Iron-catalyzed directed C2-alkylation and C2-alkenylation of indole via C–H bond activation

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2016

Wong, M. Y. (2016). Iron-catalyzed directed C2-alkylation and C2-alkenylation of indole via C–H bond activation. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/66002>

<https://doi.org/10.32657/10356/66002>

NANYANG
TECHNOLOGICAL
UNIVERSITY

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SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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A thesis submitted to the Nanyang Technological University

in partial fulfillment of the requirement for the degree of

Doctor of Philosophy

2015

Acknowledgements

First and foremost, I would like to express my deep appreciation to my supervisor, Nanyang Assistant Professor Naohiko Yoshikai, for giving me the opportunity to pursue my PhD studies in his research group. I am very grateful for his motivation, guidance and patience towards my work. His dedications and commitments to students, profession and research will continue to inspire me.

I would also like to thank Singapore International Graduate Award (SINGA) by Agency for Science, Technology and Research (A*STAR), for the generous financial support towards my PhD studies in Singapore. Additionally, I am grateful and proud to be part of Nanyang Technological University, as the university is among one of the top leading universities in Asia as well as the world.

As for the technical assistants, I would like to thank Ms Goh Ee Ling and Mr Derek Ong (NMR laboratory), Dr Zhu Wen Wei (GC and Mass Spectrometry laboratory), Dr Rakesh Ganguly and Dr Li Yongxin (X-ray Crystallographic facilities) from the School of Physical and Mathematical Sciences for their support.

I would like to express my appreciation to all teachers, lecturers and professors, whom I have known throughout my academic life in schools, college and universities. They have inspired me to follow my dreams and taught me to have passion for learning. On top of that, they always ensure that I have a pleasant learning experience.

I would like to take this opportunity to thank the Division of Chemistry and Biological Chemistry for the “Most Outstanding Teaching Assistant Award”. I am truly humbled, honored and grateful to have been selected as a recipient of the award during my postgraduate studies. It was a great experience to facilitate the undergraduate students as well as providing them with a good laboratory experience.

Next, I would like to thank all past and present members of Dr Yoshikai's group for their motivation, support and friendship. I am truly grateful for their help and discussions whenever I needed it.

I would also like to thank my amazing friends, near and far, for all the great times we shared. They have always been a huge part of my life and I cherish them the most.

Finally, I would like to extend my gratitude to my loving and caring family for their endless support and encouragement. Words cannot express the level of my appreciation for all they have done for me throughout my life.

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List of Abbreviations

β	<i>beta</i>
δ	Chemical shift (ppm)
$^{\circ}\text{C}$	Degree Celsius
η	<i>eta</i>
μL	Microliter
Ac	Acetyl
acac	Acetylacetonate
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Ar	Aryl (substituted aromatic ring)
app.	Apparent
Atm	Standard atmosphere
br	Broad
BARF	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	Benzyl
BQ	Benzoquinone
Boc	<i>tert</i> -Butyloxycarbonyl
<i>n</i> Bu	<i>n</i> -Butyl
<i>t</i> Bu	<i>tert</i> -Butyl
Bz	Benzoyl
cat.	Catalyst
cod	1,5-Cyclooctadiene
C	Carbon

Cy	Cyclohexyl
<i>p</i> -Cym	<i>p</i> -Cymene
Cyp	Cyclopentyl
d	Doublet
D	Deuterium
DCE	1,2-Dichloroethane
DCIB	1,2-Dichloro-2-methylpropane
DCM	Dichloromethane
dd	Doublet of doublet
DG	Directing group
DMA	<i>N,N</i> -Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMPE	1,2-Bis(dimethylphosphino)ethane
DMPU	<i>N,N'</i> -Dimethylpropylene urea
(<i>S</i>)-DM-SEGPPOS	(<i>S</i>)-(-)-5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
DMSO	Dimethyl sulfoxide
dtbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridine
ESI	Electrospray ionization
equiv	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
GC	Gas Chromatography
h	Hour

H	Hydrogen
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IMes	1,3-Dimesitylimidazol-2-ylidene
IXyl•HCl	1,3-Bis(2,6-dimethylphenyl)imidazolium chloride
<i>J</i>	Coupling constants
L	Ligand
LA	Lewis Acid
m	Multiplet
<i>m</i>	<i>meta</i>
M	Concentration (mol/L)
M ⁺	Molecular ion
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute(s)
mL	Milliliter
mmol	Millimole
mol %	Mole percent
m.p.	Melting point
NHC	<i>N</i> -heterocyclic carbene
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
Np	2-Naphthyl
<i>o</i>	<i>ortho</i>

<i>p</i>	<i>para</i>
Ph	Phenyl
phen	1,10-Phenanthroline
PMP	<i>p</i> -Methoxyphenyl
ppm	Parts per million
<i>n</i> Pr	<i>n</i> -Propyl
<i>i</i> Pr	<i>iso</i> -Propyl
py	Pyridine
q	Quartet
s	Singlet
(<i>R</i>)-SDP	(<i>R</i>)-(+)-7,7'-Bis(diphenylphosphino)-2,2',3,3'- tetrahydro-1,1'-spirobiindene
Sext	Sextet
SIMes•HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolinium chloride
SIPr•HCl	1,3-Bis(2,6-diisopropylphenyl)imidazolinium chloride
SIXyl•HCl	1,3-Bis(2,6-dimethylphenyl)imidazolinium chloride
<i>R_f</i>	Retention factor
rt	Room temperature
t	Triplet
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
<i>p</i> -Tol	<i>p</i> -Tolyl
Ts	<i>p</i> -Toluenesulfonyl

Abstract

Over the past decades, transition metal-catalyzed directed C–H bond functionalization has been developed as a highly effective method to resolve regioselectivity issues in the field of organic synthesis. Recently, a variety of low-valent transition metal complexes have played an important role to promote directed hydroarylation or hydroheteroarylation of unsaturated hydrocarbon molecules.

In general, iron is known as one of the most naturally abundant, inexpensive and environmentally friendly transition metals that could exhibit high reactivity and selectivity under mild reaction conditions. These remarkable features have attracted our attention in exploring and developing hydroarylation reactions through directed C–H bond activation.

Following a general outline (Chapter 1) of the recent advances in directed hydroarylation and hydroheteroarylation reactions as well as iron-mediated reactions, Chapter 2 details the discovery and development of iron-catalyzed directed C2-alkylation of indole with vinylarenes. The reaction afforded 1,1-diarylalkane derivatives in good yields with exclusive regioselectivity.

Next, Chapter 3 describes iron-catalyzed C2-alkenylation of indole with internal alkynes *via* directed C–H bond activation. The reaction proceeded under mild conditions to afford C2-alkenylated products in good yields with high *syn*-stereoselectivity. Lastly, Chapter 4 is a concluding chapter that summarizes this thesis research.

Chapter 1. Introduction

1.1 General Introduction

Developing efficient, mild and selective synthetic methods have always been highly desired in the field of catalysis and synthesis. Functionalization of C–H bond is an alternative atom-economical approach to the classical cross-coupling strategies that require the presence of organic halides and organometallic reagents for carbon–carbon bond formation.¹ Additionally, the C–H bond functionalization reactions could also reduce the amount of toxic by-products. Hence, researchers have made rapidly advances in exploring catalytic reactions that involved C–H bond cleavage for direct transformation of non-functionalized substrates into complex molecules.²

Over the past several decades, a variety of transition metal catalysts have showed significant robust catalytic ability that allowed transformations to proceed in a highly efficient and selective manner.^{2,3,4,5} Transition metal-catalyzed aromatic C–H bond functionalization reactions were initially achieved by the respective research groups of Lewis,⁶ Jordan,⁷ and Moore.⁸ In 1993, Murai and co-workers have emerged the groundbreaking discovery of ruthenium-catalyzed directed alkylation of aromatic compounds.⁹ Since then, the use of heteroatom directing group is commonly known as one of the most effective strategies to resolve regioselectivity issues.¹⁰

In recent years, a growing number of C–H bond functionalization reactions have been demonstrated including alkylation,^{3e,3c} alkenylation,¹¹ arylation,¹ amination,¹² and borylation.¹³ Furthermore, synthetically useful catalytic functionalization of unactivated C–H bonds has been applied in methodologies for the production of natural products and pharmaceuticals as well as recent progresses in the field of materials and polymers.¹⁴

Lately, second- and third-row transition metals have played an important part for directed hydroarylation of alkenes and alkynes. Nevertheless, the limitation of possible improvements and applications by using such transition metal catalysts, which may due to their substantial toxicity and high price, will eventually lead to severe drawback for large-scale synthesis.¹⁵ Therefore, the importance of using an inexpensive, readily available and less hazardous transition metal catalyst has been a potential goal in modern organic synthesis.

Since the discovery of iron catalysis by Kharasch in the middle of twentieth century,¹⁶ the use of first-row transition metal catalysts has increasingly attracted the interest of chemists.¹⁷ In the 1970s, Kochi has contributed a series of extensive studies on iron-catalyzed cross-coupling reactions.¹⁸ Nevertheless, iron catalysts were surprisingly underrepresented in comparison to other transition metals despite its notable advantages in the field of catalysis.¹⁵

Recently, the research groups of Cahiez,¹⁹ Fürstner,^{17c,20} Nakamura,²¹ and others²² have established efficient strategies for iron-catalyzed reactions in organic synthesis. Based on their research findings, iron catalysts showed high reactivity and selectivity under mild reaction conditions, which were unattainable in other transition metal catalysis.

To the best of our knowledge, iron-catalyzed hydroarylation involving directed C–H bond activation is yet to be developed and explored.^{23,24} We wondered whether iron catalyst could be an alternative transition metal to effectively promote heteroatom-directed hydroarylation of unsaturated hydrocarbon compounds.

1.2 Hydroarylation of Alkenes

Insertion of alkenes into unactivated aromatic C–H bonds (hydroarylation) represents a straightforward and atom-economical approach to introduce alkyl groups onto arenes.^{25,26} In general, hydroarylation of alkenes can be categorized into two major types of reactions that could lead to different regioselectivities and substrate scopes (Scheme 1.1).

Scheme 1.1. Hydroarylation of Alkenes

One of which is Friedel-Crafts type alkylation reaction that could be promoted by Lewis or Brønsted acid catalyst.^{27,28} The classical alkylation reaction is only applicable to electron-rich arenes and heteroarenes. Branched product is afforded selectively in a Markovnikov fashion involving activation of an alkene through a carbocationic species.²⁹

On the other hand, transition metal-catalyzed C–H bond activation typically requires the presence of a directing group or other electronic perturbations on the aromatic ring, which could preferably afford linear addition product.^{2b,9,14a,29,30,31} In 1993, Murai and co-workers have successfully developed ruthenium-catalyzed hydroarylation of sterically hindered styrene to afford linear product in the presence of ketone as a directing group (Scheme 1.2).⁹

Scheme 1.2. Addition of Aromatic Ketone to Styrene

Overalkylation could occur in the absence of an *ortho*-blocking substituent (Scheme 1.3).⁹ However, this limitation was overcome by Genet and Darses, who reported on *anti*-Markovnikov monosubstituted hydroarylation of triethoxyvinylsilane that can be effectively catalyzed by an *in-situ* generated ruthenium complex (Scheme 1.3).^{31f} Recently, the use of ruthenium(II) catalytic species could promote C–H bond functionalization reactions.^{10,32,33,34,35} However, these reactions involved in a rather different C–H bond activation mechanism, which was a deprotonation mechanistic pathway.

Scheme 1.3. Ruthenium-Catalyzed Hydroarylation Reactions of Vinylsilane

Pioneer work of rhodium-catalyzed C–H alkylation reaction has demonstrated by Lim and Kang.³⁶ A more recent example, Jun and co-workers reported that linear adduct was achieved when the reaction of *N*-benzyl aryl ketimine with *tert*-butylethylene was catalyzed by an air- and moisture-stable Wilkinson's catalyst, $\text{RhCl}(\text{PPh}_3)_3$ (Scheme 1.4a).³⁷ In 2010, Nakao and Hiyama reported hydroheteroarylation of vinylarene in the presence of $\text{Ni}(\text{cod})_2$ catalyst and 1,3-

dimesitylimidazol-2-ylidene (IMes) ligand that exclusively afforded 1,1-diarylethane derivative as a branched product (Scheme 1.4b).³⁸

Scheme 1.4. Rhodium- and Nickel-Catalyzed Hydroarylation of Alkene Derivatives

In general, structural motifs of 1,1-(branched) and 1,2-(linear) diarylethane derivatives are often found in biologically active compounds.³⁹ Recently, our group has developed cobalt-catalyzed hydroarylation of styrene derivatives under mild reaction conditions. Interestingly, the use of ligands could control regioselectivity of the reaction. Branched product was afforded by the Co-PCy₃ catalysis, whereas linear product was afforded by the Co-IMes catalysis (Scheme 1.5).^{40,41,42}

Scheme 1.5. Regiodivergent Addition of 2-Arylpyridines to Styrenes

Furthermore, Shibata and co-workers have reported on iridium-catalyzed alkylation of *N*-substituted indoles with a variety of alkenes to selectively form linear

or branched 2-alkylindoles.⁴³ The use of *N*-acetyl directing group afforded linear product, whereas the use of *N*-benzoyl directing group afforded branched product (Scheme 1.6).

Scheme 1.6. Reactions of *N*-Acetylindole and *N*-Benzoylindole with Styrene

In recent years, a few examples were reported on a tandem alkene isomerization–hydroarylation process. One of the reports was demonstrated by Jun and co-workers on isomerization of internal to terminal alkenes, which was then followed by hydroarylation reaction in the presence of rhodium catalyst at 150 °C to afford corresponding linear alkylation products (Scheme 1.7a).^{31c,44} In addition, Nakamura and co-workers have developed cobalt-catalyzed alkylation of benzamide derivative with (*E*)-2-octene or 1-phenyl-1-propene. After isomerization, the reaction took place predominantly at the terminal position of the corresponding alkene that selectively formed an *ortho*-alkylated product (Scheme 1.7b).⁴⁵ Furthermore, our group has reported that a cobalt–*N*-heterocyclic carbene (NHC)–Grignard catalytic system could promote alkylation of indole with non-conjugated arylalkenes, which exclusively afforded 1,1-diaryllkane derivatives (Scheme 1.7c).⁴⁶

Scheme 1.7. Alkene Isomerization–Hydroarylation Tandem Catalysis

A general reaction mechanism for chelation-assisted C–H alkylation is shown (Scheme 1.8).^{2d,14a} Most of the chelation-driven processes undergo the similar standard reaction pathway regardless of some mechanistic details that may be varied in certain cases. Initial coordination of a transition metal to the chelating heteroatom of substrate **1**, which is then followed by C–H bond activation to give a heterometallacyclic intermediate **2**. Next, the mechanistic pathway proceeds through ligand dissociation, alkene coordination and subsequent insertion of the alkene into the M–H bond to form intermediate **3**. Reductive elimination of the resulting intermediate **3** affords corresponding product **4**, which then closes the catalytic cycle. In most of the directed C–H alkylation reactions, reductive elimination step has been exhibited as a rate-limiting process.

Scheme 1.8. Proposed Mechanism for Chelation-Assisted C–H Alkylation

1.3 Hydroarylation of Alkynes

Catalytic addition of an aromatic C–H bond to an alkyne is one of the most efficient and straightforward approaches for synthesizing an arylalkene derivative with perfect atom efficiency.^{2b} This method provides a simpler protocol than Heck reactions⁴⁷ and other cross-coupling reactions,^{48, 49} which involve halogenated compounds as starting materials.⁵⁰ In general, hydroarylation of alkynes can take place through two mechanistic pathways, that is activation of the alkyne $C\equiv C$ triple bond (Scheme 1.9a) and activation of the arene C–H bond (Scheme 1.9b).⁵¹

Scheme 1.9. Transition Metal-Catalyzed Hydroarylation of Alkynes Through Direct Functionalization of Aromatic C–H Bonds

For a reaction involving an alkyne activation pathway (Scheme 1.9a),⁵² a cationic metal coordinates with a triple bond of an alkyne, which then undergoes an electrophilic aromatic substitution to give an arylvinylmetal complex.⁵¹ Subsequently, the vinyl complex is protonated to form an arylalkene product in a *trans*-selective manner. Regioselectivity of the addition reaction is controlled by the electronic factor of substituents on the alkyne. On the other hand, the second reaction pathway proceeds through aromatic C–H bond activation (Scheme 1.9b). The reaction typically gives regio- or stereoisomeric mixture of products. However, the presence of a directing group on an aromatic ring could accelerate C–H bond activation and control regioselectivity of the reaction.

In 1979, Hong and co-workers were the first to report on hydroarylation of alkynes that proceeded through aromatic C–H bond activation.⁵³ The alkenylation of arenes with diphenylacetylene took place in the presence of $\text{Rh}_4(\text{CO})_{12}$ under carbon monoxide atmosphere at 220 °C to afford the corresponding arylalkene products (Scheme 1.10). Notably, the reaction of anisole with diphenylacetylene gave *ortho*-alkenylated product as a major regioisomer.

Scheme 1.10. Addition of Arenes to Diphenylacetylene

In 2001, Lim and Kang reported another example of rhodium-catalyzed hydroarylation of alkynes in the presence of Wilkinson's catalyst.⁵⁴ The reaction of 2-phenylpyridine with 2-butyne gave the *ortho*-alkenylated and dialkenylated products in a ratio of 19:81 (Scheme 1.11a). Unfortunately, terminal alkynes were not successful under the same reaction conditions. In addition to Lim's studies, Jun and co-workers have extended the scope of rhodium catalysis by using a ketimine with a terminal alkyne (Scheme 1.11b).⁵⁵ Monoalkenylated products were afforded when linear alkyl acetylenes and diphenylacetylene were used, respectively.

Scheme 1.11. Rhodium(I)-Catalyzed *ortho*-Alkenylation Reactions

To date, ruthenium and rhodium catalysts have played an important and effective role in hydroarylation of alkynes with the aid of various directing groups.^{2f,14a, 56} In addition to the development of transition metal-catalyzed

hydroarylation reactions, Nakao and Hiyama have reported that hydroheteroarylation of an unsymmetrical internal alkyne (4-methyl-2-pentyne) proceeded effectively in the presence of $\text{Ni}(\text{cod})_2$ and PCyp_3 under mild reaction conditions to afford an alkenylated product in excellent yield with high regio- and stereoselectivity (Scheme 1.12a).⁵⁷ Another example was described by Kuninobu and Takai that the reaction of a heteroaryl aldimine with diphenylacetylene could take place in the presence of $[\text{ReBr}(\text{CO})_3(\text{THF})]_2$ catalyst to give an *ortho*-alkenylated product in good yield (Scheme 1.12b).⁵⁸

Scheme 1.12. Transition Metal-Catalyzed Directed Alkenylation Reactions

Furthermore, our group has successfully developed the reaction of an aromatic ketimine with an internal alkyne by using a quaternary catalytic system that consisting of CoBr_2 precatalyst, a triarylphosphine ligand, a Grignard reagent and pyridine as an additive to afford a *syn*-addition product (Scheme 1.12c).⁵⁹ Recently, Chen and Wang have reported the first example of an aromatic C–H alkenylation with a terminal alkyne in the presence of the commercially available $\text{MnBr}(\text{CO})_5$ and dicyclohexylamine (Scheme 1.12d).⁶⁰ The reaction proceeded in a highly regio-, chemo- and stereoselective manner to afford *anti*-alkenylated product.

A general proposed mechanism for transition metal-catalyzed directed alkenylation is shown (Scheme 1.13).⁵⁵ Oxidative addition of an *ortho* C–H bond of substrate **5** to a metal center forms complex **6**. The mechanistic pathway is followed by insertion of an alkyne into the M–H bond. Subsequent reductive elimination of resulting intermediate **7** affords *ortho*-alkenylated product **8** with regeneration of the active catalyst species.

Scheme 1.13. Proposed Mechanism for Transition Metal-Catalyzed *ortho*-Alkenylation Reaction

1.4 Aromatic C–H Bond Activation by Iron Complexes

Activation of aromatic C–H bonds is one of the key elementary steps for organometallic reactions that has been greatly utilized in organic synthesis.^{3b,4b,11a,61} The increased number of reactions for C–H bond cleavage can be promoted by either catalytic or stoichiometric amount of transition metal complexes.^{1,61,62}

An early fundamental work of aromatic C–H bond cleavage by an iron complex was achieved in the late 1970s.⁶³ Tolman, Ittel and co-workers reported that a transient 16-electron iron(0) species **9**, $\text{Fe}(\text{DMPE})_2$ could involve in C–H bond activation. The generation of the reactive iron species **9** was initiated by reductive elimination of naphthalene from *cis*- $\text{Fe}(\text{DMPE})_2(\text{Np})\text{H}$ complex. Later on, Field and Baker have found that photolysis of $\text{Fe}(\text{DMPE})_2\text{H}_2$ dihydride complex **10** underwent C–H bond activation of alkenes to form a mixture of *cis*-alkenyl iron hydrides **11** and π -complexes **12** *via* generation of the transient iron intermediate **9**, $\text{Fe}(\text{DMPE})_2$ at a low reaction temperature (Scheme 1.14).⁶⁴

Scheme 1.14. Reaction of Iron Dihydride Complex **10** with Alkenes

Cyclometalation reactions are known to transform carbon–hydrogen bonds into carbon–metal bonds that usually form five-membered metallacyclic ring species.⁶⁵ In ruthenium and rhodium catalysis, the carbon–carbon bond-forming reactions proceed preferentially by using an anchoring group, which contains nitrogen, phosphorus,

oxygen or sulfur donor atom, in each substrate molecule.^{3b,14a} In 2005, Klein and co-workers have performed cyclometalation reactions using low-valent iron complexes to obtain iron(II) complexes **13**, **14** and **15** (Figure 1),⁶⁶ that could mimic the intermediate of oxidative addition step in the proposed catalytic cycle of rhodium-catalyzed C–H bond functionalization reactions (Scheme 1.8).^{14a}

Figure 1. Cyclometalated Iron(II) Complexes by Klein

Recently, Camadanli and co-workers have extended the studies of *ortho*-metalated hydrido- and methyl-iron complexes.⁶⁷ Stoichiometric amount of diphenylketimine or *tert*-butylphenylketimine was reacted with $\text{Fe}(\text{PMe}_3)_4$ under mild reaction conditions to afford the corresponding cyclometalated iron(II) complex (Scheme 1.15).^{66,67}

Scheme 1.15. Reaction of Ketimines with $\text{Fe}(\text{PMe}_3)_4$ Complex

Interestingly, the reaction of diphenylketimine with $\text{Fe}(\text{CH}_3)_2(\text{PMe}_3)_4$ gave a methyl iron(II) complex **16** (Scheme 1.16).⁶⁷ The reaction is proposed to undergo an

ortho-metalation pathway for the formation of intermediate **17** along with the elimination of methane and one molecule of trimethylphosphine. Then, reductive elimination occurs to give intermediate (2-methylbenzophenone imine) **18**. Subsequent reinsertion of $\text{Fe}(\text{PMe}_3)_3$ into an *ortho* C–H bond of a non-substituted aromatic ring to afford the hydrido–iron(II) complex **16**. Furthermore, Camadanli and co-workers have also reported that the reaction of benzylic imines with $\text{Fe}(\text{CH}_3)_2(\text{PMe}_3)_4$ was performed in pentane at -70°C to form the corresponding iron(II) complexes **15**, **19** and **20** (Scheme 1.17).

Scheme 1.16. Reaction of Diphenylketimine with $\text{Fe}(\text{CH}_3)_2(\text{PMe}_3)_4$ Complex

Scheme 1.17. Reaction of Benzylic Imines with $\text{Fe}(\text{CH}_3)_2(\text{PMe}_3)_4$ Complex

In 2008, Nakamura and co-workers have developed the first example of iron-catalyzed direct arylation through C–H bond activation.^{3d,22f,23,68,69} In general, the use of diarylzinc reagent, that generated *in situ* from an equivalent of $\text{ZnCl}_2 \cdot \text{TMEDA}$ (where TMEDA = *N,N,N',N'*-tetramethylethylenediamine) and two equivalents of arylmagnesium reagent, was crucial for the success of the arylation reaction.^{22f} In the presence of $\text{Fe}(\text{acac})_3$ precatalyst, 1,10-phenanthroline (phen) ligand, diphenylzinc reagent and 1,2-dichloro-2-methylpropane (DCIB) as an oxidant, the reaction of 2-arylpiperidine derivative proceeded efficiently under mild reaction conditions (0 °C) to afford the corresponding arylated product in 89% yield (Scheme 1.18).

Scheme 1.18. Iron-Catalyzed Directed Arylation of 2-Arylpiperidine Derivative with Diphenylzinc Reagent

Later on, Nakamura and co-workers have extended their research to direct arylation of aromatic ketimines in the presence of $\text{Fe}(\text{acac})_3$ catalyst (Scheme 1.19).⁷⁰ They have found that 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) ligand exhibited better reactivity than phen ligand.^{22f,70} The iron-catalyzed arylation proceeded under similar reaction conditions (Scheme 1.18) by using diphenylzinc reagent, which was then followed by hydrolysis to afford the corresponding ketones in high yields (Scheme

1.19).⁷⁰ Interestingly, a unique feature of such direct arylation was that its tolerance of various electrofugal leaving groups on the same aromatic ring.

Scheme 1.19. Iron-Catalyzed Arylation of Aryl Imines *via* Directed C–H Bond Activation

In 2012, Nakamura and co-workers have further expanded the scope to secondary benzamide under mild reaction conditions (Scheme 1.20).⁷¹ The reaction selectively afforded *ortho*-monoarylated product in 78% isolated yield.

Scheme 1.20. Iron-Catalyzed Oxidative Monoarylation of *N*-Methylbenzamide

A proposed catalytic cycle (Scheme 1.21) is initiated by an *in situ* reduction of an iron salt, which leads to the formation of a low-valent organoiron species **21**.⁷¹ Coordination of a deprotonated benzamide to the iron center **21** generates an intermediate **22**. Subsequent C–H bond activation to give a ferracycle species **23** with the elimination of an arene molecule. Oxidation of the ferracycle species **23** by 1,2-

dichloro-2-methylpropane (DCIB), which then undergoes reductive elimination to afford *ortho*-arylated benzamide as well as the generation of isobutene and dichloroiron species **24**. Subsequent transmetalation of the dichloroiron species **24** with organozinc reagent regenerates the active iron species **21**.

Scheme 1.21. Proposed Catalytic Cycle for Iron-Catalyzed *ortho*-Monoarylation of Benzamide with Organozinc Reagent

A very recent example reported by Sunada and Nagashima that a stoichiometric iron complex could effectively mediate directed C–H bond alkylation of arenes with alkenes.⁷² Having to be inspired by the reactivity and design of ruthenium dihydride complex, $\text{Ru}(\text{H})_2(\eta^2\text{-H}_2)(\text{PCy}_3)_2$ in ruthenium-catalyzed C–H bond functionalization reactions,⁷³ Nagashima and co-workers have successfully developed an iron carbonyl complex **25** consisting of two weakly coordinating $\eta^2\text{-(H-Si)}$ moieties. The iron complex **25** can be easily dissociated from its metal center to form

an active disilaferracycle dicarbonyl, $[o\text{-(SiMe}_2)_2\text{C}_6\text{H}_4]\text{Fe}(\text{CO})_2$ catalytic species.⁷⁴ The reaction of 2-phenylpyridine with an excess of 2-norbornene proceeded smoothly at 80 °C for 12 h by using a stoichiometric amount of the well-defined iron complex **25** to afford the desired *ortho* C–H alkylated product in high yield (Scheme 1.22).⁷² Apart from the stoichiometric C–H bond functionalization of arenes, iron complex **25** could also demonstrate high catalytic activity towards hydrogenation and hydrosilylation of alkenes at room temperature.⁷⁴

Scheme 1.22. Stoichiometric Iron-Mediated C–H Bond Alkylation of 2-Phenylpyridine

1.5 Iron-Promoted Reduction Reactions

Iron hydride complexes typically act as key intermediates in catalytic cycles for hydrogenation, hydrosilylation, and carbon–carbon or carbon–heteroatom bond-forming reactions.⁷⁵ In 2004, Chirik and co-workers discovered a 14-electron $\text{L}_3\text{Fe}(0)$ fragment consisting of a tridentate pyridinediimine (PDI) ligand that successfully served as an active catalytic species for hydrogenation of alkenes and alkynes.^{76,77}

A wide variety of alkenes including terminal, internal, *gem*-disubstituted and dienes were effectively hydrogenated at room temperature in the presence of complex **26** to give the corresponding alkanes (Scheme 1.23a).⁷⁶ Moreover, Chirik and co-workers have found that the use of iron complex **26** could also undergo hydrogenation of internal alkynes, such as diphenylacetylene and 2-butyne, to afford alkanes *via* the

corresponding *cis*-alkene intermediates (Scheme 1.23b). However, hydrogenation of terminal alkynes was unsuccessful under the standard reaction condition.

Scheme 1.23. Hydrogenation of Alkenes and Alkynes Catalyzed by Iron Complex **26**

A proposed catalytic cycle (Scheme 1.24) for hydrogenation of an alkene involves a loss of two equivalents of N_2 from the iron complex **26** that leads to the formation of an active $\text{L}_3\text{Fe}(0)$ species **27**.⁷⁶ Coordination of an alkene with the iron species **27** to give an intermediate **28**, which is followed by oxidative addition of H_2 to form an alkene dihydride intermediate **29**. Subsequent insertion of the alkene to give an iron alkyl complex **30**, which then undergoes reductive elimination to afford an alkane product along with regeneration of the catalytically active species **27**. It is noted that isomerization of the double bond on alkene complex **28** could occur in the absence of dihydrogen.

Scheme 1.24. Proposed Mechanism for Catalytic Hydrogenation using Complex **26**

Furthermore, Chirik and co-workers reported that the reaction of unsaturated organic substrates, such as alkenes and alkynes, with hydrosilanes was able to undergo hydrosilylation reaction to form alkyl- and vinylsilanes, respectively (Scheme 1.25).⁷⁶ The bis(imino)pyridine iron complex **26**, which served as a precatalyst for hydrogenation of alkenes and alkynes, could also effectively promote hydrosilylation reaction. Moreover, Chirik and co-workers have proposed that these catalytic hydrosilylation reactions (Scheme 1.25) are most likely to undergo a mechanism that is similar to the hydrogenation reaction (Scheme 1.24).

Scheme 1.25. Hydrosilylation Reactions Catalyzed by Iron Complex **26** **1.6 Iron-Catalyzed Cross-Coupling Reactions**

A cross-coupling reaction typically involves the reaction of an organic halide with an organometallic reagent in the presence of a transition metal catalyst for the formation of a new carbon–carbon bond (Scheme 1.26).^{78,79,80,81} Although the use of economically and environmentally friendly iron catalysts was reported by Kochi and co-workers as early as the 1970s,¹⁸ these catalysts have attracted very little attention in the following decades.⁸²

Scheme 1.26. Transition Metal-Catalyzed Cross-Coupling Reaction

With the recent advances in the field of “inorganic Grignard reagents”, it is now well established that a reaction of FeCl₂ with four equivalents of Grignard reagent could form an iron species **31**, [Fe(MgX)₂] (Scheme 1.27).^{83,84} This indicates that the reduction process could generate an Fe(-II) center, instead of obtaining a zero-valent iron species.⁸⁴

Scheme 1.27. Formation of an Inorganic Grignard Reagent, **31**

In accordance with the reports by Bogdanović and Schwickardi,^{84, 85} the research group of Fürstner has proposed a reaction mechanism for iron-catalyzed cross-coupling reaction of aryl halides and alkylmagnesium halides (Scheme 1.28).^{20a, 20b} The low-valent and highly nucleophilic species **31** is believed to undergo oxidative addition with an aryl halide to give an aryl–Fe(0) intermediate **32** and is then followed by transmetalation with an organomagnesium reagent. Subsequent reductive elimination of the resulting intermediate **33** affords a cross-coupled product with regeneration of the catalytically active Fe(-II) species **31**. In general, the carbon–carbon reductive elimination step is a typical catalytic step in iron-catalyzed cross-coupling reactions.^{68, 81}

Scheme 1.28. A Simplified Proposed Fe(-II)–based Mechanism by Fürstner in 2002

1.7 Designs and Summary of Thesis Research

With the recent progress on cobalt-catalyzed directed hydroarylation of alkynes and alkenes by our group,⁴² we have driven our new interest towards the development of iron catalysis for the C–H bond functionalization reactions, given the fact that some reported examples on the parallelism between iron and cobalt stoichiometric C–H bond activation.^{66,86}

As discussed previously, aromatic C–H bonds in the presence of a directing group would generally undergo oxidative addition to low-valent iron complexes. Furthermore, migratory insertion of an alkene or alkyne into Fe–H bond is a common step in iron-catalyzed hydrogenation and hydrosilylation reactions, whereas reductive elimination of C–C bond is a typical mechanistic pathway in iron-catalyzed cross-coupling reactions. With the aforementioned background in mind, we hypothesized that the use of environmentally and economically attractive iron catalyst could be an alternative potential transition metal to undergo chelation-assisted hydroarylation of alkenes and alkynes since each of the three elementary steps appeared to be feasible.

A proposed catalytic cycle (Scheme 1.29) for iron-catalyzed directed hydroarylation involves oxidative addition of an *ortho* C–H bond to the low-valent iron center, migratory insertion of an unsaturated hydrocarbon molecule into the Fe–H bond and subsequent reductive elimination of the resulting diorganoiron species to afford corresponding product with regeneration of the iron active catalyst.

Scheme 1.29. Hypothetical Catalytic Cycle for Iron-Catalyzed Directed Hydroarylation

By having this proposed reaction mechanism, we embarked the research projects on iron-catalyzed *ortho*-directed C–H bond functionalization reactions that will be discussed in detail in the following chapters. In Chapter 2, we described the discovery and development of iron-catalyzed imine-directed C2-alkylation of indole with vinylarenes. In Chapter 3, we described an extension of the iron catalysis to imine-directed C2-alkenylation of indole with internal alkynes.

Throughout our research, we have found that the unique reactivity of iron has emerged as a promising transition metal catalyst for C–H bond functionalization reactions. More importantly, this would probably lead to a more diverse range of molecules that might not be easily achievable by other methods.

1.8 References

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Chapter 2. Iron-Catalyzed Imine-Directed C2-Alkylation of Indole with Vinylarenes

2.1 Introduction

Indole is commonly found in a myriad of biologically active compounds and natural products.¹ The nitrogen-containing heterocycle has played an important role as a key structural motif in many research areas such as pharmaceuticals, material sciences, agrochemicals and fragrances.^{1a,2} Hence, enormous efforts have been made to the development of direct and selective functionalization of the benzopyrrole unit.^{1k,2b,3}

Over the past decade, a variety of transition metal catalysts were used to promote regioselective C–H bond arylation at the C2– and C3–position of indoles.^{4,5} In the case of alkylation, several catalytic methods have been reported on C3-alkylation of indole, which are Friedel-Crafts alkylation, conjugated addition and allylic alkylation.^{1k,2b,6,7} In 2007, Jana and co-workers have reported on iron-catalyzed C3-selective alkylation of indole by using allylic and benzylic alcohols, respectively (Scheme 2.1).⁸ These reactions were performed in nitromethane under mild conditions to afford the corresponding products in good yields.

Scheme 2.1. Iron-Catalyzed C3-Selective Friedel-Crafts Alkylation of Indole with Alcohols

Direct C2-alkylation of indoles can be achieved by two main classical methods. One of which is lithiation at the C2-position of *N*-protected indoles, followed by trapping with a variety of electrophiles to give the corresponding 2-substituted indole products (Scheme 2.2a).⁹ On the other hand, Jones reported that the reaction of 2-iodoindoles with electron-deficient alkenes could afford the desired C2-substituted indoles *via* generation of indol-2-yl radicals (Scheme 2.2b).¹⁰

Scheme 2.2. Conventional Methods for C2-Alkylation of Indoles

Transition metal-catalyzed C–H bond activation is arising as a powerful and efficient synthetic method for direct C2-alkylation of indole.¹¹ In 2011, Yi and co-workers have successfully developed C2-selective alkylation of *N*-methylindole with benzylic alcohol by using a highly effective cationic ruthenium–hydride complex (Scheme 2.3a).^{11b,12} Simultaneously, Bach has demonstrated the regioselective C2-alkylation of free N–H indole with various alkyl bromides, that involved in a palladium-catalyzed norbornene-mediated cascade C–H bond activation process (Scheme 2.3b).^{11c}

Scheme 2.3. Transition Metal-Catalyzed C2-Alkylation of Indoles

In recent years, the use of a transition metal catalyst to promote hydroheteroarylation of vinylarenes represents a highly atom-economical approach to selectively afford 1,1-diarylalkane (branched) or 1,2-diarylalkane (linear) adducts.¹³ In particular, construction of a 1,1-diarylalkane structural unit has attracted great attention among chemists due to its occurrence in various pharmaceuticals and biologically active indole-containing molecules.¹⁴

Initially, our group has developed a cobalt-catalyzed alkylation of 2-phenylpyridine with styrene. In order to achieve 1,1-diarylalkane derivative (branched product), the use of a phosphine ligand was essential to control regioselectivity of the reaction (Scheme 2.4a).¹⁵ Later on, our group has extended the scope to aromatic aldimines. The aldimine-directed addition of indole to styrene was performed in the presence of a cobalt catalyst and a triarylphosphine ligand under mild reaction conditions (Scheme 2.4b).¹⁶

Scheme 2.4. Cobalt-Catalyzed Branched-Selective Hydroarylation of Styrene in the Presence of a Phosphine Ligand

A proposed mechanistic pathway consists of reversible chelation-assisted oxidative addition of an *ortho* C–H bond to the low-valent cobalt center, reversible insertion of a styrene into the Co–H bond leading to a branched intermediate that involves an intrinsically favorable η^3 -benzyl type coordination, and subsequent reductive elimination to afford the desired 1,1-diarylethane derivative as a branched product (Scheme 2.5).^{13d,15,16,17,18}

Scheme 2.5. Proposed Catalytic Cycle for Nitrogen-Assisted Cobalt-Catalyzed Hydroarylation of Styrene

Another example was reported by Shibata and co-workers on iridium(I)-catalyzed C2-alkylation of *N*-benzoyl indole with styrene. The reaction was performed in the presence of a bidentate phosphine ligand that selectively gave the corresponding branched product in excellent yield (Scheme 2.6).¹⁹

Scheme 2.6. Iridium-Catalyzed Branched-Selective Hydroheteroarylation of Styrene

Besides the well-studied and widely applied phosphine ligands, *N*-heterocyclic carbenes (NHCs) have been established as one of the most important and versatile ligands in modern organometallic chemistry.^{20, 21} Due to their strong σ -donor properties, the NHC ligands typically form strong bonds with metal centers that could lead to high resistance towards decomposition and enhance catalytic performances.²²

In 2010, Nakao and Hiyama have developed a nickel-catalyzed hydroheteroarylation of various vinylarenes, including β -methylstyrene (Scheme 2.7), to afford the corresponding 1,1-diarylalkane derivatives.²³ They have found that the use of 1,3-dimesitylimidazol-2-ylidene (IMes) carbene ligand was crucial to achieve the desired products in high yields. However, phosphine ligands, such as PCyp₃ and P(*n*Bu)₃, were completely ineffective to promote the reaction.

Scheme 2.7. Nickel-Catalyzed Hydroheteroarylation of Vinylarene using NHC Ligand

A proposed catalytic cycle (Scheme 2.8) is initiated by reversible oxidative addition of a heteroaromatic C2–H bond to the Ni(0)–IMes catalyst through η^2 -arenenickel complex **A** to form Ni–H complex **B**.²³ Reversible coordination of a vinylarene to give complex **C** and is then followed by reversible hydronicellation to form 1-arylethynickel complex **D**. Subsequent reductive elimination to afford the desired 1,1-diarylethane product as well as regeneration of complex **A**.

Scheme 2.8. Plausible Mechanism for Nickel-Catalyzed Hydroheteroarylation of Vinylarenes

Recently, our group has reported on C2-alkylation of indole with allylbenzene by using a cobalt–*N*-heterocyclic carbene–Grignard catalytic system in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) to promote a tandem alkene isomerization–hydroarylation process that exclusively gave 1,1-diarylpropane derivative in high yield (Scheme 2.9).²⁴

Scheme 2.9. Cobalt-Catalyzed Tandem Alkene Isomerization–Hydroarylation

Thus far, a variety of low-valent late transition metal complexes have played an important role in directed hydroarylation or hydroheteroarylation of alkenes.^{13a,13b,13d,19,25,26,27} However, such reaction involving a catalytic amount of an iron complex is still yet to be developed, despite being one of the most abundant and environmentally friendly transition metals.^{28,29,30} In light of the aforementioned backgrounds in Chapter 1, which are iron-mediated cyclometalation reactions,³¹ iron-catalyzed hydrogenation or hydrosilylation reactions,³² and iron-catalyzed cross-coupling reactions,³³ we have envisioned that the potential reactivity of iron complexes could probably undergo direct alkylation with alkenes through chelation-assisted C–H bond activation.

In this chapter, we report that an iron–*N*-heterocyclic carbene catalyst could promote imine-directed C2-alkylation of indole with vinylarenes to selectively afford corresponding 1,1-diarylalkane derivatives as branched products (Scheme 2.10).³⁴ To the best of our knowledge, this represents the first example of iron-catalyzed hydroheteroarylation of vinylarenes involving directed C–H bond activation process.^{28,29} The reaction is proposed to undergo the typical chelation-assisted C–H alkylation mechanistic pathway, which consists of oxidative addition, migratory insertion and reductive elimination steps.

Scheme 2.10. Iron-Catalyzed Imine-Directed C2-Alkylation of Indole with Vinylarenes

2.2 Results and Discussion

With the recent development on cobalt-catalyzed pyridine- or imine-directed hydroarylation of styrene by our group,^{15,16,35} we began the present study with attempts to perform the reaction by using an iron complex as an alternative catalyst. Through an extensive screening of reaction conditions, we have found that a simple replacement of the cobalt precatalyst with an iron salt could not effectively promote in most of the chelation-assisted hydroarylation reactions.

To our delight, the addition of 1-methyl-3-iminomethylindole **1** to styrene **2a** was found to be feasible (Table 2.1).²⁴ An iron catalytic system, consisting of Fe(acac)₃ (99% purity, 10 mol %), 1,3-bis(2,6-dimethylphenyl)imidazolium chloride (IXyl•HCl, 10 mol %), cyclohexylmagnesium chloride (CyMgCl, 100 mol %) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 2 equiv) as an additive, was able to promote the reaction in THF at 60 °C for 6 h (Table 2.1, entry 1).³⁴ The reaction afforded 1,1-diarylethane derivative **3a** as an exclusive regioisomer in 72% yield. Regioisomeric 1,2-diarylethane derivative was not detected under the present iron catalysis. The carbene ligand, IXyl•HCl is known to be effective in the recently reported C2-alkylation of indole derivatives with non-conjugated arylalkenes.²⁴

Saturated *N*-heterocyclic carbene (NHC) ligands have received much attention compared to its unsaturated analogues due to the increased in Lewis basicity which could enhance the catalytic activity.³⁶ When a saturated NHC ligand, 1,3-bis(2,6-dimethylphenyl)imidazolinium chloride (SIXyl•HCl) was used instead of the unsaturated IXyl•HCl ligand in our iron catalytic system, the reaction was further improved to achieve the desired product **3a** in 90% yield (Table 2.1, entry 2).

After carefully investigation, we have found that the reaction yield was dramatically decreased to 59% when 2-methylstyrene **2b** was used in THF (Table 2.1,

entry 3). Fortunately, the reaction of **1** with **2b** achieved substantial improvement in Et₂O as solvent rather than in THF, to afford the desired branched product **3b** in 65% yield (Table 2.1, entry 4). Hence, subsequent screening experiments were performed using the less reactive 2-methylstyrene **2b** in place of styrene **2a**.

However, increasing the steric bulkiness of saturated NHC ligands, such as 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (SIMes•HCl) and 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr•HCl), resulted the hydroheteroarylation product **3b** in much lower yields (57% and 20%, respectively) as compared to the presence of SIXyl•HCl ligand (Table 2.1, entries 4, 5 and 6).

Besides *N*-heterocyclic carbenes, the effect of phosphine ligands, such as PCy₃ and PPh₃, were investigated in the iron catalytic system (Table 2.1, entries 7 and 8). We have found that such monodentate phosphine ligands were ineffective to promote the reaction. Only trace amount of product **3b** was achieved when a phosphine ligand was used. Bipyridine ligand, which proved to be effective for iron-catalyzed directed arylation reactions,^{28a,37} was unfortunately not able to undergo in our present imine-directed iron-catalyzed hydroheteroarylation reaction (Table 2.1, entry 9).

The presence of a NHC ligand was essential for the reaction to take place smoothly (Table 2.1, entry 10). Furthermore, the reaction was completely shut down in the absence of TMEDA (Table 2.1, entry 11). Additionally, the choice and the amount of Grignard reagent were also critical for the reaction to proceed in our present iron catalysis. The use of other Grignard reagents, for example neopentylmagnesium bromide (*t*BuCH₂MgBr), instead of CyMgCl inhibited the hydroheteroarylation reaction (Table 2.1, entry 12). It is noted that reducing the amount of CyMgCl could diminish the catalytic activity of the reaction.

Table 2.1. Screening of Reaction Conditions^a

Fe(acac)_3 (10 mol %)
 ligand (10 mol %)
 CyMgCl (100 mol %)
 TMEDA (2 equiv)
 solvent, 60 °C, 6 h

entry	styrene	ligand	solvent	yield (%) ^b
1	2a	IXyl•HCl	THF	72
2	2a	SIXyl•HCl	THF	90
3	2b	SIXyl•HCl	THF	59
4	2b	SIXyl•HCl	Et ₂ O	65
5	2b	SIMes•HCl	Et ₂ O	57
6	2b	SIPr•HCl	Et ₂ O	20
7	2b	PCy ₃	Et ₂ O	4
8 ^c	2b	PPh ₃	Et ₂ O	2
9	2b	dtbpy	Et ₂ O	0
10	2b	none	Et ₂ O	6
11 ^d	2b	SIXyl•HCl	Et ₂ O	0
12 ^e	2b	SIXyl•HCl	Et ₂ O	0
13 ^f	2b	SIXyl•HCl	Et ₂ O	67
14 ^g	2b	SIXyl•HCl	Et ₂ O	0

IXyl•HCl

SIXyl•HCl (R¹ = Me, R² = H)
 SIMes•HCl (R¹ = R² = Me)
 SIPr•HCl (R¹ = *i*-Pr, R² = H)

dtbpy

^aThe reaction was performed using **1** (0.2 mmol), **2a** or **2b** (0.3 mmol). Fe(acac)₃ (99% purity) was used. PMP = *p*-methoxyphenyl. ^bDetermined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^c20 mol % of PPh₃ was used. ^dTMEDA was omitted. ^e*t*-BuCH₂MgBr was used instead of CyMgCl. ^fFe(acac)₃ (≥99.9% purity) was used. ^gCoBr₂ (0.5 mol %) was used instead of Fe(acac)₃.

Recently, Buchwald and Bolm have reported that iron-catalyzed reactions were positively affected by trace amount of other metals.³⁸ Cognizant of this possibility, we have employed a higher purity iron source to our catalytic system. As a result, we have found that the use of a higher purity Fe(acac)₃ precatalyst (>99.9% purity) gave the same outcome with respect to the reagent-grade Fe(acac)₃ under the standard reaction conditions (Table 2.1, entry 13). Moreover, the desired product was not obtained when a small amount of CoBr₂ (0.5 mol %) was used instead of Fe(acac)₃ precatalyst (Table 2.1, entry 14). In addition, the observation was the same for other metal salts, such as Mn(acac)₃ and Ni(acac)₂, under the standard reaction conditions. Hence, these experiments indicated that the C–H activation reaction was exclusively catalyzed by an iron source and the trace metal impurity is most unlikely to be responsible for the observed reactivity.

With the optimized reaction conditions (Table 2.1, entry 4) in hand, we next explored the scope of vinylarenes (Scheme 2.11). A variety of substituted styrene derivatives were able to participate in the reaction under the iron–NHC catalysis.

The iron-catalyzed reaction of indole **1** with styrene **2a** was followed by acidic hydrolysis to afford 1,1-diarylethane derivative bearing a C3-formyl group **4a** in 93% isolated yield. In the case of **2b**, the corresponding branched product **4b** was achieved in 77% yield upon isolation after acidic hydrolysis.

A styrene derivative bearing an electron-withdrawing fluoro-substituent at *para*-position on the aromatic ring **2c** gave the desired branched product **4c** in excellent yield (91%) with an exclusive regioselectivity. Furthermore, the presence of an electron-donating methoxy-substituent **2d** was tolerated under the iron catalysis to afford the corresponding product **4d** in 88% yield. In addition, 3,4-methylenedioxystyrene **2e** was able to undergo the hydroheteroarylation reaction

affording the 1,1-diarylethane derivative **4e** in good yield (83%). The reaction of **1** with 2-vinylnaphthalene **2f** gave the corresponding branched product **4f** in 91% yield.

Scheme 2.11. Imine-Directed C2-Alkylation of Indole with Vinylarenes^a

^aThe reaction was performed on a 0.2 mmol scale. ^bDetermined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

In addition to the scope of vinylarenes, we also explored the scope of β -substituted styrene derivatives with **1**. We have found that *cis*- β -substituted styrenes bearing alkyl, aryl and silyl substituents were amenable to the present reaction. The reaction of **1** with *cis*- β -methylstyrene **2g** under the Fe–NHC catalysis, which was then followed by acidic hydrolysis to give the corresponding 1,1-diaryllalkane derivative **4g** in moderate yield (58%). However, it is noted that *trans*- β -methylstyrene has shown much poorer reactivity than its *cis*-isomer **2g**. A *cis*- β -methylstyrene derivative bearing an electron-withdrawing group at *para*-position on the aromatic ring **2h** reacted smoothly to form the desired branched product **4h** in good yield (77%). In contrast, the reaction of *cis*-1-(*p*-methoxyphenyl)propene **2i** was performed rather sluggishly under the standard reaction conditions, affording the hydroheteroarylation product **4i** in low yield.

Moreover, the reaction was also applicable to *cis*- β -substituted styrenes bearing a butyl group **2j** and a phenyl group **2k**, that gave the corresponding products **4j** and **4k** with similar results (39% and 34% yields, respectively). The reaction of *cis*- β -trimethylsilylstyrene **2l** took place smoothly to give the desired branched product **4l** in 67% yield.

Additionally, an indole substrate **1'** with an *N*-benzyl protecting group was proceeded well with styrene **2a** to afford the adduct **4a'** in good yield (89%). On the other hand, an *N*-Boc protecting group of an indole derivative failed to undergo the imine-directed hydroheteroarylation reaction. Besides the indole substrates, we have found that imines derived from acetophenone and tetralone, could also participate in the reaction with styrene **2a** under our present iron–NHC catalytic system, albeit in low yields (**4m** and **4n**).^{35b}

Furthermore, we have investigated the compatibility of our iron-catalyzed reaction in the presence of other functional groups by using a robustness screen method, which was developed by Glorius and co-workers in 2013.³⁹ As a result, the imine-directed C2-alkylation of indole with vinylarenes has turned out to be incompatible with most of the functional groups.

Table 2.2. Robustness Screen to Examine Functional Group Compatibility^a

<div style="text-align: center;"> <p> Fe(acac)_3 (10 mol %) SiXyl-HCl (10 mol %) CyMgCl (100 mol %) TMEDA (2 equiv) additive (1 equiv) Et_2O, 60 °C, 6 h </p> </div>				
entry	additive	yield of 3a (%) ^b	additive remaining (%) ^c	starting material 1 remaining (%) ^c
1	none	93	-	-
2		56	N.D.	N.D.
3		0	60	67
4		0	45	85
5		44	N.D.	N.D.
6		0	12	73

^aThe reaction was performed using **1** (0.2 mmol), **2a** (0.3 mmol). Fe(acac)_3 (99% purity) was used. ^bDetermined by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

^cDetermined by GC using *n*-tridecane as an internal standard. N.D. = not determined.

Chapter 2

The reaction of indole **1** with styrene **2a** was performed under the standard iron–NHC catalytic system in the presence of an additional additive, consisting of a particular functional group on the aromatic ring (Table 2.2). The desired product **3a** was obtained in moderate yield when chlorobenzene or methyl benzoate was used as an additional additive in the reaction (Table 2.2, entries 2 and 5). On the contrary, the presence of other additional additives, such as bromobenzene, iodobenzene and benzonitrile, completely inhibited the reaction (Table 2.2, entries 3, 4 and 6). Consequently, the formation of product **3a** was not achieved, however the indole starting material **1** was almost fully recovered.

Based on the results of the robustness screen method, we have further examined the reaction of **1** with 4-chlorostyrene **2o** as well as methyl 4-vinylbenzoate **2p** (Table 2.3, entries 1 and 2). Unfortunately, only the former styrene derivative could afford the desired product **3o**, albeit in low yield (Table 2.3, entry 1).

In addition, the use of an organozinc reagent, that generated *in situ* from a mixture of $\text{ZnCl}_2 \cdot \text{TMEDA}$ with two equivalents of the Grignard reagent, could not promote the hydroheteroarylation of 4-chlorostyrene **2o** and methyl 4-vinylbenzoate **2p** (Table 2.3, entries 3 and 4). In contrast, this protocol has been frequently utilized in iron-catalyzed directed aromatic C–H bond activation.^{28a,40}

Table 2.3. Reaction of **1** with Functionalized Styrene Derivatives^a

entry	styrene	yield (%) ^b
1	2o	18
2	2p	0
3 ^c	2o	0
4 ^c	2p	0

^aThe reaction was performed using **1** (0.2 mmol), **2o** or **2p** (0.3 mmol). Fe(acac)₃ (99% purity) was used. ^bDetermined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^cA mixture of ZnCl₂·TMEDA (200 mol %) and CyMgCl (400 mol %) was used in place of CyMgCl (100 mol %) and TMEDA (2 equiv).

The iron-catalyzed reaction of **1** with allylbenzene **5** (Scheme 2.12) gave the desired 1,1-diarylpropane derivative **4g** albeit in low yield (23%). The reaction presumably proceeded through an alkene isomerization–hydroheteroarylation sequence, which is similar to the previously reported cobalt-catalyzed reaction by our group.²⁴ Under our present reaction conditions, the iron-catalyzed imine-directed hydroheteroarylation of terminal alkenes, such as 1-octene and vinyltrimethylsilane, were not successful when these were employed as the reaction partner.

Scheme 2.12. Isomerization–Hydroheteroarylation of Allylbenzene **Scheme 2.13.** Deuterium-Labeling Experiment^a

^aThe yields and the proton contents were determined by ^1H NMR spectroscopy.

To gain mechanistic insights into the present hydroheteroarylation reaction, a deuterium-labeling experiment was performed (Scheme 2.13). The reaction of C2-deuterated indole substrate **1-d** with 4-methoxystyrene **2d** was quenched at the reaction time of 3 min in the presence of the iron–NHC catalyst to afford the hydroheteroarylation product **3d-d** in 51% yield along with recovery of the starting materials both in 32% yields. The ^1H NMR spectroscopic analysis revealed that the deuterium content of **1-d** decreased only slightly to 0.9D, while the deuterium incorporation into the olefinic position of **2d** was marginal (approximately 0.1D for each position). In accordance with these observations, the methyl position of **3d-d** was

substantially deuterated ($>0.7D$), whereas the methine position was not deuterated ($<0.1D$).

We have speculated that the present hydroheteroarylation reaction is initiated by the generation of a low-valent iron–NHC complex from the reduction of the Fe(III) precatalyst by the Grignard reagent in the presence of the imidazolinium salt.³⁴ The reason behind the requirement of an excessive amount of the Grignard reagent is still ambiguous. Nevertheless, this might be attributed to the formation of a ferrate species.⁴¹

Based on the results of the deuterium-labeling experiment, a catalytic cycle is proposed to involve chelation-assisted oxidative addition of the indole C2–H bond to the iron center,³¹ migratory insertion of a vinylarene into the Fe–H bond and reductive elimination of the resulting diorganoiron species (Scheme 2.14). Formation of branched intermediate may involve the favorable η^3 -benzyl type coordination. The observation of H/D scrambling in the reaction of **1-d** with **2d** (Scheme 2.13) may indicate that the oxidative addition and migratory insertion steps are reversible. Furthermore, the regioselectivity and reaction rate are controlled in the reductive elimination step.^{15,16}

Scheme 2.14. Proposed Catalytic Cycle for Iron-Catalyzed Imine-Directed C2-Alkylation of Indole with Vinylarenes

2.3 Conclusion

In summary, we have developed an iron–NHC catalytic system for directed C2-alkylation of indole with vinylarenes.³⁴ Unlike the recent progresses in iron-catalyzed C–H functionalization reactions by Nakamura and others,²⁹ the present reaction appears to be involving C–H oxidative addition rather than undergoing deprotonative C–H metalation. To our best knowledge, this represents the first example of iron-catalyzed directed hydroheteroarylation *via* C–H activation.

2.4 Experimental Section

General. All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash chromatography was performed using 40–63 μm (Silica 60 M, Macherey-Nagel) silica gel. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECA-400 (400 MHz) NMR spectrometer. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and CHCl_3 (77.0 ppm), respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column, DB-5 (Agilent J&W, 0.2 mm i.d. x 30m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-ToF Premier LC-HR mass spectrometer. Melting points of solid materials were determined on an Optimelt Automated Melting Point System apparatus and were uncorrected.

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous iron(III) acetylacetonate was purchased from Strem Chemicals (99%) or Aldrich ($\geq 99.9\%$), and was used as received. The commercial source and purity of iron(III) acetylacetonate did not significantly affect the catalytic activity (see Table 2.1). Et_2O and THF were distilled over Na/benzophenone. TMEDA was distilled over CaH_2 . Grignard reagents were prepared from the corresponding halides and magnesium turnings in anhydrous Et_2O or THF, and titrated before use. The indole substrates (*E*)-4-methoxy-*N*-((1-methyl-1*H*-indol-3-yl)methylene)aniline (**1**), (*E*)-*N*-

((1-benzyl-1*H*-indol-3-yl)methylene)-4-methoxyaniline (**1'**), and (*E*)-1-(2-deuterio-1-methyl-1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (**1-*d***) were synthesized as described before.²⁴ Among vinylarenes, vinylbenzo[*d*][1,3]dioxole (**2e**),⁴² (*Z*)-1-phenylpropene (**2g**),⁴³ (*Z*)-1-(4-fluorophenyl)propene (**2h**),⁴³ (*Z*)-1-(*p*-methoxyphenyl)propene (**2i**),⁴⁴ (*Z*)-1-phenyl-1-hexene (**2j**),⁴³ and (*Z*)-1-phenyl-2-(trimethylsilyl)ethylene (**2l**)⁴⁵ were prepared according to the literature procedures. Bis(2,6-dimethylphenyl)imidazolium chloride (IXyl•HCl) and bis(2,6-dimethylphenyl)imidazolium chloride (SIXyl•HCl) were prepared according to the literature procedures.^{46,47}

Iron-Catalyzed Imine-Directed Alkylation of Indole with Vinylarene

Typical Procedure: In a Schlenk tube were placed the indole substrate **1** (52.9 mg, 0.20 mmol), Fe(acac)₃ (7.1 mg, 0.020 mmol), SIXyl•HCl (6.3 mg, 0.020 mmol), vinylarene **2** (0.30 mmol), TMEDA (60 μ L, 0.40 mmol), and Et₂O (0.39 mL). To the mixture was added an Et₂O solution of CyMgCl (1.74 M, 0.115 mL, 0.20 mmol) at room temperature. The resulting mixture was stirred at 60 °C for 6 h. The reaction mixture was allowed to room temperature, diluted with Et₂O (0.5 mL), and quenched with water (1.0 mL). The subsequent workup protocol depends on the vinylarene.⁴⁸

For β -unsubstituted vinylarenes (**2a–2f**), the quenched aqueous mixture was stirred for 5 min, followed by the addition of CH₂Cl₂ (3 mL) and 6M HCl (2 mL). The resulting mixture was heated to 45 °C, and the progress of the acidic hydrolysis was monitored by thin-layer chromatography (TLC). Upon completion of the hydrolysis, the mixture was cooled to room temperature. The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel

chromatography to afford the hydroarylation product.

For β -substituted vinylarenes (**2g–2l**), the quenched aqueous mixture was directly treated with 3M HCl (0.5 mL) at room temperature with stirring for 1 h. The aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford the hydroarylation product.

1-Methyl-2-(1-phenylethyl)-1H-indole-3-carbaldehyde (4a): The typical procedure was applied to **1** and styrene (**2a**, 34.5 μ L, 0.30 mmol). The hydrolysis was performed at 45 °C for 3 h after the addition of 6M HCl. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow oil (49.2 mg, 93%). R_f 0.32 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl₃): δ 1.87 (d, J = 7.2 Hz, 3H), 3.44 (s, 3H), 5.21 (q, J = 7.4 Hz, 1H), 7.22-7.34 (m, 8H), 8.36-8.39 (m, 1H), 10.26 (s, 1H); ^{13}C NMR (100 MHz, CDCl₃): δ 18.6, 31.1, 34.4, 109.2, 114.5, 121.3, 123.0, 123.4, 125.7, 126.8, 126.9, 128.8, 137.3, 140.9, 153.4, 184.7; HRMS (ESI) Calcd for C₁₈H₁₈NO [M + H]⁺ 264.1383, found 264.1389. The ^1H and ^{13}C NMR spectra showed good agreement with the literature data.¹⁶

1-Methyl-2-(1-(*o*-tolyl)ethyl)-1H-indole-3-carbaldehyde (4b): The typical procedure

was applied to **1** and 2-vinyltoluene (**2b**, 39.0 μ L, 0.30 mmol). The hydrolysis was performed at 45 °C for 36 h after the addition of 6M HCl. Silica gel chromatography (eluent: hexane/EtOAc = 100/15) of the crude product afforded the title compound as an orange solid (42.8 mg, 77%). m.p. 124.3–126.3 °C; R_f 0.34 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.85 (d, J = 7.6 Hz, 3H), 2.06 (s, 3H), 3.53 (s, 3H), 5.03 (q, J = 7.4 Hz, 1H), 7.13 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.24–7.29 (m, 4H), 7.47 (d, J = 7.6 Hz, 1H), 8.31–8.35 (m, 1H), 10.11 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.8, 20.2, 30.5, 34.3, 109.2, 114.0, 121.4, 122.9, 123.2, 125.9, 126.37, 126.44, 127.3, 131.1, 136.7, 136.9, 139.3, 153.0, 185.2; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}$ $[\text{M} + \text{H}]^+$ 278.1540, found 278.1564.

2-(1-(4-Fluorophenyl)ethyl)-1-methyl-1H-indole-3-carbaldehyde (4c): The typical procedure was applied to **1** and 4-fluorostyrene (**2c**, 36.0 μ L, 0.30 mmol). The hydrolysis was performed at 45 °C for 12 h after the addition of 6M HCl. Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a brown oil (51.1 mg, 91%). R_f 0.25 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.86 (d, J = 7.6 Hz, 3H), 3.46 (s, 3H), 5.20 (q, J = 7.2 Hz, 1H), 7.01 (t, J = 8.8 Hz, 2H), 7.20–7.23 (m, 2H), 7.26–7.33 (m, 3H), 8.34–8.38 (m, 1H), 10.25 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.7, 31.1, 33.8, 109.3, 114.4, 115.8 (d, $^2J_{\text{C-F}}$ = 21 Hz), 121.2, 123.0, 123.5, 125.8, 128.5 (d, $^3J_{\text{C-F}}$ = 8 Hz), 136.8 (d, $^4J_{\text{C-F}}$ = 3 Hz), 137.3, 152.8, 162.8 (d, $^1J_{\text{C-F}}$ = 245 Hz), 184.6; HRMS (ESI) Calcd for $\text{C}_{18}\text{H}_{17}\text{NOF}$ $[\text{M} + \text{H}]^+$ 282.1289, found 282.1297.

2-(1-(4-Methoxyphenyl)ethyl)-1-methyl-1*H*-indole-3-carbaldehyde (4d): The typical procedure was applied to **1** and 1-methoxy-4-vinylbenzene (**2d**, 40.0 μ L, 0.30 mmol). The hydrolysis was performed at 45 °C for 36 h after the addition of 6M HCl. Silica gel chromatography (eluent: hexane/EtOAc = 4/1) of the crude product afforded the title compound as an orange oil (51.4 mg, 88%). R_f 0.24 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.84 (d, J = 7.2 Hz, 3H), 3.45 (s, 3H), 3.77 (s, 3H), 5.13 (q, J = 7.4 Hz, 1H), 6.85 (app. d, J = 8.8 Hz, 2H), 7.15 (app. d, J = 8.8 Hz, 2H), 7.24-7.32 (m, 3H), 8.34-8.39 (m, 1H), 10.24 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.8, 31.0, 33.7, 55.2, 109.2, 114.1, 114.4, 121.4, 122.9, 123.3, 125.7, 128.0, 132.9, 137.3, 153.8, 158.4, 184.7; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 294.1489, found 294.1497.

2-(1-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-1-methyl-1*H*-indole-3-carbaldehyde (4e): The typical procedure was applied to **1** and 5-vinylbenzo[*d*][1,3]dioxole (**2e**, 40.5 μ L, 0.30 mmol). The hydrolysis was performed at 45 °C for 36 h after the addition of 6M HCl. Silica gel chromatography (eluent: hexane/EtOAc = 4/1) of the crude product afforded the title compound as a brown oil (51.1 mg, 83%). R_f 0.23 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.82 (d, J = 7.2 Hz, 3H), 3.49 (s, 3H), 5.11 (q, J =

7.2 Hz, 1H), 5.92 (s, 2H), 6.70-6.77 (m, 3H), 7.25-7.32 (m, 3H), 8.35-8.38 (m, 1H), 10.24 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.8, 31.0, 34.1, 101.1, 107.7, 108.3, 109.2, 114.4, 119.8, 121.3, 123.0, 123.4, 125.7, 134.8, 137.3, 146.4, 148.2, 153.4, 184.7; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 308.1282, found 308.1292.

1-Methyl-2-(1-(naphthalen-2-yl)ethyl)-1H-indole-3-carbaldehyde (4f): The typical procedure was applied to **1** and 2-vinylnaphthalene (**2f**, 46.3 mg, 0.30 mmol). The hydrolysis was performed at 45 °C for 12 h after the addition of 6M HCl. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange solid (57.3 mg, 91%). m.p. 154.4–156.4 °C; R_f 0.29 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 2.00 (d, J = 7.6 Hz, 3H), 3.46 (s, 3H), 5.39 (q, J = 7.6 Hz, 1H), 7.27-7.36 (m, 4H), 7.46-7.52 (m, 2H), 7.76-7.82 (m, 4H), 8.39-8.41 (m, 1H), 10.33 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 18.6, 31.0, 34.6, 109.3, 114.6, 121.3, 123.0, 123.4, 124.9, 125.7, 125.8, 126.0, 126.4, 127.6, 127.8, 128.6, 132.2, 133.3, 137.3, 138.5, 153.2, 184.7; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{20}\text{NO}$ $[\text{M} + \text{H}]^+$ 314.1540, found 314.1546.

1-Methyl-2-(1-phenylpropyl)-1H-indole-3-carbaldehyde (4g): The typical procedure was applied to **1** and (Z)-1-phenylpropene (**2g**, 40.5 μL , 0.30 mmol). Silica

gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange solid (32.3 mg, 58%). The same product was obtained by performing the reaction using allylbenzene (**5**, 40.0 μ L, 0.30 mmol) instead of (*Z*)-1-phenylpropene (23% yield). m.p. 110.8–112.6 °C; R_f 0.41 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.00 (t, J = 7.4 Hz, 3H), 2.15–2.27 (m, 1H), 2.47–2.58 (m, 1H), 3.49 (s, 3H), 4.93 (dd, J = 10.4, 6.0 Hz, 1H), 7.21–7.34 (m, 8H), 8.37–8.42 (m, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.6, 25.4, 31.1, 42.2, 109.3, 116.0, 121.4, 123.0, 123.4, 125.7, 126.9, 127.4, 128.8, 137.4, 140.4, 151.8, 185.0; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}$ $[\text{M} + \text{H}]^+$ 278.1540, found 278.1546. The ^1H and ^{13}C NMR spectra showed good agreement with the literature data.²⁴

2-(1-(4-Fluorophenyl)propyl)-1-methyl-1*H*-indole-3-carbaldehyde (4h**):** The typical procedure was applied to **1** and (*Z*)-1-(4-fluorophenyl)propene (**2h**, 40.9 mg, 0.30 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange solid (45.5 mg, 77%). m.p. 113.4–115.2 °C; R_f 0.31 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.00 (t, J = 7.4 Hz, 3H), 2.17–2.25 (m, 1H), 2.45–2.55 (m, 1H), 3.49 (s, 3H), 4.93 (dd, J = 10.4, 6.0 Hz, 1H), 7.01 (t, J = 8.6 Hz, 2H), 7.22–7.35 (m, 5H), 8.36–8.39 (m, 1H), 10.31 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.6, 25.6, 31.1, 41.5, 109.3, 115.7 (d, $^2J_{\text{C-F}}$ = 22 Hz), 115.9, 121.2, 123.0, 123.5, 125.8, 128.9 (d, $^3J_{\text{C-F}}$ = 8 Hz), 136.2 (d, $^4J_{\text{C-F}}$ = 3 Hz), 137.3, 151.2, 162.8 (d, $^1J_{\text{C-F}}$ = 245 Hz), 184.8; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{19}\text{NOF}$ $[\text{M} + \text{H}]^+$ 296.1446, found 296.1456. The ^1H and ^{13}C NMR spectra showed good

agreement with the literature data.²⁴

2-(1-(4-Methoxyphenyl)propyl)-1-methyl-1*H*-indole-3-carbaldehyde (4i): The typical procedure was applied to **1** and (*Z*)-1-(*p*-methoxyphenyl)propene (**2i**, 46.5 μ L, 0.30 mmol) were subjected to the typical reaction procedure. Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as a brown oil (24.0 mg, 39%). R_f 0.31 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 1.00 (t, J = 7.4 Hz, 3H), 2.15-2.25 (m, 1H), 2.44-2.54 (m, 1H), 3.50 (s, 3H), 3.78 (s, 3H), 4.87 (dd, J = 10.0, 6.0 Hz, 1H), 6.85 (app. d, J = 8.8 Hz, 2H), 7.18 (app. d, J = 8.4 Hz, 2H), 7.26-7.34 (m, 3H), 8.38-8.41 (m, 1H), 10.30 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 12.7, 25.6, 31.1, 41.5, 55.3, 109.2, 114.1, 115.9, 121.4, 122.9, 123.3, 125.7, 128.4, 132.3, 137.4, 152.2, 158.4, 185.0; HRMS (ESI) Calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 308.1646, found 308.1650. The ^1H and ^{13}C NMR spectra showed good agreement with the literature data.²⁴

1-Methyl-2-(1-phenylhexyl)-1*H*-indole-3-carbaldehyde (4j): The typical procedure was applied to **1** and (*Z*)-1-phenyl-1-hexene (**2j**, 59.5 μ L, 0.3 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title

compound as an orange oil (25.0 mg, 39%). R_f 0.53 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 0.85 (t, J = 7.0 Hz, 3H), 1.22-1.45 (m, 6H), 2.14-2.24 (m, 1H), 2.40-2.49 (m, 1H), 3.49 (s, 3H), 5.01 (dd, J = 9.8, 6.2 Hz, 1H), 7.21-7.34 (m, 8H), 8.38-8.42 (m, 1H), 10.32 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.0, 22.4, 27.8, 31.2, 31.8, 32.4, 40.6, 109.3, 115.7, 121.4, 123.0, 123.4, 125.8, 126.9, 127.4, 128.8, 137.4, 140.5, 152.1, 184.9; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{26}\text{NO}$ $[\text{M} + \text{H}]^+$ 320.2009, found 320.2013.

2-(1,2-Diphenylethyl)-1-methyl-1*H*-indole-3-carbaldehyde (4k): The typical procedure was applied to **1** and (*Z*)-stilbene (**2k**, 53.5 μL , 0.3 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a yellow oil (23.4 mg, 34%). R_f 0.38 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 3.38 (s, 3H), 3.46 (dd, J = 13.2, 10.8 Hz, 1H), 3.83 (dd, J = 13.2, 5.6 Hz, 1H), 5.19 (dd, J = 10.2, 5.8 Hz, 1H), 6.97-6.99 (m, 2H), 7.12-7.15 (m, 3H), 7.20-7.29 (m, 4H), 7.30-7.35 (m, 4H), 8.26-8.31 (m, 1H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 30.8, 39.5, 43.1, 109.3, 115.2, 121.5, 122.9, 123.3, 125.7, 126.8, 127.1, 127.4, 128.55, 128.61, 128.8, 137.0, 138.4, 140.4, 151.3, 185.0; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{22}\text{NO}$ $[\text{M} + \text{H}]^+$ 340.1696, found 340.1700. The ^1H and ^{13}C NMR spectra showed good agreement with the literature data.²⁴

1-Methyl-2-(1-phenyl-2-(trimethylsilyl)ethyl)-1*H*-indole-3-carbaldehyde (4l): The typical procedure was applied to **1** and (*Z*)-1-phenyl-2-(trimethylsilyl)ethylene (**2l**, 64.5 μ L, 0.30 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 20/1) of the crude product afforded the title compound as a yellow oil (44.8 mg, 67%). R_f 0.56 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ -0.19 (9H), 1.47 (dd, J = 14.8, 10.8 Hz, 1H), 1.68 (dd, J = 14.8, 6.0 Hz, 1H), 3.41 (s, 3H), 5.20 (dd, J = 10.8, 6.4 Hz, 1H), 7.14-7.28 (m, 8H), 8.31-8.33 (m, 1H), 10.34 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ -1.5, 20.0, 31.4, 35.5, 109.2, 114.6, 121.3, 123.0, 123.5, 125.7, 126.7, 127.2, 128.6, 137.4, 141.7, 153.1, 184.7; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{26}\text{NOSi}$ [$\text{M} + \text{H}$] $^+$ 336.1779, found 336.1784. The ^1H and ^{13}C NMR spectra showed good agreement with the literature data.²⁴

1-Benzyl-2-(1-phenylethyl)-1*H*-indole-3-carbaldehyde (4a'): The typical procedure was applied to (*E*)-*N*-((1-benzyl-1*H*-indol-3-yl)methylene)-4-methoxyaniline (**1'**, 68.1 mg, 0.20 mmol) and styrene (**2a**, 34.5 μ L, 0.30 mmol). The hydrolysis was performed at 45 $^\circ\text{C}$ for 12 h after the addition of 6M HCl. Silica gel chromatography (eluent: hexane/EtOAc = 5/1) of the crude product afforded the title compound as an orange solid (60.1 mg, 89%). R_f 0.40 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ

1.74 (d, $J = 7.6$ Hz, 3H), 5.05 (q, $J = 7.2$ Hz, 1H), 5.22 (s, 2H), 6.89-6.91 (m, 2H), 7.14 (app. d, $J = 8.4$ Hz, 1H), 7.20-7.33 (m, 10H), 8.42 (d, $J = 8.0$ Hz, 1H), 10.23 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 19.8, 35.0, 47.5, 110.2, 114.8, 121.7, 123.1, 123.7, 125.7, 125.9, 126.9, 127.0, 127.6, 128.76, 128.84, 135.9, 137.0, 141.2, 153.9, 185.3; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{22}\text{NO}$ $[\text{M} + \text{H}]^+$ 340.1696, found 340.1696.

Deuterium-Labeling Experiment

Reaction of C2-Deuterated Indole (1-*d*) with 4-Methoxystyrene (2d): To a mixture of 1-*d* (53.1 mg, 0.20 mmol, 98% D), $\text{Fe}(\text{acac})_3$ (7.1 mg, 0.020 mmol), $\text{SiXyl}\cdot\text{HCl}$ (6.3 mg, 0.020 mmol), 1-methoxy-4-vinylbenzene (2d, 27.0 μL , 0.20 mmol), TMEDA (60 μL , 0.40 mmol) and Et_2O (0.39 mL), an Et_2O solution of CyMgCl (1.74 M, 0.115 mL, 0.20 mmol) was added at room temperature. The resulting mixture was stirred at 60 $^\circ\text{C}$ for 3 min, and immediately cooled in an ice-bath followed by the addition of water (1.0 mL) and Et_2O (0.5 mL). The mixture was stirred at room temperature for 1 h and then the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude product mixture. The yields of recovered starting materials and hydroarylation product were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The crude mixture was then subjected to silica gel chromatography to separate the starting materials and the product, each of which was analyzed by ^1H NMR to determine the distribution of the deuterium atoms.

2.5 References

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48. Note that careful control and monitoring of the acidic hydrolysis were particularly essential for the reaction using vinylarenes **2a–2f**. Otherwise, the yield of the desired product was substantially lower than reported.

Chapter 3. Iron-Catalyzed Imine-Directed C2-Alkenylation of Indole with Internal Alkynes

3.1 Introduction

Alkenyl-substituted heteroaromatic moieties are commonly found in a wide diversity of natural products,¹ biologically active substances,² and organic materials.³ Consequently, effective and reliable approaches for synthesizing alkenyl-substituted heteroarenes are extensively developed by chemists.⁴

Over the past several decades, a variety of methods have been established for transition metal-catalyzed alkenylation of indoles, including oxidative coupling,⁵ decarboxylative alkenylation,⁶ and addition reactions of indole to alkynes, also known as hydroheteroarylation.⁷ These processes have eventually shortened the synthetic routes for the production of alkenyl-substituted indole compounds,⁸ as compared to the classical cross-coupling methods involving organic halides with organometallic reagents.^{9,10,11,12} Additionally, the use of readily available and environmentally benign starting materials could benefit the chemical and pharmaceutical industries.⁸

In the 1970s, Fujiwara and Moritani were the first to have successfully developed intermolecular oxidative couplings of aromatic heterocycles with alkenes by using a stoichiometric amount of palladium(II) acetate.¹³ Later on, Fujiwara and co-workers reported that indole substrate could undergo oxidative coupling with methyl acrylate by using a catalytic amount of palladium(II) acetate, benzoquinone (BQ) and *tert*-butyl hydroperoxide as an oxidant to afford regio- and stereoselective *trans*-C3-alkenylated indole product in moderate yield (Scheme 3.1).¹⁴

Scheme 3.1. Palladium-Catalyzed Oxidative Coupling of Indole with Alkene

In 2005, Gaunt and co-workers have developed a solvent-controlled regioselective intermolecular alkenylation of free N-H indole in the presence of palladium catalyst (Scheme 3.2).¹⁵ The alkenylation of indole with *tert*-butyl acrylate in dioxane-acetic acid, as a protic solvent, gave C2-alkenylated derivative in 57% yield.^{15,16} On the other hand, a C3-alkenylated indole product was afforded in 91% yield when the reaction was performed in a mixture of *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) aprotic solvent. However, oxidative alkenylation of indole is applicable for the synthesis of disubstituted *trans*-alkenylindole compounds in most cases.⁴

Scheme 3.2. Switchable Solvent-Controlled Regioselective Palladium-Catalyzed Alkenylation of Indole

In recent years, transition metal-catalyzed intermolecular hydroheteroarylation of alkynes has received much attention among chemists.¹⁷ The catalytic, highly atom-economical and environmentally benign approach provides facile access to achieve direct synthesis of regio- and stereo-defined trisubstituted alkenylated products, which

complementing the limitation of other conventional alkenylation methods. The reaction mechanism is predominantly depending on the nature of the transition metal catalyst, which may involve oxidative addition, electrophilic/deprotonative metalation or electrophilic activation of an alkyne with a subsequent Friedel-Crafts type process.

Recently, the research group of Nakao and Hiyama has established a wide range of nickel-catalyzed hydroheteroarylation of alkynes under mild reaction conditions to achieve regio-, chemo- and stereoselective alkenyl-substituted heteroarenes.^{18,19,20} In 2006, an addition reaction bearing an electron-withdrawing substituent at the C3-position of *N*-protected indole substrates to internal alkynes has demonstrated by Nakao, Hiyama and co-workers (Scheme 3.3).¹⁸ They have found that a nickel(0)–PCyp₃ catalytic system in toluene at 35 °C could effectively promote the addition reaction to afford the corresponding hydroheteroarylation products in excellent yields (Scheme 3.3a). Moreover, unsymmetrical internal alkynes, such as 1-methyl-2-isopropylacetylene, 1-(trimethylsilyl)propyne and 1-phenyl-2-(trimethylsilyl)acetylene, were also able to achieve the desired *E*-adducts with excellent regioselectivities by having a larger substituent distal to the heteroarene (Scheme 3.3b).

Scheme 3.3. Nickel-Catalyzed Hydroheteroarylation of Alkynes

Furthermore, a catalytic cycle (Scheme 3.4) is proposed to involve an alkyne-coordinating nickel(0) species **A** that subsequently undergoes oxidative addition of an indole C2–H bond to give an indole–Ni(II) intermediate **B**.¹⁸ Insertion of the alkyne into the Ni–H bond in a *syn*-fashion to form a Ni(II)–alkenyl intermediate **C**, which then proceeds reductive elimination to afford *syn*-hydroheteroarylation product along with regeneration of the Ni(0) active species **A**.

Scheme 3.4. Plausible Mechanism for Hydroheteroarylation of Alkynes under Nickel Catalysis

In 2008, Kuninobu and Takai reported that the use of an imine moiety as a directing group could promote activation of an *ortho* C–H bond in a variety of hydroheteroarylation reactions under rhenium catalysis.²¹ The reaction of 3-imino indole derivative with diphenylacetylene in the presence of $[\text{ReBr}(\text{CO})_3(\text{THF})]_2$ catalyst and 1,2-dichloroethane (DCE) as solvent at 135 °C for 24 h, was then followed by hydrolysis of the imino group during column chromatography (Scheme 3.5). The desired regioselective 2-alkenylated indole product bearing a carbonyl group at the C3-position was afforded in 72% isolated yield.

Scheme 3.5. Rhenium-Catalyzed Hydroheteroarylation of Alkyne

A proposed mechanism involves oxidative addition of an indole C2–H bond to the rhenium(I) center, insertion of an alkyne into the rhenium–carbon bond and subsequent reductive elimination to afford the desired hydroheteroarylation product as well as regeneration of the rhenium catalyst (Scheme 3.6).²¹

Scheme 3.6. Proposed Mechanism for Rhenium-Catalyzed Hydroheteroarylation of Alkyne

In 2010, our group has initially developed a ternary catalytic system consisting of a cobalt precatalyst (CoBr_2), a phosphine ligand (PMePh_2) and a reducing agent (MeMgCl), that promoted an addition reaction of 2-phenylpyridine to an unactivated internal alkyne at 100 °C through a *syn*-addition fashion (Scheme 3.7a).²² The cobalt-catalyzed hydroarylation reaction gave the *ortho*-dialkenylated product in high yield. In light of the success on cobalt-catalyzed hydroarylation reactions,²³ our group has expanded the research to indole substrates with the aid of a removable 2-pyrimidyl directing group.²⁴ The directed hydroheteroarylation proceeded in the presence of CoBr_2 precatalyst, 2-[2-(diphenylphosphino)ethyl]pyridine (pyphos) ligand and

neopentylmagnesium bromide ($t\text{-BuCH}_2\text{MgBr}$) at room temperature to effectively afford the desired C2-alkenylated indole product in 96% yield with an exclusive *E*-stereoselectivity (Scheme 3.7b).

Scheme 3.7. Cobalt-Catalyzed Hydroarylation and Hydroheteroarylation of 4-Octyne

Furthermore, the cobalt-catalyzed C2-alkenylation of indole with an internal alkyne (Scheme 3.7b) is most likely to undergo the same mechanistic pathway as the addition reaction of aromatic imines to alkynes, which is also reported by our group.^{23c} A proposed catalytic cycle (Scheme 3.8) is initiated by precoordination of an alkyne to a low-valent cobalt species, which is generated by the reduction of the cobalt(II) precatalyst with the Grignard reagent. Next, oxidative addition of an indole C2–H bond to the cobalt center and then migratory insertion of the alkyne into the Co–H bond. Subsequent reductive elimination affords the desired alkenylated indole product as well as regeneration of the active cobalt species. Based on the reported results of deuterium-labeling experiments and kinetic analysis for cobalt-catalyzed directed

hydroarylation of alkynes, the mechanistic investigation has indicated that oxidative addition is the rate-limiting step for the reaction.

Scheme 3.8. Proposed Catalytic Cycle for Cobalt-Catalyzed Addition of *N*-Pyrimidylindole to Alkyne *via* Directed C–H Bond Activation

Upon extension of the scope of cobalt catalysis, our group has also reported on a C2-alkenylation of indole with diphenylacetylene, which was promoted by a cobalt precatalyst, a triarylphosphine ligand and isopropylmagnesium bromide (Scheme 3.9).²⁵ The reaction proceeded under mild reaction conditions and subsequent acidic hydrolysis to afford the corresponding product in 82% yield with an extensive *E/Z* isomerization.

Scheme 3.9. Cobalt-Catalyzed C2-Alkenylation of Indole *via* Directed C–H Bond Activation

As described in Chapter 2, we have developed an iron–*N*-heterocyclic carbene–Grignard catalytic system that could effectively promote C2-alkylation of indole with vinylarenes *via* directed C–H bond activation (Scheme 3.10). With the previous reported examples on transition metal-catalyzed hydroheteroarylation of alkynes by our group and others, these studies have prompted us to explore the feasibility of an addition reaction of indole to alkynes under our newly established iron catalytic system.

Scheme 3.10. Iron-Catalyzed Directed C2-Alkylation of Indole with Vinylarenes

In this chapter, we report that an iron–*N*-heterocyclic carbene catalyst could promote imine-directed C2-alkenylation of indole with internal alkynes *via* C–H bond

activation (Scheme 3.11).²⁶ The present directed hydroheteroarylation of alkynes is proposed to undergo three main catalytic steps, which are oxidative addition, migratory insertion and reductive elimination steps.

Scheme 3.11. Iron-Catalyzed Imine-Directed C2-Alkenylation of Indole with Internal Alkynes

3.2 Results and Discussion

Our present study began with the screening of reaction conditions for iron-catalyzed imine-directed alkenylation of indole. An addition reaction of indole **1** to diphenylacetylene **2a** (1.2 equiv) was performed in THF at 60 °C for 6 h in the presence of an iron catalytic system consisting of Fe(acac)₃ (10 mol %), 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (SIMes•HCl, 10 mol %) and cyclohexylmagnesium bromide (CyMgBr, 100 mol %). After acidic hydrolysis, we have found that the reaction gave the desired C2-alkenylated indole product bearing a C3-formyl group **3a** in 21% yield (Table 3.1, entry 1).

Moreover, the use of isopropylmagnesium bromide (*i*-PrMgBr) as a reducing agent, which was reported to undergo cobalt-catalyzed *ortho*-alkenylation of aromatic aldimines,²⁵ resulted in a similar yield (28%) as compared to the reaction involving cyclohexylmagnesium bromide (Table 3.1, entries 1 and 2). In addition to the alkyl Grignard reagents, we have found that phenylmagnesium bromide (PhMgBr) showed better catalytic activity and gave the desired product in 42% yield (Table 3.1, entry 3). However, the use of neopentylmagnesium bromide (*t*-BuCH₂MgBr), which proved to be effective for cobalt-catalyzed C2-alkenylation of indoles with alkynes,²⁴ was unfortunately not able to promote in our present iron-catalyzed hydroheteroarylation reaction (Table 3.1, entry 4). Thus, only trace amount of product was achieved.

Next, the use of 1,3-bis(2,6-dimethylphenyl)imidazolinium chloride (SIXyl•HCl) ligand in place of SIMes•HCl ligand showed comparable catalytic performance in the presence of CyMgBr (Table 3.1, entries 1 and 5), albeit in low yield (20%). On the contrary, a sterically more demanding saturated *N*-heterocyclic carbene (NHC) ligand, for example 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr•HCl), inhibited the hydroheteroarylation reaction (Table 3.1, entry 6).

As a result, only trace amount of product was detected by gas chromatography (GC) analysis.

Table 3.1. Screening of Reaction Conditions^a

entry	x	ligand	RMgX	additive	solvent	time (h)	yield (%) ^b
1	1.2	SIMes•HCl	CyMgBr	–	THF	6	21
2	1.2	SIMes•HCl	<i>i</i> -PrMgBr	–	THF	6	28
3	1.2	SIMes•HCl	PhMgBr	–	THF	6	42
4	1.2	SIMes•HCl	<i>t</i> -BuCH ₂ MgBr	–	THF	6	9
5	1.2	SIXyl•HCl	CyMgBr	–	THF	6	20
6	1.2	SIPr•HCl	CyMgBr	–	THF	6	2
7 ^c	1.2	SIXyl•HCl	CyMgBr	TMEDA	Et ₂ O	6	4
8	2	SIMes•HCl	PhMgBr	–	THF	18	59
9	2	SIXyl•HCl	PhMgBr	–	THF	18	61
10 ^d	2	SIXyl•HCl	PhMgBr	–	THF	18	84 (<i>E/Z</i> = 94:6) ^e

^aThe reaction was performed on a 0.2 mmol scale at a 0.4 M concentration. PMP = *p*-methoxyphenyl. ^bDetermined by GC using *n*-tridecane as an internal standard. ^cTMEDA (2 equiv) was used. ^dSIXyl•HCl (20 mol %) and PhMgBr (110 mol %) were used. ^eIsolated yield. The *E/Z* ratio was determined by ¹H NMR.

With the success of our previously developed iron-catalyzed imine-directed hydroheteroarylation of vinylarenes,²⁶ it was natural for us to examine and apply the reaction conditions to the present alkenylation reaction. The reaction of **1** with **2a** was

carried out in Et₂O at 60 °C for 6 h in the presence of Fe(acac)₃ precatalyst, SIXyl•HCl ligand, CyMgBr and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as an additive (Table 3.1, entry 7). Unfortunately, we have found that the catalytic system was ineffective in our present alkenylation reaction.

Further screening of reaction conditions was performed by using PhMgBr since the reducing agent exhibited a better catalytic performance than alkyl Grignard reagents (Table 3.1, entries 1 – 4). Next, increasing the amount of diphenylacetylene (from 1.2 equiv to 2 equiv) and extending the reaction time (from 6 h to 18 h) in the presence of SIMes•HCl ligand, have further improved the reaction to give the desired product in 59% yield (Table 3.1, entry 8).

Similarly, the reaction has improved to 61% yield when SIXyl•HCl ligand was used under the modified reaction conditions (Table 3.1, entry 9). The use of SIXyl•HCl ligand showed slightly better reactivity in comparison to the case of SIMes•HCl ligand (Table 3.1, entries 8 and 9). Thus, the SIXyl•HCl ligand was used in further optimization of the reaction conditions. To our delight, increasing the ligand loading of SIXyl•HCl to 20 mol % as well as increasing the amount of PhMgBr to 110 mol % (in order to deprotonate the additional amount of NHC ligand) could effectively promote the reaction to afford the desired hydroheteroarylation product **3a** in 84% isolated yield with high *syn*-stereoselectivity (Table 3.1, entry 10).

With the optimized reaction conditions (Table 3.1, entry 10) in hand, we next explored the scope of internal alkynes under the iron–NHC catalysis (Scheme 3.12). The reaction of indole **1** with a symmetrical alkyne bearing an electron-donating methoxy-substituent at the *para*-position on each aromatic ring **2b** was proceeded smoothly to give the desired alkenylated product **3b** in good yield (83%) with high *syn*-stereoselectivity. On the contrary, an internal alkyne in the presence of electron-

withdrawing fluoro-substituents **2c** was performed rather sluggishly. Hence, the reaction afforded the product **3c** in low yield (25%), however high stereoselectivity was achieved. In addition, the symmetrical di(*o*-tolyl)acetylene **2d** could also participate in the reaction to afford the hydroheteroarylation product **3d** in 40% yield with a modest *E/Z* ratio (about 3:2 stereoselectivity).

Scheme 3.12. Imine-Directed C2-Alkenylation of Indole with Internal Alkynes^a

^aThe reaction was performed on a 0.2 mmol scale. The yields are referred to the isolated products. The *E/Z* ratio of each product was determined by ¹H NMR and shown in parentheses.

Furthermore, an unsymmetrical diarylacetylene bearing phenyl and mesityl groups **2e** proceeded regioselectively at the less hindered acetylenic carbon position that was proximal to the phenyl substituent. Hence, the formation of corresponding alkenylated product **3e** was achieved in 70% yield with an exclusive *E*-stereoselectivity. The regio- and stereochemistry of **3e** was unambiguously confirmed by single crystal X-ray diffraction analysis (See the Experimental Section).

Additionally, the carbon–carbon bond-forming reaction of unsymmetrical silyl-substituted alkynes proceeded regioselectively at the position distal to the silyl substituents. The reaction of **1** with dimethylphenyl(phenylethynyl)silane **2f** was performed smoothly to give the desired product **3f** in 79% yield with a moderate stereoselectivity, while the reaction of **1** with 1-(trimethylsilyl)-1-propyne **2g** was able to form the regio- and stereoselective alkenylated product **3g** in moderate yield (59%).

Moreover, an addition reaction of **1** to 4-octyne **2h** in the presence of the iron–NHC catalyst could also participate in the directed hydroheteroarylation reaction. However, the reaction was performed sluggishly and gave the corresponding alkenylated product **3h** in low yield (18%) with a moderate stereoselectivity. Under our present reaction conditions, the hydroheteroarylation of terminal alkynes, such as phenylacetylene and 1-octyne, were not successful when these were employed as the reaction partner.

To gain mechanistic insights into the present iron-catalyzed imine-directed hydroheteroarylation of internal alkynes, a deuterium-labeling experiment was performed. The reaction of C2-deuterated indole substrate **1-d** with 1-(trimethylsilyl)-1-propyne **2g** under the iron–NHC catalysis and subsequent acidic hydrolysis could afford the product **3g-d** in 29% yield (Scheme 3.13). The ¹H NMR spectroscopic analysis revealed that there was a virtually complete transfer of the C2-deuterium atom

to the vinylic position on the alkenylated product **3g-d**. The yield of deuterated product **3g-d** was much lower (29%) compared with the yield of **3g** (59%) that was obtained from the parent substrate.

Scheme 3.13. Deuterium-Labeling Experiment^a

^aThe proton content was determined by ^1H NMR spectroscopy.

As mentioned in Chapter 2, we have speculated that our present hydroheteroarylation is initiated by the generation of a low-valent iron–NHC complex from the reduction of the iron(III) precatalyst by the Grignard reagent in the presence of the imidazolium salt.²⁶ A proposed catalytic cycle involves chelation-assisted oxidative addition of the indole C2–H bond to the low-valent iron center, migratory insertion of an internal alkyne into the Fe–H bond and subsequent reductive elimination to form the desired product as well as regeneration of the iron active species (Scheme 3.14). Based on the mechanistic investigation with the aid of deuterium-labeling experiment, the poorer reactivity of **1-d** with **2g** suggested that C–H oxidative addition is the rate-limiting step in our present directed alkyne hydroheteroarylation reaction. For reactions that involved an unsymmetrical alkyne, the regioselectivity is rationalized by the size of the substituent in order to prevent steric repulsion with the iron center during the alkyne migratory insertion step.

Scheme 3.14. Proposed Catalytic Cycle for Iron-Catalyzed Imine-Directed C2-Alkenylation of Indole with Internal Alkynes

3.3 Conclusion

In conclusion, we have developed an iron catalyst, that generated from Fe(acac)₃ precatalyst, SIXyl•HCl ligand and PhMgBr as a reducing agent, to promote directed C2-alkenylation of indole with various internal alkynes under mild reaction conditions. The reaction afforded trisubstituted alkenylation indole products in moderate to good yields with excellent regioselectivity and high *syn*-stereoselectivity.

3.4 Experimental Section

General. All reactions dealing with air- or moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash chromatography was performed using 40–63 μm (Silica 60 M, Macherey-Nagel) silica gel. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECA-400 (400 MHz) NMR spectrometer. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and CHCl_3 (77.0 ppm), respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column, DB-5 (Agilent J&W, 0.2 mm i.d. x 30m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-ToF Premier LC-HR mass spectrometer. Melting points of solid materials were determined on an Optimelt Automated Melting Point System apparatus and were uncorrected.

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Anhydrous iron(III) acetylacetonate was purchased from Strem Chemicals (99%). Et_2O and THF were distilled over Na/benzophenone. TMEDA was distilled over CaH_2 . Grignard reagents were prepared from the corresponding halides and magnesium turnings in anhydrous Et_2O or THF, and titrated before use. The indole substrates (*E*)-4-methoxy-*N*-((1-methyl-1*H*-indol-3-yl)methylene)aniline (**1**) and (*E*)-1-(2-deuterio-1-methyl-1*H*-indol-3-yl)-*N*-(4-methoxyphenyl)methanimine (**1-*d***) were synthesized as described before.²⁷ Among alkynes, 1,2-bis(4-methoxyphenyl)ethyne

(**2b**),²⁸ 1,2-bis(4-fluorophenyl)ethyne (**2c**),²⁹ 1,2-di-*o*-tolylethyne (**2d**),²⁸ 2,4,6-trimethylphenylethynylbenzene (**2e**),³⁰ and dimethylphenyl(phenylethynyl)silane (**2f**)³¹ were prepared according to the literature procedures. Bis(2,6-dimethylphenylimidazolium) chloride (SIXyl•HCl) was prepared according to the literature procedures.³²

Iron-Catalyzed Imine-Directed Alkenylation of Indole with Alkynes

Typical Procedure: In a Schlenk tube were placed the indole substrate **1** (52.9 mg, 0.20 mmol), Fe(acac)₃ (7.1 mg, 0.020 mmol), SIXyl•HCl (12.6 mg, 0.040 mmol), alkyne **2** (0.40 mmol), and THF (0.21 mL). To the mixture was added a THF solution of PhMgBr (0.76 M, 0.29 mL, 0.22 mmol) at room temperature. After stirring for 5 min, the resulting mixture was heated to 60 °C and stirred for 18 h. The reaction mixture was allowed to room temperature, diluted with THF (1.0 mL), and quenched with water (0.5 mL) and 1M HCl (0.5 mL). The mixture was stirred at room temperature for 1 h and then the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford the alkenylation product.

(E)-2-(1,2-Diphenylvinyl)-1-methyl-1H-indole-3-carbaldehyde (3a): The typical procedure was applied to **1** and diphenylacetylene (**2a**, 71.3 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title

compound as an orange oil (57.0 mg, 84%), consisting of a 94:6 mixture of *E/Z* isomers as determined by ^1H NMR analysis. The *E/Z* ratio was based on the ratio from the integration of the aldehyde peak of the major and minor isomers, respectively, which then normalized the ratio to a total of 100. The *E*-stereochemistry of the major isomers of this and other reactions was assumed on the basis of the *E*-stereochemistry of **3g**, which was confirmed by NOESY analysis. R_f 0.46 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3 , *E*-isomer): δ 3.46 (s, 3H), 6.93-6.96 (m, 2H), 7.10-7.16 (m, 3H), 7.31-7.35 (m, 5H), 7.36-7.38 (m, 3H), 7.53 (s, 1H), 8.38-8.42 (m, 1H), 9.78 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3 , *E*-isomer): δ 30.4, 109.9, 115.0, 122.5, 123.2, 123.8, 125.4, 126.3, 128.5, 128.5, 128.5, 128.8, 128.9, 129.7, 135.2, 135.4, 137.6, 140.4, 149.1, 185.9; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{20}\text{NO}$ $[\text{M} + \text{H}]^+$ 338.1540, found 338.1547.

(*E*)-2-(1,2-Bis(4-methoxyphenyl)vinyl)-1-methyl-1*H*-indole-3-carbaldehyde (3b):

The typical procedure was applied to **1** and 1,2-bis(4-methoxyphenyl)ethyne (**2b**, 95.3 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a brown oil (66.1 mg, 83%), consisting of a 96:4 mixture of *E/Z* isomers as determined by ^1H NMR analysis. R_f 0.29 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3 , *E*-isomer): δ 3.46 (s, 3H), 3.68 (s, 3H), 3.78 (s, 3H), 6.63 (app. d, J = 8.8 Hz, 2H), 6.84 (dd, J = 9.0, 1.8, Hz, 4H), 7.22 (app. d, J = 8.8 Hz, 2H), 7.34-7.37 (m, 4H), 8.38-8.42 (m, 1H), 9.78 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3 , *E*-isomer): δ 30.3, 55.1, 55.3, 109.9, 114.2, 114.3, 114.8, 122.4,

123.1, 123.7, 125.4, 125.6, 127.3, 128.3, 130.1, 132.8, 133.3, 137.6, 149.9, 159.4, 159.6, 186.1; HRMS (ESI) Calcd for $C_{26}H_{24}NO_3$ $[M + H]^+$ 398.1751, found 398.1765.

(*E*)-2-(1,2-Bis(4-methoxyphenyl)vinyl)-1-methyl-1*H*-indole-3-carbaldehyde (3c):

The typical procedure was applied to **1** and 1,2-bis-(4-fluorophenyl)ethyne (**2c**, 85.7 mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange solid (18.7 mg, 25%), consisting of a 95:5 mixture of *E/Z* isomers as determined by 1H NMR analysis. m.p. 192.1–194.1 °C; R_f 0.51 (hexane/EtOAc = 3/1); 1H NMR (400 MHz, $CDCl_3$, *E*-isomer): δ 3.47 (s, 3H), 6.84 (app. t, J = 8.6 Hz, 2H), 6.92 (dd, J = 8.8, 5.6 Hz, 2H), 7.04 (app. t, J = 8.4 Hz, 2H), 7.30 (dd, J = 8.4, 5.2 Hz, 2H), 7.37–7.40 (m, 3H), 7.43 (s, 1H), 8.38–8.40 (m, 1H), 9.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, *E*-isomer): δ 30.4, 110.0, 115.0, 116.1 (d, $^2J_{C-F}$ = 22 Hz), 116.1 (d, $^2J_{C-F}$ = 22 Hz), 122.5, 123.5, 124.1, 125.3, 127.4, 128.0 (d, $^3J_{C-F}$ = 8 Hz), 130.6 (d, $^3J_{C-F}$ = 8 Hz), 131.6 (d, $^4J_{C-F}$ = 4 Hz), 133.7, 136.5 (d, $^4J_{C-F}$ = 4 Hz), 137.6, 148.2, 163.6 (d, $^1J_{C-F}$ = 249 Hz), 164.1 (d, $^1J_{C-F}$ = 249 Hz), 185.6; HRMS (ESI) Calcd for $C_{24}H_{18}NOF_2$ $[M + H]^+$ 374.1351, found 374.1356.

(E)-2-(1,2-Di-*o*-tolylvinyl)-1-methyl-1*H*-indole-3-carbaldehyde (3d): The typical procedure was applied to **1** and di-*o*-tolylethyne (**2d**, 73.0 μ L, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a brown oil (30.0 mg, 40%), consisting of a 57:43 mixture of *E/Z* isomers as determined by ^1H NMR analysis. R_f 0.57 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3 , *E*-isomer): δ 2.16 (s, 3H), 2.40 (s, 3H), 3.31 (s, 3H), 6.67 (d, J = 8.0 Hz, 1H), 6.78-6.90 (m, 2H), 7.03-7.36 (m, 9H), 8.31-8.33 (m, 1H), 9.76 (s, 1H); ^1H NMR (400 MHz, CDCl_3 , *Z*-isomer): δ 1.93 (s, 3H), 2.35 (s, 3H), 3.36 (s, 3H), 6.78-6.90 (m, 1H), 7.03-7.36 (m, 11H), 8.47-8.50 (m, 1H), 10.13 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3 , *E*- and *Z*-isomers): δ 19.9, 20.1, 20.2, 20.6, 30.6, 30.9, 109.2, 109.4, 109.7, 115.3, 117.1, 122.2, 122.4, 123.1, 123.2, 123.8, 124.2, 125.4, 125.4, 125.6, 125.7, 126.2, 126.4, 126.5, 128.1, 128.3, 128.4, 128.9, 129.1, 129.9, 130.1, 130.3, 130.4, 130.9, 131.1, 131.5, 135.0, 135.0, 135.8, 136.2, 136.7, 136.9, 137.0, 137.4, 137.4, 137.7, 138.6, 141.4, 149.3, 153.2, 186.0, 186.9; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{24}\text{NO}$ $[\text{M} + \text{H}]^+$ 366.1853, found 366.1858.

(E)-2-(2-Mesityl-1-phenylvinyl)-1-methyl-1*H*-indole-3-carbaldehyde (3e): The typical procedure was applied to **1** and 2,4,6-trimethylphenylethynylbenzene (**2e**, 88.1

mg, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange solid (53.2 mg, 70%), consisting of a >99:1 mixture of *E/Z* isomers as determined by ^1H NMR analysis. Recrystallization from hexane/EtOAc (10:1) afforded single crystals suitable for X-ray diffraction analysis, which unambiguously confirmed the regio- and stereochemistry of **3e** (see Figure S1).³³ m.p. 198.3–199.9 °C; R_f 0.68 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3): δ 2.13 (s, 6H), 2.29 (s, 3H), 3.44 (s, 3H), 6.85 (s, 2H), 6.91–6.94 (m, 2H), 6.96 (s, 1H), 7.11–7.20 (m, 3H), 7.31–7.37 (m, 3H), 8.48–8.51 (m, 1H), 10.25 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 20.5, 21.0, 30.9, 109.5, 117.2, 122.2, 123.1, 124.1, 125.2, 128.1, 128.3, 128.6, 128.7, 130.9, 131.7, 137.0, 137.2, 137.5, 137.8, 152.9, 186.2, 186.2; HRMS (ESI) Calcd for $\text{C}_{27}\text{H}_{26}\text{NO}$ $[\text{M} + \text{H}]^+$ 380.2009, found 380.2014.

Figure S1. Molecular structure of **3e**

(E)-2-(2-(Dimethyl(phenyl)silyl)-1-phenylvinyl)-1-methyl-1H-indole-3-

carbaldehyde (3f): The typical procedure was applied to **1** and dimethylphenyl(phenylethynyl)silane (**2f**, 93 μ L, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as a brown oil (62.5 mg, 79%), consisting of a 76:24 mixture of *E/Z* isomers as determined by ^1H NMR analysis. R_f 0.65 (hexane/EtOAc = 3/1); ^1H NMR (400 MHz, CDCl_3 , *E*-isomer): δ 0.28 (s, 6H), 3.37 (s, 3H), 6.44 (s, 1H), 7.04-7.36 (m, 11H), 7.50-7.52 (m, 2H), 8.39-8.45 (m, 1H), 10.02 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3 , *E*-isomer): δ -1.3, 30.9, 109.5, 116.2, 122.2, 123.1, 124.1, 125.1, 128.0, 128.3, 128.8 (two signals are overlapped), 129.2, 133.3, 133.5, 138.5, 139.7, 141.4, 146.0, 154.1, 186.5; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{26}\text{NOSi}$ $[\text{M} + \text{H}]^+$ 396.1779, found 396.1787.

(E)-1-Methyl-2-(1-(trimethylsilyl)prop-1-en-2-yl)-1H-indole-3-carbaldehyde (3g):

The typical procedure was applied to **1** and 1-(trimethylsilyl)-1-propyne (**2g**, 59.5 μ L, 0.40 mmol) was subjected to the typical reaction procedure. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange solid (32.0 mg, 59%), consisting of a >99:1 mixture of *E/Z* isomers as determined by ^1H NMR analysis. m.p. 90.0–91.7 $^{\circ}\text{C}$; R_f 0.61 (hexane/EtOAc = 3/1); ^1H

NMR (400 MHz, CDCl₃): δ 0.27 (s, 9H), 2.21 (s, 3H), 3.68 (s, 3H), 5.91 (s, 1H), 7.28-7.33 (m, 3H), 8.33-8.36 (m, 1H), 9.89 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ -0.4, 23.1, 30.6, 109.5, 113.5, 122.1, 123.0, 123.7, 125.1, 136.8, 140.6, 140.7, 156.8, 185.9; HRMS (ESI) Calcd for C₁₆H₂₂NOSi [M + H]⁺ 272.1466, found 272.1470.

(*E*)-1-Methyl-2-(oct-4-en-4-yl)-1*H*-indole-3-carbaldehyde (3h): The typical procedure was applied to **1** and 4-octyne (**2h**, 59 μ L, 0.40 mmol). Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded the title compound as an orange solid (9.7 mg, 18%), consisting of a 3:1 mixture of *E/Z* isomers as determined by ¹H NMR analysis. *R_f* 0.64 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃, *E*-isomer): δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H), 1.32-1.38 (m, 2H), 1.53 (sext, *J* = 7.4 Hz, 2H), 2.31 (q, *J* = 7.6 Hz, 2H), 2.42 (br s, 2H), 3.67 (s, 3H), 5.75 (t, *J* = 7.6 Hz, 1H), 7.28-7.38 (m, 3H), 8.35-8.38 (m, 1H), 9.88 (s, 1H); ¹³C NMR (100 MHz, CDCl₃, *E*-isomer): δ 13.9, 14.1, 21.5, 22.6, 30.4, 30.7, 33.7, 109.4, 115.6, 122.0, 122.9, 123.6, 125.2, 128.8, 137.0, 139.3, 154.8, 186.4; HRMS (ESI) Calcd for C₁₈H₂₄NO [M + H]⁺ 270.1853, found 270.1858.

Deuterium-Labeling Experiment

Reaction of C2-Deuterated Indole (1-*d*) with 1-Trimethylsilylprop-1-yne (2g): 1-*d* (53.1 mg, 0.20 mmol, 98% D) and 1-trimethylsilyl-1-propyne (**2g**, 59.5 μ L, 0.40 mmol) were subjected to the typical conditions for the alkenylation reaction. Silica gel chromatography (eluent: hexane/EtOAc = 10/1) of the crude product afforded (*E*)-2-

(1-deuterio-1-(trimethylsilyl)prop-1-en-2-yl)-1-methyl-1*H*-indole-3-carbaldehyde (**3g-d**) as a brown solid (15.8 mg, 29%), consisting of a >99:1 mixture of *E/Z* isomers as determined by ¹H NMR analysis. m.p. 88.4–89.6 °C; *R_f* 0.53 (hexane/EtOAc = 3/1); ¹H NMR (400 MHz, CDCl₃): δ 0.27 (s, 9H), 2.21 (s, 3H), 3.69 (s, 3H), 7.28-7.34 (m, 3H), 8.33-8.36 (m, 1H), 9.89 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ -0.4, 23.0, 30.6, 109.5, 113.6, 122.1, 123.0, 123.7, 125.1, 136.8, 140.6, 156.7, 185.9 (the signal of deuterium-bonded carbon appeared as a small bump near the 140.6 ppm signal); HRMS (ESI) Calcd for C₁₆H₂₁DNOSi [M + H]⁺ 273.1528, found 273.1530. The ¹H NMR analysis indicated >97% deuterium incorporation into the olefinic position.

3.5 References

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Chapter 4. Conclusion

In summary, we have successfully developed an Fe–SIXyl catalyst in combination with cyclohexylmagnesium chloride (CyMgCl) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) that can effectively promote C2-alkylation of 1-methyl-3-iminomethylindole with a variety of vinylarenes, such as substituted styrene and β -substituted styrene derivatives. The imine-directed reaction proceeded at a mild temperature of 60 °C and the subsequent acidic hydrolysis afforded 1,1-diarylalkane derivatives in good yields with exclusive regioselectivity.

Furthermore, an addition reaction of the indole substrate to allylbenzene could take place under the standard reaction conditions to afford 1,1-diarylpropane derivative, albeit in low yield. The reaction presumably proceeded through an alkene isomerization–hydroheteroarylation sequence.

In addition, we have also demonstrated the imine-directed C2-alkenylation of indole with internal alkynes in the presence of Fe(acac)₃ precatalyst, SIXyl•HCl and phenylmagnesium bromide (PhMgBr) under mild reaction conditions. After acidic hydrolysis, the corresponding trisubstituted alkenylation indole products were afforded in moderate to good yields with high stereoselectivity.

Moreover, the deuterium-labeling experiments suggested that these reactions involved oxidative addition of the indole C2–H bond to iron center, migratory insertion of an alkene or alkyne into the Fe–H bond and subsequent carbon–carbon reductive elimination to afford the corresponding hydroheteroarylation product.

To the best of our knowledge, this represents the first example of iron-catalyzed hydroheteroarylation reactions involving directed C–H bond activation. The newly developed economically attractive iron-catalyzed carbon–carbon bond-forming

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reactions through activation of unreactive C–H bonds could be synthetically useful in chemical and pharmaceutical industries.