity-determining step. Transmetalation of the L*$Fe^{II}Cl_2$ **31** with aryl Grignard reagent generated a L*ArFe^{II}Cl species **33**, which bonded with the alkyl radical **32** to afford a L*Fe^{III} species **34**. The reductive elimination afforded the coupling product **27** and regenerated the L*Fe^{I}Cl complex **30** that enabled the halogen atom abstraction process. The theoretical study provided important mechanistic insights into the iron-catalyzed cross-coupling reactions and is very important for the development of iron-based catalysts for highly stereoselective synthetic organic transformations. At the same time, Gutierrez and coworkers have also performed DFT studies on this iron-catalyzed Kumada coupling and further supported the proposed mechanism [106].

In 2023, Gutierrez and coworkers reported an iron-catalyzed enantioselective three-component coupling reaction (Scheme 1.12) [107]. In the presence of $Fe(acac)_3$/BenzP* as the catalytic system, the cross-couplings of vinyl boronates **35**, (fluoro)alkyl halides **36**, and Grignard reagents reacted well to produce the enantioenriched boro-products, which were transferred into the corresponding chiral alcohols **37** with high efficiency. The α-boryl radicals **38** generated from the addition of alkyl radicals to vinyl boronates was supposed to be involved.



Scheme 1.12 Iron-catalyzed radical asymmetric three-component coupling.

In 2019, the Nakamura group reported an iron-catalyzed Suzuki–Miyaura coupling reaction (Scheme 1.13) [108]. In the presence of catalytic amounts of $FeCl_2$ and (*R*,*R*)-QuinoxP* **41**, the cross-coupling of *tert*-butyl α-bromopropionate **39** and lithium arylborates **40** took place to afford various optically active α-arylpropionic acids after cascade hydrolysis.