Summer 7-10-2018

Catalytic Functionalization of Organoaluminum Reagents and Olefins by Cross-Coupling with Copper and Nickel

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M.S., Organic Chemistry, Tribhuvan University, 2008

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of

Doctor of Philosophy
Chemistry

The University of New Mexico
Albuquerque, New Mexico

July, 2018

ACKNOWLEDGEMENTS

First and foremost, I would like to express my sincere gratitude to my advisor Professor Ramesh Giri for his continuous encouragement, guidance and support through my Ph. D. study. It is my fortune to explore the beauty of chemistry under his direction. I benefit a lot from his guidance not only for the current, but also for my future life and career.

Also, I am very grateful to all my committee members, Professor Richard Kemp, Professor Wei Wang, Professor Jeffrey J. Rack and Dr. Timothy J. Boyle for their precious time and insightful comments.

I would like to offer my regards to all the current and previous members in Dr. Giri's group, especially Dr. Santosh Kumar Gurung, Surendra Thapa, Prakash Basnet, Shekhar KC, Roshan Kumar Dhungana, Namrata Khanal, Robert Leburn and Ryan Pike for their help in my research. I am especially grateful to Brad Watson for his relentless help in proofreading with very constructive suggestion.

Last but not the least, I would like to thank my family: my parents, my wife Roshni Shrestha and my daughter Kyra Shrestha. Without their unconditional support and love, it would be hard for me to go through the whole Ph. D. study.

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Abstract

This thesis is divided into two parts. The first part focuses on the Cu-catalyzed cross-coupling of organoaluminum reagents with organohalides. One of the most powerful tools for the construction of C-C bonds is cross-coupling. But, this reaction is predominantly catalyzed by Pd, a rare and expensive transition metal, which inevitably makes the process unsustainable in the long-term. Furthermore, Pd-catalyzed cross-coupling also shows low tolerance for alkyl and heteroaryl substrates because of β-hydride elimination and catalyst deactivation, respectively. Although these issues remain largely solved by using sterically hindered and electron-rich ligands, however making these types of ligands is synthetically challenging and often involves multi-step processes. As such, the use of these ligands in large scale productions is also cost-prohibitive. In order to alleviate these problems, we have developed the cross-coupling reaction with Cu, an earth-abundant and inexpensive transition metal. Regarding this, we have been able to discover

the Cu-catalyzed coupling of alkyl-, aryl- and alkynylaluminum reagents with organohalides. This Cu-catalyzed cross-coupling does not suffer from β-hydride elimination and no rearrangement is seen when secondary alkylaluminum reagents are used. It also shows tolerance with heteroaromatic substrates. Unexpectedly, no ligand is needed when heteroaryl halides are used for cross-coupling. We have also conducted mechanistic studies through radical clock experiments, competition experiments and kinetic studies, and proposed a catalytic cycle for the Cu-catalyzed coupling of organoaluminum reagents with aryl halides. These mechanistic studies designate that the reaction proceeds through an oxidative addition-reductive elimination pathway.

The second part of this thesis is about the development of Ni-catalyzed regioselective dicarbofunctionalization of olefins in styrene derivatives by intercepting Heck C(sp3)-NiX intermediates with arylzinc reagents. This method utilizes a readily removable imine as a coordinating group that plays a dual role of intercepting oxidative addition species derived from aryl halides and triflates to promote Heck carbometallation, and stabilizing the Heck C(sp3)-NiX intermediates as transient metallacycles to suppress β-hydride elimination and facilitate transmetalation/reductive elimination steps. This approach affords diversely-substituted 1,1,2-triarylethyl products that occur as structural motifs in various natural products and bioactive molecules like cassigarol B, 4-[1-(p-hydroxyphenyl)-2-phenylethyl]phenoxyacetic acid, etc.

Table of Contents

List of Schemes

Chapter 1

Chapter 2

Chapter 3

Chapter 4

List of Tables

Chapter 2

Chapter 4

Chapter 5

List of Figures

Chapter 1

Chapter 2

Chapter 5

List of Abbreviations

Å	angstrom
APPI	atmospheric pressure photoionization
aq.	aqueous
cat.	catalyst
$CDCl_3$	deuterated chloroform
CG	coordinating group
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CMOS	complementary metal–oxide–semiconductor
COSY	COrelated SpectroscopY
d	doublet
dd	doublet of doublet
DCE	1,2-dichloroethane
δ	chemical shift
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplet
ESI	electrospray ionization
EtOAc	ethyl acetate
equiv	equivalent
g	gram(s)
GC	gas chromatography

GC-MS	gas chromatography-mass spectrometry
h	hour(s)
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	hertz
J	coupling constants
L	liter
λ	wavelength
m	multiplet
m	meta
M	molar
MeCN	acetonitrile
mg	milligram(s)
MHz	megahertz
min	minute(s)
μL	microliter
mL	milliter
mm	millimiter
mmol	millimole
Mol	mole
mp	melting point
N	normal
NHC	N-heterocyclic carbene
$Ni(cod)_2$	bis(1,5-Cyclooctadiene)nickel(0)
NMR	nuclear magnetic resonance

NMP	1-methyl-2-pyrrolidinone
NN-1	1,10-phenanthroline
NN-2	N^1,N^1,N^2,N^2-tetramethylbenzene-1,2-diamine
NN-3	1,2-di(pyrrolidin-1-yl)cyclohexane
NN-4	N^1,N^2-dimethylcyclohexane-1,2-diamine
NO-1	quinolin-8-ol
o	ortho
OO-1	2,2,6,6-tetramethylheptane-3,5-dione
OTf	trifluoromethanesulfonate
p	para
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium(0)
PN-1	2-(diphenylphosphaneyl)-N,N-dimethylaniline
PN-2	2-(di-tert-butylphosphaneyl)-N,N-dimethylaniline
PN-3	1-(2-(diphenylphosphaneyl)phenyl)piperidine
PN-4	4-(2-(diphenylphosphaneyl)phenyl)morpholine
PN-5	8-(diphenylphosphaneyl)quinoline
PN-6	2-(diphenylphosphaneyl)pyridine
PN-7	9-(2-(dicyclohexylphosphaneyl)phenyl)-9H-carbazole
PN-8	2'-(dicyclohexylphosphaneyl)-N,N-dimethyl-[1,1'-biphenyl]-2-amine
PN-9	1-(diphenylphosphaneyl)-1,3,4,6,7,8-hexahydro-2H-pyrimido[1,2-a]pyrimidine
PP-1	1,2-bis(diphenylphosphaneyl)benzene

ppm	parts per millions
R_f	retention factor
rt	room temperature
s	singlet
SCE	saturated calomel electrode
SET	single electron transfer
SIMes HCl	1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TM	transition metal
V	volt

Chapter 1: Transition Metal Catalyzed Cross-Coupling Reactions

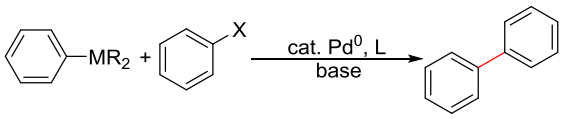
1.1. Background

"*Organic synthesis is considered, to a large extent, to be responsible for some of the most exciting and important discoveries of the twentieth century in chemistry, biology and medicine and continues to fuel the drug discovery and development processes with myriad processes and compounds for new medical breakthroughs and applications.*'' These words from K. C. Nicolaou[1] shows the significance of synthetic organic chemistry over the last two centuries since Wöhler's synthesis of urea in 1828 AD. There are lots of issues organic chemists are facing in the twenty-first century: responding to an ever-growing demand for new, efficient and environmentally friendly methods to perform chemical transformations.[2] Among these transformations, the selective carbon-carbon bond formation is certainly of great significance because it acts as a unique tool for the construction of complex molecules.

Cross-coupling is one of the main synthetic methods for the formation of C-C bond, which involves the coupling of organometallic reagents with organic halides or related electrophiles in presence of transition metal catalyst. In this transformation, generally catalyzed by Pd, a wide variety of organometallic reagents, such as those of Zn (Negishi), B (Suzuki-Miyaura), Mg (Kumada), Si (Hiyama) and Sn (Stille), are utilized as coupling partners along with organohalides (Scheme 1.1).[3] As such, this Nobel Prize-winning (2010) reaction remains one of the most versatile transformations in organic synthesis. The versatility of cross-coupling is nicely summarized recently by Roughley and co-worker in

the pursuit of drug candidates, who reported that about 62% of the total C-C bond forming processes involved cross-coupling.[4]

Scheme 1.1. Various types of cross-coupling

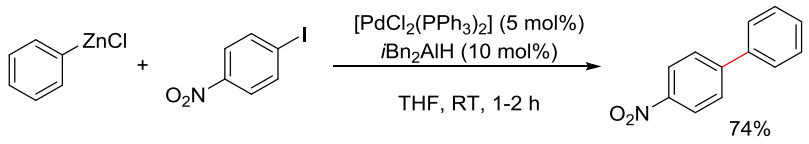


M = B, Zn, Si, Mg, Al, etc
R = alkyl, OR, F_3K etc; X = halide, OTf, etc
Coupling: aryl-aryl, alkyl-aryl, alkyl-alkyl, aryl-vinyl, etc

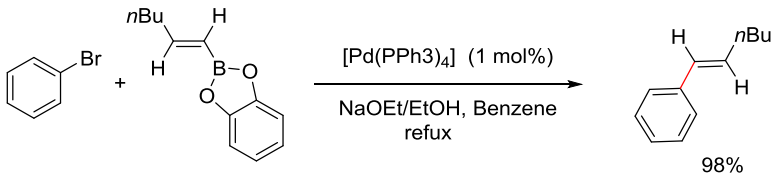
Negishi reported the first Ni-catalyzed cross-coupling of organoaluminum reagents with aryl halides in 1976 to form arylated alkenes.[5] Later, Pd was used which helped to increase the stereospecificity. Subsequently, Negishi[6] (Scheme 1.2) and Fauvarque and Jutand[7] used the organozinc to carried out the cross-coupling. In 1979, Suzuki reported the first example of Pd-catalyzed cross-coupling between 1-alkenylboranes and aryl halides (Scheme 1.3).[8] The beauty of this Suzuki-Miyaura coupling was this reaction uses the air and moisture sensitive organoboron reagent and this reaction could be done under mild reaction conditions. Corriu[9] and Kumada[10] independently developed the Ni-catalyzed cross-coupling of Grignard reagents with alkenyl and aryl halides in 1972 (Scheme 1.4). Later, Kumada used the phosphorus based ligand to tune the reactivity of the metal to improve the cross-coupling. In 1988, Hiyama developed the Pd- and Ni-catalyzed cross-coupling of organosilanes and aryl halides and triflates activated by fluoride source like tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) (Scheme 1.5).[11] Later, Denmark[12] and DeShong[13] improved this reaction using siloxanes. In 1976, Eaborn was the first who reported the Pd-catalyzed cross-coupling of organodistannane reagent with aryl iodide.[14] In 1977, Migita reported the Pd-catalyzed cross-coupling of organotin

reagents with aryl bromides.[15] In 1978, Stille synthesized the ketone using aroyl chlorides with organotin in much more milder condition than reported by Eaborn and Migita (Scheme 1.6).[16]

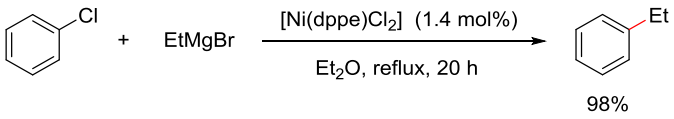
Scheme 1.2. Pd-catalyzed Negishi coupling



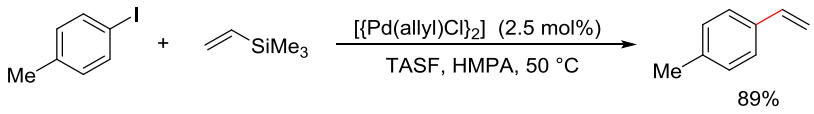
Scheme 1.3. Pd-catalyzed Suzuki-Miyaura coupling



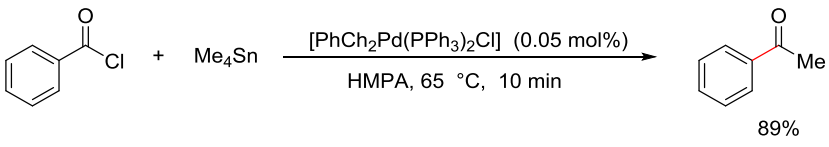
Scheme 1.4. Ni-catalyzed Corriu-Kumada coupling



Scheme 1.5. Ni-catalyzed Hiyama coupling

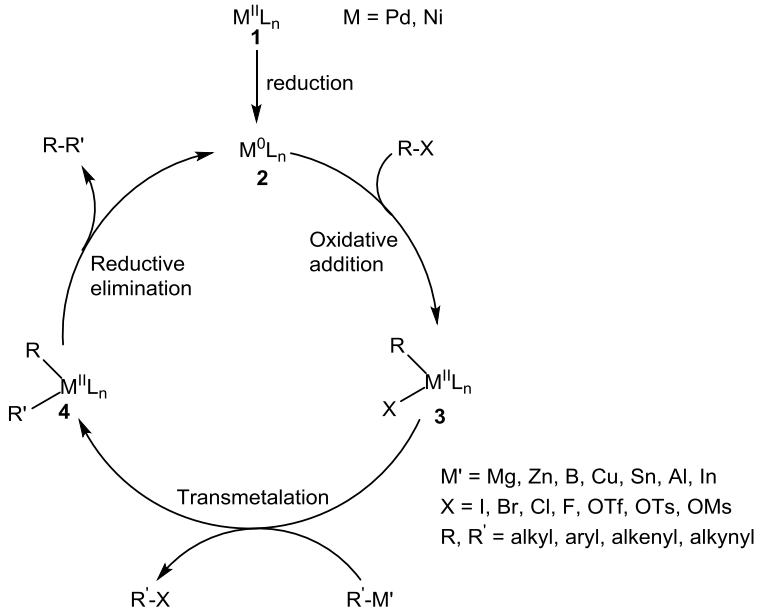


Scheme 1.6. Pd-catalyzed Stille coupling



Most of the cross-coupling reactions are catalyzed by Pd or Ni and these cross-coupling reactions have similar catalytic cycle (Scheme 1.7). Initially, off the catalytic cycle involves the *in situ* reduction of the catalyst precursor $M^{II}Ln$ (**1**) to the reactive species $M^{0}Ln$ (**2**), either with the organometallic reagent or with an additional reducing agent. In the case of metal (**0**) precursors, such as $Pd(dba)_2$ or $Ni(cod)_2$ no preliminary reduction is required. The first step is an oxidative addition to the C-X bond of the electrophile R-X, affording the organometallic complex **3**. Subsequent ligand exchange reaction with the organometallic reagent R'-M' leads to the complex **4**. Reductive elimination provides the desired cross-coupling product R-R' and regenerates the active catalyst $M^{0}Ln$ (**2**). The structure of the ligand Ln plays an essential role among all the factors influencing the catalysts efficiency. For instance, electron-rich ligands facilitate the oxidative addition step, whereas sterically demanding ligands enhance the reductive elimination step.[17]

Scheme 1.7. Catalytic cycle of the transition metal catalyzed cross-coupling reaction



The majority of these transition metal-catalyzed cross-couplings were catalyzed by Pd and very few of them were done with other transition metals (Figure 1.1). So, there is still much more need to be done in this field with inexpensive metals like copper, nickel, iron and cobalt.

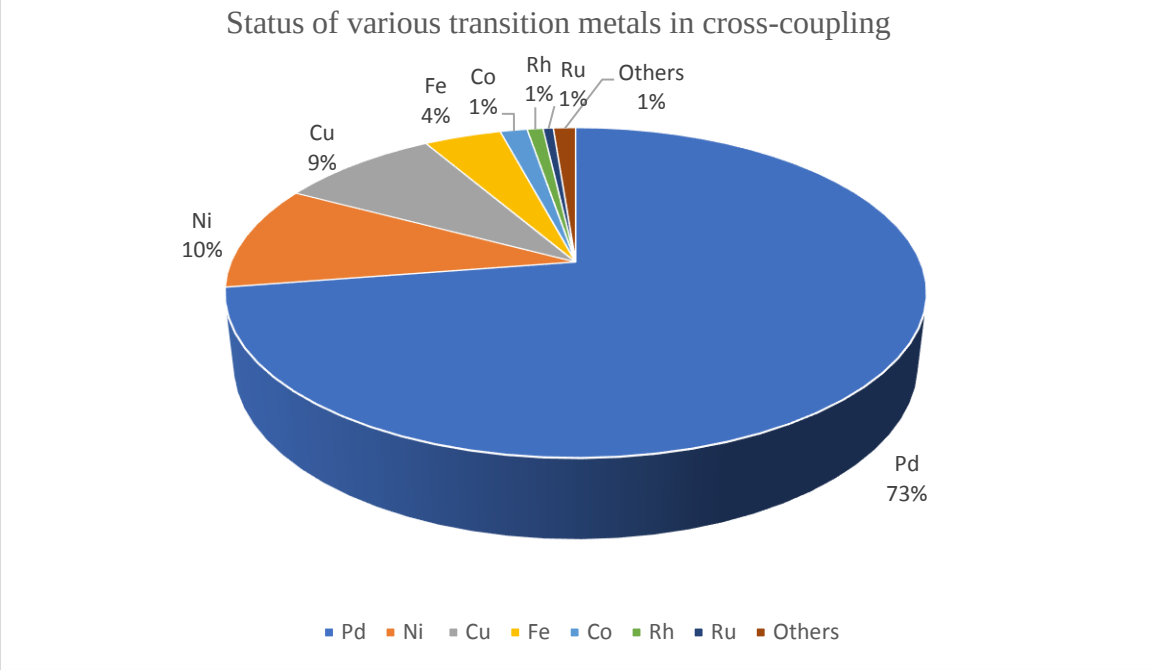


Figure 1.1. Status of various transition metals in cross-coupling (Source: Scifinder citation index; search criteria: cross-coupling; duplicates removed; data until 05/25/2018)

As expected, the transition metal catalyzed cross-coupling has been utilized in the synthesis of a variety of marketed drugs and materials, among others. For example, the Suzuki coupling is employed for the synthesis of COX-2 inhibitor, a drug used for the treatment of rheumatoid arthritis and osteoarthritis. Pharmaceutical company Pfizer uses the Kumada and Negishi couplings to synthesize PDE472, a phosphodiesterase type 4D inhibitor, which was being investigated as a drug lead for the treatment of asthma.[18] Negishi coupling is applied towards the synthesis of VEGFR kinase inhibitor, a bioactive

molecule that shows antitumor activity.[18] Kumada coupling is utilized for the synthesis of polymers such as polyalkylthiophenes, which are used for making organic solar cells and solar diodes (Figure 1.2).[19] Similarly, Negishi coupling has found use in the preparation of teranthrylethynylene (D3ANT) for use in the preparation of thin film transistor (TFT).[20]

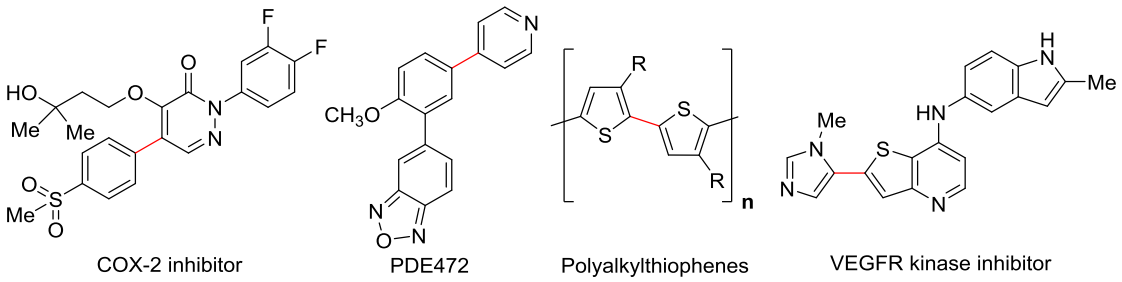


Figure 1.2. Different types of drugs and polymer obtained from cross-coupling

1.2. Nickel, Iron and Cobalt as Sustainable Metals for Cross-Coupling

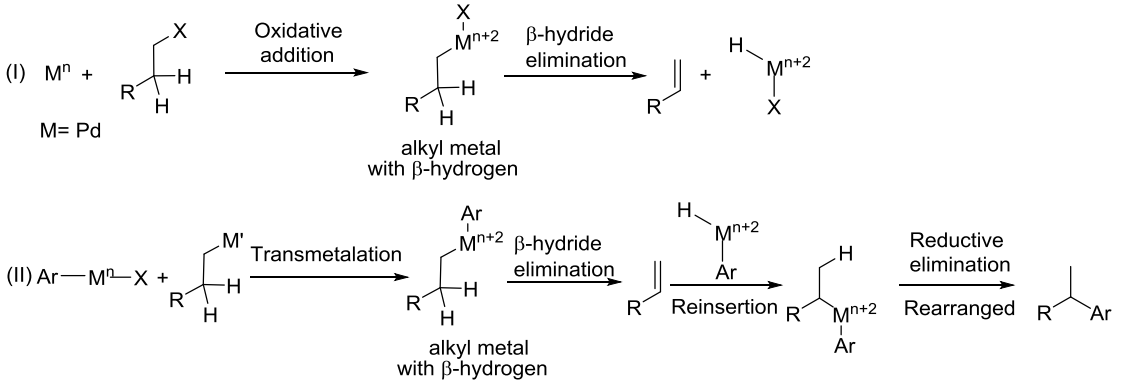
In spite of being well-developed with wide applications in both academia and industry, cross-coupling reactions are mainly catalyzed by the precious and rare transition metal Pd. Consequently, large scale production of drugs and commodity chemicals in the long term will be challenging. Alternative strategies like catalyst recycling are also being used[21] as a sustainable approach but it will only be practical for short term due to loss of catalyst during recycling. Therefore, there is a need for practical solutions that can be used for cross-coupling in order to make this chemical process sustainable in the long-term.

Despite being widely used, challenges remain for Pd-catalyzed cross-coupling reactions. Firstly, in spite of the widespread application of Pd in cross-coupling reactions, its natural abundance and cost has always remained a major concern for the long-term sustainability and large-scale use of this transformation. Pd exists only in a very low concentration on the earth's crust (6.3×10^{-7} ppm) while its demand remains on constant

rise.[4] It is likely that Pd becomes even more scarce, development of an alternative catalyst based on the earth-abundant transition metals such as Ni (9.0×10^{-3} ppm), Fe (6.3 ppm), and Co (3.0×10^{-3} ppm), is crucial. The price of Pd is much higher than Ni, Fe and Co.[22,23] Iron is less toxic in comparison to Pd and is present in the large number of the biological system as metalloproteins like hemoglobin.[24] In the recent times, earth-abundant and inexpensive transition metals like iron, cobalt and nickel have been used in cross-coupling.[25,26]

The next challenge associated with C-C bond forming reaction is β-hydride elimination. Although β-hydride elimination plays a vital role in the formation of Heck products,[27] this process does not help in the formation of desired products in many cases of cross-coupling reactions catalyzed by Pd. Alkyl halides or organometallic reagents with β-hydrogens will undergo β-hydride elimination upon reaction to Pd to give undesired olefins, thereby derailing the cross-coupling pathway (Scheme 1.8).[28] Secondary alkylmetal reagents containing β-hydrogens also cause further challenges due to rearrangement by sequential β-hydride elimination and migratory insertion processes giving undesired products.[29]

Scheme 1.8. Problems due to β-hydride elimination



In order to prevent or slow down this process, or to accelerate reductive elimination, various types of well-designed, but difficult to synthesize, bulky and expensive ligands are required.[30] Bulky ligands prevent β-hydride elimination by forcing β-hydrogens out of co-planarity with the transition metals, a required geometry for such a process (Figure 1.3).[31,32] Sterically hindered ligands facilitate the reductive elimination by forming low coordinate transition metals.[33]

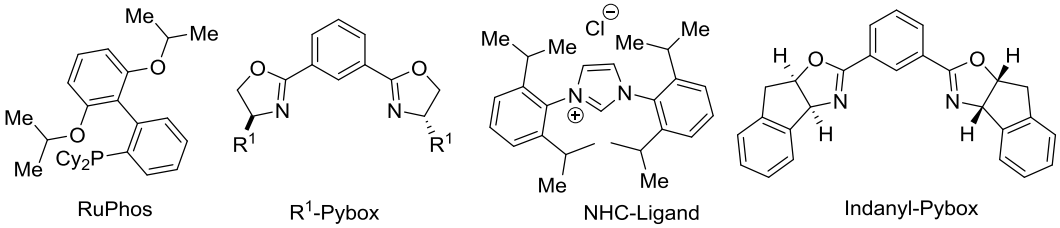
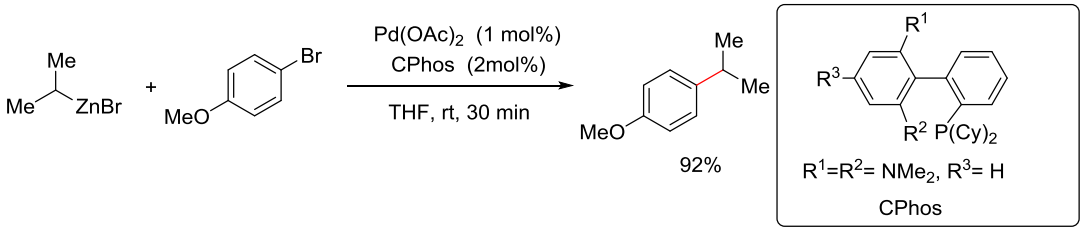


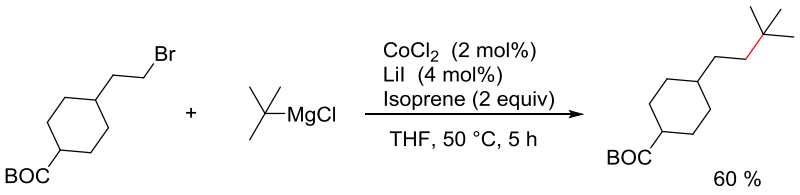
Figure 1.3. Sterically demanding electron-rich ligands

Buchwald and co-workers have reported the Pd-catalyzed Negishi coupling of secondary alkylzinc halides with aryl halides. They have used sterically hindered bulky biaryl phosphine CPhos ligand in order to prevent the β-hydride elimination (Scheme 1.9).[34] But in case of Co-catalyzed Kumada coupling reported by Kambe's group no such sterically hindered bulky ligands were needed and the cross-coupling between tertiary alkyl Grignard reagents with primary alkyl halides proceeded in presence of LiI and 2 equivalents of isoprene. No Heck product was reported due to the β-hydride elimination (Scheme 1.10).[35] Furthermore, Knochel's group had reported that Co-catalyzed cross-couplings did not suffer from rearrangement of secondary alkylhalides to unbranched products.[36]

Scheme 1.9. Pd-catalyzed Negishi coupling using CPhos ligand

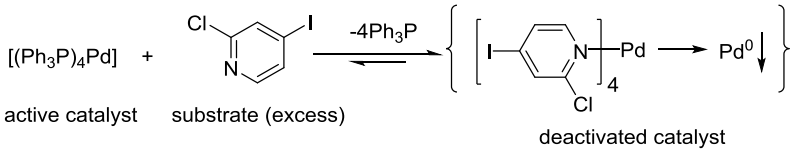


Scheme 1.10. Cobalt-catalyzed cross-coupling of alkyl halides with tertiary alkyl Grignard reagents

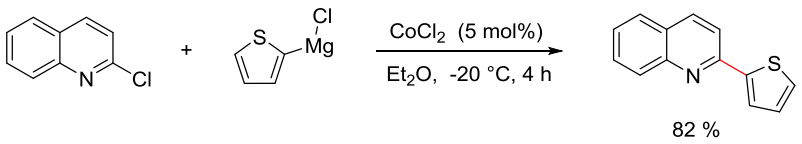


Another challenge linked with the use of Pd based catalyst is its low tolerance with the heteroaromatic substrates. Heteroarenes widely occur in natural products, pharmaceuticals, drug candidates and bioactive molecules,[18] and play vital roles in the biological system.[37] However, heteroaromatic substrates are less tolerated by Pd-catalyzed cross-couplings as they bind to Pd-catalysts competitively over the ligands causing catalyst deactivation that leads to reaction termination (Scheme 1.11).[32,38] To address these problems, application of complex electron-rich bidentate and sterically hindered ligands, similar to those discussed above (Figure 1.3), are needed.[39] But Co-catalyzed cross-couplings between heteroaryl chlorides and aryl- or heteroarylmagnesium halides do not required such complex electron-rich bidentate and sterically hindered ligands (Scheme 1.12).[40]

Scheme 1.11. Problems due to heteroaryl substrates



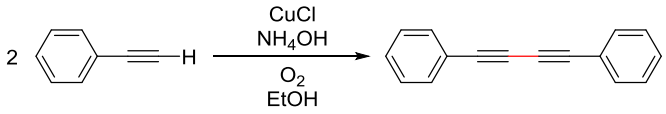
Scheme 1.12. Co-catalyzed cross-coupling between heteroaromatic chloride and heteroaromatic Grignard reagent



1.3. Copper as a Sustainable Metal for Cross-Coupling

The use of Cu in cross-coupling reactions is clearly not unprecedented. The journey of Cu-catalyzed coupling began with the development of the Glaser coupling (Scheme 1.13), later modified by Hay in 1962,[41] when Glaser reported his work in 1869 for the homocoupling of alkynes with Cu(I)-salts.[42] In 1963, Castro and Stephens developed Castro-Stephens cross coupling between Cu(I) acetylide and aryl halide forming a disubstituted alkyne and copper halide.[43] Organocuprates (the Gilman reagents) are well known to couple with alkyl halides.[44] Cu is also widely used for coupling processes such as oxidative Heck,[45] Sonogashira,[46] and Ullmann reactions.[47]

Scheme 1.13. Cu-catalyzed Glaser coupling

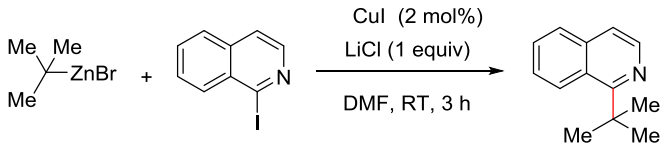


Iron-catalyzed cross-coupling generally works with highly reactive but less functional group tolerant Grignard reagents.[48] While nickel has been shown to have somewhat broader use, its toxicity has remained a major concern.[49] Cobalt is also known to be toxic to plant, animal and humans.[50,51] Removal of these metals from the finished products requires stringent and cost-intensive protocols in order to meet their threshold concentrations (<10 ppm) mandated by the Federal Drug Administration (FDA).[52] In this

scenario, we expect that copper would offer a realistic alternative owing to its low cost, earth abundance and low toxicity relative to Ni and Co.[53]

Ni and Fe-catalyzed cross-couplings are also known to undergo β-hydride elimination with a similar degree of facility.[54-56] But the Cu-catalyzed cross-coupling does not suffer from β-hydride elimination. Recently, our group reported Cu-catalyzed cross-coupling between tertiary alkylzinc halides with aryl halides in absence of ligand. No Heck product was reported due to the β-hydride elimination (Scheme 1.14).[57] In addition to this, Cu-catalyzed cross-coupling shows tolerance to heteroaromatic substrate.[58,59]

Scheme 1.14. Cu-catalyzed Negishi coupling without ligand

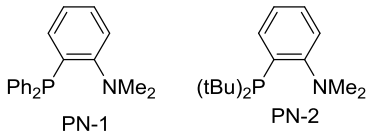


67%

Since Cu(I) (d^{10}) is isoelectronic to Pd(0), Cu(I) catalysts are expected to have reactivity similar to that of Pd(0) catalysts. In addition, several research findings in Cu-catalyzed reactions have shown that Cu catalysts demonstrate some reactivity patterns that are uniquely different from, and sometimes better than, Pd catalysts.[58,59] Therefore, Cu-based catalysts are expected to offer not only a sustainable and cost-effective alternative to Pd but also facilitate in simplifying many reaction protocols for the cross-coupling of alkyl- and heteroaryl-based substrates.

Despite the long history of Cu-catalyzed cross-coupling in C-C bond forming reaction, Cu-catalyzed cross-couplings are poorly developed. Most reactions require high catalyst loadings, high temperatures and proceed with a limited substrate scope. These reactions are also largely limited to aryl iodides[60] with exceptions of some electron

deficient aryl bromides that have been shown to react with organomagnesium,[58] aryltin,[61] arylindium,[62] and arylboron reagents.[63] These issues are generally ascribed to low stability of organocopper(I) species. Cu(I) complexes tend to undergo single electron transfer and disproportionation reactions.[64] The Cu-C and Cu-ligand bonds are also comparatively weaker than those of the second and third row late transition metals. As a result, organocopper(I) species can readily undergo ligand dissociation and decomposition during catalytic reactions. In addition, Cu complexes form aggregates. Due to decomposition and aggregation, high and low valent organocopper intermediates are hard to isolate in stable forms and characterize, which makes it difficult to study the mechanisms of Cu-catalyzed reactions.[64-67] In quest of solving these problems, our group found that the P,N-based hybrid ligands PN-1 (2-(diphenylphosphaneyl)-N,N-dimethylaniline) and PN-2 (2-(di-tert-butylphosphaneyl)-N,N-dimethylaniline) (Figure 1.4) where P-atom helps as π–acceptor to stabilize Cu in a low oxidation state Cu(I) while both P- and N- acts as σ-donors which could help to increase the reactivity of the Cu(I). This strategy helped our group to generate very stable P,N-ligated Cu(I) complexes such as dimeric forms of (PN)CuI, (PN)CuF and (PN)CuOMe, and the three-coordinate monomeric (PN)CuPh in order to conduct mechanistic studies.[62,68] With the use of these ligands, our group was able to develop Cu-catalyzed Hiyama coupling,[69,70] Suzuki-Miyaura coupling[68,71] and Negishi coupling.[72,73] Similarly, our group developed the Cu-catalyzed cross-coupling of organoindium[62], arylzirconium[74] and arylaluminum[75] reagents with aryl iodides and bromides.

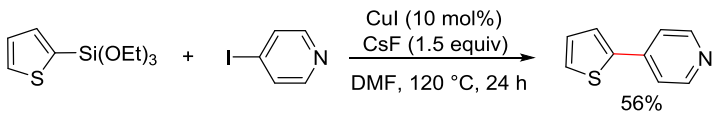


PN-1 PN-2

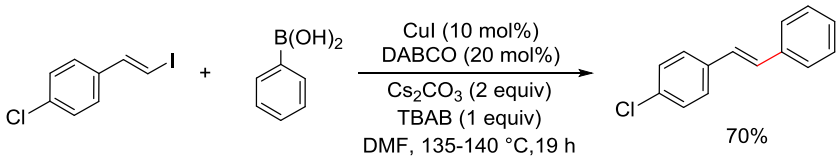
Figure 1.4. Structure of P,N-ligands used for cross-couplings

Despite the difficulties in developing the Cu-catalyzed cross-coupling processes, the Cu-salts were successfully used to form C-C bond in conjugate addition, 1,2-addition, and allylic reactions of Grignard and organozinc reagents.[76,77] These Cu-catalyzed transformations work well with the reactive and traditional organometallic reagents such as the Grignard and organozinc[76,78-80] reagents as well as stable organometallic compounds of Si[81-93] and B.[94-107] Our group first reported Cu-catalyzed Hiyama coupling of aryl- and heteroaryltriethoxysilanes with aryl and heteroaryl iodides in good to excellent yields (Scheme 1.15).[69] Li and co-workers reported Cu-catalyzed Suzuki-Miyaura coupling of arylboronic acids with vinyl iodides and bromides using 1,4-diazabicyclo[2.2.2]octane (DABCO), Cs_2CO_3 and tetrabutylammonium bromide (TBAB) (Scheme 1.16).[108] Zhang and co-workers had shown that Cu_2O nanoparticles can be used to perform the Stille coupling of vinyl- and alkynyltin reagents with aryl iodides, bromides and chlorides in the presence of KF and TBAB to give excellent yields (Scheme 1.17).[61] Kambe and co-workers reported the Cu-catalyzed Kumada coupling of Grignard reagents with generally unreactive primary alkyl fluorides in the presence of 1,3-butadiene as an additive (Scheme 1.18).[59] Our group had successfully developed the Cu-catalyzed cross coupling of diarylzinc with aryliodides to give good to excellent yields (Scheme 1.19).[73]

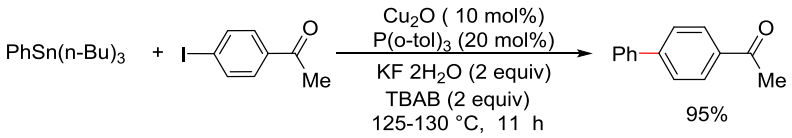
Scheme 1.15. Cu-catalyzed Hiyama coupling



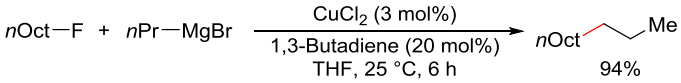
Scheme 1.16. Cu-catalyzed Suzuki-Miyaura coupling



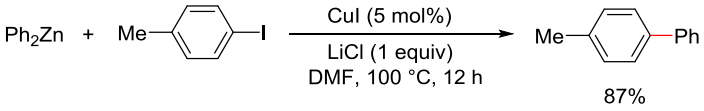
Scheme 1.17. Cu-catalyzed Stille coupling



Scheme 1.18. Cu-catalyzed Kumada coupling



Scheme 1.19. Cu-catalyzed Negishi coupling



1.4. Summary

Cross-coupling is the powerful tool for forming C-C bond and is mainly catalyzed by Pd. In order to develop cross-coupling transformations into a sustainable chemical process with particular emphasis placed on replacing rare, expensive, and toxic Pd with earth abundant, inexpensive, and non-toxic TM, Cu can in particular be regarded as the TM of choice that fulfils these requirements. Cu-catalysts are known to execute cross-couplings of a variety of organometallic reagents, such as organomagnesium, organoboron, organosilicon, organoindium and organomanganese, with alkyl, aryl and heteroaryl halides which clearly demonstrate the potential application of Cu as an alternative to Pd. Cu-catalysts displays the reactivity pattern that is unique from Pd, Ni and Fe as demonstrated, for example, in the "ligandless" Cu-catalyzed aryl–heteroaryl and heteroaryl–heteroaryl coupling, an otherwise difficult transformation when utilizing Pd, Ni and Fe-catalysts. Cu-

catalyzed cross-couplings do not suffer from β-hydride elimination and are known to tolerate the heteroaromatic substrates as well.

1.5. References

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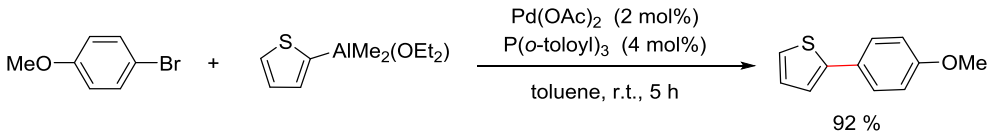
Chapter 2: Cross-Coupling of Organoaluminum Reagents

2.1. Introduction

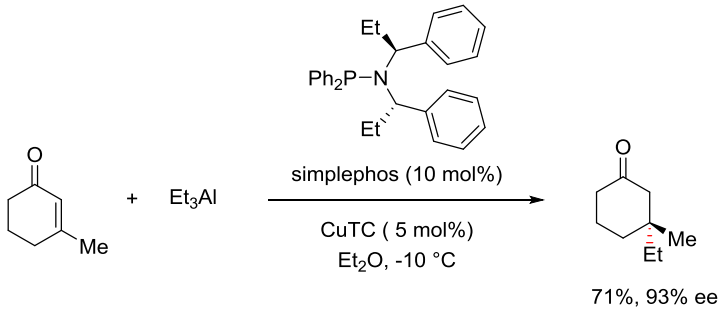
Aluminum remains one of the most earth abundant, inexpensive and low toxic metals. Organoaluminum reagents not only can easily transmetalate with Cu-salts but also has high chemoselectivity and Lewis acidity which helps to improve the yield.[1] Knochel and co-workers developed a convenient method for the synthesis of functionalized organoalanes from metallic aluminum, which could potentially widen the scope of organoaluminum in organic synthesis. Zhou and co-workers reported an efficient method for the synthesis of heteroaryl compounds through Pd-catalyzed cross-coupling reactions of (hetero)aryl bromides or benzyl halides with heteroarylaluminum reagents (Scheme 2.1).[2]

Scheme 2.1. Cross-coupling of thienylaluminium reagent with aryl bromides



There are some cases where direct transmetalation of organoalanes to Pd has been found to be slow and Pd required mediators like $ZnCl_2$ or $CdCl_2$ to enable sequential transmetalations.[3] In some cases intramolecular co-ordination of heteroatoms to Al is necessary for efficient cross-couplings of alkylalanes with organohalides.[4] In contrast, organoaluminum reagents are also known to transmetalate with Cu-salts based on their participation in the allylic and conjugate addition reactions, a required first step in developing Cu-catalyzed cross-coupling (Scheme 2.2).[5-7]

Scheme 2.2. Cu-catalyzed conjugate addition of a trialkyl aluminum reagent with a simplephos ligand



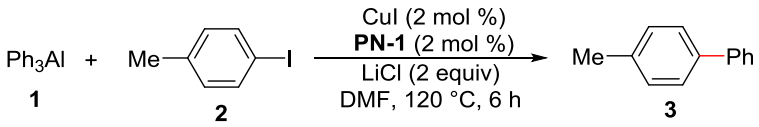
There are a lot of examples of cross-coupling of organometallic reagents derived from Si, B, Mg, Zn and Sn with Pd and Ni but there are limited cases of utility of similar organometallic complexes of Al. There are some examples of coupling of arylalanes and alkenylalanes while those of alkylalanes are still limited.[4,8-13] Inspired by these literature reports and our recent work on Cu-catalyzed cross-couplings, we explored the feasibility of using organoalumium reagents as coupling partners in order to broaden the scope of Cu-catalyzed cross-couplings.[14]

2.2.Copper-Catalyzed Cross-Coupling of Organoaluminum Reagents with C(sp2)-Halides

Our initial investigation began with the reaction of triphenylaluminum with *p*-iodotoluene in presence of 2 mol% 2-(diphenylphosphino)-*N*,*N*-dimethylaniline (PN-1) ligand, 2 mol% CuI in DMF at 120 °C, which gave the coupled product, 4-phenyltoluene, only in 45% GC yield. But when 3 equivalents of LiCl was added, the yield increased to 88% in 6 h. However, 2 equivalents of LiCl remained optimal for the standard reaction with the commercially available Ph_3Al. Lower product yields resulted by increasing or decreasing the amounts of LiCl to 1 or 4 equivalents. The reaction did not proceed in the absence of CuI and gave lower yield (26%) in absence of PN-1 ligand. The reaction gave

only 17% yield in absence of both PN-1 and LiCl. When the reaction time was decreased to 3 h, the product was formed in 73% yield. When CuO*t*Bu purified through sublimation was used instead of CuI, the product was obtained in 73% yield. When the reaction was performed with Pd- or Ni-catalysts instead of CuI, low yields were obtained, which suggest that the current reaction is unlikely to be catalyzed by low levels of Pd and Ni contaminants. When Co- and Fe-catalysts were used instead of CuI, the product was formed only 11% and 0%, respectively (Table 2.1).

Table 2.1. Optimization of reaction conditions[a]



entry	modified conditions	yield (%)[b]	entry	modified conditions	yield (%)[b]
1	without LiCl	45	9	3 h	73
2	none	88 (82)	10	[CuO*t*Bu] (sublimed) instead of CuI	73
3	3 equiv LiCl	82	11	1 mol % $Pd(OAc)_2$ instead of CuI	33[c]
4	1 equiv LiCl	60	12	1 mol % $Pd(dba)_2$ instead of CuI	9[c]
5	4 equiv LiCl	39	13	1 mol % $NiBr_2$ instead of CuI	24[c]
6	without CuI	0	14	1 mol % $(Ph_3P)_4Ni$ instead of CuI	18[c]
7	without **PN-1**	26	15	1 mol % $(Ph_3P)_3CoCl$ instead of CuI	11[c]
8	without LiCl and **PN-1**	17	16	1 mol % $Fe(OAc)_2$ instead of CuI	0[c]

[a]Reactions were run 0.1 mmol scale in 0.5 mL DMF. One equiv of **1** was used with respect to **2**. [b]Calibrated GC yields (average of at least two parallel runs). Value in parenthesis is the isolated yield (1.0 mmol). [c]1 mol % $Fe(OAc)_2$, $Co(OAc)_2$, $Ni(OAc)_2$ or $(Ph_3P)_4Ni$ was used.

Next, we looked at the effect of various ligands on the reaction that are either analogous to PN-1 or are well known for Cu-based catalytic reactions. Various types of ligands used in the reaction are shown in Figure 2.1 and the corresponding yields of the product **3** are presented in the bar diagram in Figure 2.2. Replacing Ph_2P- group in PN-1 with $(tBu)_2P$- group (PN-2) decreased the product yield significantly (56%). Use of PN-3 and PN-4 in which the dimethylamino goup of PN-1 was replaced by piperidinyl (PN-3) and morpholinyl (PN-4) groups afforded significantly low product yields (54% and 72%, respectively). Changing the dimethylamino group of PN-1 to pyridinyl (PN-5 and PN-6) and carbazolyl (PN-7) groups also furnished the product **3** only in 30%, 36% and 21% yields, respectively. Use of rotationally flexible ligand PN-8 also afforded the product **3** in 35% yield. Diphenylphosphorus amide ligand PN-9 provided the product **3** in a reasonable yield (65%). Bidentate phosphine-based ligands such as bis(diphenylphosphino)benzene (PP-1) afforded the product **3** in lower yield (29%) than the reaction without a ligand (45%). Phenanthroline (NN-1) and bidentate amine-based ligands (NN-2, NN-3 and NN-4) that are known to generate excellent Cu-catalysts for arylation of amines and phenols[15-19] also affected reaction adversely and decreased the product yields to 32%, 23%, 35% and 28%, respectively. Similarly, anionic ligands such as 8-hydroxyquinoline (NO-1) and 2,2,6,6-tetramethyl-3,5-heptanedione (OO-1), which are also excellent ligands for C-N and C-O bond formation,[15-19] afforded lower product yields (27% and 26%, respectively) than without a ligand. *N*-heterocyclic carbene (NHC) ligands, such as 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (SIMes•HCl), also decreased the product yield (25%).

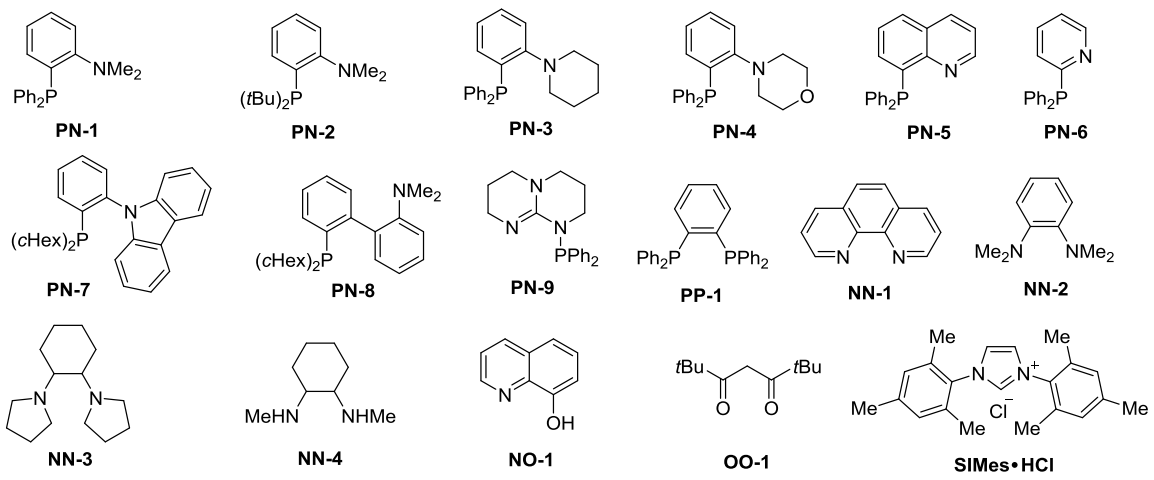


Figure 2.1. Ligands used for reaction optimization

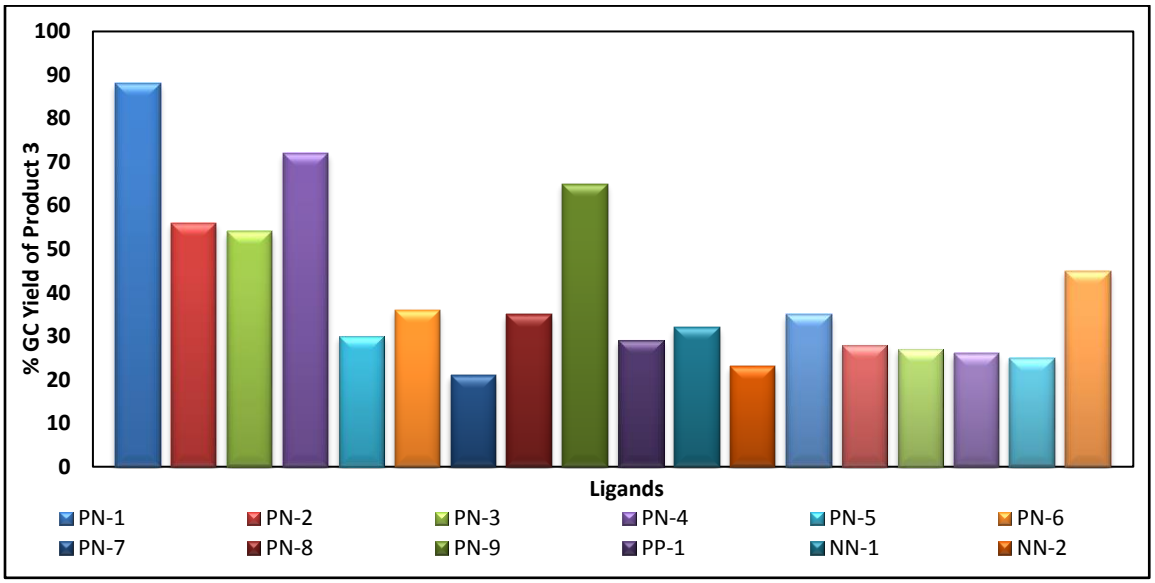
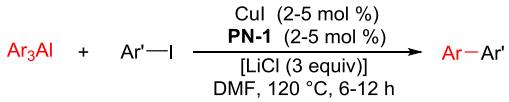
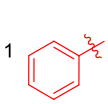
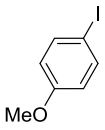
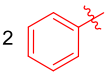
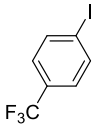
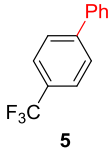
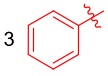
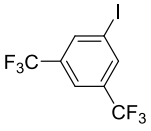
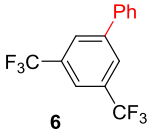
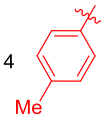
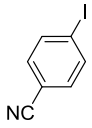
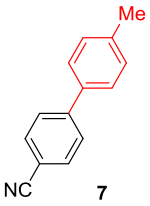
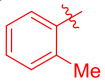
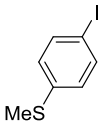
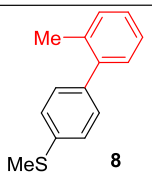
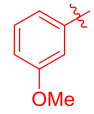
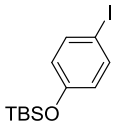
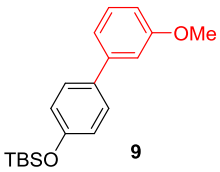
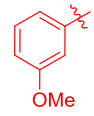
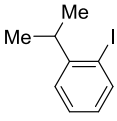
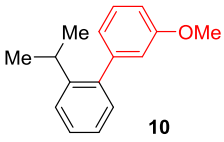
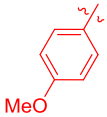
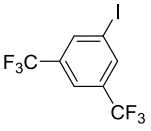
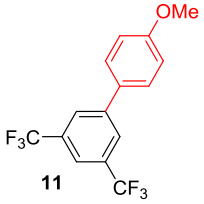


Figure 2.2. Bar diagram showing the percentage yields of 4-phenyltoluene (**3**) from the reaction of triphenylaluminum reagent with 4-iodotoluene in the presence of various types of ligands instead of PN-1 under the standard reaction conditions from Table 2.1, entry 2. Yields are GC yields (average of at least two parallel runs) of the product **3** calibrated against 2-nitrobiphenyl as an external standard.

Once we found that the combination of PN-1 and CuI as the best catalyst, we commenced to explore the substrate scope of the reaction. The reaction proceeds with electron-neutral and electron-rich triarylaluminum reagents (Table 2.2). The reactions of these triarylaluminum reagents proceed with both electron-poor and electron-rich aryl iodides and afford corresponding biaryl products in good yields. The reaction tolerates sensitive functional groups such as nitrile, thiomethoxy and TBS-protected alcohol (entries 4-6) and sterically hindered substituents like *iso*-propyl group at the *ortho*-position of iodoarenes (entry 7).

Table 2.2. Coupling of triarylaluminum reagents with aryl iodides[a]



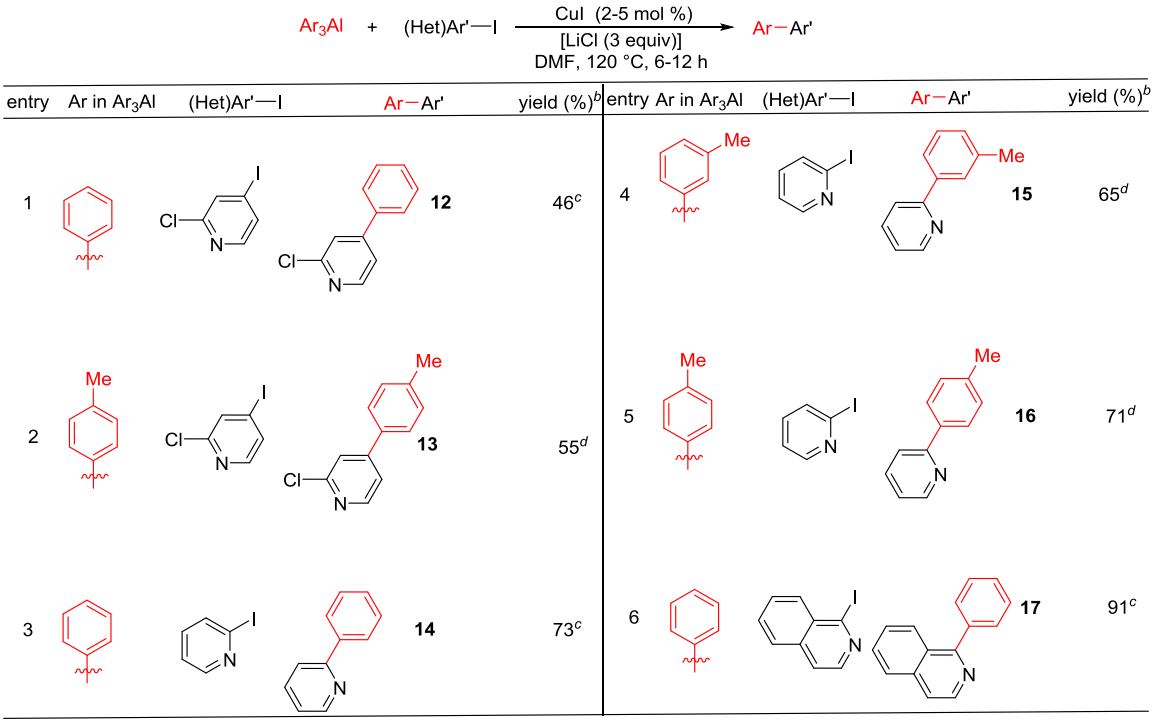
entry	Ar in Ar_3Al	Ar'—I	Ar—Ar'	yield (%)[b]
1			 **4**	87[c]
2			 **5**	83[d]
3			 **6**	54[d]
4			 **7**	70[d]
5			 **8**	62[c]
6			 **9**	40[d]
7			 **10**	38[c]
8			 **11**	49[c]

[a]Reactions were run in 1.0 mmol scale in 0.5 mL DMF. One equiv of Ar_3Al was used with respect to ArI. Reactions for entries 1, 4, 6 and 8 were run for 12 h. Reactions for entries 2, 3, 5 and 7 were run for 6 h. Each reaction contains 3 equivalents of LiCl, written in parenthesis below the reaction arrow, which is generated during the preparation of triarylaluminum reagents. [b]Yields are for analytically pure products isolated by column chromatography from a 1.0 mmol scale reaction. [c]5 mol% CuI/PN-1 was used. [d]2 mol% CuI/PN-1 was used.

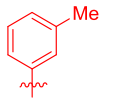
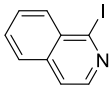
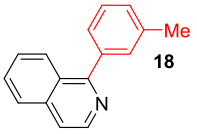
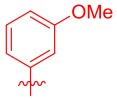
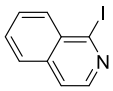
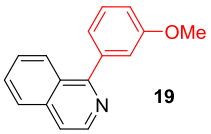
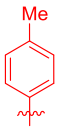
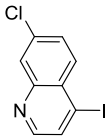
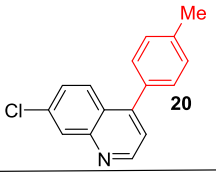
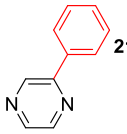
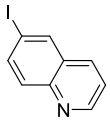
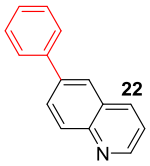
Our current reaction conditions can be applied for the arylation of heteroaryl iodides for the synthesis of a variety of heterobiaryl compounds (Table 2.3). However, heteroarenes did not require any ligand for the best product yields. Reactions with heteroaryl iodides under the standard conditions that contain PN-1 ligand afford the cross-coupled products in lower yields. Reactions can be performed with nitrogen-containing heteroaryl iodides such as 2-iodopyridine, 2-chloro-4-iodopyridine, 6-iodoquinoline, 7-chloro-4-iodiquinoline, 1-iodoisoquinoline and 2-iodopyrazine and the corresponding heterobiaryl compounds are obtained in good to excellent yields. This reactivity pattern of Cu^I-catalysts is in contrast to the reactivity of established metals Pd and Ni for cross-coupling with heteroaryl halides. Generally, the known Pd- and Ni-catalyzed cross-coupling reactions are less tolerant of heteroarenes because the heteroaryl substrates compete with ligands to bind with these transition metals. Consequently, the Pd- and Ni-catalysts are deactivated eventually leading to the termination of the cross-coupling reactions.[20,21] Therefore, Pd- and Ni-based catalytic systems for coupling with heteroaryl halides generally require sterically hindered, bulky phosphine- or carbene-based ligands[22-26] in order to suppress multiple ligations of heteroaryl substrates to prevent the untoward

deactivation pathway. In this respect, Cu^{I}-based catalysts, which are d^{10} congeners of Pd^{0} and Ni^{0}, display a unique property in the current cross-coupling reactions with heteroaryl substrates. This unique reactivity pattern is very general, and was observed previously by our group in the cross-couplings of arylboron,[27,28] arylsilicon,[29,30] organoindium,[31] arylzirconium,[32] and organozinc reagents[33] with heteroaryl halides. In addition, Hintermann and coworkers[34] have previously demonstrated that Grignard reagents could be coupled with heteroaryl chlorides under 'ligand-free' conditions using CuI as a catalyst. Nitrogen-based molecules are known to be excellent ligands in many Cu-catalyzed arylation of amines, amides and phenols.[15-19] Catalytically competent discrete Cu^{I}-complexes that contain nitrogen-based ligands have also been synthesized and fully characterized structurally.[35-39] Therefore, we believe that the *N*-based heteroaryl substrates and products function as ligands in our current reaction.

Table 2.3. Coupling of triarylaluminum reagents with heteroaryl iodides [a]



Continuation of table 2.3.

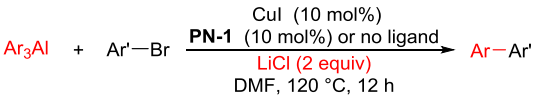
entry	Ar in Ar_3Al	(Het)Ar'—I	Ar—Ar'	yield (%)[b]
7			 **18**	82[d]
8			 **19**	71[d]
9			 **20**	92[c]
10			 **21**	41[c]
11			 **22**	68[d]

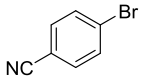
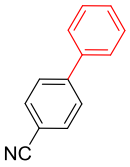
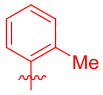
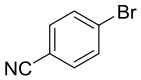
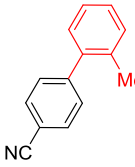
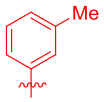
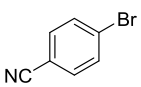
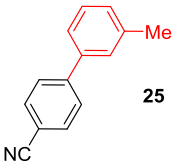
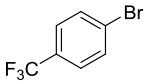
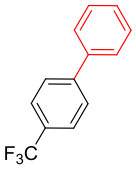
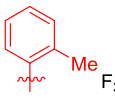
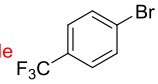
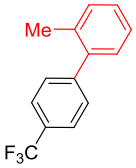
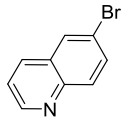
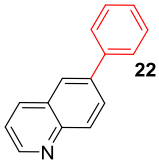
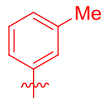
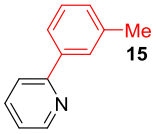
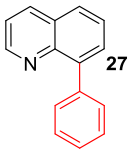
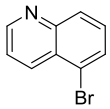
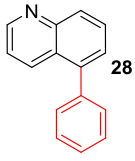
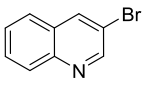
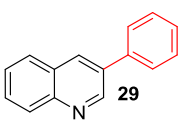
[a]Reactions were run in 1.0 mmol scale in 0.5 mL DMF. One equiv of Ar_3Al was used with respect to ArI. Reactions for entries 1, 3, 6, 9 and 10 were run for 6 h. Reactions for entries 2, 4, 5, 7, 8 and 11 were run for 12 h. Each reaction contains 3 equivalents of LiCl, written in parenthesis below the reaction arrow, which is generated during the preparation of triarylaluminum reagents. [b]Yields are for analytically pure products isolated by column chromatography from a 1.0 mmol scale reaction. [c]2 mol% CuI was used. [d]5 mol% CuI was used.

Our current reaction conditions enable the cross-coupling of electron-deficient aryl and heteroaryl bromides and afford products in good to excellent yields when 10 mol% CuI or CuI/PN-1 was used as a catalyst (Table 2.4). However, in situ generated triarylaluminum reagents usually gave lower product yields than purified triarylalumimun reagents. As such, pure triarylaluminum reagents were used for all the reactions with aryl bromides, which gave the best product yields. The triarylaluminum reagents were prepared and purified according to the literature procedure.[40] Consistent with the reactivity with aryl

iodides, the reaction of aryl bromides requires PN-1 ligand. The reaction proceeds well with electron-deficient aryl bromides such as 4-bromobenzonitrile and 4-bromobenzotrifluoride affording the cross-coupled products in 62-90% yields (entries 1-5). The reaction also proceeds with a variety of nitrogen-based heteroaryl bromides and afford the heterobiaryl products in good yields in the absence of the PN-1 ligand (entries 6-10). Heteroaryl bromides such as 2-bromopyridine, 3-bromoquinoline, 5-bromoquinoline, 6-bromoquinoline and 8-bromoquinoline are good substrates for the current reaction.

Table 2.4. Coupling of triarylaluminum reagents with electron-deficient aryl and heteroaryl bromides [a]

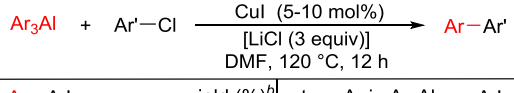


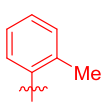
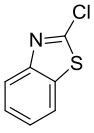
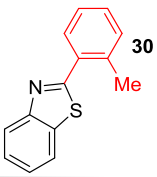
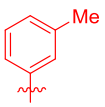
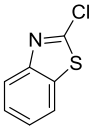
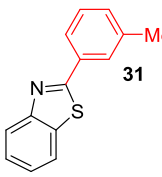
entry	Ar in Ar_3Al	Ar'—Br	Ar—Ar'		yield (%)[b]
1				**23**	90
2				**24**	66
3				**25**	69
4				**5**	75
5				**26**	62
6				**22**	59
7				**15**	65
8				**27**	79
9				**28**	61
10				**29**	73

[a]Reactions were run 1.0 mmol scale in 0.5 mL DMF. One equiv of Ar_3Al was used with respect to ArBr. Reactions for entries 1-5 require 10 mol% PN-1 ligand. No ligand was added to the reactions for entries 6-10. Since pure triarylaluminum reagents were used, 2 equivalents of LiCl were added to the reactions. [b]Yields are for analytically pure products isolated by column chromatography from a 1.0 mmol scale reaction.

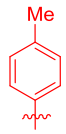
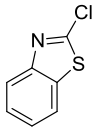
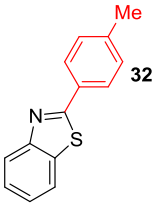
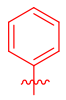
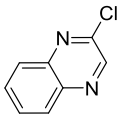
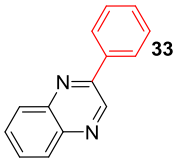
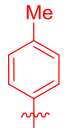
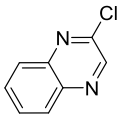
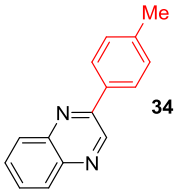
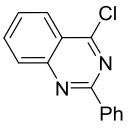
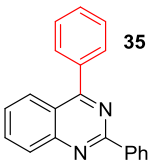
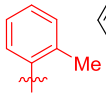
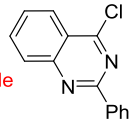
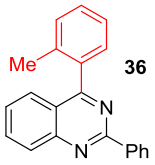
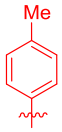
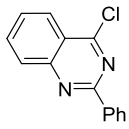
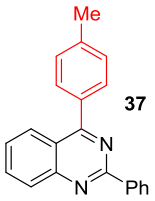
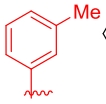
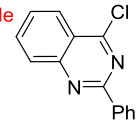
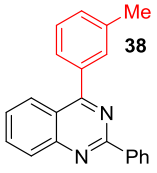
Cu-catalyzed cross-coupling that involves aryl chlorides as coupling partners are formidably challenging and therefore are rare. Hintermann and co-workers demonstrated that Grignard reagents could be coupled with a variety of nitrogen-based heterocyclic chlorides in the presence of catalytic amounts of CuI.[34] It has also been reported that Cu-nanoparticles can catalyze the coupling of arylboronic acids with aryl chlorides.[41] However, the reaction requires the addition of molecular iodine, which is proposed to convert aryl chlorides to aryl iodides *in situ* as reactive species via an iodide-chloride (I/Cl) exchange (aromatic Finkelstein reaction).[42] Therefore, this reaction only represents a 'formal' reaction with aryl chlorides. Pleasingly, our current reaction condition can also be applied for cross-couplings with heteroaryl chlorides (Table 2.5). The reaction provides products in good to excellent yields for the cross-couplings of arylaluminum reagents with nitrogen-based heteroaryl chlorides such as 2-chlorobenzothiazole, 2-chloroquinoxaline and 4-chloro-2-phenylquinazoline.

Table 2.5. Coupling of triarylaluminum reagents with heteroaryl chlorides [a]



entry	Ar in Ar_3Al	Ar'—Cl	Ar—Ar'	yield (%)[b]	entry	Ar in Ar_3Al	Ar'—Cl	Ar—Ar'	yield (%)[b]
1			 **30**	65[c]	2			 **31**	89[d]

Continuation of table 2.5.

entry	Ar in Ar_3Al	Ar'—Cl	Ar—Ar'	yield (%)[b]
3			 **32**	63[d]
4			 **33**	75[c]
5			 **34**	66[d]
6			 **35**	91[c]
7			 **36**	59[c]
7			 **37**	80[d]
9			 **38**	73[d]

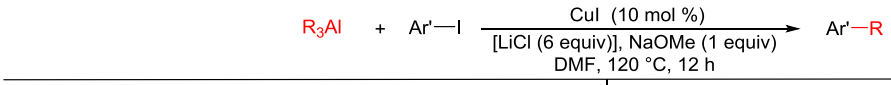
[a]Reactions were run in 1.0 mmol scale in 0.5 mL DMF. One equiv of Ar_3Al was used with respect to ArCl. Each reaction contains 3 equivalents of LiCl, written in parenthesis below the reaction arrow, which is generated during the preparation of triarylaluminum reagents. [b]Yields are for analytically pure products isolated by column chromatography from a 1.0 mmol scale reaction. [c]5 mol% CuI was used. [d]10 mol% CuI was used.

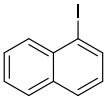
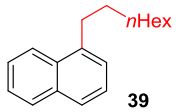
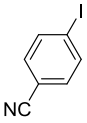
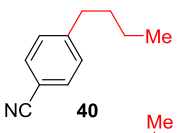
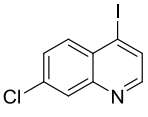
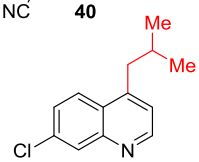
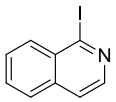
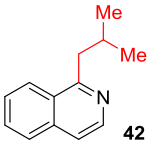
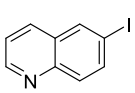
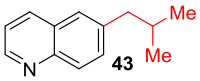
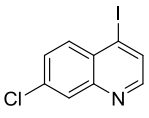
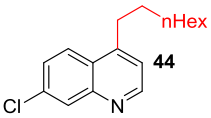
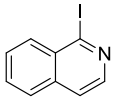
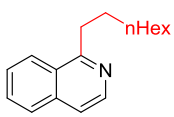
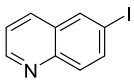
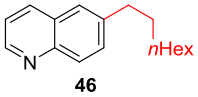
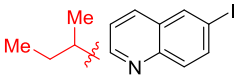
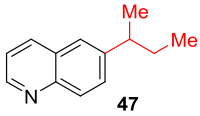
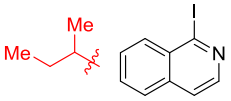
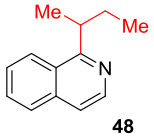
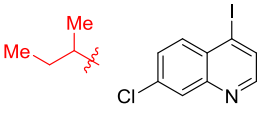
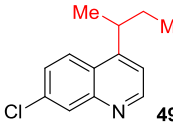
In case of Cu-catalyzed cross-coupling between alkyl aluminum reagents and organohalides, we first tried to optimize the reaction. We started our work with the reaction of commercial trioctylaluminum reagents with 1-iodonapthalene to get the alkylated product in 39% GC yield. Further optimization of the reaction showed that 10 mol% CuI, 1 equivalent of NaOMe and 6 equivalents of LiCl with DMF as solvent at 120°C gave the

best yield (55% GC and 46% isolated). PN-1 ligand is required for non-heteroaryl halide while no ligand is required for the heteroaryl halides.

This optimized condition worked for the coupling of electron-neutral and electron deficient aryl iodides (Table 2.6) such as 1-iodonapthalene and 4-iodobenzonitrile with trialkylaluminum reagents affording products in good yields (entries 1 and 2). The reactions also proceed in good yields with heteroaryl iodides such as 6-iodoquinoline, 7-chloro-4-iodoquinoline and 1-iodoisoquinoline (entries 3-11). Both primary and secondary alkylaluminum reagents undergo coupling reaction with aryl iodides under the current condition. The new conditions can also be used for the couplings of primary alkylaluminum reagents with heteroaryl chlorides such as 2-chlorobenzothiazole, 1-chloroisoquinoline and 4-chloro-2-phenylquinazoline, which afford the coupled products in good yields (Table 2.7). It is well known that coupling of secondary alkylorganometallic reagents with organohalides using metal catalyst like Pd and Ni suffers from β-hydride elimination and results in the formation of rearranged products.[43] The coupling of alkylorganometallic reagents with heteroaryl halides is further challenging due to complications arising for the catalyst deactivation in addition to β-hydride elimination.[44] Due to these complications, reactions require sterically hindered phosphine- or carbene-based ligands to prevent both β-hydride elimination and catalyst deactivation.[22,23] In sharp contrast, our current reaction protocol does not suffer from these complications. So, Cu-catalyzed cross-coupling can be expected to offer a convenient and practical method for the coupling of alkylorganometallic reagents with heteroaryl halides.

Table 2.6. Coupling of trialkylaluminum reagents with electron-deficient aryl and heteroaryl iodides [a]

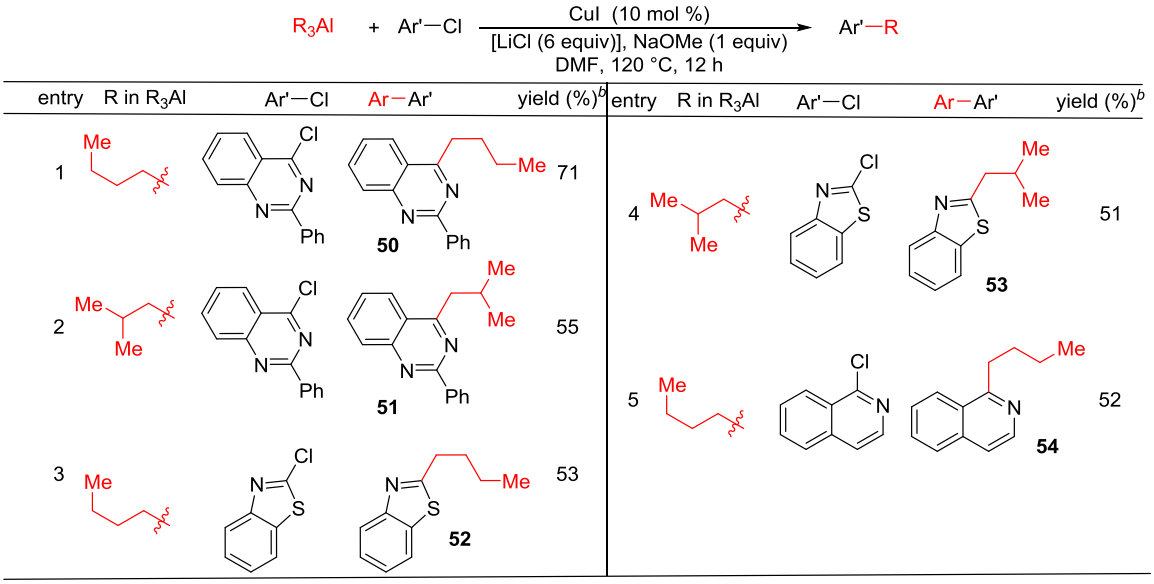


entry	R in R_3Al	Ar'—I	Ar—Ar'	yield (%)[b]
1	*n*Hex		 **39**	46 (39)
2	Me		 **40**	59
3	Me, Me		 **41**	75
4	Me, Me		 **42**	62
5	Me, Me		 **43**	59
6	*n*Hex		 **44**	51
7	*n*Hex		 **45**	91
8	*n*Hex		 **46**	78
9	Me, Me		 **47**	76
10	Me, Me		 **48**	64
11	Me, Me		 **49**	63

[a]Reactions were run 1.0 mmol scale in 0.5 mL DMF. One equiv of R_3Al was used with respect to ArI. Reactions for entries 1 and 2 require 10 mol% PN-1 ligand. No ligand was added to the reactions for entries 3-11. 6 equivalents of LiCl was added to the reactions of commercially available tri-*n*-octylbutyl- and tri-*iso*-butylaluminum reagents. Reactions of tri-*n*-butyl- and tri-*sec*-butylaluminum reagents also contain 6 equivalents of LiCl, 3 equivalents generated during the preparation of trialkylaluminum reagents plus extra 3 equivalents added separately. [b]Yields are for analytically pure products isolated by column

chromatography from a 1.0 mmol scale reaction. Value in parenthesis is the calibrated GC yield.

Table 2.7. Coupling of trialkylaluminum reagents with heteroaryl chlorides [a]

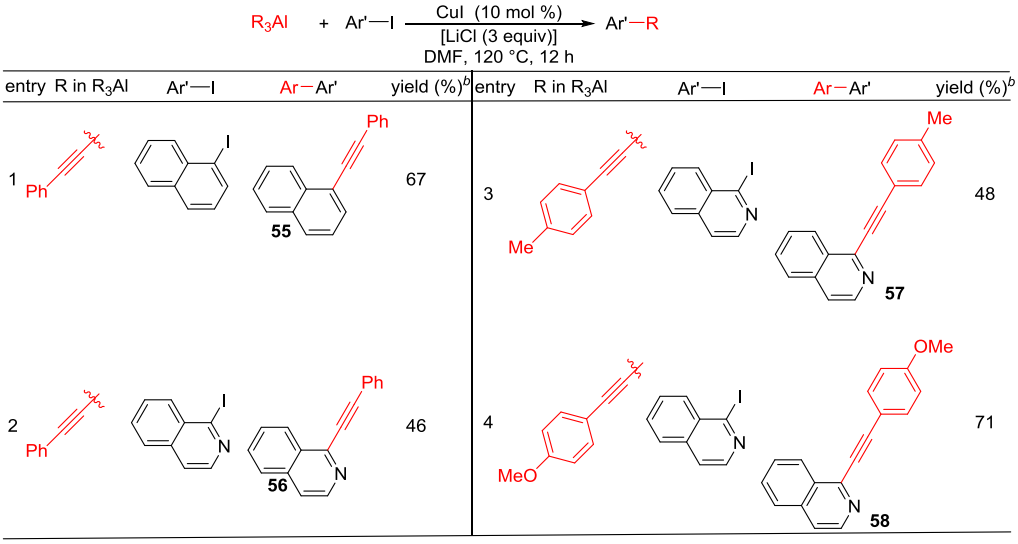


[a]Reactions were run in 1.0 mmol scale in 0.5 mL DMF. One equiv of R_3Al was used with respect to ArCl. 6 equivalents of LiCl was added to the reactions of commercially available tri-*iso*-butylaluminum reagent. Reaction of tri-*n*-butylaluminum reagent also contain 6 equivalents of LiCl, 3 equivalents generated during the preparation of tri-*n*-butylaluminum reagent plus extra 3 equivalents added separately. [b]Yields are for analytically pure products isolated by column chromatography from a 1.0 mmol scale reaction.

Pd-[45] or Cu-catalyzed[46-55] Sonogashira coupling of alkynes with aryl halides is one of the straightforward methods to synthesize arylalkynes. Alternatively, Cahiez and coworkers have shown that alkynyl halides can also be used as a coupling partner in Cu-catalyzed cross-coupling with aryl halides to afford arylalkynes.[56] A similar reaction was also recently reported by Riant and co-workers for the cross-coupling of vinyltriethoxysilanes with alkynyl bromides.[57] A combination of CuI and 8-

hydroxyquinoline was also shown to be an active catalyst that facilitated cross-coupling between arylboronic acids and alkynyl bromides.[58] Pd-catalyzed cross-couplings of alkynylsilane,[59-62] alkynylboron,[63,64] alkynylzinc[65,66] and alkynyltin[67,68] reagents with aryl halides are also powerful methods to synthesize arylalkynes. Similarly, *in situ* generated alkynylcopper(I) intermediates are also used as coupling partners in Pd-catalyzed Sonogashira couplings co-catalyzed by Cu-salts.[45] A few examples of Ni-catalyzed cross-couplings of alkynylalanes with benzylic and aryl halides have also been reported.[69,70] Nishihara demonstrated that alkynylboron[71] and alkynylsilane[72] reagents could be coupled with aryl iodides using a CuI/Ph_3P catalyst. We have demonstrated that trialkynylaluminum reagents are also viable nucleophiles that undergo transmetalation with CuI and subsequently react with aryl iodides to offer arylalkynes as cross-coupled products (Table 2.8). In these reactions, neutral and electron-rich triarylaluminum reagents, such as triphenylaluminum, tri-*p*-tolylaluminum and tri-*p*-anisolylaluminum, can be utilized as coupling partners to react with aryl iodides such as iodonaphthalene and 1-iodoisoquinoline, which afford cross-coupled products in good yields.

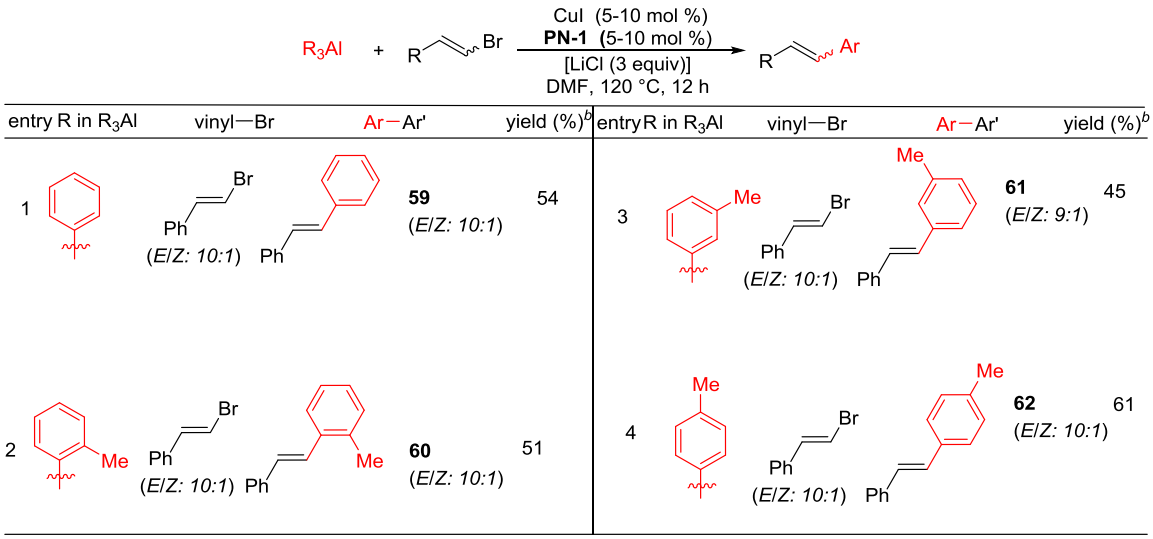
Table 2.8. Coupling of trialkynylaluminum reagents with aryl and heteroaryl iodides [a]



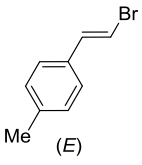
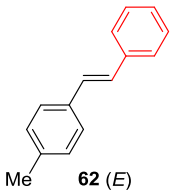
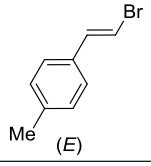
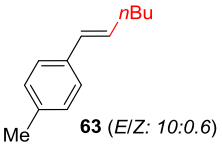
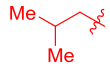
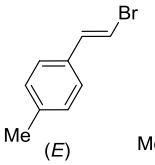
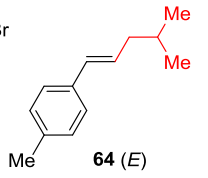
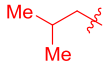
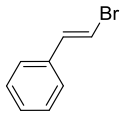
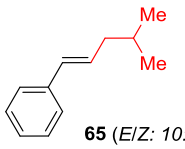
[a]Reactions were run in 1.0 mmol scale in 0.5 mL DMF. One equiv of R_3Al was used with respect to ArI. Reaction for entry 1 requires 10 mol% PN-1 ligand. No ligand was added to the reactions for entries 2-4. Each reaction contains 3 equivalents of LiCl, written in parenthesis below the reaction arrow, which is generated during the preparation of trialkynylaluminum reagents. [b]Yields are for analytically pure products isolated by column chromatography from a 1.0 mmol scale reaction.

There are only few papers which reported the Cu-salts for the couplings of organometallic reagents with vinyl halides.[73-75] We were also able to develop a simple protocol for the coupling of alkylaluminum reagents with vinyl halides in good yields (Table 2.9). The reactions proceed well for the couplings of triphenylaluminum, tri-*o*-tolylaluminum, tri-*m*-tolylaluminum and tri-*p*-tolylaluminum reagents with *trans*-β-bromostyrene and *trans*-4-methyl-β-bromostyrene (entries 1-5). Similarly, the reactions also work well for the couplings of tri-*n*-butylaluminum and tri-*iso*-butylaluminum reagents with *trans*-β-bromostyrene and *trans*-4-methyl-β-bromostyrene (entries 6-8).

Table 2.9. Coupling of triaryl- and trialkylaluminum reagents with vinyl bromides [a]



Continuation of table 2.9.

entry	R in R_3Al	vinyl—Br	Ar—Ar'	yield (%)[b]
5			 **62** (*E*)	41
6			 **63** (*E*/*Z*: 10:0.6)	50[c,d]
7			 **64** (*E*)	49[c,d]
8			 **65** (*E*/*Z*: 10:1)	45[c]

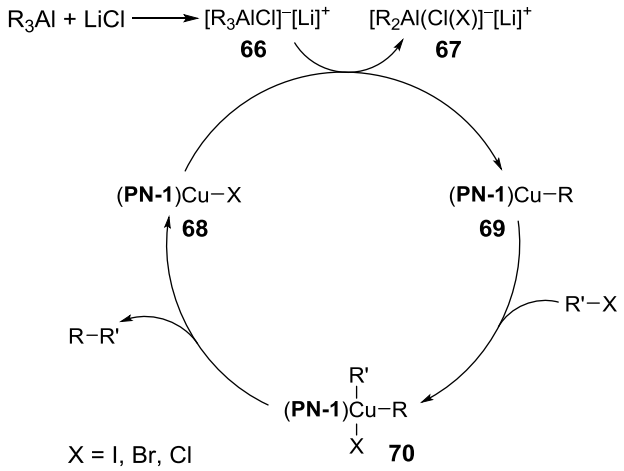
[a]Reactions were run in 1.0 mmol scale in 0.5 mL DMF. One equiv of R_3Al was used with respect to vinyl bromides. 5 mol% CuI/PN-1 was used for the reactions of arylaluminum reagents (entries 1-5). 10 mol% CuI/PN-1 was used for the reactions of alkylaluminum reagents (entries 6-8). 3 equivalents of LiCl was added to the reactions of commercially available tri-*iso*-butylaluminum reagent. Reaction of tri-*n*-butyl- and triarylaluminum reagents contain 3 equivalents of LiCl, which is generated during the preparation of tri-*n*-butyl- and triarylaluminum reagents. *E*/*Z* ratios of the products were determined by ^{1}H NMR. [b]Yields are for analytically pure products isolated by column chromatography from a 1.0 mmol scale reaction. [c]Reactions require 1 equiv of NaOMe. [d]Reactions were run for 24 h.

2.2.1. Mechanistic Studies

Proposed Catalytic Cycle: Based on our work and literature reports, we have proposed the catalytic cycle for the coupling organoaluminum reagents with aryl halides (Scheme 2.3). We believe that triorganoaluminum reagents first react with LiCl forming active organoaluminate complexes (**66**) due to the Lewis acidity of triorganoaluminums. Thus,

formed triorganoaluminates will transmetallate with PN-bound CuX to form (PN)CuR intermediates, which will then undergo oxidative addition with organohalides followed by reductive elimination to give cross-coupled products. Evidence for the existence of these steps can be garnered from the literature. Triorganoaluminate complexes have previously been isolated and synthesized.[40] It is known that, during allylic and conjugate addition reactions, the triorganoaluminum reagents undergo transmetalation with Cu salts to form organocopper(I) intermediates.[76] In addition, our group has recently synthesized and fully characterized a three coordinate (PN)CuPh complex and shown that it readily reacts with Ar-I at 120 °C to give biaryl products.[27]

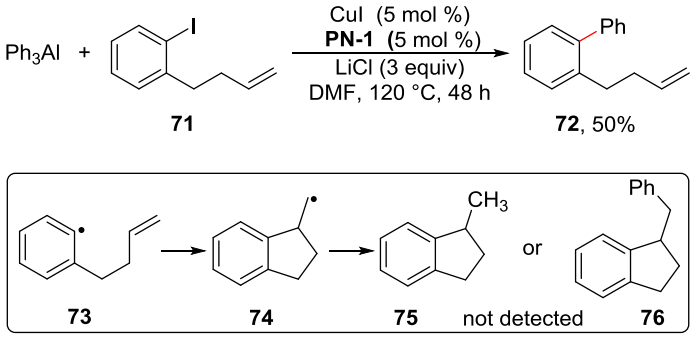
Scheme 2.3. Proposed catalytic cycle



Radical Clock Experiment: In order to confirm that the reaction does not involve any free radicals produced from a single electron transfer (SET) to aryl halides, we carried out a radical clock experiment. It is known that the radical probe (**71**) undergoes cyclization at the rate of 5.0 x 10^8 s^{-1} in DMF at 50 °C.[77] When there is absence of a free radical, we can expect to form only the direct coupling product without cyclization.[36] Therefore, when we

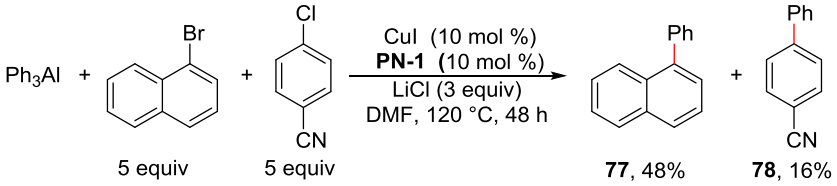
carried out the reaction of triphenylaluminum reagents with the radical probe (**71**), we obtained only the direct cross-coupling product (**3**) in 50% GC yield, suggesting the absence of free aryl radicals in the reaction (Scheme 2.4).

Scheme 2.4. Radical clock experiment



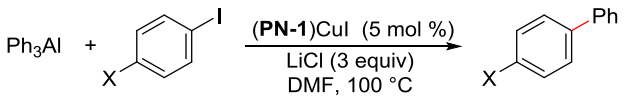
Competition Experiment: Further evidence to show that our current reaction does not proceed through SET pathway, we carried out a competition experiment. Here, we performed the reaction between triphenylaluminum reagent with 1-bromonapthalene and 4-chlorobenzonitrile. As 4-chlorobenzonitrile has higher reduction potential (-2.03 V vs SCE in DMF) than 1-bromonapthalene (-2.17 V vs SCE in DMF), 4-chlorobenzonitrile is expected to reduce by SET to form a radical anion faster, which later forms aryl radical after the cleavage of the halide anion.[78] Despite the favorable condition, 1-bromonapthalene reacted faster than 4-chlorobenzonitrile and afforded the corresponding products in 48% and 16% GC yields (3:1), respectively (Scheme 2.5). This result is consistent with previously reported Cu-catalyzed coupling in which reaction was shown to proceed via oxidative addition-reductive elimination route[36] and in sharp contrast to another similar reaction which was shown to proceed via SET pathway.[79]

Scheme 2.5. Competition experiment



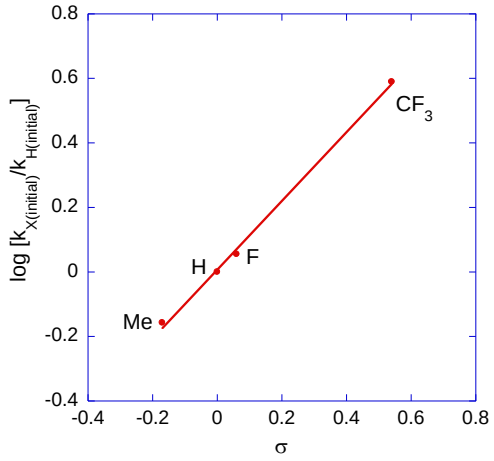
Hammett Plot: We obtained the Hammett plot to show the effect of electronic properties of the substituted iodoarenes on the rate of the reaction with triarylaluminum reagents to form biaryl products. The initial rates of reaction for <30% GC yield of triphenylaluminum reagents with iodobenzene, p-iodotoluene, p-iodoflurobenzene and p-iodobenzotrifluoride showed a linear curve when 2-nitrobiphenyl was used as a calibration standard (Table 2.10). The log values of the ratio of initial rates of substituted iodoarenes to unsubstituted iodoarene (iodobenzene) versus σ were plotted and was found to be linear (R^2=0.99) with a ρ value of +1.06 (Figure 2.3). These results are consistent with the oxidative addition of aryl halides to electron-rich metal centers where electron-deficient aryl halides oxidize low valent to high valent metals faster than electron rich aryl halides.[80,81]

Table 2.10. Iodoarenes used for the Hammett plot and the values for the initial rates of reactions



iodoarenes	$k_{X(initial)}$ (M s^{-1})	log[$k_{X(initial)}$/ $k_{H(initial)}$]	σ
X = H	1.9×10^{-5}	0.0000	0.00
X = Me	1.3×10^{-5}	-0.1576	-0.17
X = F	2.2×10^{-5}	0.05541	0.06
X = CF_3	7.5×10^{-5}	0.5894	0.54

Figure 2.3. The Hammett plot for the reaction of Ph_3Al with 5.0 equivalents of iodobenzene, *para*-iodotoluene, *para*-iodofluorobenzene and *para*-iodobenzotrifluoride. The curve depicts the result of an unweighted least-square fit to y = a*x + b (a = +1.06, b = 7.27×10^{-3}, $R^2 = 0.99$).



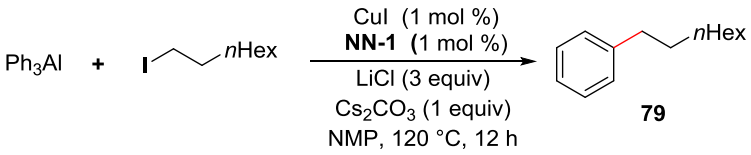
2.3.Copper-Catalyzed Cross-Coupling of Organoaluminum Reagents with C(sp3)-Halides

As discussed above (Section 2.2), we successfully developed Cu-Catalyzed cross-coupling of trialkylaluminum reagents and aryl halides to form alkylarenes.[14] An alternative route to form arylalkanes would be the coupling of triarylaluminum reagents with alkyl halides. In order to realize this goal, we started our work with our previously established conditions for the coupling of triphenylaluminum reagent with 1-iodooctane in presence of 1 mol% of CuI and 1 mol% of 2-(dihenylphosphino)-N,N-dimethylaniline (PN-1) and 3 equivalent LiCl in DMF at 120°C. However, the reaction afforded the coupled product, phenyloctane, only 34% GC yield (Table 2.11 entry 1). Therefore, we started screening for solvents and bases, and found that when the reaction was carried out in NMP

in the presence of 1 equivalent of Cs_2CO_3, phenyloctane was formed in 66% GC yield (Table 2.11 entry 2).

A variety of ligands (Figure 2.4) were screened and found that *N,N,N',N'*-tetramethyl-o-phenylenediamine (NN-1) was an effective ligand for CuI that enabled us to increase the product yield to 81% GC yields (76% isolated) (Table 2.11 entry 3).[76,82-84] Reactions containing other PN- and NN-based ligands that are analogous to PN-1 and NN-1 afforded cross-coupled product octylbenzene (**79)** in lower yields than the reaction performed in the absence of NN-1. Reactions containing bisphosphine ligand, *o*-bis(diphenylphosphine)benzene (PP) and anionic ligands such as 8-hydroxyquinoline (NO) and 2,2,6,6-tetramethyl-3,5-heptanedione (OO) (Figure 2.4) also formed the product octylbenzene in lower yields than the reaction performed in the absence of NN-1. The reaction does not proceed in the absence of CuI (Table 2.11 entry 4). The cross-coupled product octylbenzene is formed in 50% and 54% yields, respectively, in the absence of LiCl and Cs_2CO_3 (Table 2.11 entries 5 and 6). The reactions with 2 and 4 equivalents of LiCl also afford the product octylbenzene in comparable yields (78% and 76%, respectively) to that of the standard reaction (Table 2.11 entries 7 and 8). However, excess of LiCl is detrimental to the reaction (Table 2.11 entry 9). The reaction can also be performed at as low as 80 °C affording the coupled product octylbenzene only in slightly lower yields than that of the standard reaction (Table 2.11 entries 10 and 11). The cross-coupled product is formed in 78% at 100 °C (Table 2.11 entry 10). The reaction of Ph_3Al with 1-iodooctane using the Schlenk technique afforded cross-coupled product octylbenzene in 72% yield.

Table 2.11. Optimization of reaction conditions[a]



entry	deviation from the standard conditions	yield (%)[b]	entry	deviation from the standard conditions	yield (%)[b]
1	PN-1 instead of NN-1 in DMF, no Cs_2CO_3	34	7	2 equiv LiCl	78
2	No NN-1	66	8	4 equiv LiCl	76
3	none	81 (76)	9	6 equiv LiCl	35
4	without CuI	0	10	100 °C	78
5	without LiCl	50	11	80 °C	75
6	without Cs_2CO_3	54			

[a]Reactions were run in 0.5 mL DMF. Commercially available Ph_3Al was used. [b]GC yields (average of at least two parallel runs) calibrated against pyrene as an internal standard. Value in parenthesis is the isolated yield (1.0 mmol).

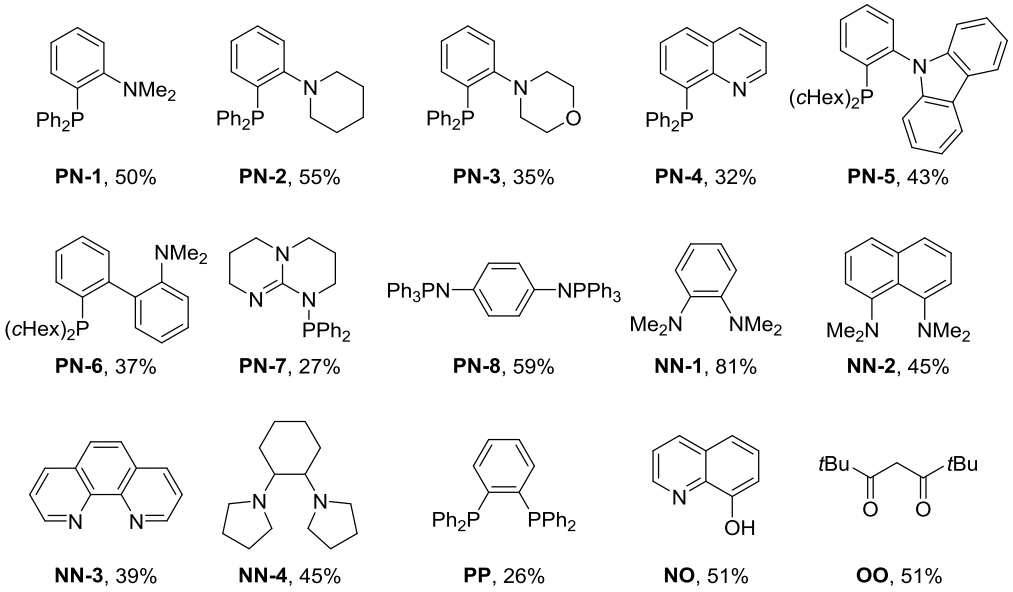
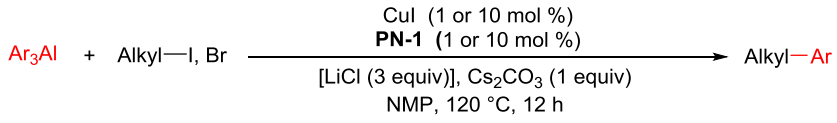
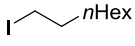
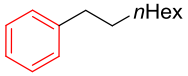
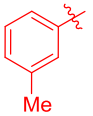
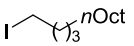
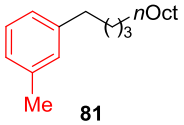
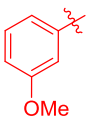
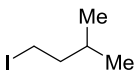
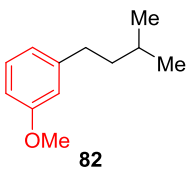


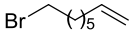
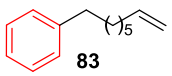
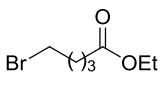
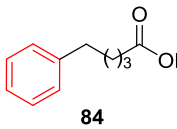
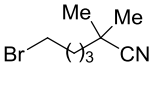
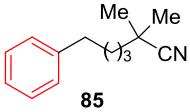
Figure 2.4. Ligands used for reaction optimization

Once we found out that NN-1 and CuI as the best catalyst, we began to explore the substrate scope of the reaction. While the reaction proceeded in good yields with alkyl iodides (Table 2.12, entries 1-3) by using 1 mol% of the catalyst, reactions with alkyl bromides, which are more readily available and less expensive than alkyl iodides, required 10 mol% of NN-1/CuI (entries 4-15). The reaction can be performed with electron-neutral and electron-rich triarylaluminum reagents. Cross-coupling of electron-deficient (4-$FC_6H_4)_3Al$ with benzyl bromide afforded the product only in 18% yield. The reaction tolerates a variety of functional groups on alkyl halides including highly sensitive esters (entries, 5, 9 and 11), nitriles (entries 6 and 7) and olefins (4, 8, 10, 13 and 15). The conversion of bromoolefins is generally over 90%. The low to moderate yields could result from protodebromination of the bromoolefins.With 10 mol% catalyst loading, the reaction can also be extended to the coupling of triarylaluminum reagents with benzyl bromides (entries 12 and 14).[76]

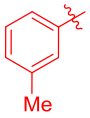
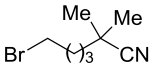
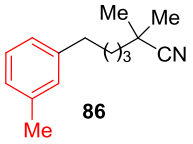
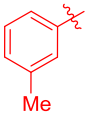
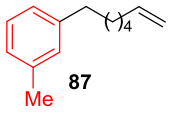
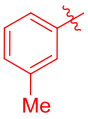
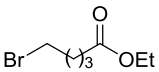
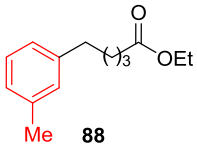
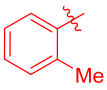
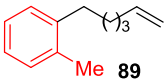
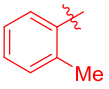
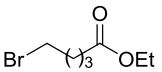
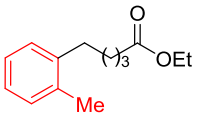
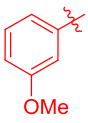
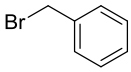
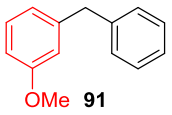
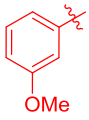
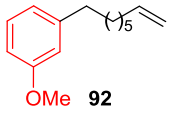
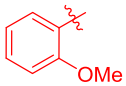
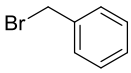
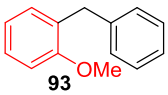
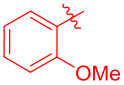
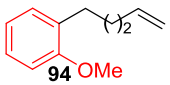
Table 2.12. Coupling of triarylaluminum reagents with alkyl iodides and bromides[a]



	Ar in Ar_3Al	Alkyl—I, Br	Alkyl—Ar	yield (%)[b]
1			 **80**	76
2			 **81**	61
3			 **82**	49

	Ar in Ar_3Al	Alkyl—I, Br	Alkyl—Ar	yield (%)[b]
4			 **83**	60
5			 **84**	58
6			 **85**	71

Continuation of table 2.12.

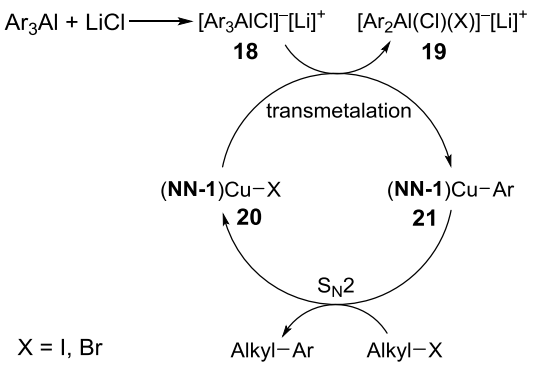
entry	Ar in Ar_3Al	Alkyl—I, Br	Alkyl—Ar	yield (%)[b]
7			 **86**	88
8			 **87**	53
9			 **88**	59
10			 **89**	46
11			 **90**	92
12			 **91**	53
13			 **92**	52
14			 **93**	68
15			 **94**	47

[a]Reactions were run in 5 mL DMF. Reactions for entries 1-3 were run with 1 mol% NN-1/CuI. Reactions for entries 4-15 were run with 10 mol% NN-1/CuI. Triaylaluminum reagents, except the commercially available Ph_3Al, were prepared from the reaction of 3 equivalents of ArLi reagents with $AlCl_3$ (99.99% purity) in THF at room temperature and were used without further purification. Each reaction contains 3 equivalents of LiCl, written in parenthesis below the reaction arrow, which is generated during the preparation

of triarylaluminum reagents. [b]Yields are for products isolated by column chromatography from a 1.0 mmol scale reaction.

We proposed a catalytic cycle for the current reaction (Scheme 2.6) depending upon the literature reports and our recent mechanistic works on Cu-catalyzed cross-couplings.[27,29,31] The optimization of reaction conditions shows that both NN-1 and LiCl improve product yields for the current coupling of triarylaluminum reagents with alkyl halides. As such, we believe that organoaluminate complexes such as **18**, generated from the binding of LiCl to three-coordinate triarylaluminum reagents, are the actual species in solution that undergo transmetalation with NN-bound CuX (X = I, Br) to generate (NN)CuAr complexes as the reaction intermediates. There are literature reports on the synthesis and characterization of catalytically competent Cu^{I}-complexes that contain nitrogen-based ligands.[35,36,38,39,85] Triorganoaluminum complexes are also known to form triorganoaluminate species in the presence of anions in solution.[40,86-89] We analyzed a mixture of Ph_3Al and LiCl using Al-NMR. No significant change was observed in the Al-NMR spectra. However, due to strong Lewis acidic nature of Ph_3Al, formation of a small amount of $[Ph_3AlCl]^-[Li]^+$ cannot be ruled out without further experiments. Furthermore, there are cases where organoaluminum reagents have been demonstrated to undergo transmetalation with Cu-salts based on their participation in allylic and conjugate addition reactions.[6,76,90] There are some examples where similar Cu-catalyzed couplings of organometallic reagents with alkyl electrophiles have previously been shown to proceed via S_N2 process.[82,91] Thus, we believe that a similar mechanistic scenario can also be envisioned in the current Cu-catalyzed cross-coupling of triarylaluminum reagents with primary alkyl halides that involves (NN)CuAr as the reaction intermediates.

Scheme 2.6. Proposed catalytic cycle



2.4. Summary

Over the past decades, the transition metals catalyzed cross-couplings have been developing tremendously and are mainly catalyzed by precious and earth scarce metal like Pd. So, in order to find alternatives for Pd, our group is working with earth abundant and cheap Cu metal as a catalyst. We have developed the first Cu-catalyzed cross-coupling of organoaluminum reagents with organohalides. The reactions can be performed using various organoaluminum reagents, such as alkyl-, aryl- and alkynylaluminum, and a variety of organohalides like aryl and heteroaryl iodides, aryl and heteroaryl bromides, heteroaryl chlorides and vinyl bromides. Reactions proceed with both the primary and secondary alkylaluminum reagents in good yields. The reactions for alkyl-aryl, aryl-aryl and aryl-vinyl coupling require the addition of PN-1 ligand to obtain the best yields of the products. However, the couplings with heteroaryl halides do not require PN-1 ligand even for reactions that cross-couple primary and secondary alkylaluminum reagents with heteroaryl halides. These 'ligand-free' cross-couplings are not complicated by the formation of rearranged products that are known to arise usually by rapid β-hydride elimination and olefin re-insertion process with established transition metals such as Pd and Ni. Preliminary

mechanistic studies with a radical probe and relative reactivity studies for the reactions of 1-bromonaphthalene and 4-chlorobenzonitrile indicate that the transformation does not involve aryl radicals or aryl radical anions as intermediates. These results combined with the result of the linear free-energy relationship (the Hammett plot) study suggest that the reaction is likely to proceed via an oxidative addition-reductive elimination pathway.

We have developed a Cu-catalyzed coupling of triarylaluminum reagents with primary alkyl iodides and bromides. The reaction proceeds in the presence of NN-1/CuI as an effective catalyst. This reaction condition works for electron-neutral and electron-rich triarylaluminum reagents. The reaction tolerates various functional groups on alkyl halides including highly sensitive esters, nitriles and olefins. Our reaction condition can be used for the coupling of triarylaluminum reagents with benzyl bromides as well.

2.5. References

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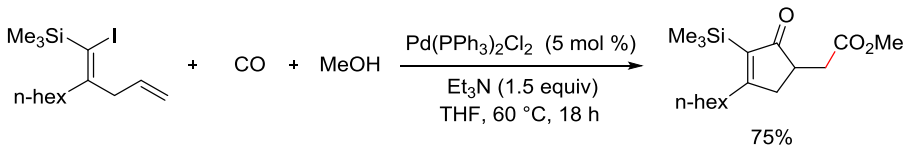
Chapter 3: Transition Metal-Catalyzed Olefin Dicarbofunctionalization

3.1. Introduction

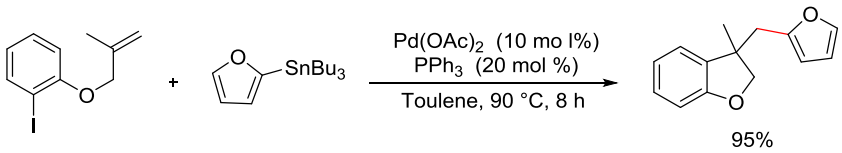
Alkenes are one of the most significant and readily available building blocks of the natural products, pharmaceuticals and materials. Many reactions like oxidation, hydroformylation, hydrogenation, oligomerization, Wacker oxidation,[1] polymerization[2] are applied in the chemical industry. Functionalization of simple olefin has become powerful tool for chemists to generate highly functionalized skeleton in organic synthesis. Particularly, intermolecular and intramolecular difunctionalization of simple alkenes help to increase molecular complexity and opens new doors for the formation of unconventional bonds.[3] The classic Sharpless dihydroxylation[4] is the simple example of olefin difunctionalization where two hydroxyl groups are added in adjacent carbons simultaneously.[5,6] There are few literature reports regarding transition metal (TM) catalyzed difunctionalization of olefins by cross-coupling[7] such as carbooxygenation[8-18] and carboamination[19-31] which have been developed as a powerful process that introduce new C-C/C-O and C-C/C-N bonds in adjacent carbons. More recently, dicarbofunctionalization which involves the installment of two carbon-based entities across an olefin to generate two C-C bonds has gained tremendous interest owing to its ability to assemble complex carbon skeletons rapidly. So far, this reaction is still among the least explored and underdeveloped difunctionalization processes to date. One of the powerful ways of achieving dicarbofunctionalization of unactivated olefins is to combine Heck carbometalation and cross-coupling. Here, aryl halides and organometallic reagents are utilized as carbon sources.

Olefin dicarbofunctionalization mostly involves cyclization. Here, the recent and past development intramolecular olefin dicarbofunctionalization is briefly described. In 1987, Balme and coworkers[32] reported the dicarbofunctionalization of olefins tethered to dicarbonyl compounds bearing an enolizable α-hydrogen (DMSO pK_a ~13) with aryl halides.[33,34] In 1985, Negishi and Tour reported Pd-catalyzed double carbonylative cyclization functionalized unactivated olefins tethered to vinyl and aryl iodides with two molecules of CO that were inserted in vinyl/aryl-PdX species before cyclization and in the resultant C(sp^3)-PdX intermediates after cyclization (Scheme 3.1).[35-38] In 1988, Grigg and coworkers reported the use of using 2,2-disubstituted tethered olefins which generate stable C(sp^3)-PdX intermediate lacking β-H, which enabled further transmetalation/reductive elimination to proceed successfully furnishing five- and six-membered cyclization/cross-coupling products. The reaction could be conducted with 1,2-disubstituted tethered olefins as well, which generated C(sp^3)-PdX species with β-H's but the substrate backbone was geometrically constrained as a result attainment of favorable geometry for β-H elimination was prevented (Scheme 3.2).[39,40]

Scheme 3.1. Pd-catalyzed cyclization/carbonylation

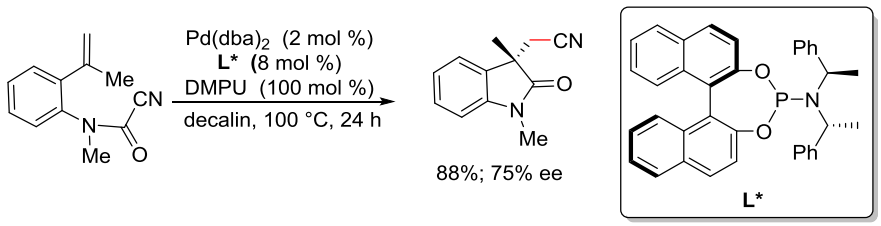


Scheme 3.2. Pd-catalyzed cyclization/cross-coupling with organotin reagents

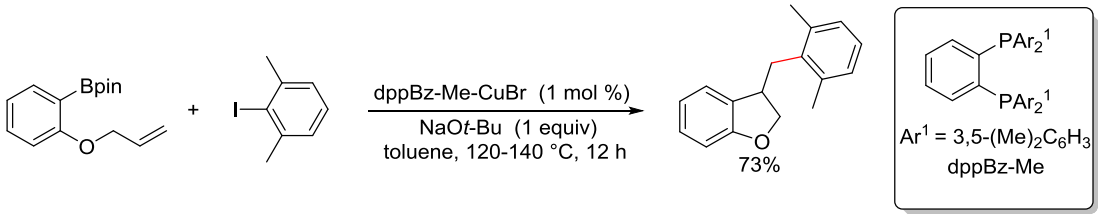


In 2008, Takemoto and coworkers reported Pd-catalyzed enantioselective cyanoacylation of (2-vinylphenyl)carbamoyl cyanide derivatives in the presence of a chiral phosphoramidite ligand and stoichiometric quantity of *N*,*N*-dimethylpropylene (DMPU) where the reaction proceeded with cleavage of the C-C bond of the carbamoyl cyanide moiety followed by the addition of both fragments across the tethered olefin (Scheme 3.3).[41] In 2014, Brown and Yu reported a Cu-catalyzed cyclization/cross-coupling of olefin-tethered aryl-9-BBN with aryl iodides where aryl-9-BBN first underwent transmetalation with CuBr/dppBz-Me followed by migratory insertion of the tethered olefin into the aryl-Cu bond (Scheme 3.4).[42] In 2004, Widenhoefer and Liu reported Pd-catalyzed cyclization/carbonylation of indoles bearing tethered olefins at C-2 position that generated a new carbocycle at the C-2/C-3 position.[43] In this reaction firstly, Lewis acidic Pd(II) will activate the tethered olefin and the attack of the coordinated olefin by the indole at C-3 which resulted in generation of C(sp^3)-PdX species bearing β-Hs, which were intercepted by CO insertion faster than β-H elimination (Scheme 3.5). There are few examples of similar reactions where the olefins are tethered to organometallic. Regarding this, our group reported a Cu-catalyzed cyclization/cross-coupling of aryl and heteroaryl iodides with alkyl and arylzinc reagents generated in situ from the reaction of alkyl and aryl halides with Zn (Scheme 3.6).[51]

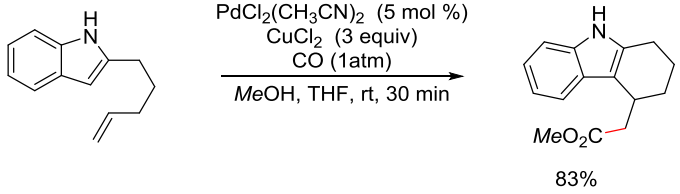
Scheme 3.3. Pd-catalyzed enantioselective intramolecular cyanoacylation



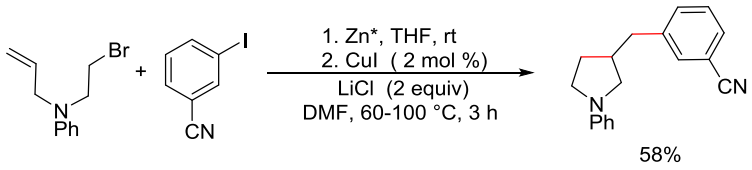
Scheme 3.4. Cu-catalyzed cyclization/cross-coupling of aryl-9-BBN reagents with aryl iodides



Scheme 3.5. Pd-catalyzed aryl C-H cyclization/carbonylation



Scheme 3.6. Cyclization/cross-coupling of olefin-tethered alkyl and arylzinc reagents



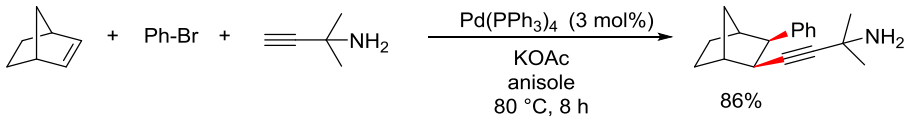
3.2. Transition Metal-Catalyzed Intermolecular Olefin Dicarbofunctionalization

The three-component dicarbofunctionalization of unactivated olefin is very hard to achieve. The three-component dicarbofunctionalization of unactivated olefin usually suffers from major side reactions such as β-H elimination, cross-coupling and protodemetallation. Various strategies which have been used to overcome these major side reactions and to achieve olefin dicarbofunctionalization are described below.

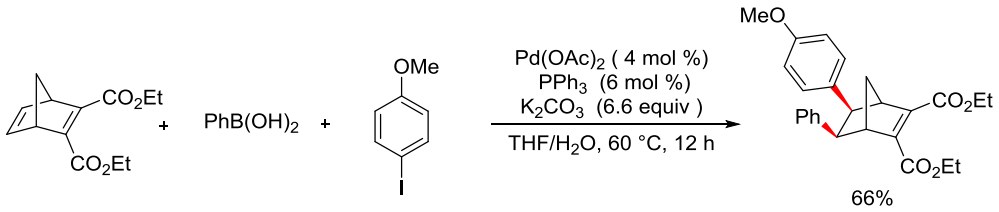
In 1982, Chiusoli and Catellani reported Pd-catalyzed dicarbofunctionalization of the olefin in norbornene with organohalides and alkynes giving cis, exo-difunctionalized products in good to excellent yields.[44] The geometric constraints bicyclic backbone of

norbornene prevents β-H elimination from the C(sp^3)-PdX intermediates generated in situ (Scheme 3.7). Later, Goodson reported the $Pd(OAc)_2$ catalyzed selective difunctionalization of one olefin in norbornadiene by using aryl halides and $ArB(OH)_2$ (Scheme 3.8).[45]

Scheme 3.7. Difunctionalization of norbornene with aryl bromides and alkyne



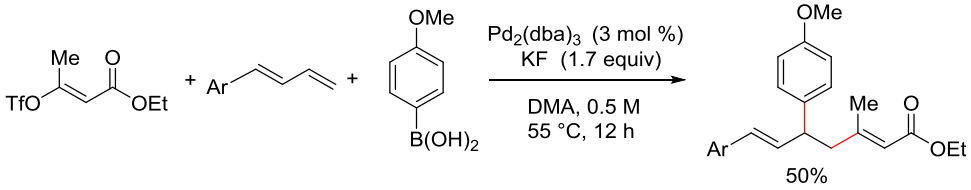
Scheme 3.8. Difunctionalization of norbornene with aryl bromides and alkyne



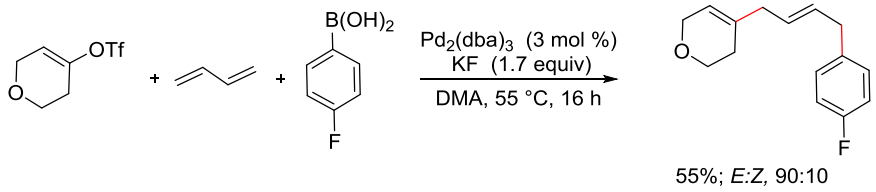
There are cases where successful difunctionalization of organohalides and organometallic reagents had been carried out in 1,3-dienes and styrenes without suffering from β-H elimination. Takai and coworkers published a paper reporting a Cr-catalyzed 1,2-difunctionalization of 1,3-dienes with alkyl halides and benzaldehyde where they used 6 equivalent of $CrCl_2$.[46] Recently in 2011, Sigman and coworkers[47,48] reported Pd-catalyzed 1,2-difunctionalization of 1,3-dienes with vinyl triflates and arylboronic acids in the presence of KF where they showed that π-allylpalladium species which is intercepted from the Heck C(sp^3)-PdX intermediates helps to avoid β-H elimination and enable transmetalation/reductive elimination to proceed as desired to form dicarbofunctionalized products (Scheme 3.9).[49] In 2013, same group also demonstrated that $Pd_2(dba)_3$ could catalyze the 1,4-difunctionalization of 1,3-butadiene with vinyl triflates and

aryl/vinylboronic acids to generate dienes and trienes (Scheme 3.10).[50,51] Song and coworkers used $Pd_2(dba)_3$ as a catalyst to carry out the 1,2-difunctionalization of styrene derivatives using vinyl triflates and arylboronic acids (Scheme 3.11).[52]

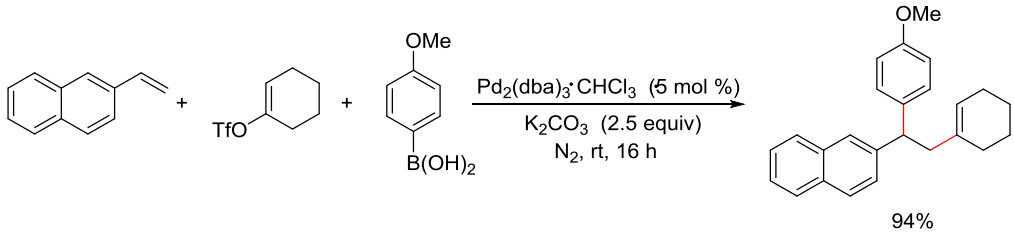
Scheme 3.9. Pd-catalyzed 1,2-difunctionalization of 1,3-dienes with vinyl triflates and arylboronic acids



Scheme 3.10. Pd-catalyzed 1,4-difunctionalization of 1,3-dienes with vinyl triflates and arylboronic acids



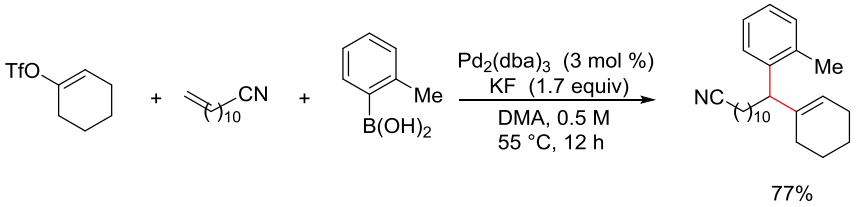
Scheme 3.11. 1,2-Difunctionalization of styrenes with vinyl triflates and arylboronic acids



Generally, difunctionalization of unactivated olefins in simple alkenes where in situ-generated Heck C(sp^3)-MX intermediates are hard to stabilized lead to the formation of 1,1-difunctionalized product. Sigman and coworkers showed that $Pd_2(dba)_3$ can be used to carry out the 1,1-difunctionalizing terminal alkenes with vinyl triflates and arylboronic acids (Scheme 3.12).[49] The reaction was anticipated to advance via β-H elimination from

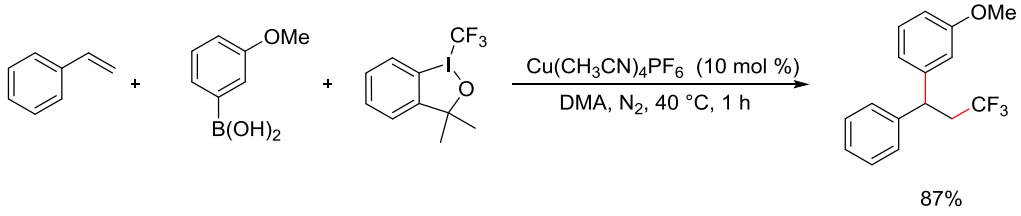
the Heck C(sp^3)-PdX intermediates followed by a Pd-H reinsertion/π-allylpalladium formation/transmetalation/reductive elimination sequence.[53]

Scheme 3.12. 1,1-Difunctionalization of terminal alkenes with vinyl triflates and arylboronic acids



There are some literature reports which showed that copper-based catalysts played vital role in the addition of carbon-centered radicals to olefins during dicarbofunctionalization reactions. In 2013, Liu and coworkers developed a Cu-catalyzed trifluoromethylarylation of both styrene derivatives and unactivated olefins with Togni's reagent and arylboronic acids (Scheme 3.13).[54] Mechanistially, they proposed that Togni's reagent would coordinate to arylboronic acids prior to the generation of •CF_3 and then transmetalation occurs in the presence of a Cu-catalyst. The •CF_3 would then add to olefins followed by radical recombination with ArCu(II) and reductive elimination from a Cu(III) species to give the desired product.

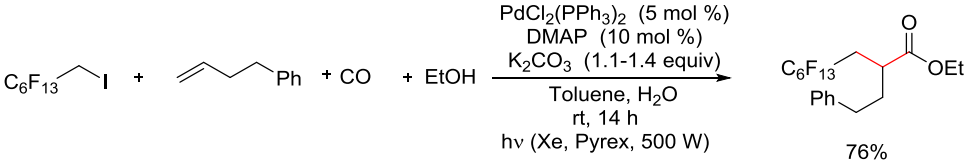
Scheme 3.13. Cu-catalyzed trifluoromethylarylation of styrenes



There are some cases of photochemically-induced transition metal-catalyzed difunctionalization of olefin. Ryu and coworkers[55] developed a photochemically-induced

Pd-catalyzed difunctionalization of unactivated olefins with α-iodocarbonyl compounds and CO/alcohols where reaction is proposed to proceed via the formation of alkyl radicals from alkyl halides and their addition to olefins(Scheme 3.14).[56]

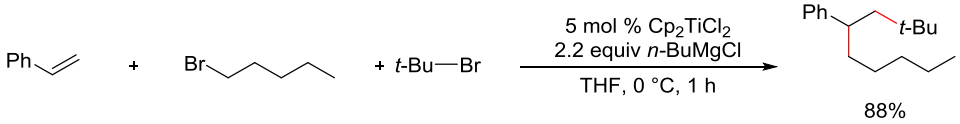
Scheme 3.14. Pd-catalyzed carbonylative alkylation of olefins



There are several research papers which showed that oxidation of low valent C(sp^3)-Pd(II) intermediates to high valent C(sp^3)-Pd(IV) intermediates assist in overcoming the complications of β-H elimination in many reactions including C-H bond activation.[57-59] Toste and coworkers recently published a research paper where 8-aminoquinoline could be used as a coordinating group for Pd-catalyzed fluoroarylation of 2-vinylbenzamides, a reaction that is proposed to proceed via a Pd(II)/Pd(IV) catalytic cycle.[60]

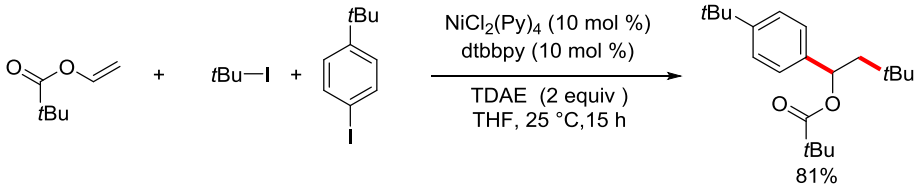
There has been some progress made in difunctionalizing olefins by reductive couplings wherein both carbon entities are derived from organohalides. In 1988, Kambe and coworkers showed that Cp_2TiCl_2 could catalyze the addition of two different types of alkyl halides across the olefin in styrene derivatives in the presence of stoichiometric quantities of *n*BuMgCl (Scheme 3.15).[61] They proposed that the reaction proceeded by the addition of alkyl radicals to styrenes followed by the transmetalation of alkyl-[Ti] intermediates to *n*BuMgCl and reaction of the resultant alkyl-MgCl with alkyl halides.

Scheme 3.15. Ti-catalyzed reductive dialkylation of styrenes with alkyl bromides

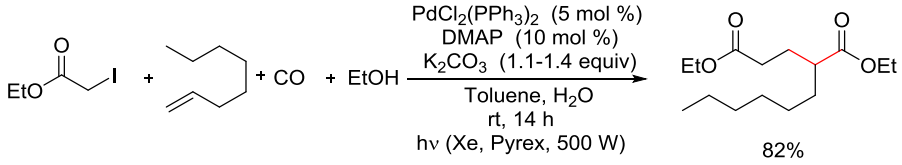


Nevado and coworkers also reported a Ni/dtbbpy-catalyzed reductive difunctionalization of unactivated and mildly activated olefins in allylic compounds, vinyl carboxylates and enamides where they proposed that the reaction to proceed via a radical process that involved four species of Ni–Ni(0)/Ni(I)/Ni(II)/Ni(III) and required tetrakis(dimethylamino)ethylene (TDAE) as a stoichiometric reductant to reduce Ni(II) to Ni(0) to turn over the catalytic cycle (Scheme 3.16).[62] There is a literature reported by Ryu and coworkers[55] where they developed the photochemically-induced Pd-catalyzed difunctionalization of unactivated olefins with α-iodocarbonyl compounds and CO/alcohols and they proposed that the reaction is proposed to proceed via the formation of alkyl radicals from alkyl halides and their addition to olefins (Scheme 3.17).[56]

Scheme 3.16. Ni-catalyzed reductive alkylarylation of olefins



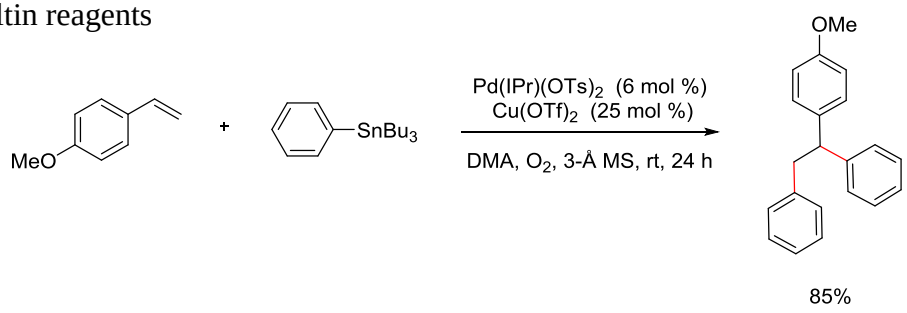
Scheme 3.17. Pd-catalyzed carbonylative alkylation of olefins



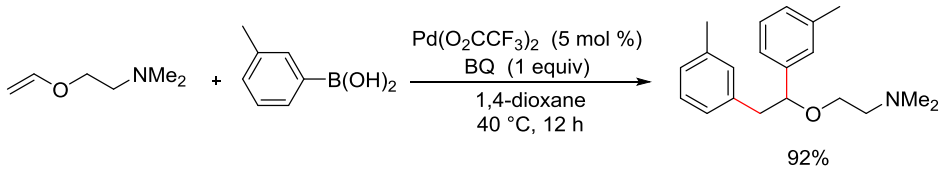
In 2009, Sigman group reported a Pd-catalyzed oxidative difunctionalization of olefins with aryl- and vinyltin reagents where same same aryl/vinyl groups from organotin reagents was added across the olefins (Scheme 3.18).[63] They reported that styrenes and dienes resulted 1,2-difunctionalized products while simple unactivated alkenes generated 1,1-difunctionalized products.[64] In the same year, Larhed and coworkers also reported a

Pd-catalyzed oxidative 1,2-diarylation of terminal olefins in vinyl ethers with $ArB(OH)_2$ where they proposed that coordination-assistance by the *N*,*N*-dimethylamino group tethered to the vinyl ethers would form a palladacycle in situ which prevent β-H elimination from a $C(sp^3)$-PdX intermediate (Scheme 3.19).[65-67]

Scheme 3.18. Pd-catalyzed oxidative functionalization of styrenes and 1,3-dienes with aryl/vinyltin reagents



Scheme 3.19. Pd-catalyzed coordination-assisted oxidative diarylation of vinyl ethers



3.3. Summary

TM-catalyzed dicarbofunctionalization of unactivated olefins results in two C-C bonds in one synthetic step which helps in building complex molecular architectures in short synthetic routes from readily available chemicals. But, this type of transformation usually suffers from β-H elimination from $C(sp^3)$-[M] species that are generated as intermediates in catalytic reactions. Various strategies like utilizing 2,2-disubstituted olefins that would generate $C(sp^3)$-[M] intermediates lacking in β-H's, conducting reactions in the presence of CO or using olefins in geometrically constrained molecules are being followed in order to address the problems of β-H elimination. Though, there is significant progress in the

development of dicarbofunctionalization but there is much more need to be done in case of dicarbofunctionalization of simple alkenes which lack any intrinsic stabilizer of C(sp^3)-[M] intermediates.

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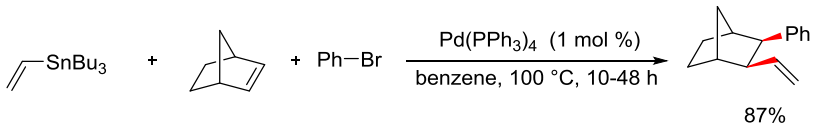
Chapter 4: Olefin Dicarbofunctionalization by Cross-Coupling

4.1. Introduction

There are only few examples of three-component dicarbofunctionalization of olefins with organohalides and organometallic reagents. Due to the intermolecular nature of the reactants, the development of three-component dicarbofunctionalization of unactivated olefins remains very challenging. Three and half decades have past but only three different strategies have been exploited in order to overcome the complications of β–H elimination and/or direct cross-coupling that function as major side reactions in the three-component dicarbofunctionalization of unactivated olefins – 1) use of geometrically constrained olefin substrates, 2) use of dienes or styrenes as substrates to stabilize alkyl-metal species as π-allyl or π-benzyl intermediates and, 3) use of heteroatom-bearing olefins as substrates to stabilize alkyl-metal species as transient metallacycles.

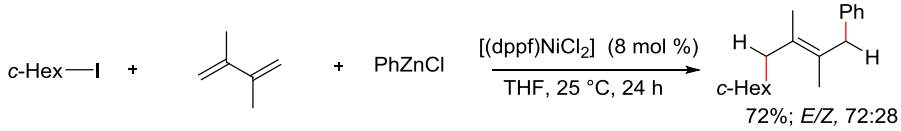
In 1987, Kosugi, Migita and coworkers[1-3] reported a regioselective aryl-vinylation of norbornene with bromobenzene and tributylvinyltin reagents by using $Pd(PPh_3)_4$ as a catalyst (Scheme 4.1).[4-6] The geometrical restriction of bond rotations in these bicyclic molecules help in suppressing β-H elimination from their corresponding Heck $C(sp^3)$-[M] intermediates that prevent the $C(sp^3)$-[M] species from attaining *syn*-coplanarity with a β-hydrogen required for β-H elimination, and enable the subsequent steps of transmetalation and reductive elimination to proceeds as desired. Chiusoli, Catellani[4] and Goodson[7] had also reported Pd-catalyzed dicarbofunctionalization of the olefin in norbornene and norbornadiene.

Scheme 4.1. Dicarbofunctionalization of norbornene



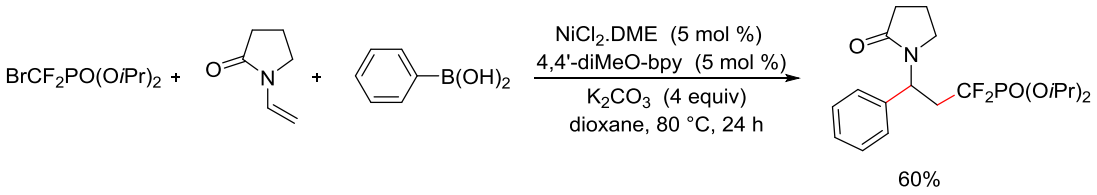
One of the approach to overcome the complications of β-H elimination is the stabilization of the C(sp^3)-[M] species as π-allyl-[M] intermediates. In this process, conjugated dienes are usually used as substrates rather than isolated olefins wherein the additional olefin of the diene forms a π-allyl complex with the C(sp^3)-[M] species generated after the Heck carbometalation process. For example, in 2004, Kambe and coworkers reported a dppf/$NiCl_2$-catalyzed 1,4-difunctionalization of 1,3-dienes with alkyl halides and PhZnCl or ArMgBr where they have shown that the 1,4-difunctionalized products also arise from the same π-allyl-[M] species as in 1,2-difunctionalization but the reductive elimination proceeds with the distal allylic carbon (Scheme 4.2).[8,9]

Scheme 4.2. Ni-catalyzed 1,4-difunctionalization of 1,3-dienes with PhZnCl reagents



Zhang and coworkers developed the Ni-catalyzed difluoroalkyl-arylation of vinyl groups in enamides where they had demonstrated a coordinating effect of amide oxygen.[10] Mechanistically, they proposed that the carbon radicals generated α to nitrogen after the addition of difluoroalkyl radical to the *N*-vinyl group would be stabilized by recombination with the Ni-catalyst coordinated to the amide (Scheme 4.3). The limitation of this work is that directing group cannot be removed.

Scheme 4.3. Ni-catalyzed difluoroalkylarylation of enamides by coordination-assistance



4.2. Ni-Catalyzed Diarylation of Vinylarenes via Imine-Assisted Formation of Transient Metallacycle

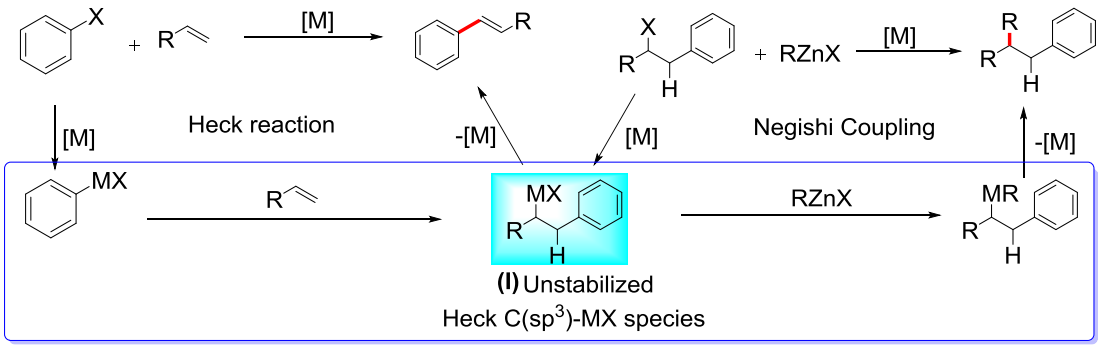
The concept of utilizing readily removable coordinating groups to stabilize the Heck C(sp^3)–[M] intermediates through the formation of transient metallacycles is widely used in directed C(sp^3)-C-H bond activation.[13-15] This concept is based on the fact that C(sp^3)-metallacycles undergo β–H elimination more slowly than their acyclic variants due to restricted bond rotations that prevent the attainment of favorable geometry for β-H elimination. This concept has never been reported to develop three-component diarylation of olefins. So, based on this idea of readily removable coordinating groups to stabilize the Heck C(sp^3)–[M] intermediates through the formation of transient metallacycles, we successfully developed a Ni(cod)$_2$-catalyzed 1,2-dicarbofunctionalization of 2-vinylbenzaldehyde derivatives with aryl halides/triflates and arylzinc reagents.[16]

4.2.1. Hypothesis and Initial Studies

Cross-coupling is one of the versatile synthetic method for generating carbon-carbon bond. One of the cross-coupling reaction is the Negishi coupling which uses organozinc as nucleophile and organohalides as electrophile in presence of transition metal like Pd to form carbon-carbon bond. Next is the Heck reaction that functionalizes olefins with organohalides through the formation of a new C-C bond with the application of a TM-

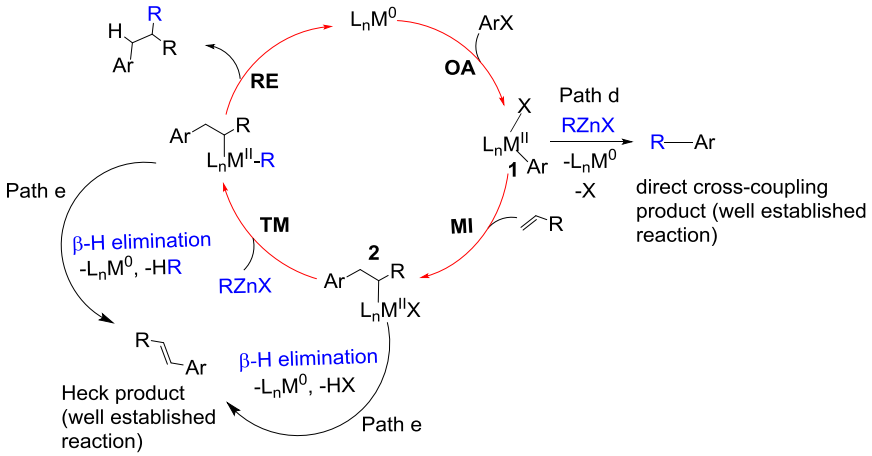
catalyst, typically Pd. Both Heck reaction and Negishi coupling gives common unstable species **I** (Scheme 4.4). The goal is to trap this Heck C(sp^3)-MX (**I**) species with the nucleophile (organozinc) to give the 1,2-difunctionalized product.

Scheme 4.4. Heck reaction and Negishi coupling



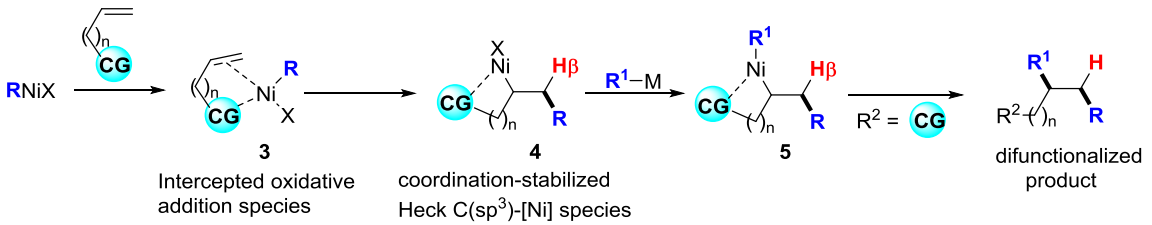
The catalytic cycle of transition metal-catalyzed olefin dicarbofunctionalization involves four elementary steps – oxidative addition (OA), carbometalation, transmetalation (TM) and reductive elimination (RE) (Scheme 4.5). An oxidative addition intermediate (Ar-M-X) (**1**) is expected to insert an olefin to generate a new C(sp^3)-MX (**2**) species,[11,12] which is subsequently intercepted by organometallic reagents (RZnX) via a transmetalation/reductive elimination sequence to form a desired product. But, this kind of transformation suffers from two major side reactions – 1) the cross-coupling between organohalides and organometallic reagents prior to olefin insertion (Path d); and 2) the Heck reaction by β-hydride (β-H) elimination from the C(sp^3)-MX intermediate (**2**) after olefin insertion (Path e). Therefore, careful strategies to intercept the Heck C(sp^3)–MX species (**2**) should be needed to enable 1,2-dicarbofunctionalization of olefins by cross-coupling.

Scheme 4.5. Catalytic cycle and side reactions



The two undesired pathways (Scheme 4.5) which are direct cross-coupling and β-H elimination to generate Heck product could be simultaneously surmounted by installing a removable coordinating group (CG) in olefin substrates (Scheme 4.6). The coordinating group (CG) perform two major functions-1) CG could initially intercept the higher valent, oxidative addition intermediate (Ar-M-X) (**1**) as species **3** via a bidentate coordination mode with the help of the vinyl group and promote Heck carbometallation onto the olefin faster than the direct cross-coupling through the entropically favorable intramolecular insertion process; 2) CG could then intercept and stabilize the Heck C(sp^3)-MX intermediates as transient metallacycles (species **4** and **5**), which are expected to slow down the process of β-H elimination due to restricted bond rotations that prevent the attainment of favorable geometry.

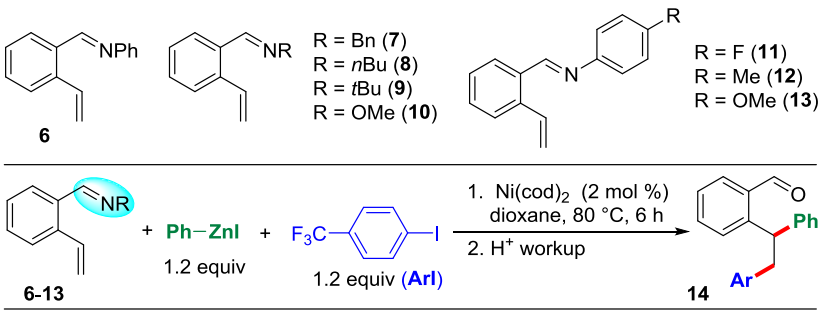
Scheme 4.6. Coordination assisted olefin dicarbofunctionalization



CG: coordinating group; R^1M: ArZnX, ArMgX, $ArBR_2$

We started our work by choosing imines as a coordinating group to test our hypothesis because of their efficacy of binding to transition metals and ease of removal by simple aqueous acidic workup. The reaction of 2-vinyl-*N*-phenylbenzylimine (**6**) with 4-iodobenzotrifluoride and PhZnI in the presence of 2 mol% $Ni(cod)_2$ in dioxane at 80 °C, gave the expected product **14** as a single regioisomer in 85% yield after acidic workup (Table 4.1, entry 1). Longer time is required when the reaction is scaled up to 0.5 mmol to get the best product yield (entry 1). No product was obtained in the absence of $Ni(cod)_2$ (entry 2). The product was formed in lower yields in shorter reaction time (entry 3). When we altered the imine group in vinylaldimine **6** to benzylimine (**7**), *n*-butylimine (**8**), *t*-butylimine (**9**) and *N*-methoxyimine (**10**), the expected product **14** is obtained in lower yield (entries 4-5). We also examined other coordinating groups such as 8-aminoqunoline, 8-hydroxyquinoline and 2-aminopyridine in *N*-allyl-*N*-benzylquinolin-8-amine, 8-(allyloxy)quinoline and *N*-allyl-*N*-(pyridin-2-yl)benzamide, which did not furnish any difunctionalized product. We then electronically modified the *N*-phenyl group in vinylimine **6** with *p*-F (**11**), *p*-Me (**12**) and *p*-OMe (**13**) groups. Among these vinylaldimines, only the *N*-anisolyl-imine **13** furnished the expected product **14** in comparable yield (entries 6-7). Other catalysts based on Pd, Co, Fe and Cu did not catalyze the reaction which shows the significance of Ni-catalyst for this transformation (entry 8). We tried other Ni-catalyst like $(Ph_3P)_4Ni$ and $NiBr_2$ which furnished the product **14** in lower yields (entries 9-10). When reaction was conducted in NMP or THF, then the product **14** was obtained in comparable yields (entry 11). Other solvents such as DMF, DMSO, benzene and MeCN afforded the product **14** in lower yields (entries 12-13).

Table 4.1. Optimization of reaction conditions[a]



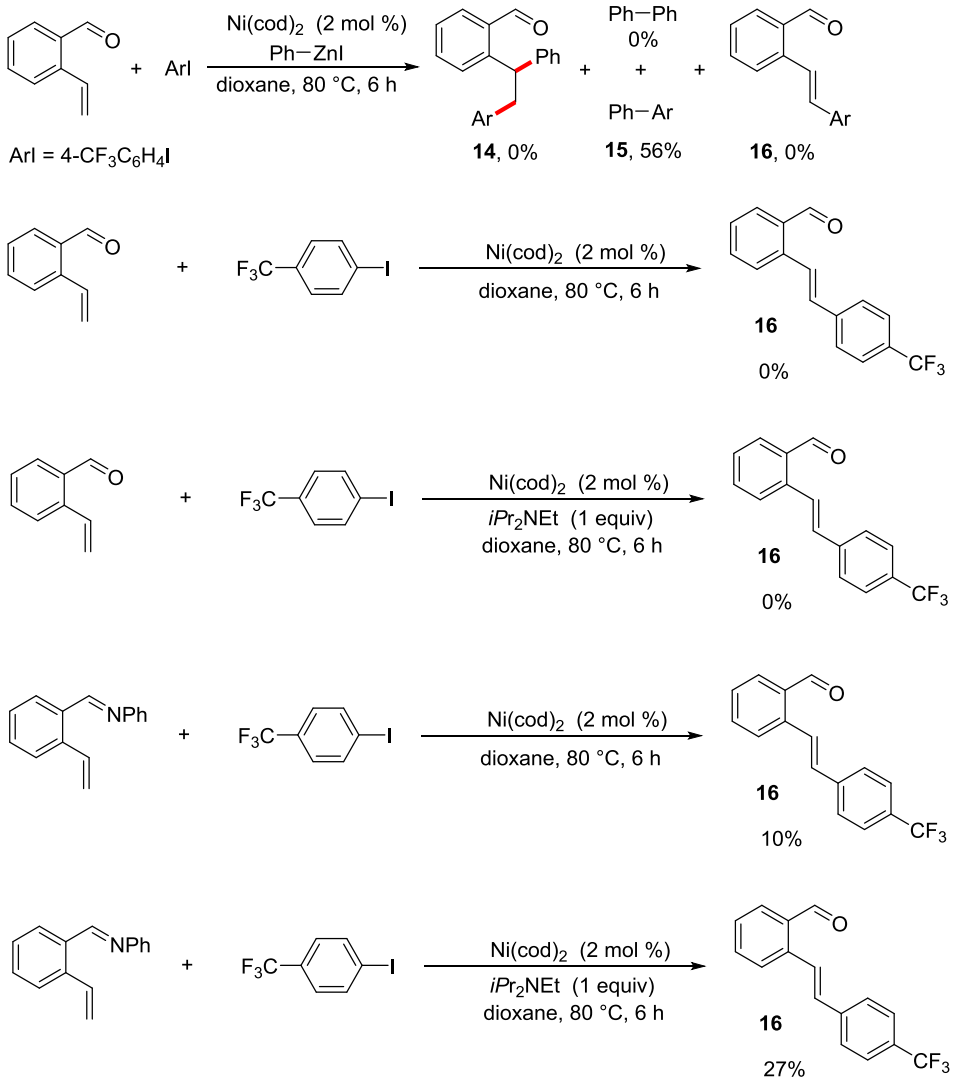
entry	reaction condition deviation	vinylimine	yield of **14** (%)[b]
1	none	**6**	85 (81)
2	without $Ni(cod)_2$	**6**	0
3	3 h	**6**	69
4	none	**7**	19
5	none	**8**, **9** or **10**	trace
6	none	**11** or **12**	34-44
7	none	**13**	78
8	Pd, Co, Fe or Cu-catalyst[c] instead of $Ni(cod)_2$	**6**	0
9	$(Ph_3P)_4Ni$ instead of $Ni(cod)_2$	**6**	9
10	$NiBr_2$ instead of $Ni(cod)_2$	**6**	42
11	NMP or THF instead of dioxane	**6**	77-78
12	DMF or DMSO instead of dioxane	**6**	48-60
13	benzene or MeCN instead of dioxane	**6**	35-49

[a]0.1 mmol scale reaction in 0.5 mL solvent. [b]Yields were determined by ^1H using pyrene as an internal standard. Value in parenthesis is the isolated yield from 0.5 mmol in 18 h. $Pd(OAc)_2$, $CoCl_2$, $FeCl_2$ or CuI was used.

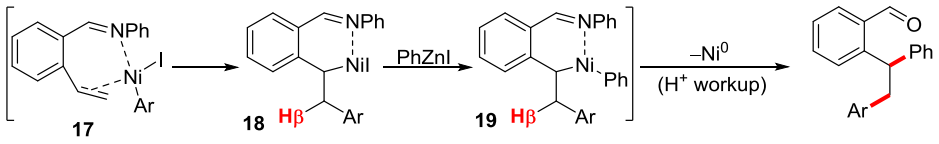
We want to investigate the role of the imine group, so we performed further studies (Scheme 4.7). The reaction of 2-vinylbenzaldehyde with 4-iodobenzotrifluoride and PhZnI under the standard conditions was carried out. In spite of Ni being a good catalyst for the Heck reaction,[17-26] 2-vinylbenzaldehyde did not afford any Heck or difunctionalized product. Only the direct cross-coupling product **15** was seen in significant amounts. Further examination of the reactions of 2-vinylbenzaldehyde and vinylaldimine **6** separately with 4-iodobenzotrifluoride under the standard conditions but in the absence of PhZnI showed

that only the reaction of vinylaldimine **6** produced the Heck product in 27% yield.[27-31] These results designated that coordination of the imine group is indeed required for both the Heck carbometallation of ArNiI on the vinyl group of 2-vinylaldimine **6** through species **17**, and stabilizing the Heck C(sp^3)-NiX intermediates **18** and **19** for further transmetallation with ArZnI to ultimately deliver the 1,2-diarylated product **14** (Scheme 4.8).

Scheme 4.7. Control experiments for establishing the role of the imine group



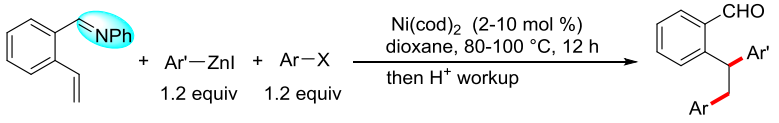
Scheme 4.8. Proposed mechanistic pathway for regioselective 1,2-dicarbofunctionalization

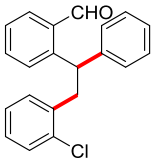


4.2.2. Scope of the Reaction

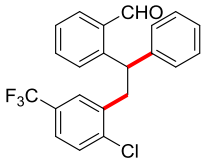
Once we got the optimized conditions and established the role of the imine group then we investigated the scope of the current reaction (Table 4.2). Variety of electron-rich, neutral and deficient aryl halides (I, Br) and arylzinc reagents can be utilized as coupling partners with the vinylaldimine **6**, which affords the 1,2-diarylated products **20**-**35** as the only regioisomers in good to excellent yields. The regioselectivity of the reaction was confirmed by the single crystal X-ray structure of product **30**, and ^{1}H-^{1}H COSY experiment of compound **26**. It was found that the reaction of aryl iodides required lower catalyst loadings (2-5 mol%) than with that of aryl bromides (5-10 mol%) but the latter generally provided products in better yields (**23**-**26**). Likewise, aryl bromides also required higher temperature than aryl iodides (80 °C) and typically proceeded at 100 °C to afford the best product yield. It was found that chloride (**20**-**21**), and other sensitive functional groups such as nitrile (**22**-**23**), ester (**24**), ketone (**25**), dioxolyl (**32**), thioether (**33**), silyl ether (**34**) and benzyl ether (**35**) were well tolerated. Electron-rich aryl iodides containing multiple electron-donating groups like 3,5-dimethyliodobenzene (**28**), 3,4,5-trimethoxyiodo-benzene (**31**), 5-iodobenzo[*d*][1,3]dioxole (**32**) and 2-(benzyl-oxy)-4-iodo-1-methoxybenzene (**35**) worked well for this reaction. The reaction furnishes products in good yields for aryl halides containing functional groups such as Cl, CF_3 and sterically bulky *i*-Pr at the *ortho*-position (**20**-**22**, **26**, **27**).

Table 4.2. Scope with aryl iodides and bromides[a]

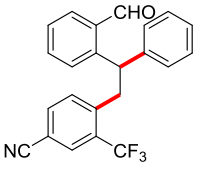




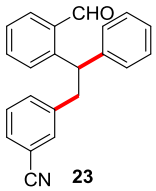
20, X = I, 72%[b]



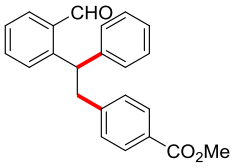
21, X = I, 62%[c]



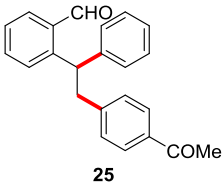
22, X = I, 61%[c,e,f]



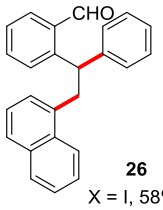
23
X = I, 70%[b]; X = Br, 78%[b]



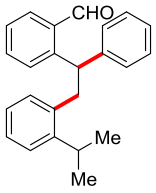
24, X = I, 61%[c];
X = Br, 72%[b]



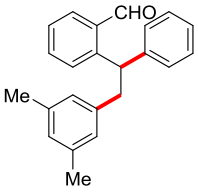
25
X = I, 60%[c]; X = Br, 63%[d]



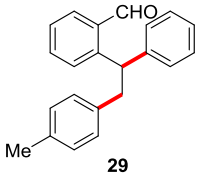
26
X = I, 58%[c];
X = Br, 70%[c]



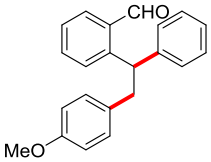
27, X = I, 66%[b]



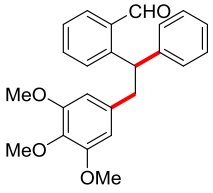
28
X = I, 69%[b]; X = Br, 56%[d]



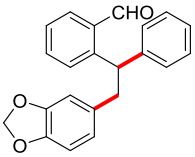
29
X = I, 69%[b,f];
X = Br, 53%[d]



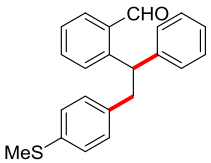
30
X = I, 56%[c,e]; X = Br, 58%[d]



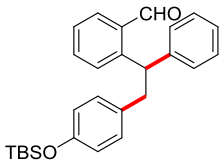
31, X = I, 59%[c,f]



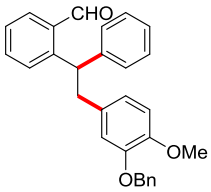
32
X = I, 66%[c]



33
X = I, 60%[c]; X = Br, 68%[b]



34
X = I, 61%[b]

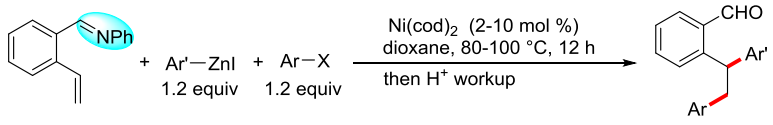


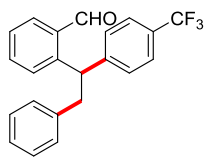
35
X = I, 46%[c]

[a]Isolated from 0.5 [a]Isolated from 0.5 mmol.80 °C for ArI and 100 °C for ArBr unless stated otherwise. [b]2 mol% $Ni(cod)_2$. [c]5 mol% $Ni(cod)_2$. [d]10mol% $Ni(cod)_2$. [e]$NiBr_2$. [f]18 h.

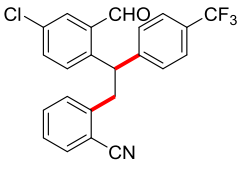
Further examination for the scope of the reaction with functionalized vinylaldimines and arylzinc reagents (Table 4.3) showed that vinylaldimines containing both electron-withdrawing and donating groups such as Cl, F, Me and OMe could be used as a substrate with a variety of electron-rich and deficient aryl halides and arylzinc reagents (**36-58**). Vinylaldimine containing internal olefins, such as 2-(1-propenyl)-N-phenylbenzylimine (*trans*:*cis*/2:1), furnished difunctionalized products only in less than 10% NMR yields. Arylzinc reagents containing F, CF_3, CN, CO_2Me, Me and OMe furnishes products in good to excellent yields. The reaction also tolerates *ortho*-substituted vinylaldimines (**43**) and arylzinc reagents (**49-50**).

Table 4.3. Scope with vinylaldimines and arylzinc reagents[a]

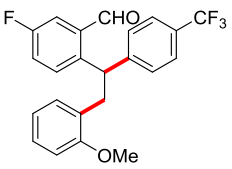




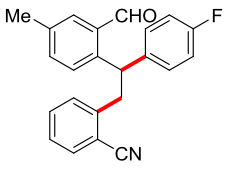
36
X = I, 65%[b]



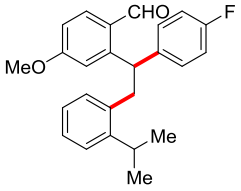
37
X = I, 72%[c]
X = Br, 70%[b]



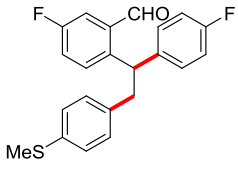
38
X = I, 67%[c,h]
X = Br, 48%[d]



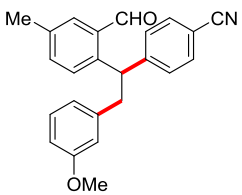
39
X = I, 64%[c]
X = Br, 65%[d]



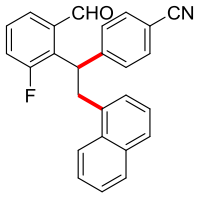
40
X = I, 55%[b]



41
X = I, 72%[b,g]
X = Br, 60%[d]

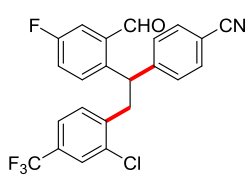


42
X = I, 61%[c]



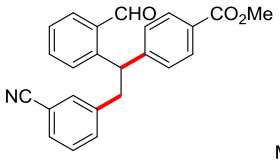
43
X = I, 68%[c]

Continuation of table 4.3.



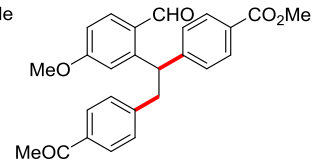
44

X = I, 58%[c]



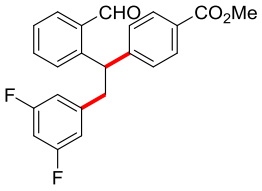
45

X = I, 60%[c];
X = Br, 63%[c]



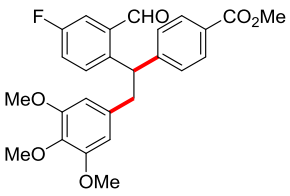
46

X = I, 60%[b]
X = Br, 49%[d]



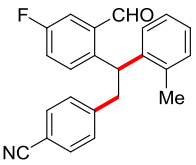
47

X = I, 61%[c,e,f,h]



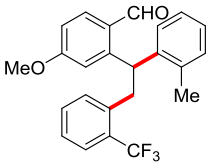
48

X = I, 70%[c,h]



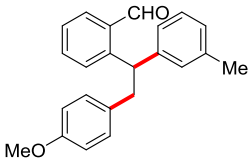
49

X = I, 64%[c]; X = Br, 45%[d]



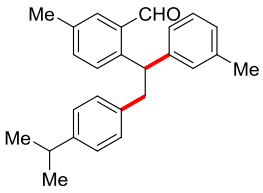
50

X = I, 57%[b]



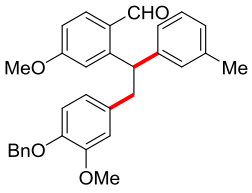
51

X = I, 72%[b,f];
X = Br, 65%[d]



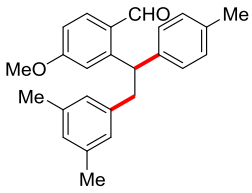
52

X = I, 63%[c]



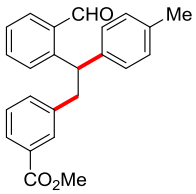
53

X = I, 45%[b]



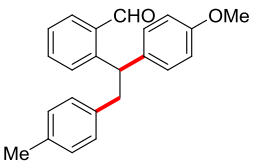
54

X = I, 67%[b]
X = Br, 54%[d]



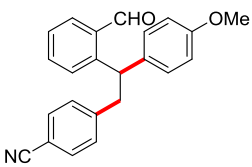
55

X = I, 53%[c]



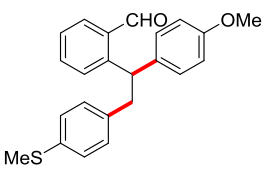
56

X = I, 47%[c,g]



57

X = I, 55%[b,f]; X = Br, 68%[d]



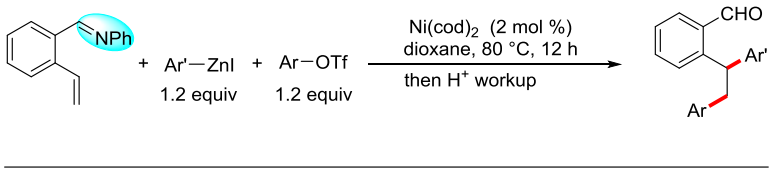
58

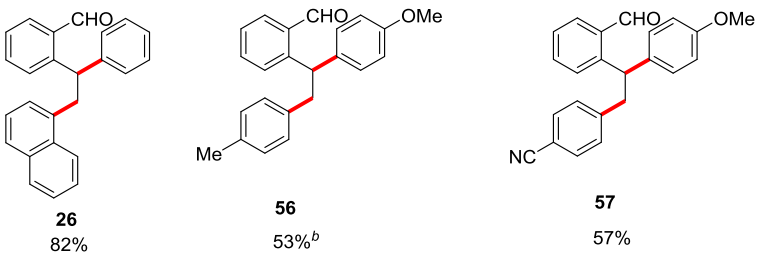
X = I, 56%[c]; X = Br, 52%[d]

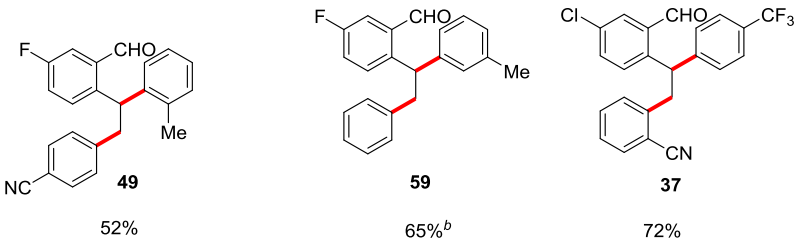
[a]Isolated from 0.5 mmol.80 ^{0}C for ArI and 100 ^{0}C for ArBr unless stated otherwise. [b]2 mol% $Ni(cod)_2$. [c]5 mol% $Ni(cod)_2$. [d]10mol% $Ni(cod)_2$. [e]$NiBr_2$. [f]18 h. [g]24 h. [h]100 ^{0}C.

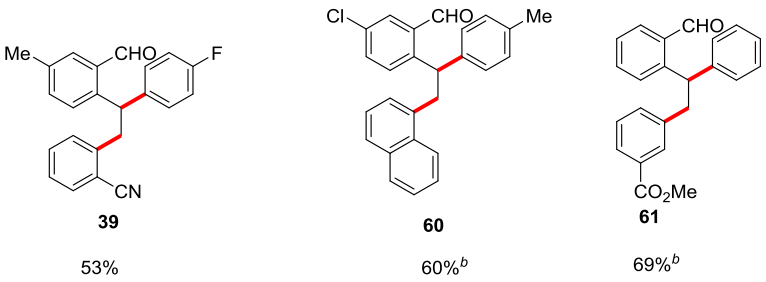
The reaction protocol also worked for aryl triflates instead of aryl halides along with a variety of arylzinc reagents and substituted vinylaldimines, which affords products in good yields (Table 4.4). The reaction generally works well with moderately electron-rich, neutral and deficient aryl triflates. The reaction required 2-5 mol% of catalyst loading and temperature of 80 °C.

Table 4.4. Scope with aryl triflates[a]





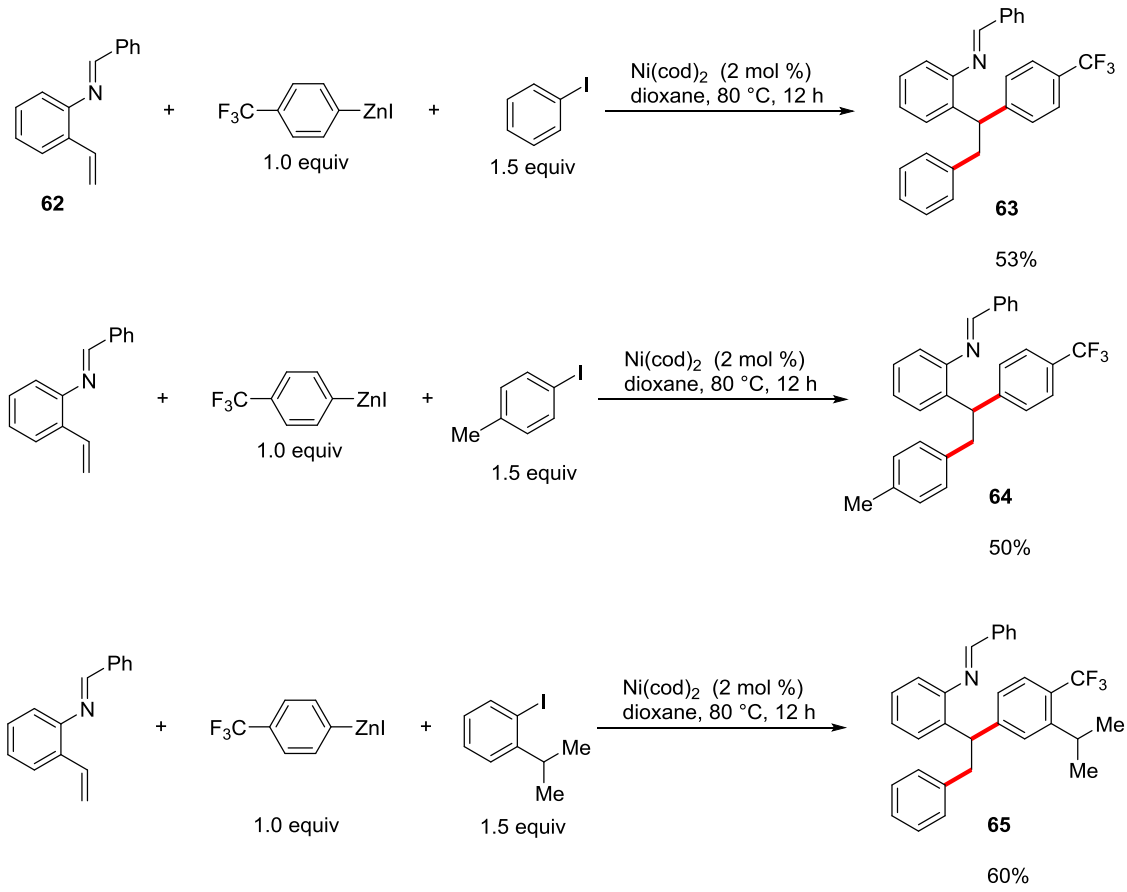




[a]Isolated from 0.5 mmol. [b]5 mol% $Ni(cod)_2$, 100 ^0C.

We also inspected the scope of the current transformation with vinylimines derived from 2-vinylanilines and benzaldehyde (Scheme 4.9). The reaction of vinylimine **62** and (4-(trifluoro-methyl)phenyl)zinc iodide with iodobenzene, 4-iodotoluene and 2-isopropyliodobenze gave the corresponding diarylated imine products **63-65** in good yields. Unlike the products of vinylimines derived from 2-vinylbenzaldehydes, these products were surprisingly resistant to acidic hydrolysis and the product **63** hydrolyzed in <20% GC yield in dioxane:4N H_2SO_4 in 15 h at 120 °C.

Scheme 4.9. Scope with vinylimines derived from 2-vinyl-anilines



4.3. Summary

In conclusion, we were able to develop a Ni-catalyzed regioselective dicarbofunctionalization of olefins in styrene derivatives with aryl halides/triflates and arylzinc reagents, the success of which arise from the stabilization of Heck C(sp^3)-NiX intermediates as transient metallacycles by imine coordination. The reaction displayed high functional group and steric tolerance and gave products in good to excellent yields. The current reaction affords an expedient route to differently-substituted 1,1,2-triarylethyl products that widely occur as structural scaffolds in a variety of natural products and bioactive molecules.[32,33]

4.4. References

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Chapter 5: Experimental

5.1. Cu-Catalyzed Cross-Coupling of Organoaluminum Reagents

5.1.1. General Information

All the reactions and handling of chemicals were done inside a nitrogen-filled glovebox unless stated otherwise. All glassware including the 4-dram borosilicate scintillation (Wheaton), 1-dram borosilicate (Kimble-Chase) vials, and pressure vessels were properly dried in an oven before use. Bulk solvents were obtained from EMD and 99.8% pure anhydrous solvents (DMF, DMSO, NMP, HMPA, toluene, dixoane) were obtained from Sigma-Aldrich and were used directly without further purification. Deuterated solvents were purchased from the Cambridge Isotope. Aryl halides, vinyl bromides, alkynyl bromides, and triphenylaluminum were purchased from Acros, Sigma-Aldrich, Oakwood, TCI-America, Matrix and Alfa-Aesar. Pure triarylaluminum reagents other than Ph_3Al were synthesized following the reported procedure.[1] CuI (99.999%), LiCl (99.9%) and NaOMe (99.9%) were procured from Sigma-Aldrich, Alfa-Aesar and EMD, respectively. Ligands **PN-2**, **PN-6**, **PN-7**, **PN-8**, **PP-1**, **NN-2**, **NN-4**, **NO-1**, **OO-1** and **SIMes•HCl** were purchased from commercial sources (Sigma-Aldrich and Alfa-Aesar) and were used as received. Ligands **PN-1**, **PN-3**, **PN-4**, **PN-5**, **PN-9**,[2] **NN-1**,[3] and **NN-3**[4] were synthesized following the reported procedures.[5] [CuO*t*Bu] was prepared and purified as reported.[6] 4-Phenyltoluene (**3**) (Table 5.1, entry 2) arising from the cross-coupling of triphenylaluminum (**1**) with *p*-iodotoluene (**2**) was identified by comparing ^{1}H and ^{13}C NMR spectra of the isolated compound with that of the commercially available sample. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker instrument (300, 75 and 282 MHz, respectively) and internally referenced to the residual solvent signals of $CDCl_3$ for ^{1}H and

^{13}C NMR at 7.26 and at 77.16 ppm, respectively, and C_6F_6 for ^{19}F NMR at −164.9 ppm. NMR chemical shifts and the coupling constants (*J*) for ^{1}H, ^{13}C and ^{19}F NMR are reported in δ parts per millions (ppm) and in Hertz (Hz), respectively. The following conventions are used for multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; dt, double of triplet. High resolution mass and NMR spectra for new compounds were recorded at the Mass Spectrometry and NMR Facilities, Department of Chemistry and Chemical Biology, University of New Mexico (UNM).

5.1.2. Procedure for Reaction Screening

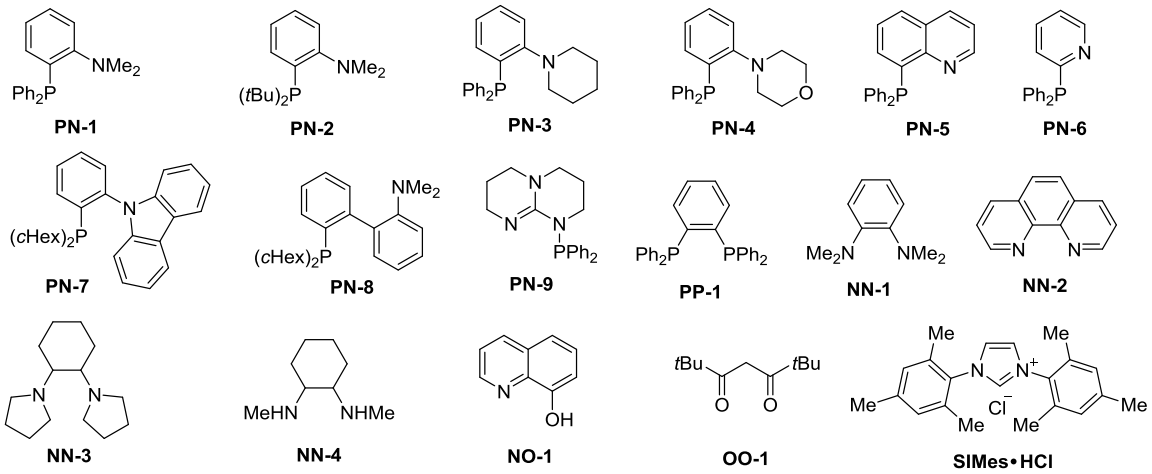


Figure 5.1. Ligands used for reaction screening

5.1.2.1. For Aryl-Aryl Coupling

In a glovebox, triphenylaluminum (0.10 mmol, 0.10 mL from a 1.0 M solution in dibutyl ether), *p*-iodotoluene (21.8 mg, 0.10 mmol), CuI (0.4 mg, 0.0020 mmol), ligand (0.0020 mmol) and LiCl (0.10 – 0.40 mmol) were added to a 1-dram vial and dissolved in DMF (0.5 mL). The vial was then tightly capped, taken out of the glovebox and placed in a hotplate pre-heated to 120 °C with vigorous stirring. After 6 h, the reaction mixture was

allowed to cool down to room temperature, 20 μL of 2-nitrobiphenyl (0.010 mmol, 0.5 M stock solution) was added as a standard, diluted with EtOAc (1 mL) and filtered through a short pad of silica gel in a pipette. The reaction mixture was then analyzed by GC. The formation of the cross-coupled product, 4-phenyltoluene, was confirmed by comparison of the GC trace of the reaction mixture with that of the commercially available sample.

5.1.2.2. For Alkyl-Aryl Coupling

In a glovebox, tri-*n*-octylaluminum (0.10 mmol, 36.7 mg), 1-iodonaphthalene (25.4 mg, 0.10 mmol), CuI (0.4 mg, 0.0020 mmol) and LiCl (8.4 mg, 2 equiv) were added to a 1-dram scintillation vial and dissolved in DMF (0.5 mL). Reaction conditions were varied as shown in Table 5.2. The vial was then tightly capped, taken out of the glovebox and placed in a hotplate pre-heated to 120 °C with vigorous stirring. After 6 h, the reaction mixture was cooled down to room temperature, 20 μL of 2-nitrobiphenyl (0.010 mmol, 0.5 M stock solution) as was added a standard, diluted with EtOAc (1 mL) and filtered through a short pad of silica gel in a pipette. The reaction mixture was then analyzed by GC. The formation of the cross-coupled product, 1-octylnaphthalene, was confirmed by comparison of the GC trace of the reaction mixture with that of the standard sample.

5.1.2.3. General Procedure for Cross-Coupling with Triarylaluminum Reagents

To a suspension of $AlCl_3$ (133.3 mg, 1.0 mmol) in THF (2 mL) was added dropwise a solution of aryllithium (3.0 mmol) (generated from the lithiation of aryl iodides with *n*-BuLi in THF) at room temperature. After 45 minutes, the solvent was removed to obtain a triarylaluminum reagent containing 3 equivalents of LiCl, which was then dissolved in DMF (5 mL). Aryl halide (1.0 mmol) and CuI (3.8 – 19.0 mg, 0.020 – 0.10 mmol) were then added to the solution of the triarylaluminum reagent. For reactions containing non-

heteroaryl halides, **PN-1** (6.1 – 30.5 mg, 0.020 – 0.10 mmol) was added to the reaction mixture. For reactions containing heteroaryl halides, no ligand was added. The reaction mixture was then tightly capped, taken out of the glovebox, placed in an oil bath pre-heated to 120°C and vigorously stirred. After 6-24 h, the reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography using hexanes as an eluting solvent for non-heterocyclic products and 10–20% ethylacetate/hexanes for heterocyclic products.

5.1.2.4. General Procedure for Cross-coupling with Trialkylaluminum Reagents

To a suspension of $AlCl_3$ (133.3 mg, 1.0 mmol) in THF (2 mL) was added dropwise a solution of alkyllithium (3.0 mmol) at room temperature. After 45 minutes, the solvent was removed to obtain a trialkylaluminum reagent containing 3 equivalents of LiCl, which was then dissolved in DMF (5 mL). Aryl halide (1.0 mmol), NaOMe (54.0 mg, 1.0 mmol), CuI (19.0 mg, 0.10 mmol) and LiCl (127.2 mg, 3.0 mmol, except for reactions with vinyl bromides, which do not need additional LiCl) were then added to the solution of the trialkylaluminum reagent. For reactions containing non-heteroaryl halides, **PN-1** (30.5 mg, 0.10 mmol) was added to the reaction mixture. For reactions containing heteroaryl halides, no ligand was added. The reaction mixture was then tightly capped, taken out of the glovebox, placed in an oil bath pre-heated to 120°C and vigorously stirred. After 12-24 h, the reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl

acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography using hexanes as an eluting solvent for non-heterocyclic products and 10–20% ethylacetate/hexanes for heterocyclic products.

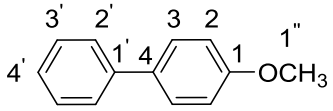
5.1.2.5. General Procedure for Cross-coupling with Trialkynylaluminum Reagents

To a suspension of $AlCl_3$ (133.3 mg, 1.0 mmol) in THF (2 mL) was added dropwise a solution of alkynyllithium (3.0 mmol) (generated from the lithiation of arylacetylene with *n*-BuLi in THF) at room temperature. After 45 minutes, the solvent was removed to obtain a trialkynylaluminum reagent containing 3 equivalents of LiCl, which was then dissolved in DMF (5 mL). Aryl halide (1.0 mmol), NaOMe (54.0 mg, 1.0 mmol) and CuI (19.0 mg, 0.10 mmol) were then added to the solution of the trialkynylaluminum reagent. For reactions containing non-heteroaryl halides, **PN-1** (30.5 mg, 0.10 mmol) was added to the reaction mixture. For reactions containing heteroaryl halides, no ligand was added. The reaction mixture was then tightly capped, taken out of the glovebox, placed in an oil bath pre-heated to 120°C and vigorously stirred. After 12 h, the reaction mixture was cooled down to room temperature, diluted with ethyl acetate (15 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography using 5–20% ethylacetate/hexanes for heterocyclic products.

5.1.2.6. General Procedure for Cross-Coupling with C(sp3)-Halides

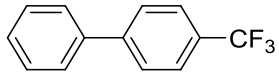
To a suspension of $AlCl_3$ (133.3 mg, 1.0 mmol) in THF (2 mL) was added dropwise a solution of aryllithium (3.0 mmol) (generated from the lithiation of aryl iodides with *n*-BuLi in THF) at room temperature. After 45 minutes, the solvent was removed to obtain a triarylaluminum reagent containing 3 equivalents of LiCl, which was then dissolved in NMP (5 mL). Alkyl halide (1.0 mmol), CuI (1.9 mg, 0.010 mmol, for alkyl iodides; 19.0 mg, 0.10 mmol, for alkyl bromides) and NN-1 (1.6 mg, 0.010 mmol, for alkyl iodides; 16.4 mg, 0.10 mmol, for alkyl bromides) were then added to the solution of the triarylaluminum reagent. The reaction mixture was then tightly capped, taken out of the glovebox, placed in an oil bath pre-heated to 120°C and vigorously stirred. After 12 h, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fraction was dried over Na_2SO_4 and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography using 0–5% ethylacetate in hexanes.

5.1.3. Characterization Data for New Compounds

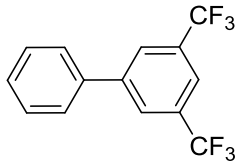


4-Phenylanisole[7] was obtained as a white solid (160 mg, 87% yield) after purification by silica gel column chromatography, mp 83 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H, H_3C(1'')), 7.04-7.09 (m, 2H, HC(3)), 7.36-7.42 (m, 1H, HC(4')), 7.47-7.54 (m, 2H, HC(3')), 7.60-7.67 (m, 4H, HC(2), HC(2')); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4 (C(1")),

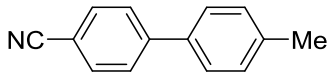
114.3 (C(3)), 126.8 (C(4')), 126.8 (C(2')), 128.2 (C(2)), 128.8 (C(1)), 133.8 (C(3')), 140.9 (C(1')), 159.3 (C(4')); HRMS (APPI) Calcd for $C_{13}H_{12}O$ $(M)^+$ 184.0888, found 184.0892.



4-Trifluromethyl-1,1'-biphenyl was obtained as a white solid (184 mg, 83% yield from the reaction of 1-Iodo-4-(trifluoromethyl)benzene with triphenylaluminium reagent and 167 mg, 75% yield from the reaction of 1-Bromo-4-(trifluoromethyl)benzene with triphenylaluminium reagent) after purification by silica gel column chromatography, mp 64 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-3.52 (m, 3H), 7.58-7.63 (m, 2H), 7.70 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.6 (q, J_{CF} = 3.8 Hz), 125.9, 127.4, 127.6, 127.8, 128.3, 129.1, 139.9, 144.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -65.0; HRMS (APPI) Calcd for $C_{13}H_{19}F_3$ $(M)^+$ 222.0656, found 222.0660.

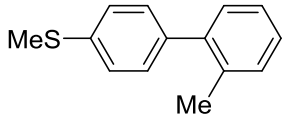


3,5-Bis(trifluromethyl)-1,1'-biphenyl was obtained as colorless oil (157 mg, 54% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.55 (m, 2H), 7.60-7.64 (m, 2H), 7.87 (s, 1H), 8.01-8.04 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.1, 121.8, 125.4, 127.4, 129.0, 129.4, 132.3 (q, J_{CF} = 33.0 Hz), 138.4, 143.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.9; GC-MS (m/z) 291.1.

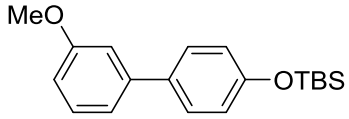


4-Tolylbenzonitrile was obtained as a white solid (135 mg, 70% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.29 (d,

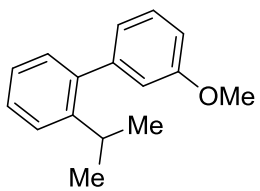
J = 8.1 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.65-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 110.7, 119.2, 127.2, 127.6, 130.0, 132.7, 136.4, 138.9, 145.7; HRMS (APPI) Calcd for $C_{14}H_{11}N$ $(M)^+$ 193.0891, found 193.0895.



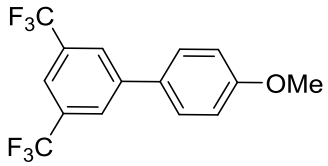
4-(2-Methylphenyl)thioanisole was obtained as colorless oil (133 mg, 62% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.53 (s, 3H), 7.21-7.33 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 20.6, 125.9, 126.4, 127.4, 129.8, 129.9, 130.5, 135.5, 137.0, 138.9, 141.4; HRMS (APPI) Calcd for $C_{14}H_{14}S$ $(M)^+$ 214.0816, found 214.0818.



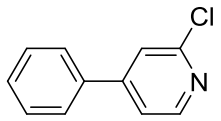
4'-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-methoxy-1,1'-Biphenyl was obtained as yellow oil (126 mg, 40% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (s, 6H), 1.02 (s, 9H), 3.87 (s, 3H), 6.84-6.93 (m, 3H), 7.09-7.10 (m, 1H), 7.13-7.16 (m, 1H), 7.31-7.36 (m, 1H), 7.44-7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.2, 18.4, 25.9, 55.4, 112.2, 112.7, 119.5, 120.4, 128.3, 129.8, 134.3, 142.6, 155.6, 160.1; HRMS (APPI) Calcd for $C_{19}H_{26}O_2Si$ $(M)^+$ 314.1702, found 314.1712.



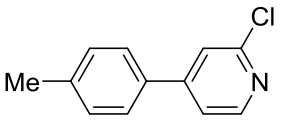
2-Isopropyl-3'-methoxy-1,1'-biphenyl was obtained as colorless oil (86 mg, 38% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.0 Hz, 6H), 3.04-3.17 (m, 1H), 3.85 (s, 3H), 6.87-6.95 (m, 3H), 7.31-7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 29.5, 55.3, 112.4, 115.1, 121.9, 125.4, 125.7, 127.8, 129.1, 129.9, 141.1, 143.6, 146.5, 159.3; HRMS (APPI) Calcd for $C_{16}H_{18}O$ $(M)^+$ 226.1358, found 226.1362.



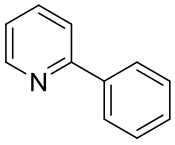
4'-Methoxy-3,5-bis(trifluromethyl)-1,1'-biphenyl was obtained as colorless oil (157 mg, 49% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.03-7.07 (m, 2H), 7.56-7.60 (m, 2H), 7.82 (s, 1H), 7.99 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 114.8, 120.3 (q, J_{CF} = 3.8 Hz), 125.4, 126.8, 128.5, 130.8, 132.2 (q, J_{CF} = 33.0 Hz), 143.0, 160.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.9; HRMS (APPI) Calcd for $C_{15}H_{10}F_6O$ $(M)^+$ 320.0636, found 320.0638.



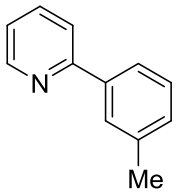
2-Chloro-4-phenylpyridine was obtained as a white solid (87 mg, 46% yield) after purification by silica gel column chromatography, mp 58 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, J = 3.0, 6.0 Hz, 1H), 7.46-7.55 (m, 4H), 7.60-7.63 (m, 2H), 8.43 (dd, J = 3.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.6, 122.2, 127.2, 129.4, 129.8, 137.0, 150.1, 151.7, 152.4; HRMS (ESI) Calcd for $C_{11}H_9ClN$ $(M+H)^+$ 190.0424, found 190.0427.



2-Chloro-4-(4-Methylphenyl)pyridine was obtained as a white solid (112 mg, 55% yield) after purification by silica gel column chromatography, mp 50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.29 (d, *J* = 6.0 Hz, 2H), 7.40 (dd, *J* = 6.0, 3.0 Hz, 1H), 7.49-7.53 (m, 3H), 8.39 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 120.3, 121.8, 126.9, 130.1, 133.9, 140.1, 150.0, 151.6, 152.3; HRMS (ESI) Calcd for $C_{12}H_{11}ClN$ $(M+H)^+$ 204.0580, found 204.0578.

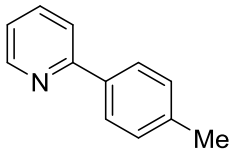


2-Phenylpyridine was obtained as a white solid (114 mg, 73% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.24 (m, 1H), 7.39-7.51 (m, 3H), 7.72-7.74 (m, 2H), 7.01 (d, *J* = 9.0 Hz, 2H), 8.71 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.6, 122.2, 126.9, 128.8, 129.0, 136.8, 139.5, 149.6, 157.6; HRMS (ESI) Calcd for $C_{11}H_{10}N$ $(M+H)^+$ 156.0813, found 156.0816.

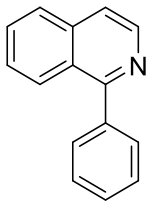


2-(3-Methylphenyl)-pyridine was obtained as colorless oil (111 mg, 65% yield from the reaction of 2-Iodo pyridine with tris(3-tolyl)aluminium reagent and 111 mg, 65% yield from the reaction of of 2-Bromo pyridine with tris(3-tolyl)aluminium reagent) after purification by silica gel column chromatography.^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s,

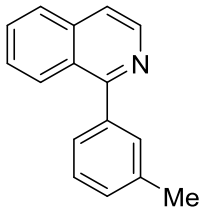
3H), 7.20-7.26 (m, 2H), 7.37 (t, *J* = 6.0 Hz, 1H), 7.71-7.78 (m, 3H), 7.84 (s, 1H), 8.68-8.71 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 120.7, 122.1, 124.1, 127.8, 128.8, 129.8, 136.8, 138.5, 139.5, 149.8, 157.8; HRMS (ESI) Calcd for $C_{12}H_{12}N$ $(M+H)^+$ 170.0970, found 170.0972.



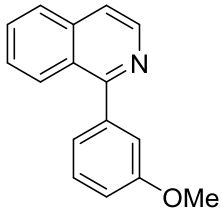
2-(4-Methylphenyl)pyridine was obtained as yellow oil (121 mg, 71% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 7.13-7.21 (m, 1H), 7.26-7.31 (m, 2H), 7.68-7.70 (m, 2H), 7.89-7.94 (m, 2H), 8.67-8.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 120.2, 121.8, 126.8, 129.5, 136.6, 138.9, 138.9, 149.6, 157.4; HRMS (ESI) Calcd for $C_{12}H_{12}N$ $(M+H)^+$ 170.0970, found 170.0971.



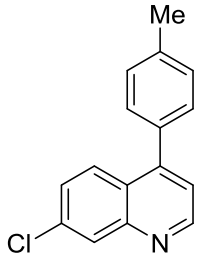
1-Phenylisoquinoline was obtained as a white solid (188 mg, 91% yield) after purification by silica gel column chromatography, mp 150 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.56 (m, 4H), 7.63-7.73 (m, 4H), 7.87 (d, *J* = 6.0 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 8.63 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.9, 126.8, 127.0, 127.2, 127.6, 128.4, 128.3, 130.0, 130.0, 136.9, 139.7, 142.3, 160.8; HRMS (ESI) Calcd for $C_{15}H_{12}N$ $(M+H)^+$ 206.0970, found 206.0970.



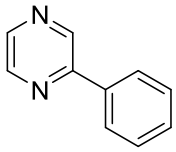
1-(3-Methylphenyl)isoquinoline was obtained as colorless oil (180 mg, 82% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.31 (d, *J* = 6.0 Hz, 1H), 7.39-7.55 (m, 4H), 7.62-7.70 (m, 2H), 7.87 (d, *J* = 9.0 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 8.62 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 119.9, 126.8, 127.0, 127.2, 127.7, 128.2, 129.4, 130.0, 130.6, 136.9, 138.2, 139.6, 142.3, 161.0; HRMS (ESI) Calcd for $C_{16}H_{14}N$ $(M+H)^+$ 220.1126, found 220.1132.



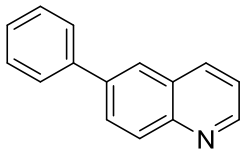
1-(3-Methoxyphenyl)isoquinoline was obtained as colorless oil (168 mg, 71% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 7.04 (dd, *J* = 9.0, 6.0 Hz, 1H), 7.26-7.28 (m, 2H), 7.40-7.52 (m, 2H), 7.60-7.67 (m, 2H), 7.84 (d, *J* = 9.0 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 8.60 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 114.6, 115.1, 119.9, 122.4, 126.6, 126.9, 127.1, 127.5, 129.3, 129.9, 136.8, 140.9, 142.1, 159.6, 160.5; HRMS (ESI) Calcd for $C_{16}H_{14}NO$ $(M+H)^+$ 236.1075, found 236.1079.



7-Chloro-4-(4-methylphenyl)quinoline was obtained as a white solid (234 mg, 92% yield) after purification by silica gel column chromatography, mp 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47(s, 3H),□7.30-7.39 (m, 5H), 7.43 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 8.16 (d, *J* = 3.0 Hz, 1H), 8.92 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 121.6, 125.5, 127.6, 127.6, 128.8, 12.5, 129.5, 134.7, 135.3, 138.8, 148.8, 149.3, 151.1; HRMS (ESI) Calcd for $C_{16}H_{13}ClN$ $(M+H)^+$ 254.0737, found 254.0740.

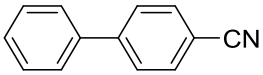


2-Phenylpyrazine was obtained as a white solid (64 mg, 41% yield) after purification by silica gel column chromatography, mp 66 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.55 (m, 3H), 8.00-8.04 (m, 2H), 8.52 (d, *J* = 3.0 Hz, 1H), 8.64 (dd, *J* = 2.4, 1.8 Hz, 1H), 9.03 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.1, 129.2, 130.1, 136.5, 142.4, 143.1, 144.3, 153.0; HRMS (ESI) Calcd for $C_{10}H_9N_2$ $(M+H)^+$ 157.0766, found 157.0769.

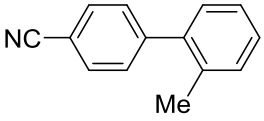


6-Phenylquinoline was obtained as a yellowish white solid (140 mg, 68% yield from the reaction of 6-Iodoquinoline with triphenylaluminium reagent and 122 mg, 59% yield from

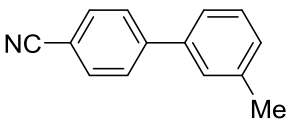
the reaction of of 6-Bromoquinoline with triphenylaluminium reagent) after purification by silica gel column chromatography, mp 106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.52 (m, 4H), 7.69.7.72 (m, 2H), 7.96.7.99 (m, 2H), 8.15-8.20 (m, 2H), 8.92 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.5, 125.5, 127.5, 127.8, 128.5, 129.0, 129.3, 130.0, 136.3, 139.4, 140.4, 147.8, 150.5; HRMS (ESI) Calcd for $C_{15}H_{12}N$ $(M+H)^+$ 206.0970, found 206.0969.



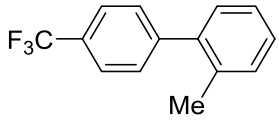
4-Phenylbenzonitrile was obtained as a white solid (161 mg, 90% yield) after purification by silica gel column chromatography, mp 78 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.54 (m, 3H), 7.60-7.64 (m, 2H), 7.69-7.77 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.1, 119.0, 127.3, 127.8, 128.8, 129.2, 132.7, 139.3, 145.8; HRMS (APPI) Calcd for $C_{13}H_9N$ $(M)^+$ 179.0735, found 179.0743.



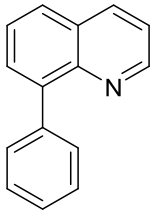
4-(2-Methylphenyl)benzonitrile was obtained as a pale yellow solid (128 mg, 66% yield) after purification by silica gel column chromatography, mp 62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 7.18-7.32 (m, 4H), 7.43-7.46 (m, 2H), 7.69-7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 110.9, 119.1, 126.2, 128.4, 129.5, 130.1, 130.8, 132.1, 135.2, 140.1, 146.9; HRMS (ESI) Calcd for $C_{14}H_{12}N$ $(M+H)^+$ 194.0976, found 194.0976.



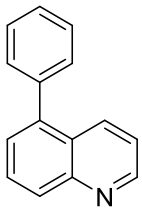
4-(3-Methylphenyl)benzonitrile was obtained as yellow oil (134 mg, 69% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.22-7.26 (m, 1H), 7.34-7.41 (m, 3H), 7.65-7.73 (m, 4); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 110.9, 119.1, 124.5, 127.9, 128.1, 129.1, 129.5, 132.7, 138.9, 139.3, 145.9; HRMS (APPI) Calcd for $C_{14}H_{11}N$ $(M)^+$ 193.0891, found 193.0900.



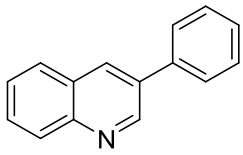
4-(2-Methylphenyl)trifluromethylbenzene was obtained as yellow oil (146 mg, 62% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 7.19-7.32 (m, 4H), 7.44 (d, J = 6.0 Hz, 2H), 7.66-7.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 125.2 (q, J_{CF} = 3.8 Hz), 126.1, 127.8, 128.0, 129.6, 130.6, 135.3, 140.6, 145.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.9; GC-MS (m/z) 236.1.



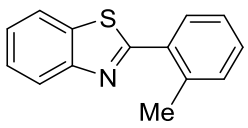
8-Phenylquinoline was obtained as colorless oil (163 mg, 79% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.64 (m, 5H), 7.72-7.77 (m, 3H), 7.84 (dd, J = 6.0, 2.1 Hz, 1H), 8.21 (dd, J = 9.0, 3.0 Hz, 1H), 8.98 (dd, J = 6.0, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.1, 126.4, 127.5, 127.6, 128.1, 128.8, 130.4, 130.7, 136.3, 139.7, 141.1, 146.2, 150.4; HRMS (ESI) Calcd for $C_{15}H_{12}N$ $(M+H)^+$ 206.0970, found 206.0975.



5-Phenylquinoline was obtained as yellow oil (126 mg, 61% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.44-7.53 (m, 6H), 7.76 (dd, *J* = 8.4, 6.9 Hz, 1H), 8.12-8.16 (m, 1H), 8.22-8.26 (m, 1H), 8.93 (dd, *J* = 4.2, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.2, 126.8, 127.4, 127.8, 128.6, 129.0, 129.1, 130.1, 134.5, 139.5, 140.6, 148.6, 150.4; HRMS (ESI) Calcd for $C_{15}H_{12}N$ $(M+H)^+$ 206.0970, found 206.0970.

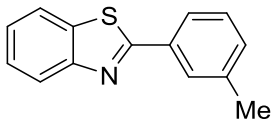


3-Phenylquinoline was obtained as yellow oil (150 mg, 73% yield) after purification by silica gel column chromatography.^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.60 (m, 4H), 7.69-7.75 (m, 3H), 7.78 (dd, *J* = 9.0, 3.0 Hz, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 8.29 (d, *J* = 2.1 Hz, 1H), 9.2 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.1, 127.5, 127.8, 128.1, 128.2, 128.5, 129.3, 129.4, 129.5, 133.3, 138.0, 147.5, 150.0; HRMS (ESI) Calcd for $C_{15}H_{12}N$ $(M+H)^+$ 206.0970, found 206.0970.

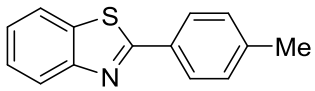


2-(2-Methylphenyl)benzothiazole was obtained as a white solid (147 mg, 65% yield) after purification by silica gel column chromatography, mp 52 °C. ^{1}H NMR (300 MHz, $CDCl_3$)

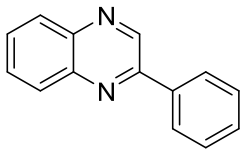
δ 2.68 (s, 3H), 7.30-7.55 (m, 5H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 8.12 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 121.5, 123.5, 125.2, 126.2, 130.1, 130.6, 131.6, 133.2, 135.7, 137.4, 153.9, 168.1; HRMS (ESI) Calcd for $C_{14}H_{12}NS$ $(M+H)^+$ 226.0690, found 226.0696.



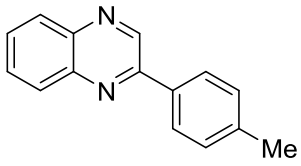
2-(3-Methylphenyl)benzothiazole was obtained as a yellow solid (201 mg, 89% yield) after purification by silica gel column chromatography, mp 68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.30 (d, *J* = 6.0 Hz, 1H), 7.35-7.40 (m, 2H), 7.47-7.52 (m, 1H), 7.86-7.91 (m, 2H), 7.95-7.97 (m, 1H), 8.08-8.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 121.7, 123.2, 124.4, 125.2, 126.3, 128.1, 128.9, 131.9, 133.6, 135.1, 138.9, 154.2, 168.4; HRMS (ESI) Calcd for $C_{14}H_{12}NS$ $(M+H)^+$ 226.0690, found 226.0689.



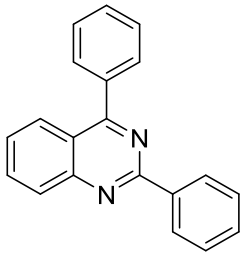
2-(4-Methylphenyl)benzothiazole was obtained as a white solid (142 mg, 63% yield) after purification by silica gel column chromatography, mp 78 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.30-7.34 (m, 2H), 7.36-7.42 (m, 1H), 7.48-7.54 (m, 1H), 7.89-7.93 (m, 1H), 8.00-8.03 (m, 2H), 8.07-8.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 121.7, 123.2, 125.1, 126.4, 127.6, 129.8, 131.1, 135.1, 141.5, 154.3, 168.3; HRMS (ESI) Calcd for $C_{14}H_{12}NS$ $(M+H)^+$ 226.0690, found 226.0692.



2-Phenylquinoxaline was obtained as a yellow solid (155 mg, 75% yield) after purification by silica gel column chromatography, mp 120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.61 (m, 3H), 7.72-7.82 (m, 2H), 8.11-8.23 (m, 4H), 9.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.7, 128.5, 129.3, 129.6, 130.3, 130.4, 136.9, 136.9, 141.7 142.4, 143.5, 151.9; HRMS (ESI) Calcd for $C_{14}H_{11}N_2$ $(M+H)^+$ 207.0922, found 207.0929.

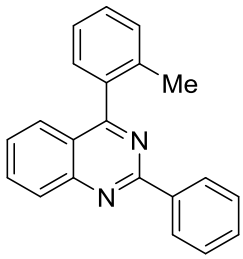


2-(4-Methylphenyl)quinoxaline was obtained as a pale brown solid (146 mg, 66% yield) after purification by silica gel column chromatography, mp 88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.35-7.38 (m, 2H), 7.69-7.80 (m, 2H), 8.08-8.16 (m, 4H), 9.31 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 127.5, 129.2, 129.4, 129.7, 130.0, 130.3, 134.1, 140.6, 141.6, 142.5, 143.4, 151.9; HRMS (ESI) Calcd for $C_{15}H_{13}N_2$ $(M+H)^+$ 221.1079, found 221.1079.

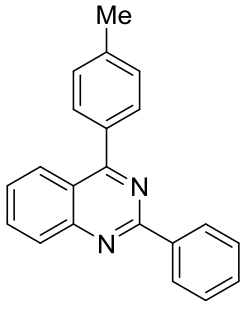


2,4-Biphenylquinazoline was obtained as a white solid (258 mg, 91% yield) after purification by silica gel column chromatography, mp 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.51-7.63 (m, 7H), 7.86-7.93 (m, 3H), 8.11-8.19 (m, 2H), 8.73-8.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.8, 127.1, 128.6, 128.8, 129.3, 130.0, 130.3, 130.6, 133.6, 137.8, 138.3, 152.1, 160.3, 166.9, 163.7, 168.4; HRMS (ESI) Calcd for $C_{20}H_{15}N_2$ $(M+H)^+$ 283.1235, found 283.1234.

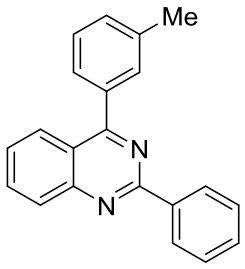


4-(2-Methylphenyl)-2-phenylquinazoline was obtained as a white solid (175 mg, 59% yield) after purification by silica gel column chromatography, mp 139 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s, 3H), 7.26-7.57 (m, 8H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.89 (t, *J* = 6.0Hz, 1H), 8.19 (d, *J* = 9.0 Hz, 1H), 8.69-8.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 122.8, 125.7, 127.1, 127.2, 128.6, 128.9, 129.2, 129.3, 129.8, 130.6, 130.8, 133.8, 136.6, 137.1, 138.4, 151.6, 160.4, 169.8; HRMS (ESI) Calcd for $C_{21}H_{17}N_2$ $(M+H)^+$ 297.1392, found 297.1398.

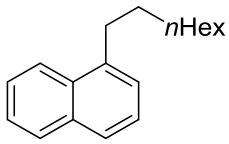


4-(4-Methylphenyl)-2-phenylquinazoline was obtained as a white solid (238 mg, 80% yield) after purification by silica gel column chromatography, mp 98 °C. ^{1}H NMR (300

MHz, $CDCl_3$) δ 2.51 (s, 3H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.50-7.58 (m, 4H), 7.80-7.91 (m, 3H), 8.14-8.17 (m, 2H), 8.70-8.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 121.8, 126.9, 127.2, 128.6, 128.8, 129.3, 129.6, 130.3, 130.6, 133.5, 135.0, 138.4, 140.3, 152.1, 160.3, 168.4; HRMS (ESI) Calcd for $C_{21}H_{17}N_2$ $(M+H)^+$ 297.1392, found 297.1396.

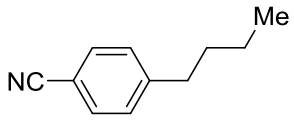


4-(3-Methylphenyl)-2-phenylquinazoline was obtained as a yellowish white solid (217 mg, 73% yield) after purification by silica gel column chromatography, mp 84 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.47-7.60 (m, 5H), 7.66-7.73 (m, 2H), 7.86-7.91 (m, 1H), 8.12-8.19 (m, 2H), 8.73-8.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 121.8, 127.0, 127.2, 127.4, 128.4, 128.6, 128.8, 129.2, 130.6, 130.7, 130.8, 133.6, 137.7, 138.4, 138.4, 152.0, 160.3, 168.7; HRMS (ESI) Calcd for $C_{21}H_{17}N_2$ $(M)^+$ 297.1392, found 297.1390.

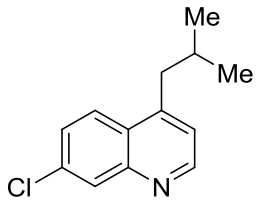


1-*n*-Octylnapthalene was obtained as yellow oil (110 mg, 46% yield) after purification by silica gel column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.0 Hz, 3H), 1.19-1.47 (m, 10H), 1.72-1.82 (m, 2H), 3.08 (t, *J* = 9.0 Hz, 2H), 7.32-7.55 (m, 4H), 7.70-7.73 (m, 1H), 7.85-7.88 (m, 1H), 8.05-8.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3,

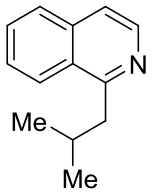
22.8, 29.5, 29.7, 29.9, 30.0, 32.1, 33.3, 124.1, 125.5, 125.7, 125.7, 126.0, 126.5, 128.9, 132.1, 134.0, 139.2; HRMS (APPI) Calcd for $C_{18}H_{24}$ $(M)^+$ 240.1878, found 240.1887.



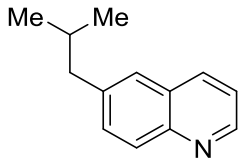
4-*n*-Butylbenzonitrile was obtained as colorless oil (94 mg, 59% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 6.0 Hz, 3H), 1.31-1.41 (m, 2H), 1.55-1.65 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 22.2, 33.1, 35.8, 109.5, 119.2, 129.2, 132.1, 148.6; HRMS (APPI) Calcd for $C_{11}H_{14}N$ $(M+H)^+$ 160.1126, found 160.1133.



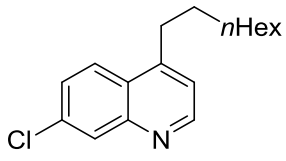
7-Chloro-4-iso-butylquinoline was obtained as yellow oil (165 mg, 75% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.0 Hz, 6H), 1.99-2.08 (m, 1H), 2.88 (d, *J* = 6.0 Hz, 2H), 7.17 (d, *J* = 4.5 Hz, 1H), 7.47 (dd, *J* = 9.0, 3 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 3.0 Hz, 1H), 8.78 (d, *J* = 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 29.6, 41.6, 122.2, 125.4, 126.5, 127.2, 129.2, 134.9, 147.9, 149.1, 151.1; HRMS (ESI) Calcd for $C_{13}H_{15}ClN$ $(M+H)^+$ 220.0893, found 220.0892.



1-iso-Butylisoquinoline was obtained as colorless oil (115 mg, 62% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.0 Hz, 6H), 2.22-2.36 (m, 1H), 3.16 (d, *J* = 6.0 Hz, 2H), 7.49 (d, *J* = 6.0 Hz, 1H), 7.54-7.67 (m, 2H), 7.80 (d, *J* = 9.0 Hz, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 8.45 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 29.1, 44.3, 119.2, 125.7, 126.9, 127.4, 127.5, 129.8, 136.4, 141.9, 161.7; HRMS (ESI) Calcd for $C_{13}H_{16}N$ $(M+H)^+$ 186.1283, found 186.1287.

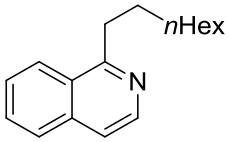


6-iso-Butylisoquinoline was obtained as colorless oil (110 mg, 59% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.0 Hz, 6H), 1.89-2.09 (m, 1H), 2.65 (d, *J* = 6.0 Hz, 2H), 7.35 (q, *J* = 6.0 Hz, 1H), 7.52-7.55 (m, 2H), 8.10-8.00 (m, 2H), 8.85 (dd, *J* = 4.5, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 30.3, 45.5, 121.1, 127.0, 128.3, 129.2, 131.7, 135.7, 140.3, 147.3, 149.7; HRMS (ESI) Calcd for $C_{13}H_{16}N$ $(M+H)^+$ 186.1283, found 186.1289.

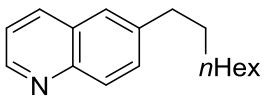


7-Chloro-4-*n*-octylquinoline was obtained as yellow oil (141 mg, 51% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t,

J = 6.3 Hz, 3H), 1.23-1.44 (m, 10H), 1.68-1.78 (m, 2H), 3.02 (t, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 3.0 Hz, 1H), 7.49 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.96 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 2.4 Hz, 1H), 8.78 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.7, 29.3, 29.5, 29.7, 30.2, 31.9, 32.2, 121.0, 125.2, 126.2, 127.3, 129.2, 134.9, 149.0, 149.1, 151.3; HRMS (ESI) Calcd for $C_{17}H_{23}ClN$ $(M+H)^+$ 276.1519, found 276.1526.

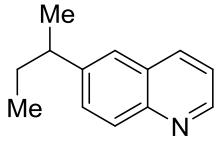


1-*n*-Octylisoquinoline was obtained as yellow oil (220 mg, 91% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* = 6.6 Hz, 3H), 1.25-1.32 (m, 10H), 1.81-1.91 (m, 2H), 3.28 (t, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 6.0 Hz, 1H), 7.61 (m, 2H), 7.78-7.82 (m, 1H), 8.14-8.17 (m, 1H), 8.43 (d, *J* = 6.0 Hz,1H); ^{13}CNMR(75MHz,$CDCl_3$) δ 14.2, 22.8, 29.4, 29.6, 29.9, 30.0, 32.0, 35.7, 119.2, 125.5, 127.0, 127.1, 127.5, 129.8, 136.4, 142.1, 162.6; HRMS (ESI) Calcd for $C_{17}H_{24}N$ $(M+H)^+$ 242.1909, found 242.1915.

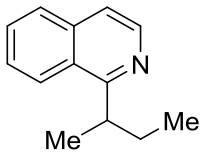


6-*n*-Octylquinoline was obtained as yellow oil (189 mg, 78% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6 Hz, 3H), 1.27-1.38 (m, 10H), 1.66-1.75 (m, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 7.35 (q, *J* = 6.0 Hz, 1H), 7.54-7.58 (m, 2H), 8.00-8.09 (m, 2H), 8.85 (dd, *J* = 6.0 , 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.8, 29.4, 29.4, 29.6, 31.4, 32.0, 36.1, 121.1, 126.1, 128.5, 129.3, 131.2,

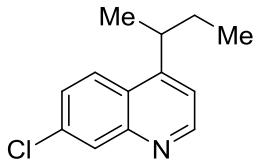
135.6, 141.5, 147.3, 149.7; HRMS (ESI) Calcd for $C_{17}H_{24}N$ $(M+H)^+$ 242.1909, found 242.1915.



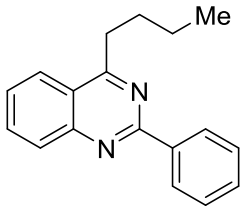
6-*sec*-Butylquinoline was obtained as yellow oil (141 mg, 76% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.5 Hz, 3H), 1.32 (d, *J* = 6.0 Hz, 3H), 1.64-1.72 (m, 2H), 2.76-2.83 (m, 1H), 7.35 (q, *J* = 4.2 Hz, 1H), 7.56 (s, 1H), 7.60 (d, *J* = 2.1 Hz, 1H), 8.03-8.11 (m, 2H), 8.85 (dd, *J* = 6.0, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 21.9, 31.1, 41.8, 121.1, 125.0, 128.4, 129.5, 129.6, 135.8, 146.1, 147.5, 149.7; HRMS (ESI) Calcd for $C_{13}H_{16}N$ $(M+H)^+$ 186.1283, found 186.1286.



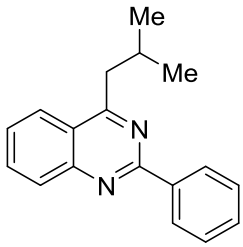
1-*sec*-Butylisoquinoline was obtained as yellow oil (119 mg, 64% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 3H), 1.41 (d, *J* = 6.0 Hz, 3H), 1.72-1.81 (m, 1H), 2.08-1.99 (m, 1H), 3.68-3.75 (m, 1H), 7.48 (d, *J* = 6.0 Hz, 1H), 7.55-7.67 (m, 2H), 7.81 (d, *J* = 6.0 Hz, 1H), 8.22 (d, *J* = 6.0 Hz, 1H), 8.50 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 20.3, 29.7, 37.9, 118.9, 124.9, 126.9, 127.0, 127.6, 129.6, 136.5, 142.1, 166.0; HRMS (ESI) Calcd for $C_{13}H_{16}N$ $(M+H)^+$ 186.1283, found 186.1286.



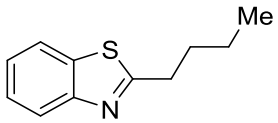
7-Chloro-4-*sec*-butylquinoline was obtained as colorless oil (167 mg, 63% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 6.0 Hz, 3H), 1.35 (d, *J* = 6.0 Hz, 3H), 1.64-1.86 (m, 2H), 3.39-3.51 (m, 1H), 7.25-7.27 (m, 1H), 7.49 (dd, *J* = 9.0, 3.0 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H), 8.11 (d, *J* = 3.0 Hz, 1H), 8.84 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 20.8, 30.2, 35.3, 118.0, 124.7, 126.0, 127.3, 129.4, 134.8, 149.1, 151.5, 153.9; HRMS (ESI) Calcd for $C_{13}H_{15}ClN$ $(M+H)^+$ 220.0893, found 220.0898.



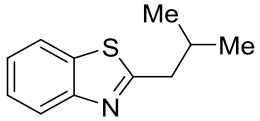
4-*n*-Butyl-2-phenylquinazoline was obtained as yellow oil (187 mg, 71% yield) after purification by silica gel column chromatography.^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, *J* = 9.0 Hz, 3H), 1.51-1.60 (m, 2H), 1.95-2.05 (m, 2H), 3.34 (t, *J* = 9.0 Hz, 2H), 7.48-7.60 (m, 4H), 7.82-7.88 (m, 1H), 8.07-8.14 (m, 2H), 8.65 (dd, *J* = 9.0, 3.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.9, 30.8, 34.4, 122.6, 124.7, 126.8, 128.6, 129.2, 129.5, 130.4, 133.3, 138.6, 150.8, 160.2, 171.6; HRMS (ESI) Calcd for $C_{18}H_{19}N_2$ $(M+H)^+$ 263.1548, found 263.1550.



4-(2-Methylpropyl)-2-phenylquinazoline was obtained as yellow oil (145 mg, 55% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.0 Hz, 6H), 2.45-2.59 (m, 1H), 3.21 (d, *J* = 6.0 Hz, 2H), 7.52-7.60 (m, 4H), 7.81-7.86 (m, 1H), 8.11 (d, *J* = 9.0 Hz, 2H), 8.69-8.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 28.7, 43.3, 123.1, 124.8, 126.7, 128.6, 128.7, 129.5, 130.4, 133.3, 138.6, 150.9, 160.1, 170.8; HRMS (ESI) Calcd for $C_{18}H_{19}N_2$ $(M+H)^+$ 263.1548, found 263.1541.

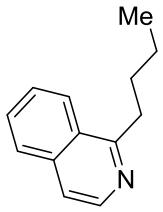


2-*n*-Butylbenzothiazole was obtained as yellow oil (102 mg, 53% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3H), 1.41-1.53 (m, 2H), 1.81-1.92 (m, 2H), 3.11 (t, 7.5 Hz, 2H), 7.26-7.36 (m, 1H), 7.41-7.47 (m, 1H), 7.81-7.85 (m, 1H), 7.96 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 22.4, 31.9, 34.2, 121.6, 122.6, 124.7, 125.9, 135.3, 153.4, 172.5; HRMS (ESI) Calcd for $C_{11}H_{14}NS$ $(M+H)^+$ 192.0847, found 192.0852.

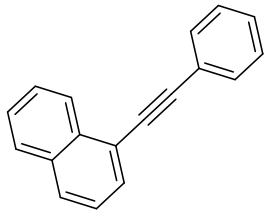


2-(2-Methylpropyl)benzothiazole was obtained as yellow oil (98 mg, 51% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d,

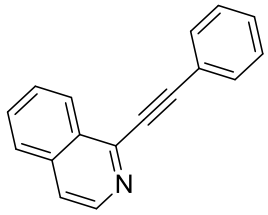
J = 6.0 Hz, 6H), 2.15-2.29 (m, 1H), 2.98 (d, *J* = 9.0 Hz, 2H), 7.30-7.35 (m, 1H), 7.41-7.46 (m, 1H), 7.80-7.84 (m, 1H), 7.96-7.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 29.8, 43.3, 121.5, 122.6, 124.7, 125.9, 135.3, 153.4, 171.3; HRMS (ESI) Calcd for $C_{11}H_{14}NS$ $(M+H)^+$ 192.0847, found 192.0849.



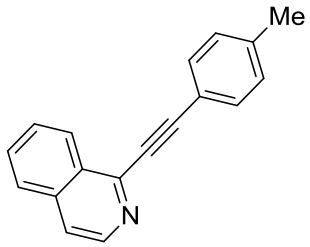
1-*n*-Butylisoquinoline was obtained as yellow oil (97 mg, 52% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, *J* = 6.0 Hz, 3H), 1.44-1.56 (m, 2H), 1.80-1.90 (m, 2H), 3.29 (t, *J* = 9.0 Hz, 2H), 7.48 (d, *J* = 6.0 Hz, 1H), 7.54-7.67 (m , 2H), 7.89 (d, *J* = 9.0 Hz, 1H), 8.15 (d, *J* = 9.0 Hz, 1H), 8.43 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 23.1, 32.0, 35.4, 119.2, 125.5, 127.0, 127.1, 127.5, 129.8, 136.4, 142.1, 162.6; HRMS (ESI) Calcd for $C_{13}H_{16}N$ $(M+H)^+$ 186.1283, found 186.1281.



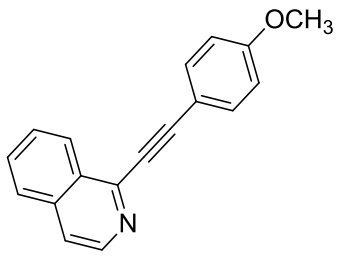
1-(2-Phenylethynyl)napthalene was obtained as yellow oil (153 mg, 67% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.69 (m, 8H), 7.77-7.90 (m, 3H), 8.47 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.7, 94.5, 121.1, 123.6, 125.4, 126.4, 126.6, 126.9, 128.5, 128.6, 128.6, 128.9, 130.5, 131.8, 133.4, 133.4; HRMS (APPI) Calcd for $C_{18}H_{12}$ $(M)^+$ 228.0939, found 228.0946.



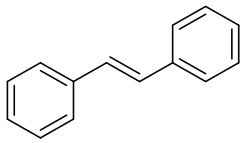
1-(2-Phenylethynyl)isoquinoline was obtained as yellow oil (106 mg, 46% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.44 (m, 3H), 7.62-7.75 (m, 5H), 7.82-7.86 (m, 1H), 8.49-8.53 (m, 1H), 8.56 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.9, 94.0, 120.6, 122.3, 126.9, 127.0, 128.0, 128.5, 129.3, 129.4, 130.6, 132.2, 135.8, 143.0, 144.4; HRMS (ESI) Calcd for $C_{17}H_{12}N$ $(M+H)^+$ 230.0970, found 230.0973.



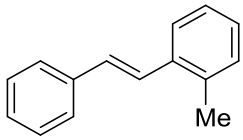
1-[2-(4-Methylphenyl)ethynyl]isoquinoline was obtained as a pale brown solid (117 mg, 48% yield) after purification by silica gel column chromatography, mp 92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.20 (d, *J* = 9.0 Hz, 2H), 7.57-7.70 (m, 5H), 7.77-7.80 (m, 1H), 8.47-8.50 (m, 1H), 8.53 (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 86.4, 94.4, 119.2, 120.4, 126.9, 127.0, 127.9, 129.3, 130.6, 132.2, 135.8, 139.6, 142.9, 144.6; HRMS (ESI) Calcd for $C_{18}H_{14}N$ $(M+H)^+$ 244.1126, found 244.1120.



1-[2-(4-Methoxyphenyl)ethynyl]isoquinoline was obtained as yellow oil (185 mg, 71% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.92-96.95 (m, 2H), 7.59-7.74 (m, 5H), 7.81-7.84 (m, 1H), 8.48-8.55 (m ,2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 86.0, 94.5, 114.3, 120.4, 127.0, 127.2, 127.9, 129.4, 130.7, 133.4, 135.9, 143.1, 144.8, 160.6; HRMS (ESI) Calcd for $C_{18}H_{14}NO$ $(M+H)^+$ 260.1075, found 260.1082.

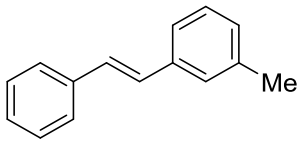


1,1'-(1E)-1,2-Ethenediylbisbenzene was obtained as a white solid (97 mg, 54% yield) after purification by silica gel column chromatography, mp 116 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 2H), 7.26-7.32 (m, 2H), 7.36-7.42 (m, 4H), 7.53-7.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.7, 127.8, 128.8, 137.5; HRMS (APPI) Calcd for $C_{14}H_{12}$ $(M)^+$ 180.0939, found 180.0942.

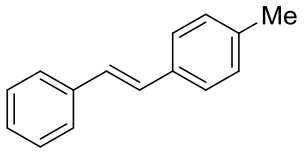


1-Methyl-2[(1E)-2-phenylethenyl]benzene was obtained as colorless oil (99 mg, 51% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.00 (d, *J* = 9.0 Hz, 1H), 7.18-7.41 (m, 7H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.61

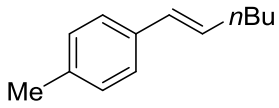
(d, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 125.5, 126.3, 126.7, 127.7, 127.7, 126.8, 130.2, 130.5, 135.9, 136.6, 137.8; HRMS (APPI) Calcd for $C_{15}H_{14}$ $(M)^+$ 194.1096, found 194.1101.



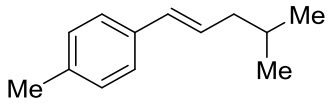
1-Methyl-3[(1E)-2-phenylethenyl]benzene was obtained as a white solid (87 mg, 45% yield) after purification by silica gel column chromatography, mp 54 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.15 (s, 3H), 7.28-7.44 (m, 6H), 7.55-5.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 123.8, 126.6, 127.3, 127.6, 128.6, 128.6, 128.7, 128.7, 128.9, 137.4, 137.5, 138.3; HRMS (APPI) Calcd for $C_{15}H_{14}$ $(M)^+$ 194.1096, found 194.1099.



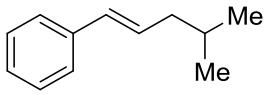
1-Methyl-4[(1E)-2-phenylethenyl]benzene was obtained as a white solid (118 mg, 61% yield from the reaction of β-bromostyrene with tris(4-tolyl)aluminium reagent and 80 mg, 41% yield from the reaction of 1-[(1*E*)-2-bromoethenyl]-4-methylbenzene with triphenyl aluminium reagent) after purification by silica gel column chromatography, mp 116 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 7.10 (d, J = 3.0 Hz, 2H), 7.19 (d, J = 9.0 Hz, 2H), 7.23-7.29 (m, 1H), 7.34-7.45 (m, 4H), 7.51-7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 126.5, 126.6, 127.5, 127.8, 128.8, 129.5, 134.7, 137.7; HRMS (APPI) Calcd for $C_{15}H_{14}$ $(M)^+$ 194.1096, found 194.1101.



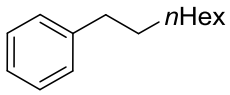
1-(1E)-1-Hexen-1-yl-4-methylbenzene was obtained as colorless oil (87 mg, 50% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, *J* = 6.0 Hz, 3H), 1.32-1.52 (m, 4H), 2.17-2.25 (m, 2H), 2.34 (s, 3H), 6.13-6.23 (m, 1H), 6.36 (d, *J* = 18.0 Hz, 1H), 7.10-7.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 21.2, 22.4, 31.7, 32.8, 125.9, 129.3, 129.7, 130.3, 135.3, 136.5; GC-MS (m/z) 174.1.



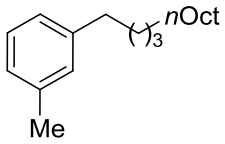
1-Methyl-4-[(1E)-4-methyl-1-penten-1-yl]benzene was obtained as colorless oil (87 mg, 49% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, *J* = 9.0 Hz, 6H), 1.65-1.78 (m, 1H), 2.06-2.11 (m, 2H), 2.32 (s, 3H), 6.11-6.21 (m, 1H), 6.34 (d, *J* = 18.0 Hz, 1H), 7.10 (d, *J* = 6.0 Hz, 2H), 7.25 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 22.5, 28.8, 42.6, 125.9, 128.9, 129.3, 130.8, 135.3, 136.6; GC-MS (m/z) 174.1.



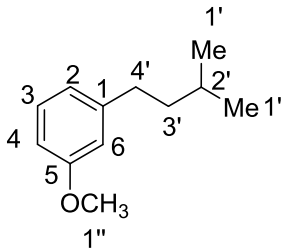
[(1E)-4-Methyl-1-penten-1-yl]benzene was obtained as colorless oil (72 mg, 45% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, *J* = 9.0 Hz, 6H), 1.69-1.83 (m, 1H), 2.10-2.15 (m, 2H), 6.19-6.29 (m, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 7.19-7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 28.7, 42.5, 126.1, 126.9, 128.6, 130.0, 130.9, 138.1; GC-MS (m/z) 160.1.



n-Octylbenzene was obtained as a colorless oil (144 mg, 76% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.6Hz, 3H), 1.29-1.32 (m, 10H), 1.58-1.68 (m, 2H), 2.62 (m, *J* = 8.1Hz, 2H), 7.18-7.20 (m, 3H), 7.25-7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.8, 29.4, 29.5, 29.6, 31.7, 32.0, 36.1, 125.7, 128.3, 128.5, 143.1; GC-MS (m/z) 190.1.

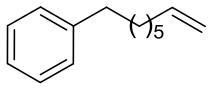


1-Dodecyl-3-methylbenzene was obtained as yellow oil (159 mg, 61% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 6.3 Hz, 3H), 1.28-1.31 (m, 18H), 1.53-1.64 (m, 2H), 2.35 (s, 3H), 2.55-2.60 (m, 2H), 6.98-7.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 21.6, 22.9, 27.1, 29.5, 29.6, 29.7, 29.8, 31.7, 32.1, 36.1, 45.3, 125.5, 126.4, 128.3, 129.4, 137.9, 143.1; GC-MS (m/z) 260.1.

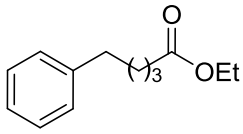


m-Isopentylmethoxybenzene[8] was obtained as colorless oil (87 mg, 49% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 6H, $H_3C(1')$), 1.46-1.64 (m, 3H, HC(2'), $H_2C(3')$), 2.6 (t, *J* = 7.8 Hz, 2H, $H_2C(4')$), 3.80 (s, 3H, $H_3C(1'')$), 6.71-7.38 (m, 4H, HC(2), HC(3), HC(4), HC(6)); ^{13}C NMR (75 MHz,

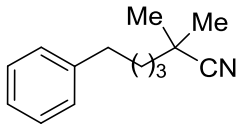
$CDCl_3$) δ 22.7 (C(1')), 27.8 (C(2')), 33.9 (C(4')), 40.8 (C(3')), 55.2 (C(1")), 110.9 (C(4)), 114.3 (C(6)), 120.9 (C(2)), 129.3 (C(3)), 144.9 (C(1)), 159.7 (C(5)); GC-MS (m/z) 178.1.



7-Octen-1-ylbenzene was obtained as a colorless oil (113 mg, 60% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33–1.41 (m, 6H), 1.60-1.65 (m, 2H), 2.00-2.08 (m, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 4.91-5.03 (m, 2H), 5.75-5.88 (m, 1H), 7.17-7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.9, 29.1, 29.2, 31.5, 33.9, 36.0, 114.3, 125.6, 128.3, 128.5, 139.2, 142.9; GC-MS (m/z) 188.1.

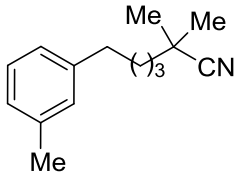


1-Ethyl-5-phenylvalerate was obtained as yellow oil (120 mg, 58% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 9.0Hz, 3H), 1.66-1.70 (m, 4H), 2.31-2.35 (m, 2H), 2.62-2.67 (m, 2H), 4.13 (q, *J* = 6.9 Hz, 2H), 7.17-7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 24.7, 33.5, 34.2, 35.6, 60.3, 125.8, 128.4, 128.4, 142.2, 173.7; GC-MS (m/z) 206.1.

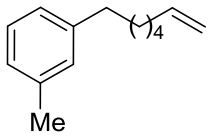


2,2-Dimethyl-6-phenylhexanenitrile was obtained as yellow oil (143 mg, 71% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.54-1.58 (m, 4H), 1.62-1.72 (m, 2H), 2.63-2.68 (m, 2H), 7.17-7.32 (m, 5H); ^{13}C

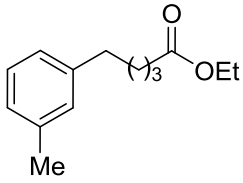
NMR (75MHz, $CDCl_3$) δ 25.0, 26.7, 31.5, 32.4, 35.7, 40.9, 125.2, 125.8, 128.4, 142.2; GC-MS (m/z) 201.1.



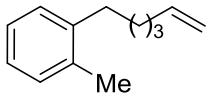
2,2-Dimethyl-6-(3-Methylphenyl)-hexanenitrile was obtained as yellow oil (189 mg, 88% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.55-1.59 (m, 4H), 1.63-1.72 (m, 2H), 2.36 (s, 3H), 2.61-2.67 (m, 2H), 6.93-7.23 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 25.0, 26.6, 31.5, 32.3, 35.6, 41.3, 125.2, 125.3, 126.5, 128.2, 129.2, 137.8, 142.1; GC-MS (m/z) 215.1.



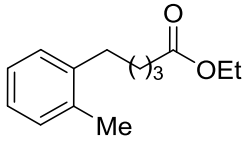
1-(6-Hepten-1-yl)-3-methylbenzene was obtained as colorless oil (100 mg, 53% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34-1.45 (m, 4H), 1.59-1.66 (m, 2H), 2.02-2.09 (m, 2H), 2.33 (s, 3H), 2.57 (t, *J* = 7.8 Hz, 2H), 4.92-5.03 (m, 2H), 5.75-5.88 (m, 1H), 6.97-7.19 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.7, 31.4, 33.7, 35.6, 114.2, 125.4, 126.3, 128.1, 129.2, 137.7, 139.1, 142.8; GC-MS (m/z) 188.2.



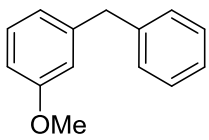
1-Ethyl-5-(3-methylphenyl)valerate was obtained as a yellow oil (130 mg, 59% yield) after purification by silica gel column chromatography. ^{1}H NMRs (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.66-1.72 (m, 4H), 2.33-2.37 (m, 5H), 2.60-2.65 (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 6.94-7.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 21.5, 24.7, 31.0, 34.3, 35.6, 60.2, 125.4, 126.5, 128.3, 129.3, 137.9, 142.2, 173.7; GC-MS (m/z) 220.2



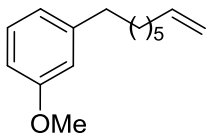
1-(5-Hexen-1-yl)-2-methylbenzene was obtained as colorless oil (80 mg, 46% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48-1.67 (m, 4H), 2.09-2.16 (m, 2H), 2.33 (s, 3H), 2.59-2.65 (m, 2H), 4.98-5.07 (m, 2H), 5.77-5.91 (m, 1H), 7.11-7.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 29.1, 29.9, 33.3, 33.8, 114.6, 125.9, 125.9, 128.9, 130.2, 135.9, 139.0, 141.0; GC-MS (m/z) 174.1.



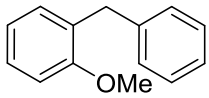
1-Ethyl-5-(2-methylphenyl)valerate was obtained as yellow oil (203 mg, 92% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.58-1.76 (m, 4H), 2.31-2.37 (m, 5H), 2.6-2.65 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 7.11-7.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 19.4, 25.1, 29.8, 33.1, 34.4, 60.4, 126.0, 128.9, 130.3, 135.9, 140.5, 173.8; GC-MS (m/z) 220.2.



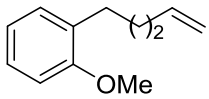
1-Benzyl-3-methoxybenzene was obtained as a light yellow oil (105 mg, 53% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82(s, 3H), 3.8 (s, 2H), 6.80-7.34 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.0, 55.2, 111.4, 114.9, 121.4, 126.2, 128.3, 128.5, 129.5, 140.9, 142.7, 159.8; GC-MS (m/z) 198.1.



1-Methoxy-3-(oct-7-en-1-yl)benzene was obtained as colorless oil (113 mg, 52% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27-1.42 (m, 4H), 1.55-1.65 (m, 4H), 2.01-2.05 (m, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.92-5.02 (m, 2H), 5.75-5.88 (m, 1H), 6.72-7.36 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 29.3, 29.6, 31.4, 33.9, 35.8, 55.2, 110.9, 114.3, 121.0, 129.3, 129.8, 139.3, 144.7; GC-MS (m/z) 218.2.



1-Benzyl-2-methoxybenzene was obtained as light yellow oil (135 mg, 68% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.04 (s, 2H), 6.90-6.96 (m, 2H), 7.11-7.14 (m, 1H), 7.23-7.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 55.4, 110.5, 120.6, 125.8, 127.5, 128.3, 129.0, 129.7, 130.4, 141.1, 157.4; GC-MS (m/z) 198.2.



1-Methoxy-2-(pent-4-en-1-yl)benzene was obtained as yellow oil (83 mg, 47% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64-1.74 (m, 2H), 2.08-2.15 (m, 2H), 2.61-2.66 (m, 2H), 3.83 (s, 3H), 5.01-5.08 (m, 2H), 5.80-5.94 (m, 1H), 6.83-7.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2, 33.8, 41.5, 55.4, 110.4, 114.5, 117.9, 120.4, 127.0, 139.1, 145.3, 157.2; GC-MS (m/z) 176.1.

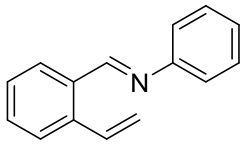
5.2. Ni-Catalyzed Olefin Dicarbofunctionalization

5.2.1. General Information

All the screening reactions were set up in a N_2 glovebox unless stated otherwise. All glassware were dried in an oven prior to use. Anhydrous DMF, NMP, DMSO, Dioxane, acetonitrile were purchased from Sigma-Aldrich and were used as received. THF and benzene were dried with PureSolv solvent purification system. Deuterated solvents were obtained from Sigma-Aldrich. Other chemical reagents such as aryl halides, amines and vinylaldehydes (for making starting materials) were purchased from Acros, Sigma-Aldrich, TCI, Matrix, OxChem, Ark Pharm, Alfa-Aesar and Oakwood. $NiBr_2$ and $Ni(cod)_2$ were purchased from Alfa-Aesar and Strem Chemicals, respectively. Except *p*-tolyl triflate (TCI), all other aryl triflates were prepared following a literature procedure.[9] Arylzinc iodides were prepared in THF according to a literature procedure.[10] The concentration of arylzinc reagents were determined by titration with molecular iodine and the final concentration of stock solution was adjusted to 1.0 molar in THF. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker instrument (300, 75, and 282, respectively). NMR samples were internally referenced to the residual solvent signals of $CDCl_3$ for ^{1}H and ^{13}C NMR at 7.26 and 77.16 ppm, respectively, and C_6F_6 for ^{19}F NMR at −164.9 ppm. NMR

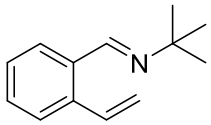
chemical shifts (δ) and the coupling constants (*J*) for ^{1}H, ^{13}C, and ^{19}F NMR are reported in parts per million (ppm) and in Hertz, respectively. The following conventions are used for multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet and dt, doublet of triplet. High resolution mass data of new compounds were collected at the Mass Spectrometry, Department of Chemistry and Chemical Biology, University of New Mexico (UNM) and University of California, Riverside, CA. NMR spectra of new compounds were collected at the NMR Facility, Department of Chemistry and Chemical Biology, UNM. X-ray diffraction was performed on Bruker Kappa APEX II CCD diffractometer at the Department of Chemistry and Chemical Biology, UNM. Infrared (IR) spectra were recorded on Bruker Alpha-P ATR-IR. ν_{max} is reported in cm^{-1}.

5.2.2. Substrate Preparation



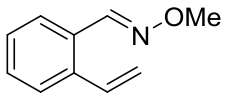
1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] 2-vinyl-N-phenylbenzylimine was prepared using 2-vinylbenzaldehyde and aniline according to the described procedure (90% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, *J* = 12.0 Hz, 1H), 5.67 (d, *J* = 18.0 Hz, 1H), 7.20-7.47 (m, 8H), 7.52 (app. d, *J* = 6.0 Hz, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ118.6, 121.0, 126.0, 127.1, 128.0, 128.1, 129.2, 131.1, 133.1, 133.9, 139.3, 152.5, 158.9; IR (neat) cm^{-1} 3019, 1619, 1585, 1486, 1197; HRMS (ESI) Calcd for $C_{15}H_{14}N$ $(M+H)^+$ 208.1126, found 208.1097.



1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] (E)-N-tert-butyl-1-(2-vinylphenyl)methanimine was prepared using 2-vinylbenzaldehyde and *tert*-butylamine according to the described procedure (79% yield).[13]

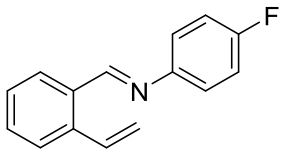
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 5.39 (d, *J* = 12.0 Hz, 1H), 5.60 (d, *J* = 18.0 Hz, 1H), 7.13-7.36 (m, 3H), 7.44 (app. d, *J* = 9.0 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 8.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ29.8, 57.8, 117.6, 126.7, 127.5, 127.9, 129.8, 134.2, 134.4, 137.9, 153.9; IR (neat) cm^{-1} 2964, 1633, 1473, 1202; HRMS (ESI) Calcd for $C_{13}H_{18}N$ $(M+H)^+$ 188.1439, found 188.1421.



1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] (E)-2-vinylbenzaldehyde O-methyl oxime was prepared using 2-vinylbenzaldehyde and methoxyamine hydrochloride according to the described procedure (91% yield).[14]

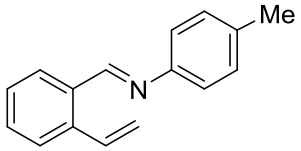
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (s, 3H), 5.38 (d, *J* = 12.0 Hz, 1H), 5.62 (d, *J* = 18.0 Hz, 1H), 7.05 (dd, *J* = 12.0, 15.0 Hz, 1H), 7.24-7.35 (m, 2H), 7.46 (app. d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 6.0 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.0, 117.8, 126.8,

127.0, 127.8, 129.3, 129.7, 134.0, 137.3, 147.2; IR (neat) cm^{-1} 2936, 1475, 1046, 987; HRMS (ESI) Calcd for $C_{10}H_{12}NO$ $(M+H)^+$ 162.0919, found 162.0921.



1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] (E)-N-(4-fluorophenyl)-1-(2-vinylphenyl)methanimine was prepared using 2-vinylbenzaldehyde and 4-fluoroaniline according to the described procedure (88% yield).[13]

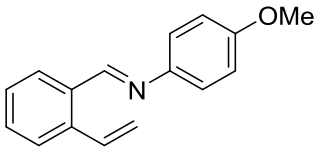
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, J = 12.0 Hz, 1H), 5.65 (d, J = 18.0 Hz, 1H), 7.04-7.46 (m, 7H), 7.51 (app. d, J = 6.0 Hz, 1H), 8.07(d, J = 6.0 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 115.8, 116.1, 118.6, 122.4 (d, J_{CF} = 8.2 Hz), 127.2, 128.0, 131.2, 133.0, 139.2, 148.5, 158.6, 161.3 (d, J_{CF} = 243.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.6; IR (neat) cm^{-1} 3061, 2911, 1619, 1498, 1193; HRMS (ESI) Calcd for $C_{15}H_{13}FN$ $(M+H)^+$ 226.1032, found 226.1005.



1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] (E)-N-p-tolyl-1-(2-vinylphenyl)methanimine was

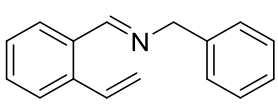
prepared using 2-vinylbenzaldehyde and *p*-toluidine according to the described procedure (91% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 5.49 (d, *J* = 12.0 Hz, 1H), 5.71 (d, *J* = 18.0 Hz, 1H), 7.19-7.26 (m, 4H), 7.33-7.48 (m, 3H), 7.55 (app. d, *J* = 6.0 Hz, 1H), 8.17(d, *J* = 6.0 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 118.3, 120.9, 127.0, 127.9, 129.7, 130.8, 133.2, 133.9, 135.7, 139.0, 149.8, 157.9; IR (neat) cm^{-1} 3021, 2918, 1620, 1504, 1196; HRMS (ESI) Calcd for $C_{16}H_{16}N$ $(M+H)^+$ 222.1283, found 222.1269.



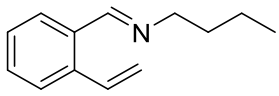
1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] (E)-N-(4-methoxyphenyl)-1-(2-vinylphenyl)methanimine was prepared using 2-vinylbenzaldehyde and *p*-anisidine according to the described procedure (87% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.44 (d, *J* = 12.0 Hz, 1H), 5.65 (d, *J* = 18.0 Hz, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.27-7.43 (m, 3H), 7.50 (app. d, *J* = 6.0 Hz, 1H), 8.81 (d, *J* = 9.0 Hz, 1H), 8.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.6, 114.5, 118.4, 122.3, 127.1, 127.8, 128.0, 130.8, 133.4, 134.0, 139.0, 145.4, 156.9, 158.4; IR (neat) cm^{-1} 2932, 2837, 1615, 1503, 1281, 1022; HRMS (ESI) Calcd for $C_{16}H_{16}NO$ $(M+H)^+$ 238.1232, found 238.1222.



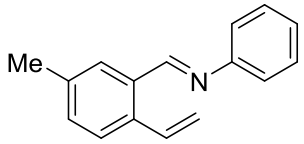
1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] (E)-N-benzyl-1-(2-vinylphenyl)methanimine was prepared using 2-vinylbenzaldehyde and benzylamine according to the described procedure (82% yield).[15]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 (s, 2H), 5.46 (d, *J* = 12.0 Hz, 1H), 5.68 (d, *J* = 18.0 Hz, 1H), 7.28-7.44 (m, 8H), 7.52 (app. d, *J* = 9.0 Hz, 1H), 8.00(d, *J* = 9.0 Hz, 1H), 8.78 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 65.5, 117.9, 126.8, 127.0, 127.8, 127.9, 128.0, 128.6, 130.4, 133.1, 134.0, 138.3, 139.4, 160.4; IR (neat) cm^{-1} 3026, 2880, 1636, 1287, 914; HRMS (ESI) Calcd for $C_{16}H_{16}N$ $(M+H)^+$ 222.1283, found 222.1327.



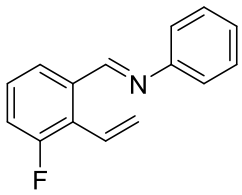
1-Bromo-2-vinylbenzene was synthesized using 2-bromobenzaldehyde according to the described procedure.[11] 2-Vinylbenzaldehyde was prepared using 1-bromo-2-vinylbenzene according to the described procedure.[12] (E)-N-butyl-1-(2-vinylphenyl)methanimine was prepared using 2-vinylbenzaldehyde and butylamine according to the described procedure (81% yield).[15]

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J* = 9.0 Hz, 3H), 1.34-1.46 (m, 2H), 1.65-1.74 (m, 2H), 3.62 (d, *J* = 6.0 Hz, 2H), 5.38 (d, *J* = 9.0 Hz, 1H), 5.61 (d, *J* = 18.0 Hz, 1H), 7.18-7.37 (m, 3H), 7.45 (app. d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 6.0 Hz, 1H), 8.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.5, 33.1, 61.9, 117.5, 126.7, 127.7, 127.8, 130.0, 133.4, 134.0, 138.0, 159.0; IR (neat) cm^{-1} 2928, 1638, 1457, 981; HRMS (ESI) Calcd for $C_{13}H_{18}N$ $(M+H)^+$ 188.1439, found 188.1423.



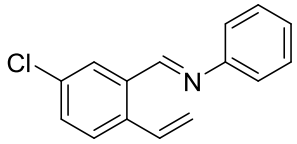
2-Bromo-4-methyl-1-vinylbenzene was synthesized using 2-bromo-4-methylbenzaldehyde according to the described procedure.[11] 5-Methyl-2-vinylbenzaldehyde was prepared using 2-bromo-4-methyl-1-vinylbenzene according to the described procedure.[12] (E)-1-(5-methyl-2-vinylphenyl)-N-phenylmethanimine was prepared using 5-methyl-2-vinylbenzaldehyde and aniline according to the described procedure (88% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 5.42 (d, *J* = 12.0 Hz, 1H), 5.65 (d, *J* = 18.0 Hz, 1H), 7.22-7.45 (m, 8H), 7.96 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 117.7, 121.0, 125.9, 127.0, 128.1, 129.2, 132.1, 132.8, 133.6, 136.6, 137.8, 152.5, 159.0; IR (neat) cm^{-1} 3020, 2918, 1623, 1490, 1162; HRMS (ESI) Calcd for $C_{16}H_{16}N$ $(M+H)^+$ 222.1283, found 222.1316.



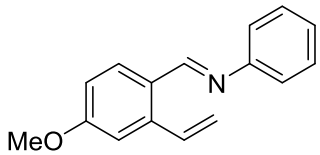
1-Bromo-3-fluoro-2-vinylbenzene was synthesized using 2-bromo-6-fluorobenzaldehyde according to the described procedure.[11] 3-Fluoro-2-vinylbenzaldehyde was prepared using 1-bromo-3-fluoro-2-vinylbenzene according to the described procedure.[12] (E)-1-(3-fluoro-2-vinylphenyl)-N-phenylmethanimine was prepared using 3-fluoro-2-vinylbenzaldehyde and aniline according to the described procedure (70% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, *J* = 18.0 Hz, 1H), 5.73 (d, *J* = 12.0 Hz, 1H), 6.96 (dd, *J* = 12.0, 18.0 Hz, 1H), 7.14-7.42 (m, 7H), 7.96 (d, *J* = 9.0 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.7 (d, J_{CF} = 23.2 Hz), 121.0, 123.7 (d, J_{CF} = 3.0 Hz), 124.0 (d, J_{CF} = 5.2 Hz), 126.3, 127.2, 127.6 (d, J_{CF} = 14.2 Hz), 128.5 (d, J_{CF} = 9.0 Hz), 129.3, 135.8 (d, J_{CF} = 3.7 Hz), 152.1, 158.4 (d, J_{CF} = 3.7 Hz), 160.6 (d, J_{CF} = 246.8 Hz); IR (neat) cm^{-1} 2969, 1598, 1464, 1127, 950; ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.2; HRMS (ESI) Calcd for $C_{15}H_{13}FN$ $(M+H)^+$ 226.1032, found 226.1054.



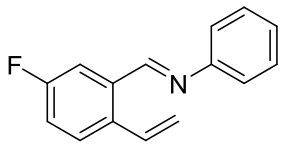
2-Bromo-4-chloro-1-vinylbenzene was synthesized using 2-bromo-4-chlorobenzaldehyde according to the described procedure.[11] 5-Chloro-2-vinylbenzaldehyde was prepared using 2-bromo-4-chloro-1-vinylbenzene according to the described procedure.[12] (E)-1-(5-chloro-2-vinylphenyl)-N-phenylmethanimine was prepared using 5-chloro-2-vinylbenzaldehyde and aniline according to the described procedure (88% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (d, *J* = 12.0 Hz, 1H), 5.66 (d, *J* = 18.0 Hz, 1H), 7.17-7.28 (m, 4H), 7.35-7.45 (m, 4H), 8.13 (d, *J* = 3.0 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.1, 121.0, 126.4, 127.5, 128.5, 129.2, 131.0, 132.7, 134.1, 134.4, 137.5, 151.9, 157.0; IR (neat) cm^{-1} 3028, 2870, 1618, 1483, 1197; HRMS (ESI) Calcd for $C_{15}H_{13}ClN$ $(M+H)^+$ 242.0737, found 242.0714.



1-Bromo-4-methoxy-2-vinylbenzene was synthesized using 2-bromo-5-methoxybenzaldehyde according to the described procedure.[11] 4-Methoxy-2-vinylbenzaldehyde was prepared using 1-bromo-4-methoxy-2-vinylbenzene according to the described procedure.[12] (E)-1-(4-methoxy-2-vinylphenyl)-N-phenylmethanimine was prepared using 4-Methoxy-2-vinylbenzaldehyde and aniline according to the described procedure (91% yield).[13]

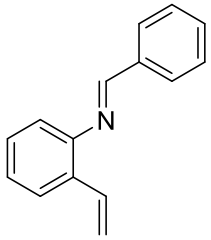
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 5.46 (d, *J* = 12.0 Hz, 1H), 5.68 (d, *J* = 18.0 Hz, 1H), 6.93 (dd, *J* = 3.0, 9.0 Hz, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 7.19-7.42 (m, 6H), 8.09 (d, *J* = 6.0 Hz, 1H), 8.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 111.6, 114.1, 118.5, 121.0, 125.6, 126.4, 129.1, 130.0, 133.9, 141.0, 152.8, 158.1, 161.8; IR (neat) cm^{-1} 2936, 2835, 1581, 1490, 1247, 1024; HRMS (ESI) Calcd for $C_{16}H_{16}NO$ $(M+H)^+$ 238.1232, found 238.1215.



2-Bromo-4-fluoro-1-vinylbenzene was synthesized using 2-bromo-4-fluorobenzaldehyde according to the described procedure.[11] 5-Fluoro-2-vinylbenzaldehyde was prepared using 2-bromo-4-fluoro-1-vinylbenzene according to the described procedure.[12] (E)-1-(5-fluoro-2-vinylphenyl)-N-phenylmethanimine was prepared using 5-fluoro-2-vinylbenzaldehyde and aniline according to the described procedure (88% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (d, *J* = 9.0 Hz, 1H), 5.62 (d, *J* = 18.0 Hz, 1H), 7.10-7.29 (m, 5H), 7.39-7.50 (m, 3H), 7.86 (dd, *J* = 3.0, 12.0 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.9 (d, J_{CF} = 23.2 Hz), 118.4 (d, J_{CF} = 21.7 Hz), 118.6, 121.0, 126.4,

129.1 (d, J_{CF} = 8.2 Hz), 129.2, 132.7, 135.1 (d, J_{CF} = 6.7 Hz), 135.5, 151.9, 157.1, 162.5 (d, J_{CF} = 246.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.0; IR (neat) cm^{-1} 3066, 1619, 1487, 1263, 1152; HRMS (ESI) Calcd for $C_{15}H_{13}FN$ $(M+H)^+$ 226.1032, found 226.1004.



2-Vinylaniline was synthesized using 2-(2-aminophenyl)ethan-1-ol and potassium hydroxide according to the described procedure.[16] (E)-1-phenyl-N-(2-vinylphenyl)methanimine was prepared using 2-Vinylaniline and benzaldehyde according to the described procedure (68% yield).[13]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.34 (d, *J* = 12.0 Hz, 1H), 5.80 (d, *J* = 15.0 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 1H), 7.22-7.35 (m, 3H), 7.50-7.52 (m, 3H), 7.64 (d, *J* = 6.0 Hz, 1H), 7.95-7.99 (m, 2H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.9, 118.5, 125.8, 125.9, 128.8, 128.8, 128.9, 131.3, 131.5, 133.4, 136.4, 149.9, 160.2; IR (neat) cm^{-1} 3060, 3023, 2875, 1623, 1199; GC-MS (m/z) 206.1.

5.2.3. General Procedure for Screening Reaction Conditions

In a glovebox, PhZnI (0.12 mmol, 0.12 mL from a 1.0 M stock solution/THF) was taken in a 1-dram vial and THF was removed under vacuum. To this PhZnI was added the catalyst (0.0020 mmol, 2 mol %), 2-vinylaldimine (0.10 mmol) and 4-iodobenzotrifluoride (32.6 mg, 0.12 mmol). The mixture was then dissolved in respective solvents (0.5 mL). The vial was then tightly capped and placed in a hotplate pre-heated to 80 °C with vigorous

stirring. After 6 h, the reaction mixture was cooled to room temperature, 1 mL of 6N HCl was added and shaken for about 2 minutes to hydrolyze the imines to aldehydes. The reaction mixture was then extracted with EtOAc (1 mL × 3), 50 µL of pyrene (0.010 mmol, 0.20 M stock solution) as an internal standard was added and the solvent was removed in a rotary evaporator. The residue was dissolved in $CDCl_3$ and NMR spectrum was acquired. The yield was determined by integrating a product peak at 5.6 ppm against the pyrene peak at 8.06 ppm.

5.2.3.1. General Procedure to Setup Large Scale Reaction

In a glovebox, ArZnI (0.60 mmol, 0.60 mL from a 1.0 M stock solution/THF) was taken in a 15-mL sealed tube and THF was removed under vacuum. To this ArZnI was added $Ni(cod)_2$ (2.70 – 13.7 mg, 0.010 – 0.050 mmol, 2 – 10 mol %), 2-vinylaldimine (0.50 mmol) and aryl halide/aryl triflate (0.60 mmol). The mixture was then dissolved in dioxane (2.5 mL). The sealed tube was then tightly capped and placed in an oil bath pre-heated to 80-100 °C with vigorous stirring. After 12-24 h, the reaction mixture was cooled to room temperature, 5 mL of 6N HCl was added and shaken for about 2 minutes to hydrolyze the imines to aldehydes. The reaction mixture was then extracted with EtOAc (3 mL × 4) and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography with a gradient elution using ethyl acetate/hexanes or diethyl ether/hexanes as solvents.

5.2.3.2. Determining the Role of Imine Group

Reaction of 2-vinylbenzaldehyde under standard reaction conditions: In a glovebox, PhZnI (0.12 mmol, 0.12 mL from a 1.0 M stock solution/THF) was taken in a 1-dram vial and

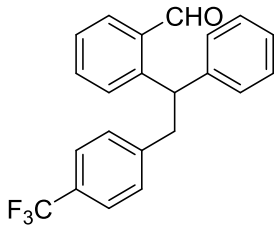
THF was removed under vacuum. To this PhZnI was added $Ni(cod)_2$ (2.7 mg, 0.0020 mmol, 2 mol %), 2-vinylbenzaldehyde (13.2 mg, 0.10 mmol) and 4-iodobenzotrifluoride (32.6 mg, 0.12 mmol). The mixture was then dissolved in dioxane (0.5 mL). The vial was then tightly capped and placed in a hotplate pre-heated to 80 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc (1 mL × 3). 50 µL of pyrene (0.010 mmol, 0.20 M stock solution) as an internal standard was added the EtOAc solution and an aliquot was analyzed by GC and GC-MS. The formation of the direct cross-coupling product, 4-phenylbenzotrifluoride (56% yield), was confirmed by comparing with a standard sample. Biphenyl, the diarylated product and the Heck product were not detected.

Reaction of 2-vinylbenzaldehyde with 4-iodobenzotrifluoride: In a glovebox, $Ni(cod)_2$ (2.7 mg, 0.0020 mmol, 2 mol %), 2-vinylbenzaldehyde (13.2 mg, 0.10 mmol) and 4-iodobenzotrifluoride (32.6 mg, 0.12 mmol) were added in a 1-dram vial. The mixture was then dissolved in dioxane (0.5 mL). Another set of a similar reaction was also set up in the presence of *N*,*N*-diisopropylethylamine (12.9 mg, 0.10 mmol). The vials were then tightly capped and placed in a hotplate pre-heated to 80 °C with vigorous stirring. After 6 h, the reaction mixtures were cooled to room temperature, diluted with water and extracted with EtOAc (1 mL × 3). 50 µL of pyrene (0.010 mmol, 0.20 M stock solution) as an internal standard was added the EtOAc solution and an aliquot was analyzed by GC and GC-MS. Heck product was not detected.

Reaction of 2-vinyl-N-phenylbenzylimine with 4-iodobenzotrifluoride: In a glovebox, $Ni(cod)_2$ (2.7 mg, 0.0020 mmol, 2 mol %), 2-vinyl-N-phenylbenzylimine (20.7 mg, 0.10 mmol) and 4-iodobenzotrifluoride (32.6 mg, 0.12 mmol) were added in a 1-dram vial. The

mixture was then dissolved in dioxane (0.5 mL). Another set of a similar reaction was also set up in the presence of *N*,*N*-diisopropylethylamine (12.9 mg, 0.10 mmol). The vials were then tightly capped and placed in a hotplate pre-heated to 80 °C with vigorous stirring. After 6 h, the reaction mixture was cooled to room temperature, 1 mL of 6N HCl was added and shaken for about 2 minutes to hydrolyze the imines to aldehydes. The reaction mixture was then extracted with EtOAc (1 mL × 3), 50 µL of pyrene (0.010 mmol, 0.20 M stock solution) as an internal standard was added and an aliquot was analyzed by GC, GC-MS and ^{1}H NMR. The Heck product was formed in 10% and 27% yields in the absence and presence of *N*,*N*-diisopropylethylamine, respectively. The formation of the Heck product was confirmed by GC-MS and comparing the NMR spectra with the spectra and data from the literature.[17]

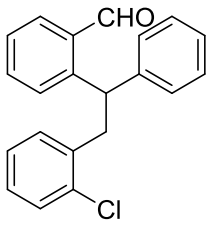
5.2.4. Characterization Data for New Compounds



2-(1-phenyl-2-(4-(trifluoromethyl)phenyl)ethyl)benzaldehyde was obtained as a white solid (144 mg, 81% yield from the reaction of 1-Iodo-4-(trifluoromethyl)benzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 18 h.

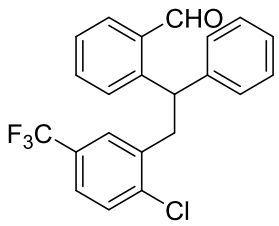
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33-3.48 (m, 2H), 5.61 (t, *J* = 9.0 Hz, 1H), 7.16-7.28 (m, 7H), 7.34-7.56 (m, 5H), 7.72 (dd, *J* = 3.0, 9.0 Hz, 1H), 10.11 (s, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 41.9, 45.4, 122.6, 125.1 (q, J_{CF} = 3.0 Hz), 126.7, 126.9,128.3, 128.6, 128.8, 129.4, 133.5, 133.8, 133.9, 142.9, 143.9, 146.2, 192.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.8; IR (neat) cm^{-1} 2927, 2864, 2737, 1690, 1319, 1109, 1017; HRMS (ESI) Calcd for $C_{22}H_{17}F_3ONa$ $(M+Na)^+$ 377.1129, found 377.1129.



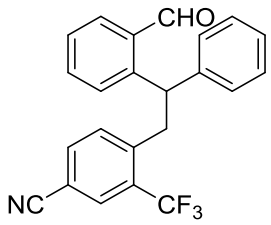
2-(2-(2-chlorophenyl)-1-phenylethyl)benzaldehyde was obtained as a colorless oil (115 mg, 72% yield from the reaction of 1-chloro-2-iodobenzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38-3.62 (m, 2H), 5.56 (t, *J* = 9.0 Hz, 1H), 7.78 (dd, *J* = 3.0, 9.0 Hz, 1H), 6.95 (dt, *J* = 0.4, 1.9 Hz, 1H), 7.06 (dt, *J* = 0.5, 1.9 Hz, 1H), 7.15-7.36 (m, 7H), 7.50-7.57 (m, 2H), 7.72 (d, *J* = 6.0 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 43.5, 126.5, 126.6, 126.8, 127.8, 128.3, 128.5, 128.9, 129.5, 131.2, 131.4, 133.9, 133.9, 134.3, 136.9, 143.5, 146.4, 191.8; IR (neat)cm^{-1} 3026, 2836, 1694, 1206, 1033; GC-MS (m/z) 320.1.



2-(2-(2-chloro-5-(trifluoromethyl)phenyl)-1-phenylethyl)benzaldehyde was obtained as a yellow oil (121 mg, 62% yield from the reaction of 1-chloro-2-iodo-4-(trifluoromethyl)benzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 9 : 1). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

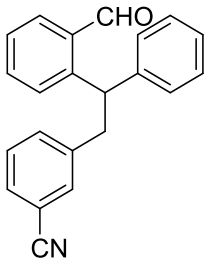
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41-3.64 (m, 2H), 5.60 (t, *J* = 9.0 Hz, 1H), 6.94 (s, 1H), 7.18-7.42 (m, 8H), 7.51-7.59 (m, 2H), 7.70 (d, *J* = 9.0, Hz, 1H), 10.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 43.3, 121.8, 124.5 (q, J_{CF} = 3.7 Hz), 125.4, 126.8, 127.1, 128.3, 128.6, 128.7, 129.0, 129.9, 132.7, 133.8, 133.9, 138.1, 142.8, 145.7, 192.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -61.3; IR (neat) cm^{-1} 2925, 2855, 1692, 1328, 1121, 1079; GC-MS (m/z) 388.1.



4-(2-(2-formylphenyl)-2-phenylethyl)-3-(trifluoromethyl)benzonitrile was obtained as a white solid (116 mg, 61% yield from the reaction of 4-iodo-3-(trifluoromethyl)benzonitrile with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.44 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $NiBr_2$, 100°C, 18 h.

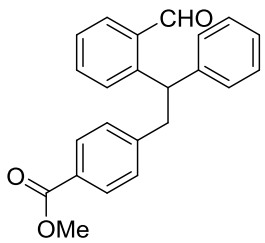
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50-3.67 (m, 2H), 5.78 (t, *J* = 9.0 Hz, 1H), 7.08-7.26 (m, 6H), 7.38-7.58 (m, 4H), 7.73 (dd, *J* = 3.0, 9.0 Hz, 1H), 7.87 (s, 1H), 10.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.2, 43.5, 110.8, 117.6, 121.6, 125.2, 126.9, 127.3, 1285, 128.7, 128.8, 129.9 (q, J_{CF} = 6.0 Hz), 130.5, 132.0, 133.4, 134.1, 134.6, 13.8, 142.1, 143.9, 145.4,

192.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -59.0; IR (neat)cm^{-1} 3065, 2859, 2742, 2233, 1690, 1316, 1120; GC-MS (m/z) 379.1.



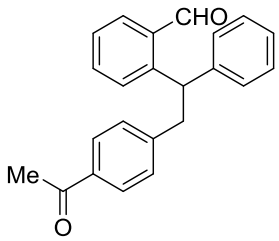
3-(2-(2-formylphenyl)-2-phenylethyl)benzonitrile was obtained as a yellow oil (109 mg, 70% yield from the reaction of 3-iodobenzonitrile with phenylzinc(II) iodide reagent and 121 mg, 78% yield from the reaction of 3-bromobenzonitrile with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 6 : 4). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 2 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28-3.42 (m, 2H), 5.57 (t, *J* = 9.0 Hz, 1H), 7.17-7.56 (m, 12H), 7.71 (d, *J* = 9.0 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.6, 45.5, 112.1, 118.9, 126.8, 127.1, 128.5, 128.6, 128.7, 129.0, 130.0, 132.7, 133.5, 133.7, 134.0, 134.2, 141.2, 142.4, 145.9, 192.9; IR (neat)cm^{-1} 3020, 2743, 2229, 1692, 1215; HRMS (ESI) Calcd for $C_{22}H_{17}NNaO$ $(M+Na)^+$ 334.1208, found 334.1199.



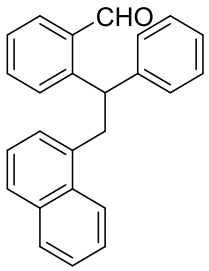
Methyl 4-(2-(2-formylphenyl)-2-phenylethyl)benzoate was obtained as a yellow oil (105 mg, 61% yield from the reaction of methyl 4-iodobenzoate with phenylzinc(II) iodide reagent and 124 mg, 72% yield from the reaction of methyl 4-bromobenzoate with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 2 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32-3.47 (m, 2H), 3.84 (s, 3H), 5.57 (t, *J* = 9.0 Hz, 1H), 7.09-7.25 (m, 7H), 7.31-7.36 (m, 1H), 7.46-7.54 (m, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 6.0 Hz, 2H), 10.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.2, 45.4, 52.0, 126.6, 126.9, 128.1, 128.4, 128.5, 128.8, 129.2, 129.5, 133.3, 133.6, 133.9, 143.0, 145.1, 146.2, 167.1, 192.6; IR (neat)cm^{-1} 2951, 2736, 1716, 1690, 1276, 1108; HRMS (ESI) Calcd for $C_{23}H_{20}NaO_3$ $(M+Na)^+$ 367.1310, found 367.1308.



2-(2-(4-acetylphenyl)-1-phenylethyl)benzaldehyde was obtained as a white solid (99 mg, 60% yield from the reaction of 1-(4-iodophenyl)ethan-1-one with phenylzinc(II) iodide reagent and 103 mg, 63% yield from the reaction of 1-(4-bromophenyl)ethan-1-one with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.43 (Hex : Ether = 1 : 1). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H), 3.32-3.47 (m, 2H), 5.58 (t, *J* = 9.0 Hz, 1H), 7.11-7.25 (m, 8H), 7.35 (dt, *J* = 0.8, 2.3 Hz, 1H), 7.46-7.55 (m, 2H), 7.69-7.75 (m, 2H), 10.09 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 42.1, 45.3, 126.6, 126.9, 128.3, 128.4, 128.5, 128.8, 129.3, 133.5, 133.6, 133.9, 135.3, 142.9, 145.4, 146.2, 192.7, 197.8; IR (neat)cm^{-1} 2918, 2748, 1691, 1673, 1263, 1180; HRMS (ESI) Calcd for $C_{23}H_{20}NaO_2$ $(M+Na)^+$ 351.1361, found 351.1343.

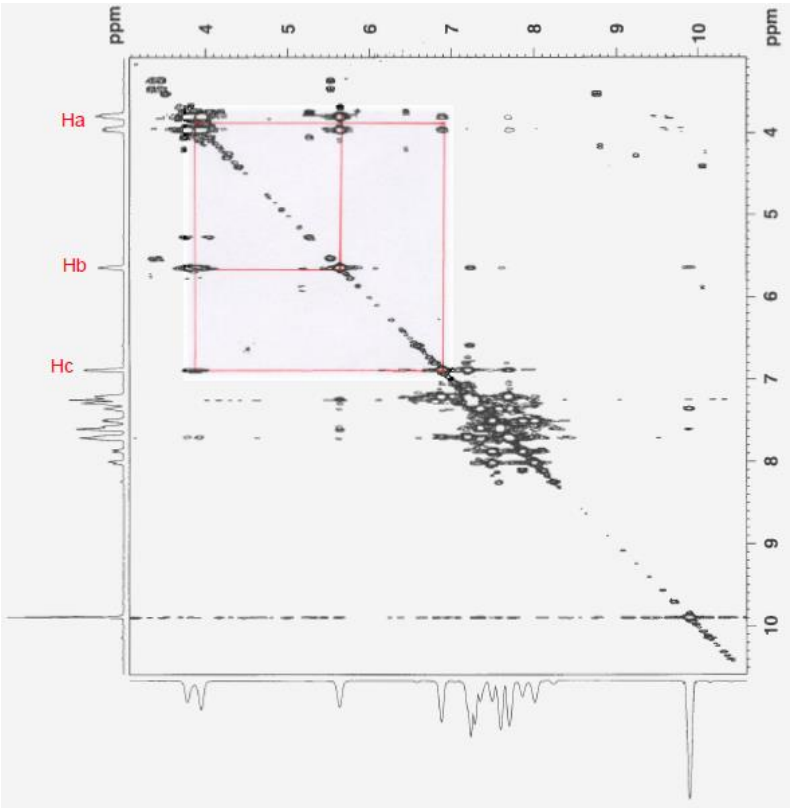


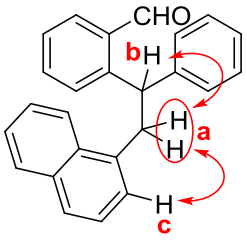
2-(2-(naphthalen-1-yl)-1-phenylethyl)benzaldehyde was obtained as a yellow oil (98 mg, 58% yield from the reaction of 1-iodonaphthalene with phenylzinc(II) iodide reagent and 118 mg, 70% yield from the reaction of 1-bromonaphthalene with phenylzinc(II) iodide reagent and 138 mg, 82% yield from the reaction of naphthalen-1-yl trifluoromethanesulfonate with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.48 (Hex : Ether = 7 : 3). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 5 mol % $Ni(cod)_2$, 100°C, 12 h; for ArOTf, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

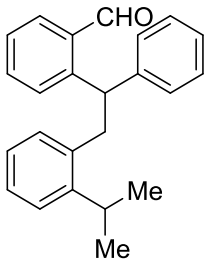
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72-3.96 (m, 2H), 5.60 (t, *J* = 9.0 Hz, 1H), 6.85 (d, *J* = 6.0 Hz, 1H), 7.15-7.35 (m, 7H), 7.45-7.59 (m, 4H), 7.65-7.70 (m, 2H), 7.91 (dd, *J* = 9.0, 39.0 Hz, 2H), 9.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 44.4, 123.3, 125.2, 125.6, 126.2, 126.6, 126.8, 127.2, 127.3, 128.4, 128.5, 128.7, 129.0, 131.0, 132.0, 133.9, 133.9, 134.0,

135.0, 144.0, 146.8, 191.4; IR (neat) cm^{-1} 3058, 2920, 2850, 2733, 1687, 1596, 1182; HRMS (ESI) Calcd for $C_{25}H_{21}O$ $(M+H)^+$ 337.1592, found 337.1585.

^1H-^1H COSY spectrum of 2-(2-(naphthalen-1-yl)-1-phenylethyl)benzaldehyde showing three-bond (Ha to Hb) and four-bond (Ha to Hc) correlations confirming the regioselective addition of two aryl groups across the olefin as shown.



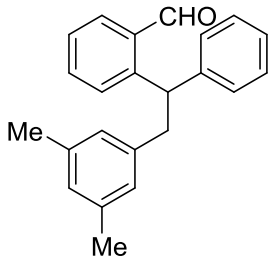




2-(2-(2-isopropylphenyl)-1-phenylethyl)benzaldehyde was obtained as a yellow oil (108 mg, 66% yield from the reaction of 1-iodo-2-isopropylbenzene with phenylzinc(II) iodide

reagent) after purification by silica gel column chromatography. R_f: 0.51 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

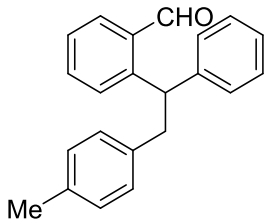
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 6.9, 3H), 2.94-3.03 (m, 1H), 3.34-3.55 (m, 2H), 5.38 (t, *J* = 9.0 Hz, 1H), 6.75 (d, *J* = 6.0, 1H), 6.94 (dt, *J* = 0.8, 2.3 Hz, 1H), 7.13-7.29 (m, 7H), 7.32-7.38 (m, 1H), 7.57 (d, *J* = 6.0 Hz, 2H), 7.73 (d, *J* = 6.0 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 24.2, 28.8, 38.7, 45.6, 125.3, 126.5, 126.7, 126.8, 128.4, 128.5, 128.8, 130.2, 131.4, 133.8, 134.0, 135.8, 143.9, 146.8, 147.0, 191.6; IR (neat)cm^{-1} 2959, 2868, 1736, 1182, 1033; GC-MS (m/z) 328.2.



2-(2-(3,5-dimethylphenyl)-1-phenylethyl)benzaldehyde was obtained as a colorless oil (108 mg, 69% yield from the reaction of 1-iodo-3,5-dimethylbenzene with phenylzinc(II) iodide reagent and 88 mg, 56% yield from the reaction of 1-bromo-3,5-dimethylbenzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.48 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

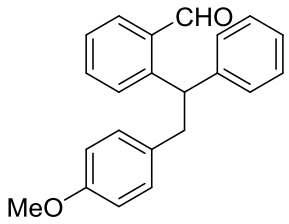
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 6H), 3.20-3.39 (m, 2H), 5.42 (t, *J* = 9.0 Hz, 1H), 6.62 (s, 2H), 6.76 (s, 1H), 7.14-7.35 (m, 6H), 7.47-7.56 (m, 2H), 7.73 (d, *J* = 9.0 Hz, 1H), 10.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 42.2, 45.7, 126.4, 126.6, 127.0, 127.8,

128.4, 128.8, 131.6, 133.8, 133.9, 137.6, 139.3, 143.8, 146.9, 192.1; IR (neat)cm^{-1} 2919, 2858, 1688, 1599, 1077; GC-MS (m/z) 314.2.



2-(1-phenyl-2-(p-tolyl)ethyl)benzaldehyde was obtained as a yellow oil (104 mg, 69% yield from the reaction of 1-iodo-4-methylbenzene with phenylzinc(II) iodide reagent and 80 mg, 53% yield from the reaction of 1-bromo-4-methylbenzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.56 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 18 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

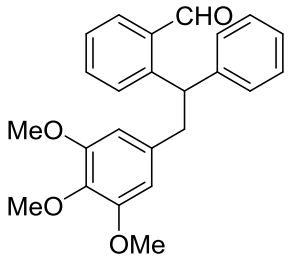
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.23-3.41 (m, 2H), 5.43 (t, *J* = 9.0 Hz, 1H), 6.87-6.97 (m, 4H), 7.12-7.34 (m, 6H), 7.46-7.54 (m, 2H), 7.71 (d, *J* = 6.0 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 41.9, 45.8, 126.4, 126.6, 128.5, 128.8, 128.9, 129.0, 131.9, 133.8, 135.6, 136.4, 143.7, 146.9, 192.2; IR (neat) cm^{-1} 3024, 2919, 2733, 1688, 1182; GC-MS (m/z) 300.1.



2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde was obtained as a white solid (89 mg, 56% yield from the reaction of 1-iodo-4-methoxybenzene with phenylzinc(II) iodide

reagent and 92 mg, 58% yield from the reaction of 1-bromo-4-methoxybenzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.56 (Hex : EtOAc = 8 : 2). The compound 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde was also crystallized from hexanes/EtOAc mixture at –35 °C. The crystals were used to acquire X-ray crystallographic data (see page 171). Conditions: for ArI, 5 mol % $NiBr_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

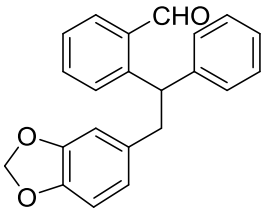
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23-3.41 (m, 2H), 3.72 (s, 3H), 5.44 (t, *J* = 9.0 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 7.15-7.35 (m, 6H), 7.48-7.55 (m, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.4, 46.0, 55.2, 113.6, 126.4, 126.6, 128.4, 128.8, 130.0, 131.5, 132.1, 133.8, 143.6, 146.9, 158.0, 192.2; IR (neat) cm^{-1} 2916, 2834, 2735, 1688, 1510, 1243, 1031; GC-MS (m/z) 316.1.



2-(1-phenyl-2-(3,4,5-trimethoxyphenyl)ethyl)benzaldehyde was obtained as a yellow oil (111 mg, 59% yield from the reaction of 5-iodo-1,2,3-trimethoxybenzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.42 (Hex : Ether = 4 : 6). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 18 h.

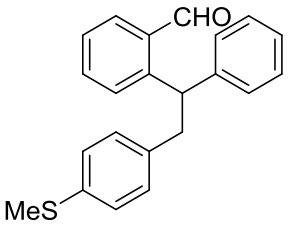
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17-3.38 (m, 2H), 3.65 (s, 6H), 3.75 (s, 3H), 5.43 (t, *J* = 9.0 Hz, 1H), 6.15 (s, 2H), 7.16-7.36 (m, 6H), 7.46-7.55 (m, 2H), 7.71 (d, *J* = 6.0 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.6, 45.8, 56.0, 60.9, 106.2, 126.5, 126.7,

128.5, 128.8, 132.5, 133.8, 133.9, 135.2, 136.4, 143.5, 146.8, 152.9, 192.3; IR (neat)cm^{-1} 2935, 2836, 1687, 1588, 1237, 1120; HRMS (ESI) Calcd for $C_{24}H_{24}NaO_4$ $(M+Na)^+$ 399.1572, found 399.1695.



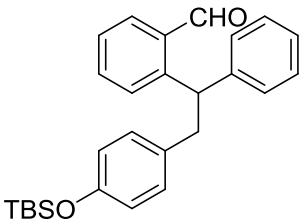
2-(2-(benzo[d][1,3]dioxol-5-yl)-1-phenylethyl)benzaldehyde was obtained as a yellow solid (109 mg, 66% yield from the reaction of 5-iodobenzo[d][1,3]dioxole with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 8 : 2). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.19-3.36 (m, 2H), 5.43 (t, *J* = 9.0 Hz, 1H), 5.84 (s, 2H), 6.46 (d, *J* = 9.0 Hz, 1H), 6.54 (s, 1H), 6.59 (d, *J* = 6.0 Hz, 1H), 7.16-7.36 (m, 6H), 7.45-7.54 (m, 2H), 7.73 (d, *J* = 9.0 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.0, 46.0, 100.8, 108.0, 109.5, 122.1, 126.5, 126.7, 128.5, 128.8, 132.4, 133.3, 133.8, 133.8, 143.4, 145.9, 146.7, 147.5, 192.3; IR (neat) cm^{-1} 2927, 2735, 1692, 1489, 1246, 1035; HRMS (ESI) Calcd for $C_{22}H_{18}NaO_3$ $(M+Na)^+$ 353.1154, found 353.1091.



2-(2-(4-(methylthio)phenyl)-1-phenylethyl)benzaldehyde was obtained as a yellow oil (100 mg, 60% yield from the reaction of (4-iodophenyl)(methyl)sulfane with phenylzinc(II) iodide reagent and 113 mg, 68% yield from the reaction of (4-bromophenyl)(methyl)sulfane with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.44 (Hex : Ether = 8 : 2). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 2 mol % $Ni(cod)_2$, 100°C, 12 h.

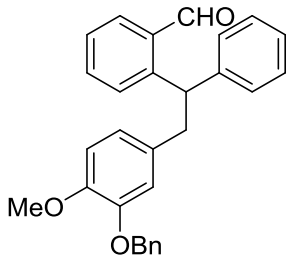
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.22-3.38 (m, 2H), 5.46 (t, *J* = 9.0 Hz, 1H), 6.93 (d, *J* = 6.0 Hz, 2H), 7.04 (d, *J* = 6.0 Hz, 2H), 7.11-7.26 (m, 5H), 7.30-7.35 (m, 1H), 7.45-7.54 (m, 2H), 7.71 (d, *J* = 6.0 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 41.7, 45.7, 126.5, 126.8, 128.5, 128.6, 128.8, 129.6, 132.7, 133.7, 133.8, 135.9, 136.6, 143.4, 146.7, 192.4; IR (neat) cm^{-1} 3022, 2918, 2856, 2738, 1687, 1492, 1181; GC-MS (m/z) 332.1.



2-(2-(4-((tert-butyldimethylsilyl)oxy)phenyl)-1-phenylethyl)benzaldehyde was obtained as a yellow oil (127 mg, 61% yield from the reaction of tert-butyl(4-iodophenoxy)dimethylsilane with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.52 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

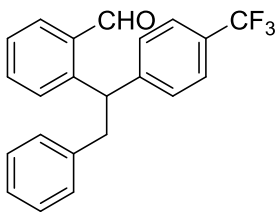
^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 6H), 0.93 (s, 9H), 3.18-3.37 (m, 2H), 5.36 (t, *J* = 9.0 Hz, 1H), 6.60 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 7.14-7.33 (m, 6H), 7.44-

7.54 (m, 2H), 7.69 (d, J = 9.0 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.3, 18.3, 25.8, 41.6, 46.1, 119.9, 126.4, 126.6, 128.4, 128.9, 130.1, 131.8, 132.3, 133.8, 133.9, 143.7, 146.9, 154.0, 192.1; IR (neat) cm^{-1} 2955, 2857, 1693, 1508, 1251; GC-MS (m/z) 416.2.



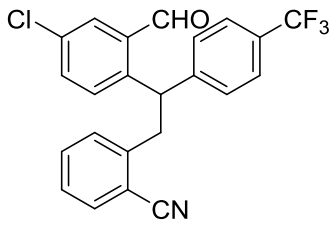
2-(2-(3-(benzyloxy)-4-methoxyphenyl)-1-phenylethyl)benzaldehyde was obtained as a yellow oil (97mg, 46% yield from the reaction of 1-(benzyloxy)-4-iodo-2-methoxybenzene with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.15-3.32 (m, 2H), 3.79 (s, 3H), 4.94 (s, 2H), 5.32 (t, J = 9.0 Hz, 1H), 6.49 (s, 1H), 6.56 (d, J = 9.0 Hz, 1H), 6.67 (d, J = 9.0 Hz, 1H), 7.13-7.38 (m, 11H), 7.43-7.53 (m, 2H), 7.71 (d, J = 6.0 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.8, 46.0, 56.0, 70.9, 111.7, 115.3, 121.8, 126.4, 126.6, 127.3, 127.8, 128.5, 128.6, 128.7, 132.0, 132.1, 133.8, 137.3, 143.6, 146.8, 147.7, 148.1, 192.2; IR (neat)cm^{-1} 3026, 2930, 1688, 1512, 1256, 1135, 1022; HRMS (ESI) Calcd for $C_{29}H_{26}NaO_3$ $(M+Na)^+$ 445.1780, found 445.1743.



2-(2-phenyl-1-(4-(trifluoromethyl)phenyl)ethyl)benzaldehyde was obtained as a yellow oil (115 mg, 65% yield from the reaction of iodobenzene with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.52 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

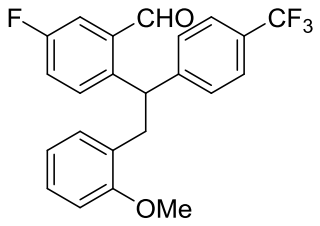
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28-3.41 (m, 2H), 5.63 (t, *J* = 9.0 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.08-7.19 (m, 3H), 7.23-7.58 (m, 7H), 7.71 (d, *J* = 6.0 Hz, 1H), 10.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.1, 45.6, 122.5, 125.3(q, J_{CF} = 3.7 Hz), 126.1, 126.4, 127.1, 128.4, 128.5, 128.8, 128.9, 129.1, 133.7, 133.9, 139.0, 145.6, 147.6, 192.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.8; IR (neat)cm^{-1} 3029, 2928, 2743, 1690, 1322, 1108, 1066; GC-MS (m/z) 354.1.



2-(2-(4-chloro-2-formylphenyl)-2-(4-(trifluoromethyl)phenyl)ethyl)benzonitrile was obtained as a yellow oil (149 mg, 72% yield from the reaction of 2-iodobenzonitrile with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent and 145 mg, 70% yield from the reaction of 2-bromobenzonitrile with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent and 149 mg, 72% yield from the reaction of 2-cyanophenyl trifluoromethanesulfonate with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 7 : 3). Conditions: for ArI, 5 mol % $Ni(cod)_2$,

80°C, 12 h; for ArBr, 2 mol % $Ni(cod)_2$, 100°C, 12 h; for ArOTf, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

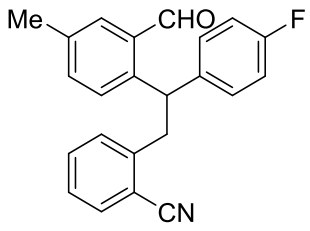
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53-3.70 (m, 2H), 5.78 (t, *J* = 9.0 Hz, 1H), 7.22-7.31 (m, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.42-7.47 (m, 1H), 7.52-7.61 (m, 5H), 7.71 (d, *J* = 3.0 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.8, 44.3, 113.0, 117.9, 125.6 (d, J_{CF} = 3.0 Hz), 127.3, 128.7, 129.0, 129.5, 130.0, 130.5, 132.8, 132.9, 133.8, 134.1, 134.8, 142.6, 142.7, 146.0,191.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -61.0; IR (neat)cm^{-1} 3069, 2865, 2740, 2224, 1697, 1323, 1110, 1067; HRMS (ESI) Calcd for $C_{23}H_{15}ClF_3NNaO$ $(M+Na)^+$ 436.0692, found 436.0695.



5-Fluoro-2-(2-(2-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)ethyl)benzaldehyde was obtained as a yellow oil (135 mg, 67% yield from the reaction of 1-iodo-2-methoxybenzene with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent and 97 mg, 48% yield from the reaction of 1-bromo-2-methoxybenzene with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.52 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 100°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

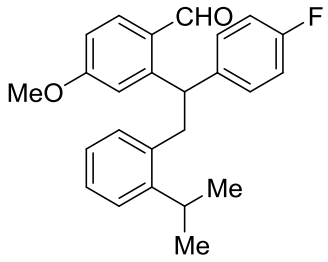
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.22-3.52 (m, 2H), 3.73 (s, 3H), 5.43 (t, *J* = 9.0 Hz, 1H), 6.70-6.80 (m, 3H), 7.12-7.27 (m, 2H), 7.32 (d, *J* = 6.0 Hz, 2H), 7.39-7.44 (m, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 10.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 43.4, 55.2, 110.3, 116.5

(d, J_{CF} = 21.7 Hz), 120.4, 120.9 (d, J_{CF} = 21.2 Hz), 122.4, 125.4 (d, J_{CF} = 3.7 Hz), 126.6, 128.1, 128.7, 129.0, 130.8, 131.1 (d, J_{CF} = 7.5 Hz), 135.7 (d, J_{CF} = 6.0 Hz), 142.0, 147.9, 157.4, 161.4 (d, J_{CF} = 246.7 Hz), 189.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.3, -61.0; IR (neat)cm^{-1} 3068, 2940, 2739, 1687, 1492, 1322, 1105, 1017; GC-MS (m/z) 402.1.



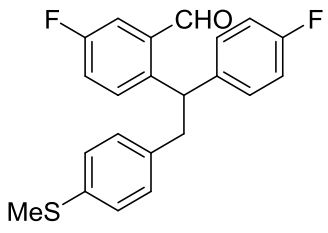
2-(2-(4-fluorophenyl)-2-(2-formyl-4-methylphenyl)ethyl)benzonitrile obtained as a yellow oil (110 mg, 64% yield from the reaction of 2-iodobenzonitrile with (4-fluorophenyl)zinc(II) iodide reagent and 112 mg, 65% yield from the reaction of 2-bromobenzonitrile with (4-fluorophenyl)zinc(II) iodide reagent and 91 mg, 53% yield from the reaction of 2-cyanophenyl trifluoromethanesulfonate with (4-fluorophenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h; for ArOTf, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.49-3.64 (m, 2H), 5.67 (t, J = 9.0 Hz, 1H), 6.89-6.95 (m, 2H), 7.16-7.26 (m, 4H), 7.37-7.53 (m, 5H), 10.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 40.2, 43.9, 112.9, 115.3 (d, J_{CF} = 21.0 Hz), 118.1, 126.9, 128.6, 129.9 (t, J_{CF} = 8.2 Hz), 132.6 (d, J_{CF} = 4.5 Hz), 133.2, 134.7, 134.8, 137.05, 138.4, 138.5, 142.3, 143.5, 161.5 (d, J_{CF} = 243.7 Hz), 192.9 ; ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.7; IR (neat)cm^{-1} 2982, 2866, 2734, 2223, 1687, 1507, 1235, 1044; HRMS (ESI) Calcd for $C_{23}H_{18}FNNaO$ $(M+Na)^+$ 366.1270, found 366.1220.



2-(1-(4-fluorophenyl)-2-(2-isopropylphenyl)ethyl)-4-methoxybenzaldehyde *w*as obtained as a yellow oil (104 mg, 55% yield from the reaction of 1-iodo-2-isopropylbenzene with (4-fluorophenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.48 (Hex : Ether = 7 : 3). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

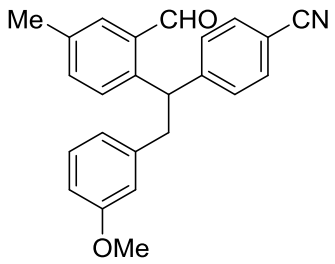
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, *J* = 14.4 Hz, 3H), 1.16 (d, *J* = 14.4 Hz, 3H), 2.95-3.04 (m, 1H), 3.36 (d, *J* = 6.0 Hz, 2H), 3.89 (s, 3H), 5.42 (t, *J* = 9.0 Hz, 1H), 6.77 (d, *J* = 6.0 Hz, 1H), 6.85-6.98 (m, 4H), 7.07-7.24 (m, 5H), 7.72 (d, *J* = 9.0 Hz, 1H), 9.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8, 24.3, 28.8, 38.7, 44.9, 55.6, 110.9, 115.0, 115.2 (d, J_{CF} = 3.7 Hz), 125.3, 126.8, 127.4, 129.8, 129.9, 130.1, 135.7, 135.8, 139.3 (d, J_{CF} = 3.0 Hz), 147.0, 149.1, 161.5 (d, J_{CF} = 243.0 Hz), 163.9, 190.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.6; IR (neat)cm^{-1} 2962, 2867, 2733, 1682, 1597, 1219, 1033; HRMS (ESI) Calcd for $C_{25}H_{26}FO_2$ $(M+H)^+$ 377.1917, found 377.1912.



5-Fluoro-2-(1-(4-fluorophenyl)-2-(4-(methylthio)phenyl)ethyl)benzaldehyde was obtained as a yellow oil (133 mg, 72% yield from the reaction of (4-

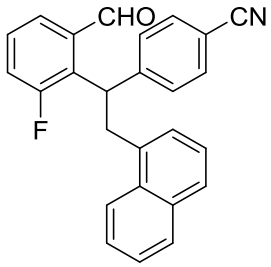
iodophenyl)(methyl)sulfane with (4-fluorophenyl)zinc(II) iodide reagent and 111 mg, 60% yield from the reaction of (4-bromophenyl)(methyl)sulfane with (4-fluorophenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.46 (Hex : Ether = 8 : 2). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 24 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.19-3.36 (m, 2H), 5.33 (t, *J* = 9.0 Hz, 1H), 6.90-6.97 (m, 4H), 7.06-7.15 (m, 4H), 7.21-7.28 (m, 1H), 7.41-7.46 (m, 2H), 10.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 41.9, 44.7, 115.4 (d, J_{CF} = 21.0 Hz), 118.1 (d, J_{CF} = 21.0 Hz), 120.9 (d, J_{CF} = 21.0 Hz), 126.7, 129.5, 129.7, 129.8, 130.6 (d, J_{CF} = 7.5 Hz), 135.2 (d, J_{CF} = 5.2 Hz), 135.8, 136.3, 138.9, 142.2, 161.3 (d, J_{CF} = 246.7 Hz), 161.5 (d, J_{CF} = 243.7 Hz), 190.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.6, 113.3; IR (neat)cm^{-1} 3037, 2920, 2738, 1685, 1490, 1222, 1094; GC-MS (m/z) 368.1.



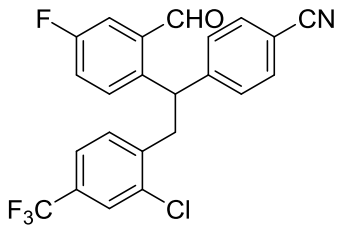
4-(1-(2-formyl-4-methylphenyl)-2-(3-methoxyphenyl)ethyl)benzonitrile was obtained as a yellow solid (108 mg, 61% yield from the reaction of 1-iodo-3-methoxybenzene with (4-cyanophenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 3.27 (d, *J* = 6.0 Hz, 2H), 3.67 (s, 3H), 5.57 (t, *J* = 9.0 Hz, 1H), 6.54-6.66 (m, 3H), 7.04-7.09 (m, 1H), 7.23-7.27 (m, 2H), 7.36 (s, 2H), 7.46-7.51 (m, 3H), 9.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 41.9, 45.5, 55.2, 110.1, 111.8, 114.8, 119.0, 121.5, 128.6, 129.3, 132.1, 133.5, 134.8, 135.2, 137.2, 140.5, 141.9, 149.4, 159.5, 193.0; IR (neat)cm^{-1} 2853, 2739, 2226, 1686, 1602, 1259, 1040; GC-MS (m/z) 355.1.



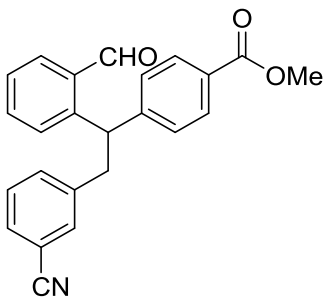
4-(1-(2-fluoro-6-formylphenyl)-2-(naphthalen-1-yl)ethyl)benzonitrile was obtained as a yellow solid (129 mg, 68% yield from the reaction of 1-iodonaphthalene with (4-cyanophenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.44 (Hex : EtOAc = 8 : 2). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83-4.16 (m, 2H), 5.99 (t, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 6.0 Hz, 1H), 7.15-7.27 (m, 2H), 7.31-7.39 (m, 2H), 7.44-7.53 (m, 4H), 7.58-7.66 (m, 3H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.98 (d, *J* = 6.0 Hz, 1H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.4, 41.1, 110.4, 119.0, 121.6, 121.9, 123.2, 125.1, 125.7, 126.3, 127.1, 127.4, 128.8, 129.0, 129.3, 131.4 (d, J_{CF} = 12.7 Hz), 131.6, 132.2, 133.8, 134.7, 136.0 (d, J_{CF} = 4.5 Hz), 148.1, 161.9 (d, J_{CF} = 248.2 Hz), 191.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ -107.6; IR (neat)cm^{-1} 3054, 2852, 2768, 2224, 1693, 1232, 1161; GC-MS (m/z) 379.1.



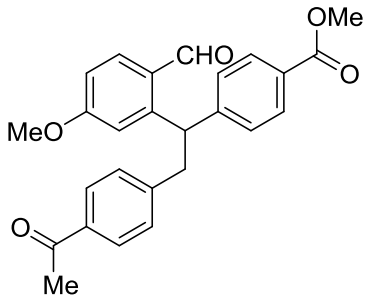
4-(2-(2-chloro-4-(trifluoromethyl)phenyl)-1-(4-fluoro-2-formylphenyl)ethyl)benzonitrile was obtained as a yellow oil (125 mg, 58% yield from the reaction of 2-chloro-1-iodo-4-(trifluoromethyl)benzene with (4-cyanophenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44-3.60 (m, 2H), 5.70 (t, *J* = 9.0 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 1H), 7.27-7.35 (m, 4H), 7.43-7.59 (m, 5H), 9.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.1, 43.2, 110.9 118.7, 120.4 (d, J_{CF} = 21.7 Hz), 121.2 (d, J_{CF} = 21.0 Hz), 123.5 (d, J_{CF} = 3.0 Hz), 125.0, 126.8 (d, J_{CF} = 3.0 Hz), 128.0, 129.1, 130.4, 130.7 (d, J_{CF} = 6.7 Hz), 131.3, 132.4, 134.8, 135.3 (d, J_{CF} = 5.2 Hz), 139.7 (d, J_{CF} = 3.0 Hz), 140.2, 148.0, 161.8 (d, J_{CF} = 249.0 Hz), 190.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.2, -62.7; IR (neat)cm^{-1} 2921, 2851, 2227, 1697, 1321, 1124, 1079; GC-MS (m/z) 431.1.



Methyl 4-(2-(3-cyanophenyl)-1-(2-formylphenyl)ethyl)benzoate was obtained as a white solid (111 mg, 60% yield from the reaction of 3-iodobenzonitrile with (4-(methoxycarbonyl)phenyl)zinc(II) iodide reagent and 116 mg, 63% yield from the reaction of 3-bromobenzonitrile with (4-(methoxycarbonyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.44 (Hex : Ether = 4 : 6). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 5 mol % $Ni(cod)_2$, 100°C, 12 h.

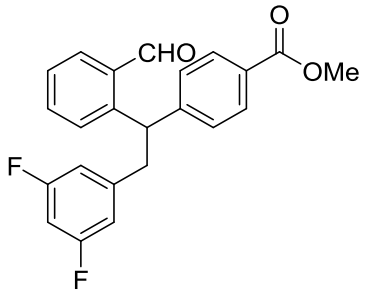
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (d, *J* = 9.0 Hz, 2H), 3.85 (s, 3H), 5.69 (t, *J* = 9.0 Hz, 1H), 7.22-7.32 (m, 5H), 7.37-7.43 (m, 3H), 7.51-7.57 (m, 1H), 7.71 (d, *J* = 6.0 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 2H), 10.02 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.4, 45.5, 52.1, 112.3, 118.9, 127.4, 128.6, 128.7, 128.8, 129.1, 129.9, 130.2, 132.6, 133.4, 133.6, 134.0, 135.2, 140.8, 144.9, 147.6, 166.8, 193.1; IR (neat)cm^{-1} 2918, 2752, 2233, 1717, 1695, 1280, 1099; HRMS (ESI) Calcd for $C_{24}H_{19}NNaO_3$ $(M+Na)^+$ 392.1263, found 392.1263.



Methyl 4-(2-(4-acetylphenyl)-1-(2-formyl-5-methoxyphenyl)ethyl)benzoate was obtained as a yellow oil (125 mg, 60% yield from the reaction of 1-(4-iodophenyl)ethan-1-one with (4-(methoxycarbonyl)phenyl)zinc(II) iodide reagent and 102 mg, 49% yield from the reaction of 1-(4-bromophenyl)ethan-1-one with (4-(methoxycarbonyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.51 (Hex :

Ether = 2 : 8). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

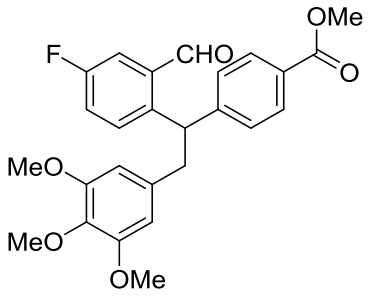
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 3.37 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 5.78 (t, *J* = 9.0 Hz, 1H), 6.86 (dd, *J* = 3.0, 9.0 Hz, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 9.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 41.7, 45.4, 52.1, 55.6, 110.9, 115.7, 127.1, 128.4, 128.5, 128.6, 129.3, 129.8, 135.4, 138.0, 145.0, 147.8, 148.0, 163.9, 166.9, 191.4, 197.8; IR (neat)cm^{-1} 3004, 2949, 2840, 2740, 1716, 1676, 1597, 1267, 1103; HRMS (ESI) Calcd for $C_{26}H_{25}O_5$ $(M+H)^+$ 417.1702, found 417.1698.



Methyl 4-(2-(3,5-difluorophenyl)-1-(2-formylphenyl)ethyl)benzoate was obtained as a white solid (116 mg, 61% yield from the reaction of 1,3-difluoro-5-iodobenzene with (4-(methoxycarbonyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.42 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $NiBr_2$, 100°C, 18 h.

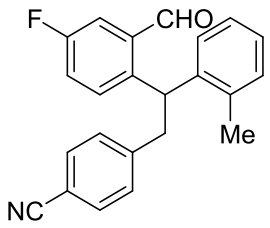
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.30 (d, *J* = 6.0 Hz, 2H), 3.84 (s, 3H), 5.67 (t, *J* = 9.0 Hz, 1H), 6.49-6.61 (m, 3H), 7.23-7.28 (m, 2H), 7.37-7.42 (m, 2H), 7.50-7.56 (m, 1H), 7.72 (d, *J* = 6.0 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 2H), 10.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

41.5, 45.3, 52.1, 101.9 (t, J_{CF} = 25.5 Hz), 111.9 (dd, J_{CF} = 7.5, 16.5 Hz), 127.3, 128.6, 128.6, 128.7, 129.8, 133.5, 134.0, 135.0, 143.2 (t, J_{CF} = 9.0 Hz), 145.0, 147.8, 162.9 (dd, J_{CF} = 12.8, 234.0 Hz), 166.9, 193.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -108.7; IR (neat)cm^{-1} 3094, 2948, 1715, 1694, 1288, 1113; GC-MS (m/z) 380.1.



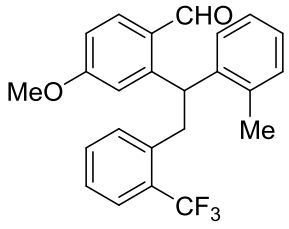
Methyl 4-(1-(4-fluoro-2-formylphenyl)-2-(3,4,5-trimethoxyphenyl)ethyl)benzoate was obtained as a yellow oil (158 mg, 70% yield from the reaction of 5-iodo-1,2,3-trimethoxybenzene with (4-(methoxycarbonyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.60 (Hex : Ether = 2 : 8). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.18-3.40 (m, 2H), 3.69 (s, 6H), 3.78 (s, 3H), 3.89 (s, 3H), 5.43 (t, *J* = 9.0 Hz, 1H), 6.16 (s, 2H), 7.22-7.30 (m, 3H), 7.40-7.45 (m, 2H), 7.94 (d, *J* = 9.0 Hz, 2H), 10.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.4, 45.4, 52.1, 56.0, 60.9, 106.1, 118.3 (d, J_{CF} = 21.7 Hz), 120.9 (d, J_{CF} = 21.0 Hz),128.4, 128.6, 129.8, 130.8 (d, J_{CF} = 6.7 Hz), 134.3, 135.5 (d, J_{CF} = 5.2 Hz), 136.6, 141.5, 148.5, 153.0, 161.3 (d, J_{CF} = 242.2 Hz), 166.8, 190.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.0; IR (neat)cm^{-1} 2940, 2838, 2740, 1716, 1690, 1277, 1119; HRMS (ESI) Calcd for $C_{26}H_{26}FO_6$ $(M+H)^+$ 453.1713, found 453.1679.



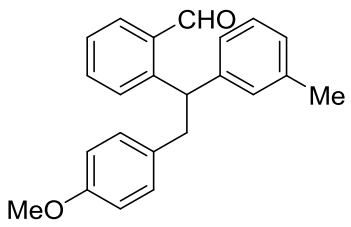
4-(2-(4-fluoro-2-formylphenyl)-2-(o-tolyl)ethyl)benzonitrile was obtained as a white solid (110 mg, 64% yield from the reaction of 4-iodobenzonitrile with *o*-tolylzinc(II) iodide reagent and 77mg, 45% yield from the reaction of 4-bromobenzonitrile with *o*-tolylzinc(II) iodide reagent and 89 mg, 52% yield from the reaction of 4-cyanophenyl trifluoromethanesulfonate with *o*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.50 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h; for ArOTf, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H), 3.23-3.45 (m, 2H), 5.64 (t, J = 9.0 Hz, 1H), 7.09-7.26 (m, 7H), 7.39-7.48 (m, 4H), 9.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 41.3, 42.3, 110.3, 118.9, 119.1 (d, J_{CF} = 21.7 Hz), 121.1 (d, J_{CF} = 21.0 Hz), 126.1, 127.0, 129.9, 131.1, 131.2, 132.1, 135.1 (d, J_{CF} = 5.2 Hz),136.8, 140.1 141.4 (d, J_{CF} = 3.7 Hz), 145.0, 161.3 (d, J_{CF} = 247.5 Hz), 190.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.0; IR (neat)cm^{-1} 2913, 2224, 1693, 1488, 1252, 1138; GC-MS (m/z) 343.1.



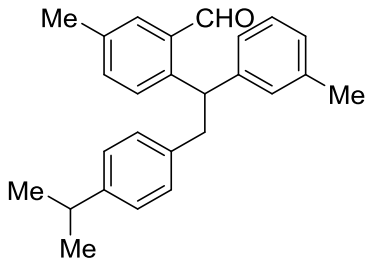
4-Methoxy-2-(1-(o-tolyl)-2-(2-(trifluoromethyl)phenyl)ethyl)benzaldehyde was obtained as a colorless oil (114 mg, 57% yield from the reaction of 1-iodo-2-(trifluoromethyl)benzene with *o*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.48 (Hex : Ether = 6 : 4). This compound contains approx. 10% of Heck product as an inseparable mixture. Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.36-3.63 (m, 2H), 3.78 (s, 3H), 5.83 (t, J = 9.0 Hz, 1H), 6.78-6.79 (m, 1H), 6.82-6.87 (m, 2H), 7.09-7.33 (m, 6H), 7.60-7.63 (m, 1H), 7.71 (d, J = 9.0 Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 38.2, 40.0, 55.5, 111.4, 115.6, 126.1 (d, J_{CF} = 6.0 Hz), 126.2, 126.4, 126.8, 127.2, 127.7, 129.1, 129.7, 130.8 (d, J_{CF} = 3.0 Hz), 131.5, 132.2, 136.1, 136.9, 137.8, 141.1, 148.7, 164.1, 190.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -58.3; IR (neat)cm^{-1} 2969, 2881, 1683, 1599, 1311, 1120, 950; HRMS (ESI) Calcd for $C_{24}H_{22}F_3O_2$ $(M+H)^+$ 399.1572, found 399.1544.



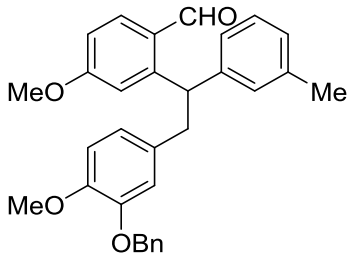
2-(2-(4-methoxyphenyl)-1-(m-tolyl)ethyl)benzaldehyde was obtained as a yellow oil (119 mg, 72% yield from the reaction of 1-iodo-4-methoxybenzene with *m*-tolylzinc(II) iodide reagent and 107 mg, 65% yield from the reaction of 1-bromo-4-methoxybenzene with *m*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 8 : 2). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 18 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.23-3.43 (m, 2H), 3.74 (s, 3H), 5.41 (t, *J* = 9.0 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.93-7.09 (m, 5H), 7.16-7.21 (m, 1H), 7.31-7.37 (m, 1H), 7.49-7.57 (m, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 41.4, 45.8, 55.2, 113.6, 125.3, 126.6, 127.2, 128.3, 128.9, 129.2, 130.0, 131.6, 131.8, 133.8, 138.0, 143.6, 147.0, 158.0, 192.2; IR (neat)cm^{-1} 2917, 2834, 2735, 1687, 1510, 1243, 1033; HRMS (ESI) Calcd for $C_{23}H_{22}NaO_2$ $(M+Na)^+$ 353.1517, found 353.1538.



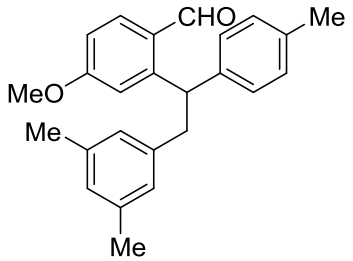
2-(2-(4-isopropylphenyl)-1-(m-tolyl)ethyl)-5-methylbenzaldehyde was obtained as a yellow oil (112 mg, 63% yield from the reaction of 1-iodo-4-isopropylbenzene with *m*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.50 (Hex : Ether = 8.5 : 1.5). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (d, *J* = 9.0 Hz, 6H), 2.30 (s, 3H), 2.38 (s, 3H), 2.80-2.89 (m, 1H), 3.26-3.44 (m, 2H), 5.35 (t, *J* = 9.0 Hz, 1H), 6.96-7.07 (m, 7H), 7.16-7.21 (m, 1H), 7.35-7.43 (m, 2H), 7.57 (s, 1H), 10.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 21.5, 24.1, 33.7, 41.9, 45.4, 125.2, 126.2, 127.1, 128.3, 128.8, 129.0, 129.2, 131.7, 133.6, 134.7, 136.2, 137.0, 138.0, 144.1, 146.7, 192.1; IR (neat)cm^{-1} 2958, 2865, 2732, 1685, 1240, 1159; HRMS (ESI) Calcd for $C_{26}H_{28}NaO$ $(M+Na)^+$ 379.2038, found 379.2022.



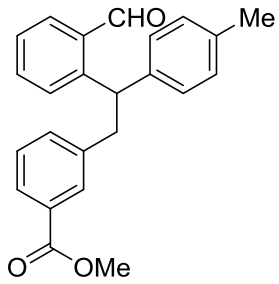
2-(2-(3-(benzyloxy)-4-methoxyphenyl)-1-(m-tolyl)ethyl)-4-methoxybenzaldehyde was obtained as a yellow oil (105 mg, 45% yield from the reaction of 2-(benzyloxy)-4-iodo-1-methoxybenzene with *m*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.62 (Hex : Ether = 3 : 7). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.16-3.31 (m, 2H), 3.82 (s, 3H), 3.83 (s, 3H), 4.99 (s, 2H), 5.37 (t, *J* = 9.0 Hz, 1H), 6.59-6.73 (m, 3H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.97-7.03 (m, 4H), 7.13-7.18 (m, 1H), 7.31-7.42 (m, 5H), 7.72 (d, *J* = 9.0 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 41.6, 45.8, 55.4, 56.0, 70.9, 110.9, 111.6, 115.1, 115.2, 121.8, 125.3, 127.2, 127.3, 127.4, 127.7, 128.3, 128.5, 129.2, 132.1, 135.1, 137.3, 137.9, 143.3, 147.7, 148.0, 149.5, 163.8, 190.7; IR (neat)cm^{-1} 2921, 1681, 1596, 1234, 1023; HRMS (ESI) Calcd for $C_{31}H_{31}O_4$ $(M+H)^+$ 467.2222, found 467.2218.



2-(2-(3,5-dimethylphenyl)-1-(p-tolyl)ethyl)-4-methoxybenzaldehyde was obtained as a yellow oil (120 mg, 67% yield from the reaction of 1-iodo-3,5-dimethylbenzene with *p*-tolylzinc(II) iodide reagent and 97 mg, 54% yield from the reaction of 1-bromo-3,5-dimethylbenzene with *p*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 8 : 2). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

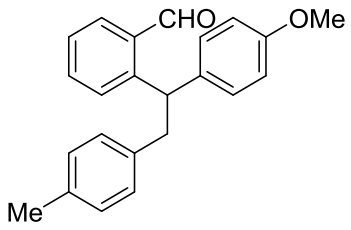
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 6H), 2.23 (s, 3H), 3.19-3.34 (m, 2H), 3.84 (s, 3H), 5.45 (t, *J* = 9.0 Hz, 1H), 6.70 (s, 2H), 6.77-6.83 (m, 2H), 6.98 (d, *J* = 3.0 Hz, 1H), 7.06-7.15 (m, 4H), 7.73 (d, *J* = 9.0 Hz, 1H), 10.04 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 21.3, 42.1, 45.2, 55.5, 111.0, 115.0, 126.9, 127.5, 127.8, 128.3, 129.1, 134.8, 135.9, 137.6, 139.5, 140.6, 149.8, 163.9, 190.7; IR (neat)cm^{-1} 3012, 2858, 2732, 1681, 1596, 1228, 1035; HRMS (ESI) Calcd for $C_{25}H_{26}NaO_2$ $(M+Na)^+$ 381.1830, found 381.1809.



Methyl 3-(2-(2-formylphenyl)-2-(p-tolyl)ethyl)benzoate was obtained as a yellow oil (95 mg, 53% yield from the reaction of methyl 3-iodobenzoate with *p*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.45 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h.

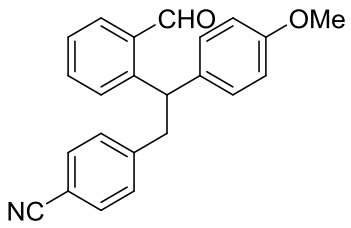
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.32-3.48 (m, 2H), 3.88 (s, 3H), 5.51 (t, *J* = 9.0 Hz, 1H), 7.05 -7.13 (m, 4H), 7.22 (d, *J* = 3.0 Hz, 2H), 7.32-7.37 (m, 1H), 7.49-7.57 (m,

2H), 7.72 (d, *J* = 6.0 Hz, 1H), 7.78-7.82 (m, 2H), 10.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 42.0, 45.2, 52.1, 126.7, 127.5, 128.3, 128.7, 129.2, 130.1, 130.3, 132.7, 133.7, 133.9, 136.1, 140.1, 146.6, 167.1, 192.4; IR (neat)cm^{-1} 2981, 2736, 1720, 1694, 1238, 1044; HRMS (ESI) Calcd for $C_{24}H_{22}NaO_3$ $(M+Na)^+$ 381.1467, found 381.1435.



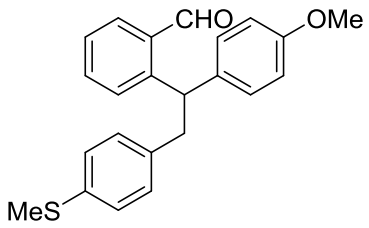
2-(1-(4-methoxyphenyl)-2-(p-tolyl)ethyl)benzaldehyde was obtained as a yellow oil (78 mg, 47% yield from the reaction of 1-iodo-4-methylbenzene with (4-methoxyphenyl)zinc(II) iodide reagent and 88 mg, 53% yield from the reaction of p-tolyl trifluoromethanesulfonate with (4-methoxyphenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.46 (Hex : Ether = 7 : 3). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 24 h; for ArOTf, 5 mol % $Ni(cod)_2$, 100°C, 12 h, 1.4 equiv each of ArOTf and ArZnI was used.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.24-3.41 (m, 2H), 3.77 (s, 3H), 5.41 (t, *J* = 9.0 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.92-7.01 (m, 4H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.31-7.36 (m, 1H), 7.48-7.57 (m, 2H), 7.74 (d, *J* = 9.0 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 42.1, 45.1, 55.2, 113.8, 126.5, 128.7, 128.9, 129.0, 129.4, 131.9, 133.7, 133.8, 135.6, 135.8, 136.5, 147.3, 158.1, 192.2; IR (neat)cm^{-1} 2920, 2834, 2734, 1688, 1509, 1246, 1033; HRMS (ESI) Calcd for $C_{23}H_{22}NaO_2$ $(M+Na)^+$ 353.1517, found 353.1527.



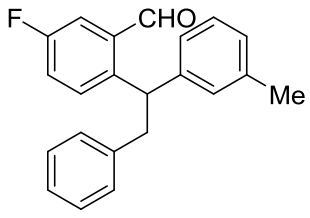
4-(2-(2-formylphenyl)-2-(4-methoxyphenyl)ethyl)benzonitrile was obtained as a yellow solid (94 mg, 55% yield from the reaction of 4-iodobenzonitrile with (4-methoxyphenyl)zinc(II) iodide reagent and 116 mg, 68% yield from the reaction of 4-bromobenzonitrile with (4-methoxyphenyl)zinc(II) iodide reagent and 97 mg, 57% yield from the reaction of 4-cyanophenyl trifluoromethanesulfonate with (4-methoxyphenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.46 (Hex : Ether = 4 : 6). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 18 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h; for ArOTf, 2 mol % $Ni(cod)_2$, 80°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29-3.43 (m, 2H), 3.76 (s, 3H), 5.55 (t, *J* = 9.0 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 2H), 7.14 (dd, *J* = 9.0, 24.0 Hz, 4H), 7.37-7.58 (m, 5H), 7.73 (d, *J* = 9.0 Hz, 1H), 10.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.3, 44.6, 55.2, 110.0, 113.9, 119.0, 126.9, 128.6, 129.4, 129.9, 132.0, 133.3, 133.9, 134.2, 134.4, 145.6, 146.4, 158.3, 193.0; IR (neat)cm^{-1} 2931, 2835, 2741, 2225, 1688, 1508, 1247, 1177, 1032; GC-MS (m/z) 341.1.



2-(1-(4-methoxyphenyl)-2-(4-(methylthio)phenyl)ethyl)benzaldehyde was obtained as a yellow oil (101 mg, 56% yield from the reaction of (4-iodophenyl)(methyl)sulfane with (4-methoxyphenyl)zinc(II) iodide reagent and 94 mg, 52% yield from the reaction of (4-bromophenyl)(methyl)sulfane with (4-methoxyphenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.48 (Hex : Ether = 6 : 4). Conditions: for ArI, 5 mol % $Ni(cod)_2$, 80°C, 12 h; for ArBr, 10 mol % $Ni(cod)_2$, 100°C, 12 h.

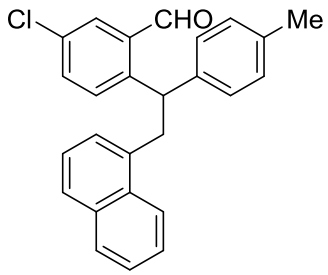
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.22-3.37 (m, 2H), 3.76 (s, 3H), 5.42 (t, *J* = 9.0 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.06-7.14 (m, 4H), 7.33-7.38 (m, 1H), 7.47-7.57 (m, 2H), 7.74 (d, *J* = 6.0 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 41.8, 44.9, 55.2, 113.8, 126.6, 126.7, 128.6, 129.4, 129.6, 132.6, 133.6, 133.8, 135.5, 135.7, 136.7, 147.1, 158.1, 192.4; IR (neat)cm^{-1} 2918, 2833, 2736, 1687, 1509, 1246, 1032; HRMS (ESI) Calcd for $C_{23}H_{22}NaO_2S$ $(M+Na)^+$ 385.1238, found 385.1214.



5-Fluoro-2-(2-phenyl-1-(m-tolyl)ethyl)benzaldehyde was obtained as a yellow oil (103 mg, 65% yield from the reaction of phenyl trifluoromethanesulfonate with *m*-tolylzinc(II)

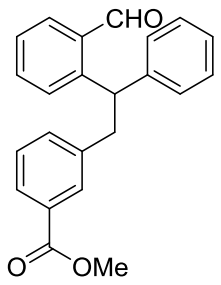
iodide reagent) after purification by silica gel column chromatography. R_f: 0.42 (Hex : Ether = 9 : 1). Conditions: for ArOTf, 5 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.22-3.50 (m, 2H), 5.27 (t, *J* = 9.0 Hz, 1H), 6.96-7.05 (m, 5H), 7.16-7.26 (m, 5H), 7.40-7.47 (m, 2H), 10.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 42.5, 45.4, 116.3 (d, J_{CF} = 21.7 Hz), 121.0 (d, J_{CF} = 21.7 Hz), 125.1, 126.4, 127.5, 128.6, 129.0, 129.1, 131.0 (d, J_{CF} = 7.5 Hz), 135.5 (d, J_{CF} = 6.0 Hz), 138.3, 139.2, 142.6, 143.4, 161.3 (d, J_{CF} = 246.0 Hz), 190.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.7; IR (neat)cm^{-1} 3027, 2921, 2734, 1685, 1489, 1252, 1144; GC-MS (m/z) 318.1.



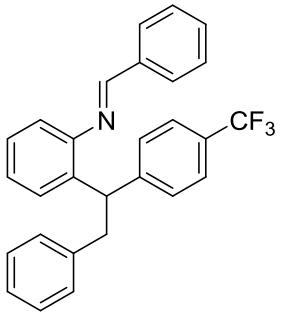
5-Chloro-2-(2-(naphthalen-1-yl)-1-(p-tolyl)ethyl)benzaldehyde was obtained as a yellow oil (115 mg, 60% yield from the reaction of naphthalen-1-yl trifluoromethanesulfonate with *p*-tolylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.60 (Hex : Ether = 8.5 : 1.5). Conditions: for ArOTf, 5 mol % $Ni(cod)_2$, 100°C, 12 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.62-3.99 (m, 2H), 5.43 (t, *J* = 9.0 Hz, 1H), 6.82 (d, *J* = 6.0 Hz, 1H), 7.11 (s, 4H), 7.17-7.22 (m, 1H), 7.43-7.51 (m, 4H), 7.63 (d, *J* = 3.0 Hz, 1H), 7.69 (d, *J* = 6.0 Hz, 1H), 7.84-7.97 (m, 2H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 39.3, 43.6, 123.1, 125.2, 125.7, 126.3, 127.4, 128.1, 129.2, 129.4, 129.5, 130.5, 131.5, 131.8, 132.9, 133.7, 133.9, 134.5, 135.3, 136.5, 140.5, 145.5, 189.5; IR (neat)cm^{-1} 3045, 2851, 2733, 1686, 1509, 1106; GC-MS (m/z) 384.1.



Methyl 3-(2-(2-formylphenyl)-2-phenylethyl)benzoate was obtained as a yellow oil (119 mg, 69% yield from the reaction of methyl 3-(((trifluoromethyl)sulfonyl)oxy)benzoate with phenylzinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.40 (Hex : Ether = 7 : 3). Conditions: for ArOTf, 5 mol % $Ni(cod)_2$, 100°C, 12 h.

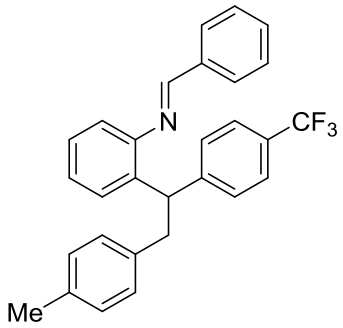
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34-3.50 (m, 2H), 3.87 (s, 3H), 5.56 (t, *J* = 9.0 Hz, 1H), 7.17-7.29 (m, 7H), 7.33-7.38 (m, 1H), 7.50-7.58 (m, 2H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.78-7.82 (m, 2H), 10.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.9, 45.6, 52.1, 126.6, 126.8, 127.5, 128.2, 128.4, 128.5, 128.7, 130.1, 130.3, 132.9, 133.6, 133.9, 139.9, 143.1, 146.3, 167.1, 192.4; IR (neat)cm^{-1} 3061, 2949, 2738, 1716, 1687, 1279, 1105; HRMS (ESI) Calcd for $C_{23}H_{20}NaO_3$ $(M+Na)^+$ 367.1310, found 367.1280.



(E)-1-phenyl-N-(2-(2-phenyl-1-(4-(trifluoromethyl)phenyl)ethyl)phenyl)methanimine was obtained as a yellow oil (113.7 mg, 53% yield from the reaction of iodobenzene with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column

chromatography. R_f: 0.47 (Hex : Ether = 9 : 1). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h, 1.5 equiv each of ArI and 1 equiv of ArZnI was used.

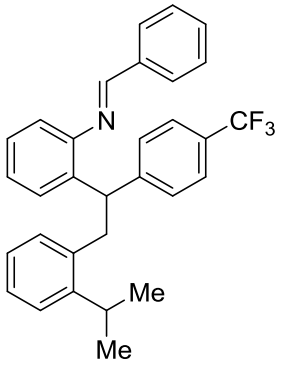
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (d, *J* = 9.0 Hz, 2H), 5.02 (t, *J* = 9.0 Hz, 1H), 6.83-6.86 (m, 1H), 6.97-7.00 (m, 2H), 7.07-7.09 (m, 3H), 7.21-7.24 (m, 2H), 7.31-7.38 (m, 3H), 7.41 (s, 1H) 7.43-7.51 (m, 4H), 7.79-7.82 (m, 2H), 7.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 41.3, 46.6, 118.2, 125.1 (d, J_{CF} = 3.0 Hz), 126.1, 126.1, 127.5, 127.7, 128.0, 128.2, 128.4, 128.5, 128.8, 128.9, 129.2, 131.4, 136.4, 137.4, 139.9, 148.8, 150.7, 160.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.7; IR (neat)cm^{-1} 3061, 3026, 2924, 2858, 1628, 1322, 1110, 1066; GC-MS (m/z) 429.1.



(E)-1-phenyl-N-(2-(2-(p-tolyl)-1-(4-(trifluoromethyl)phenyl)ethyl)phenyl)methanimine was obtained as a yellow oil (110.9 mg, 50% yield from the reaction of 1-iodo-4-methylbenzene with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.48 (Hex : Ether = 9 : 1). Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h, 1.5 equiv each of ArI and 1 equiv of ArZnI was used.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.30 (d, *J* = 9.0 Hz, 2H), 4.96 (t, *J* = 9.0 Hz, 1H), 6.80-6.83 (m, 4H), 7.17-7.24 (m, 3H), 7.29-7.31 (m, 3H), 7.38 (s, 1H), 7.40-7.46 (m, 4H), 7.75-7.78 (m, 2H), 7.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 21.1, 41.0, 46.6, 116.8,

118.1, 125.1 (d, J_{CF} = 3.8 Hz), 125.4, 126.1, 126.3, 127.5, 127.6, 127.9, 128.4, 128.9, 129.1, 131.4, 135.4, 136.5, 136.8, 137.5, 149.0, 150.7, 160.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.8; IR (neat)cm^{-1} 3022, 2983, 2927, 2870, 1629, 1323, 1238, 1119; GC-MS (m/z) 443.2.

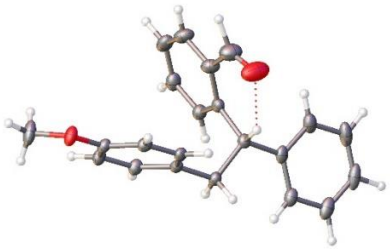


(E)-N-(2-(2-(2-isopropylphenyl)-1-(4-(trifluoromethyl)phenyl)ethyl)phenyl)-1-phenylmethanimine was obtained as a yellow oil (141.4 mg, 60% yield from the reaction of 1-iodo-2-isopropylbenzene with (4-(trifluoromethyl)phenyl)zinc(II) iodide reagent) after purification by silica gel column chromatography. R_f: 0.56 (Hex : Ether = 9 : 1). *)*: Conditions: for ArI, 2 mol % $Ni(cod)_2$, 80°C, 12 h, 1.5 equiv each of ArI and 1 equiv of ArZnI was used.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.0 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 2.96-3.09 (m, 1H), 3.42 (d, *J* = 9.0 Hz, 2H), 4.92 (t, *J* = 9.0 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 1H), 6.80-6.88 (m, 2H), 7.06-7.13 (m, 2H), 7.23-7.30 (m, 3H), 7.39 (s, 1H), 7.41-7.45 (m, 5H), 7.72-7.74 (m, 2H), 7.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.7, 24.4, 28.8, 38.1, 46.5, 118.3, 122.6, 125.1 (q, J_{CF} = 3.0 Hz), 126.0, 126.3, 126.6, 127.6, 127.7, 127.9, 128.2, 128.4, 128.7, 128.8, 128.9, 130.3, 131.4, 136.3, 137.3, 147.1, 149.0, 150.9, 1

60.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ -60.8; GC-MS (m/z) 471.2

5.2.5. X-Ray Crystallographic Data for 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde



A colorless block specimen of $C_{22}H_{20}O_2$, approximate dimensions 0.28 mm x 0.222 mm x 0.215 mm, was used for the X-ray crystallographic analysis. The X-ray intensities were measured using a Bruker-D8 Venture dual-source diffractometer (Cu Kα, λ = 1.5406 Å) and CMOS detector. Indexing and frame integration was performed using the APEX-III software suite. Absorption correction was performed using face-indexing (numerical method) also within the APEX-III software. The structures were solved using SHELXL-2014/7 and refined using OLEX2 version 1.2.8. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H., OLEX2: A complete structure solution, refinement and analysis program (2009). J. Appl. Cryst., 42, 339-341.

The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a triclinic unit cell yielded a total of 15783 reflections to a maximum θ angle of 68.24° (0.80 Å resolution), of which 3064 were independent (average redundancy 5.151, completeness = 99.6%, R_{int} = 2.86%, R_{sig} = 2.15%) and 2898 (94.58%) were greater than $2\sigma(F^2)$. The final cell constants of $\underline{a}$ = 9.1265(3) Å, $\underline{b}$ = 9.1821(3) Å, $\underline{c}$ = 11.6541(4) Å, α = 87.9160(10), β = 97.5650(10)°, γ = 62.7980(10) volume = 840.90(5) $Å^3$, are based upon the refinement of the XYZ-centroids of 14859 reflections above 20 σ(I) with 7.836° < 2θ < 136.476. Data were corrected for

absorption effects using the Multi-Scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.5944.

The final anisotropic full-matrix least-squares refinement on F^2 with 154 variables converged at R1 = 6.20%, for the observed data and wR2 = 17.54% for all data. The goodness-of-fit was 1.093. The largest peak in the final difference electron density synthesis was 1.369 $e^-/Å^3$ and the largest hole was -0.425 $e^-/Å^3$ with an RMS deviation of 0.063 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.250 g/cm^3 and F(000), 336 e^-.

Table 5.1. Crystal data and structure refinement for 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde.

Identification code	jsTp-1_a
Empirical formula	$C_{22}H_{20}O_2$
Formula weight	316.38
Temperature/K	108.85
Crystal system	triclinic
Space group	P-1
a/Å	9.1265(3)
b/Å	9.1821(3)
c/Å	11.6541(4)
α/°	87.9160(10)
β/°	76.2840(10)
γ/°	62.7980(10)
Volume/$Å^3$	840.90(5)

Z	2
ρ_{calc}g/cm^3	1.250
μ/mm^{-1}	0.618
F(000)	336.0
Crystal size/mm^3	0.28 × 0.222 × 0.215
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.836 to 136.476
Index ranges	$-10 \leq h \leq 10$, $-11 \leq k \leq 11$, $-13 \leq l \leq 14$
Reflections collected	14859
Independent reflections	3064 [R_{int} = 0.0286, R_{sigma} = 0.0215]
Data/restraints/parameters	3064/0/282
Goodness-of-fit on F^2	1.095
Final R indexes [I>=2σ (I)]	R_1 = 0.0620, wR_2 = 0.1739
Final R indexes [all data]	R_1 = 0.0638, wR_2 = 0.1754
Largest diff. peak/hole / e Å^{-3}	1.37/-0.42

Table 5.2. Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for Table 5.4. Crystal data and structure refinement for 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
O1	1196(3)	6197(3)	4190.0(18)	61.7(6)
O2	7484.4(18)	7395.9(17)	1880.5(14)	28.4(4)
C1	2276(4)	5391(3)	4715(2)	45.4(6)
C2	3754(3)	3719(3)	4371.1(18)	30.1(5)

C3	4122(2)	2713(2)	3354.0(17)	21.6(4)
C4	5458(3)	1127(3)	3213.4(18)	24.6(4)
C5	6437(3)	543(3)	4033(2)	29.6(5)
C6	6100(3)	1549(3)	5021(2)	33.9(5)
C7	4756(3)	3117(3)	5184(2)	35.7(5)
C8	3161(2)	3319(2)	2392.0(17)	21.1(4)
C9	2366(2)	2240(2)	2167.2(19)	23.5(4)
C10	1366(3)	1884(3)	3128(2)	31.0(5)
C11	562(3)	965(3)	2956(3)	38.9(6)
C12	739(3)	390(3)	1828(3)	38.4(6)
C13	1730(3)	725(3)	868(2)	33.9(5)
C14	2543(3)	1638(2)	1037(2)	26.5(5)
C15	4313(2)	3503(2)	1259.8(17)	21.3(4)
C16	5168(2)	4511(2)	1457.8(16)	19.8(4)
C17	6903(3)	3773(2)	1380.6(18)	23.0(4)
C18	7734(2)	4678(2)	1524.3(18)	23.8(4)
C19	6799(2)	6378(2)	1745.1(17)	21.0(4)
C20	5054(2)	7148(2)	1836.2(17)	21.9(4)
C21	4254(2)	6220(2)	1699.0(17)	21.1(4)
C22	9225(3)	6624(3)	1913(3)	40.3(6)

Table 5.3. Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	**U_{11}**	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**

O1	57.1(12)	51.1(12)	47.4(11)	-10.7(9)	-21.6(10)	4.9(10)
O2	22.8(7)	22.1(7)	44.6(9)	0.4(6)	-14.9(6)	-10.6(6)
C1	47.0(15)	44.5(14)	34.5(13)	-3.6(11)	-10.8(11)	-11.8(12)
C2	37.5(12)	30.6(11)	21.7(10)	3.4(8)	-7.8(9)	-15.4(10)
C3	21.1(9)	25.6(10)	20.9(9)	5.1(7)	-4.8(7)	-13.5(8)
C4	23.4(10)	26.1(10)	25.9(10)	3.3(8)	-7.5(8)	-12.1(8)
C5	24.1(10)	29.3(11)	36.6(12)	10.2(9)	-12.0(9)	-11.8(9)
C6	38.6(12)	44.4(13)	30.1(11)	15.3(10)	-19.1(10)	-24.4(11)
C7	48.6(14)	39.5(13)	22.9(11)	4.2(9)	-13.4(10)	-21.5(11)
C8	18.0(9)	19.6(9)	24.2(10)	2.1(7)	-5.8(8)	-7.2(8)
C9	15.7(9)	19.1(9)	35.6(11)	7.0(8)	-11.6(8)	-6.0(7)
C10	21.3(10)	33.1(11)	40.1(12)	12.2(9)	-11.2(9)	-12.8(9)
C11	21.9(10)	36.4(12)	63.1(17)	22.2(12)	-14.7(11)	-16.6(10)
C12	24.1(11)	23.0(11)	76.6(18)	13.6(11)	-25.5(11)	-12.5(9)
C13	25.8(11)	20.5(10)	57.2(15)	1.5(10)	-20.6(10)	-7.1(8)
C14	21.4(10)	21.3(10)	37.6(12)	3.1(8)	-11.6(9)	-8.6(8)
C15	22(1)	23.8(10)	21.5(9)	4.2(8)	-8.9(8)	-11.9(8)
C16	21.7(9)	23.3(10)	16.9(9)	5.0(7)	-7.5(7)	-11.5(8)
C17	22.3(10)	18.7(9)	27.7(10)	2.7(8)	-9.6(8)	-7.6(8)
C18	17.8(9)	22.9(10)	30.2(10)	1.8(8)	-10.0(8)	-6.9(8)
C19	22.3(10)	21.7(10)	22.5(9)	3.0(7)	-10.0(8)	-11.1(8)
C20	22.4(10)	17.9(9)	23.2(10)	1.7(7)	-8.7(8)	-6.1(8)
C21	17.8(9)	24.1(10)	21.2(9)	4.6(7)	-8.8(7)	-7.9(8)
C22	24.3(11)	31.0(12)	72.0(18)	-0.5(11)	-19.7(11)	-14.0(9)

Table 5.4. Bond Lengths for for 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde**.**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.216(3)	C9	C10	1.398(3)
O2	C19	1.372(2)	C9	C14	1.392(3)
O2	C22	1.423(3)	C10	C11	1.392(3)
C1	C2	1.494(3)	C11	C12	1.380(4)
C2	C3	1.407(3)	C12	C13	1.383(4)
C2	C7	1.396(3)	C13	C14	1.393(3)
C3	C4	1.391(3)	C15	C16	1.510(3)
C3	C8	1.520(3)	C16	C17	1.389(3)
C4	C5	1.388(3)	C16	C21	1.401(3)
C5	C6	1.387(3)	C17	C18	1.394(3)
C6	C7	1.381(3)	C18	C19	1.392(3)
C8	C9	1.531(3)	C19	C20	1.394(3)
C8	C15	1.537(3)	C20	C21	1.386(3)

Table 5.5. Bond Angles for 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C19	O2	C22	116.64(15)	C14	C9	C10	118.00(19)
O1	C1	C2	129.3(2)	C11	C10	C9	120.9(2)
C3	C2	C1	125.1(2)	C12	C11	C10	120.4(2)
C7	C2	C1	115.3(2)	C11	C12	C13	119.5(2)
C7	C2	C3	119.5(2)	C12	C13	C14	120.3(2)

C2	C3	C8	122.45(17)	C9	C14	C13	120.9(2)
C4	C3	C2	118.14(18)	C16	C15	C8	114.09(16)
C4	C3	C8	119.36(17)	C17	C16	C15	120.90(17)
C5	C4	C3	121.7(2)	C17	C16	C21	117.70(17)
C6	C5	C4	120.1(2)	C21	C16	C15	121.39(17)
C7	C6	C5	118.8(2)	C16	C17	C18	122.13(18)
C6	C7	C2	121.7(2)	C19	C18	C17	118.98(18)
C3	C8	C9	112.03(15)	O2	C19	C18	124.13(17)
C3	C8	C15	110.37(15)	O2	C19	C20	115.83(17)
C9	C8	C15	112.72(16)	C18	C19	C20	120.04(18)
C10	C9	C8	119.12(18)	C21	C20	C19	119.91(18)
C14	C9	C8	122.84(18)	C20	C21	C16	121.23(17)

Table 5.6. Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 2-(2-(4-methoxyphenyl)-1-phenylethyl)benzaldehyde.

Atom	***x***	***y***	***z***	**U(eq)**
H10	1233	2274	3909	37
H22A	9933	6019	1146	60
H22B	9393	5859	2536	60
H22C	9547	7461	2081	60
H1	2250(50)	6000(50)	5570(40)	79(11)
H4	5680(30)	460(30)	2530(20)	34(6)
H5	7320(30)	-540(30)	3900(20)	26(6)
H6	6810(30)	1120(30)	5600(20)	37(7)
H7	4500(40)	3840(40)	5860(30)	50(8)

H8	2210(30)	4420(30)	2660(20)	23(6)
H11	-50(40)	690(40)	3620(30)	43(7)
H12	140(40)	-260(40)	1680(30)	51(8)
H13	1910(40)	300(40)	10(30)	46(8)
H14	3170(30)	1860(30)	390(20)	28(6)
H15A	5200(30)	2390(30)	890(20)	26(6)
H15B	3580(30)	4070(30)	700(20)	28(6)
H17	7550(30)	2600(30)	1200(20)	27(6)
H18	8930(30)	4090(30)	1510(20)	29(6)
H20	4440(30)	8280(30)	1970(20)	21(5)
H21	3050(30)	6770(30)	1760(20)	21(5)

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