LATE TRANSITION METAL-CATALYST DEVELOPMENT FOR ALKYNE COUPLING REACTIONS

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LATE TRANSITION METAL-CATALYST DEVELOPMENT FOR

ALKYNE COUPLING REACTIONS

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

DOCTOR OF PHILOSOPHY

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ABSTRACT

Alkynes are versatile and valuable synthetic precursors in a variety of organic transformations and have found tremendous applications in materials science and pharmaceutical chemistry. In recent years, there has been a tremendous growth in the development of transition-metal catalyzed organic transformations by alkynes coupling reactions such as ring constructions (carbocycles and heterocycles), hydroarylation and hydroamination. This thesis describes the development of new transition metal catalyst for alkyne coupling reactions. The results are highlighted by chemoselective coupling between internal alkynes and N-H aromatic ketimines to synthesize indenamine, dihydroisoquinoline, and 2-aza-1,3-butadiene derivatives.

Chapter 1 introduces background for alkyne coupling reactions towards hydrometalation, hydroarylation and hydroamination. Also this chapter provides new strategies developed towards C-H activation and hydroamination by using late transition metal catalysts.

Chapter 2 describes catalytic development of rhodium catalyzed redox-neutral [4+2] annulation of N-H aromatic ketimines and alkynes to synthesize multi-substituted 3,4-dihydroisoquinolines (DHIQs) in high chemo-selectivity over competing annulation processes, exclusive *cis*-diastereoselectivity, and distinct regioselectivity for alkyne addition.

Chapter 3 describes development of earth abundant metal nickel as the catalyst for the Nickel (0)/NHC-based catalyst system for alkyne hydroimination with aromatic N–H ketimines as N-nucleophiles. To demonstrate the potential of current method for practical synthesis, we also carried out a gram-scale alkyne hydroimination with benzophenone imine.

Chapter 4 describes catalyst development for oxidative [4+2] imine/alkyne annulation with unconventional regioselectivity. Even though there are numerous methods towards the synthesis of isoquinoline derivative here in this chapter we proposed a different pathway for C-N

bond formation compared to other reported methods. In spite of moderate yields for the unsymmetrical alkynes the regioselectivity is different from other reported isoquinoline products by oxidative [4+2] annulations.

Chapter 5 describes about Ni/NHC catalyst development towards stereoselective semihydrogenation of alkynes by usig simple alcohol, isopropanol as the hydrogen source. Here we report new Ni-NHC complexes derived from Ni(0)-mediated facile C–H activation at the methyl position of IPr, one of the most commonly used NHC ligands in nickel catalysis. Results from stoichiometric transformations suggest that such cyclometalation provides a low-energy access to NHC-ligated Ni(II) hydride species that are envisioned as key reactive intermediates in many catalytic processes.

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DEDICATION

To my parents and sisters for their love, endless support and encouragement

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LIST OF ABBREVIATIONS

Å ..... Angstrom

Ac ..... Acetyl

Acac ..... Acetylacetanato

Al ..... Aluminum

Ag ..... Silver

$AgSbF_6$ ..... silver hexafluoroantimonate

Au ..... Gold

Ar ..... Aryl

Bn ..... Benzyl

BINAP ..... 2-2'-Bis(diphenylphosphino)-1,1'-binaphthyl

n-Bu ..... *normal*-Butyl

t-Bu ..... *tertiary*-Butyl

Br ..... Bromine

Bz ..... Benzoyl

Calcd ..... Calculated

$CDCl_3$ ..... deuterated chloroform

Cod 1,5-cyclooctadiene

Coe ..... cyclooctene

Co ..... Cobalt

CO ..... Carbon monoxide

Cp ..... cyclopentadienyl

Cp* ..... pentamethylcyclopentadienyl

$CrCl_2$ ..... Chromyl chloride

Cs ..... Cesium

Cu ..... Copper

Dba ..... dibenzylideneacetone

DCE 1,2-dichloroethane

DBU ..... Diazabicyclo[5.4.0]undec-7-ene

DCM ..... Dichloromethane

DG ..... Directing group

DMA ..... N,N-dimethylacetamide

DMSO ..... Dimethyl sulfoxide

DPPP ..... 1,3-bis(diphenylphosphino)propane

dr ..... Diasteromeric ratio

EDG ..... electron donating group

ee ..... Enantiomeric excess

Equiv ..... Equivalent

Et ..... Ethyl

EtOAc ..... ethyl acetate

Et_2O ..... diethylether

EWG ..... Electron-withdrawing group

Fe ..... Iron

GC ..... Gas chromatography

GC/MS ..... Gas chromatography/mass spectrometry

H_2O ..... Water

HRMS ..... High resolution mass spectrometry

h ..... Hours

HCI ..... Hydrochloric acid

Hz ..... Hertz

IMes ..... 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene

IPr ..... 1,3-bis(2,6-triisopropylphenyl)imidazole-2-ylidene

Ir ..... Iridium

J ..... Coupling constants (in NMR)

K ..... Potassium

KPF_6 ..... Potassium hexafluorophosphate

L ..... Ligand

Li ..... Lithium

m ..... *meta*

M ..... Metal

Me ..... Methyl

MeO ..... Methoxy

MeOH ..... Methanol

Mg ..... Magnesium

Mn ..... Manganese

mL ..... millilitre

mol ..... Moles

Mol.Wt ..... Molecular weight

Na ..... Sodium

Na_2SO_4 ..... Sodium sulfate

Ni ..... Nickel

NHC ..... N-heterocyclic carbene

NMR ..... Nuclear magnetic resonance

NMP ..... *N*-Methylpyrrolidine

nOe ..... Nuclear Overhauser effect

Nu ..... Nucleophile

o ..... *ortho*

OTf ..... Triflate

p ..... *para*

Ph ..... Phenyl

PivOH ..... pivalic acid

ppm ..... Parts per million

rt ..... Room temperature

Si ..... Silicon

Sn ..... Tin

Temp ..... Temperature

t-BuOK ..... Potassium *tert*-butoxide

THF ..... Tetrahydrofuran

TLC ..... Thin layer chromatography

UV ..... Ultraviolet

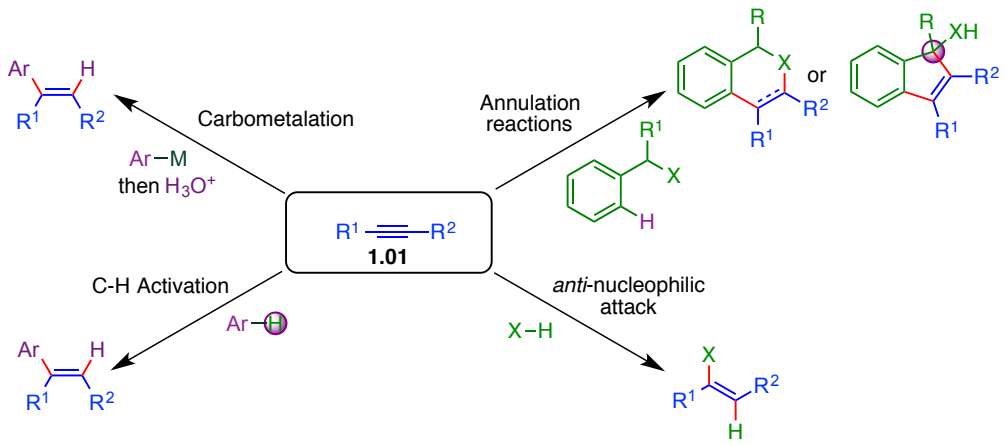
Zn ..... Zinc

Zr ..... Zirconium

CHAPTER 1. LATE TRANSITION METAL-CATALYZED ALKYNE COUPLING REACTIONS

1.1. Introduction

Alkynes are versatile and valuable synthetic precursors (synthons) in a variety of organic transformations and found tremendous applications in material and pharmaceutical chemistry. In recent years tremendous growth has been realized in the development of transition metal catalyzed organic transformations of alkyne, particularly internal alkynes, which include but are not limited to ring constructions (carbocycles and heterocycles) via oxidative annulation, hydroarylation, and hydroamination. Being more electronegative than alkenes, alkynes tend to encourage back donation and coordinate more strongly to transition metal complexes. Once π-electrons of alkyne coordinates to metal center, triple bond tends to fold back away making the metal-carbon distance slightly shorter than that of the corresponding alkene complexes. The coordination of alkynes to metals is similar to alkenes. Depending on the metal, alkynes can act as either 2-electron donor or 4-electron donor. The wider utility of internal alkynes relies on the accessibility of diversified alkynes via Sonogashira coupling reaction.[1,2] Conventionally alkynes can undergo addition reactions like, hydroboration, hydration, oxy-mercuration, ozonolysis, hydrogenation. Alkynes can be reduced to *cis* and *trans* alkenes by using lindlar's catalyst (prepared by deactivation or poisoning a conventional palladium catalyst by treating it with lead acetate and quinolone) and sodium in presence of ammonia respectively. The various reactions of internal alkyne under transition metal catalysis could be categorized as the 1) addition reactions of alkynes through carbometalation and C-H bond activation, 2) annulation reactions of alkynes, and 3) anti-nucleophilic attack to alkynes (Scheme 1.1).

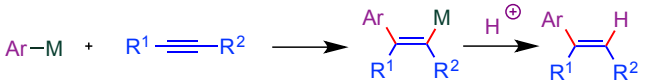


Scheme 1.1. Internal alkynes in various coupling reactions

1.2. Addition reactions of alkynes through carbometalation and C-H activation

1.2.1. Addition reactions of alkynes through carbometalation

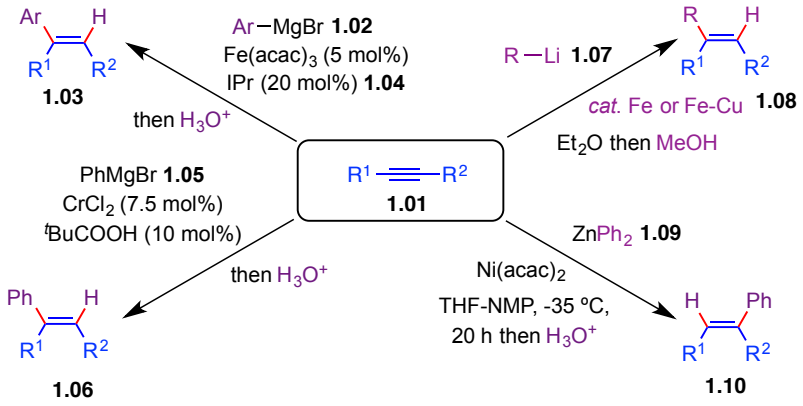
Carbometalation is an organometallic reaction involving nucleophilic addition of organometallic reagents such as Grignard, organolithium, organocopper, organoboron, organozinc and organoaluminium to the alkynes or alkenes followed by the hydrolysis of the resulting C-metal bonds to form the corresponding aryl substituted alkenes or alkanes respectively (Scheme 1.2).



Scheme 1.2. Hydroarylation of alkynes through carbometalation

Hayashi in the year 2005 reported an iron catalyzed arylmagnesiation of alkynes (**1.01**) followed by hydrolysis to give trisubstituted arylethenes (**1.03**) in highly regio- and stereoselective manner.[3] Later the same group developed an analogous reaction in the presence of catalytic IPr (13-Bis(2,6-diisopropyl-1,3-dihydro-2H-imidazol-2-ylidene) carbene (**1.04**)

(Scheme 1.3). A cooperative catalysis in presence of chromium and pivalic acid for the arylmagnesiation of alkynes (**1.01**) with PhMgBr (**1.05**) was reported by Oshima in 2007.[4] In 2009, Hayashi reported a directing group-free carbolithiation of alkynes (**1.01**) using iron catalysis[5] (Scheme 1.3). Further, arylzincation of alkynes (**1.01**) catalyzed by nickel to give disubstituted arylethenes[6] (**1.12**) regio- and stereoselectively was reported in the year 1998 (Scheme 1.3). All these discussed carbometalation reactions suffer from common drawbacks such as requirement of preactivation of starting materials, limited functional group compatibility, and generation of the stoichiometric amounts of wastes.

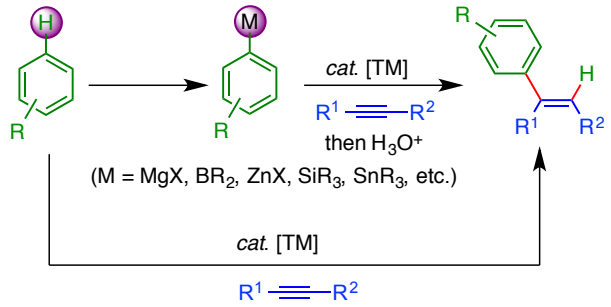


Scheme 1.3. Transition metal-catalyzed carbometalation

1.2.2. Addition reactions of alkynes through C-H bond activation

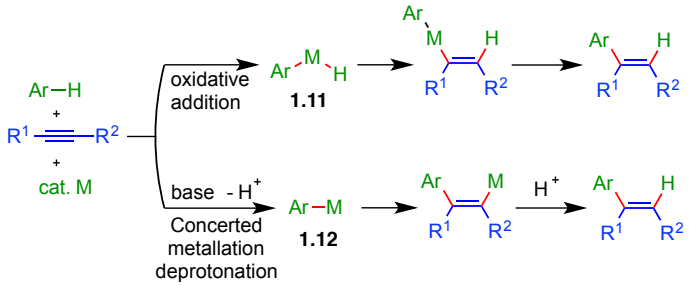
C-H bond activation is referred as the "Holy Grail" in organic chemistry and it is used as a versatile and non-conventional method for the construction of C-C and carbon-heteroatom bonds. In organic compounds these C-H bonds are ubiquitous and thus C-H bond activation is most powerful tool for sustainable synthesis by constructing carbon frameworks, and it opens new routes to synthesisis of pharmaceuticals and natural products. Compared to conventional cross-coupling reactions[7] these methods of C-H activation[8] are economically attractive and can minimize the salt byproduct formation as exemplified by trasition metal (TM) catalyzed alkyne

hydroarylation (Scheme 1.4). As we discussed above the prefunctionalized organometallics or main-group element are prepared from the corresponding arenes, which involves a number of synthetic operations and are sensitive to moisture and air (Scheme 1.4).



Scheme 1.4. Conventional cross coupling versus C-H activation

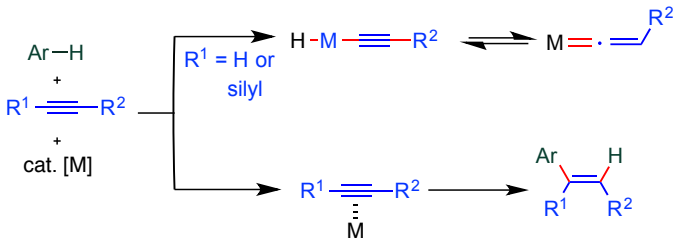
Transition metal catalyzed non-Friedel-Crafts type of hydroarylation of alkynes is mainly classified into two methods based on the mechanism of C-H activation, one method is oxidative addition and the other method is concerted metalation and deprotonation (CMD) (Scheme 1.5). Typically electron-rich low-valent complexes of late transition metals like Fe, Ru, Re, Os, Ir, Pt, Rh will promote C-H activation by oxidative addition to form M-H bond (**1.11**). In this method alkyne is inserted into M-H bond, whereas in concerted metallation deprotonation there will be simultaneous cleavage of C-H bond and carbon-metal bond formation (**1.12**) without formation of M-H bond and alkyne is inserted in to the resulting carbon-metal bond. In this concerted metalation deprotonation method generally a carbonate or acetate base is required to deprotonate the acidic C-H bond (Scheme 1.5).



Scheme 1.5. Hydroarylation of alkynes through C-H bond activation

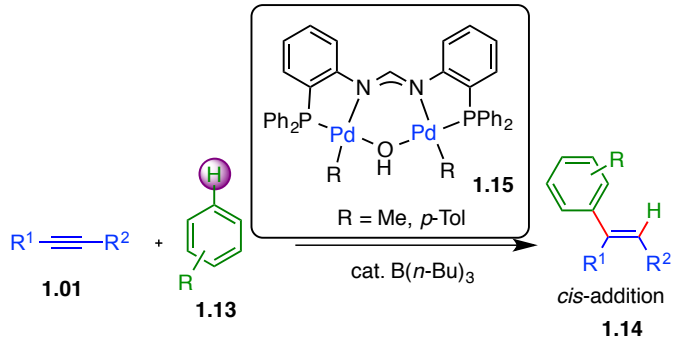
1.2.2.1. Non-directed C-H activation by oxidative addition

Internal alkynes can be activated by metals by coordinating with π-elctrons and forms π-complexes whereas if the alkyne is terminal, because of the active sp C-H bond it undergoes oxidative addition and then isomerizes to vinylidene complex, often leading to catalyst deactivation (Scheme 1.6).



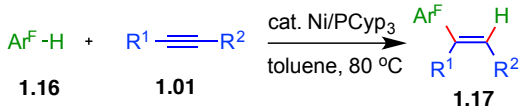
Scheme 1.6. Metal mediated activation of alkynes

In 2003, Inoue reported stereospecific *syn*-addition of aromatic C-H bonds to alkynes using a catalyst system of dinuclear palladium precursors (**1.15**) and trialkyl boranes. This catalystic system can be applied to hydroarylation of alkynes through addition of C-H bonds in a *cis*-addition manner (Scheme 1.7).[9]



Scheme 1.7. Dinuclear palladium catalyzed hydroarylation of alkynes

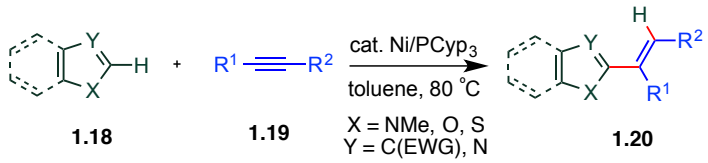
Later in the year 2008, Hiyama reported nickel-catalyzed alkyne arylation with fluoroarenes (**1.16**) via activation of C-H bond over C-F bond to give fluoroarylalkenes (**1.17**) (Scheme 1.8).[10]



1.16 **1.01** **1.17**

Scheme 1.8. Nickel catalyzed hydroarylation of perfluoroarenes

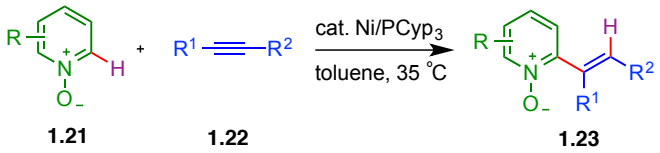
The acidic C-H bonds of electron-deficient heteroarenes can be activated to enable hydroheteroarylation of alkynes. For example, Hiyama reported nickel-catalyzed hydroheteroarylation[11] with alkynes. Mostly trans- to heteroaryl alkene products (**1.18**) is observed, and unsymmetrical alkynes (**1.19**) reacted with good regioselectivity (**1.20**) (Scheme 1.9).



1.18 **1.19** **1.20**

Scheme 1.9. Metal catalyzed hydroarylation of alkynes with heterocycles

The above catalyst system of $Ni(cod)_2$ and $PCyp_3$ can also be applied to C-H alkenylation of 6-membered pyridine N-Oxides (**1.21**) to give trisubstituted ethenes (**1.23**).[12] However the parent pyridine did not undergo this transformation even at high temperatures (Scheme 1.10).



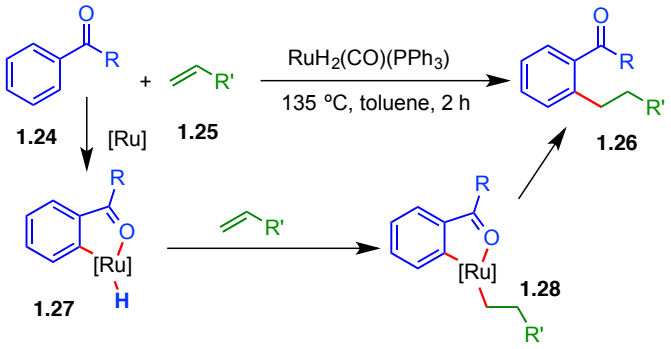
1.21 **1.22** **1.23**

Scheme 1.10. Metal catalyzed hydroheteroarylation of alkynes with pyridine-N-oxide

1.2.2.2. Directed C-H activation by oxidative addition

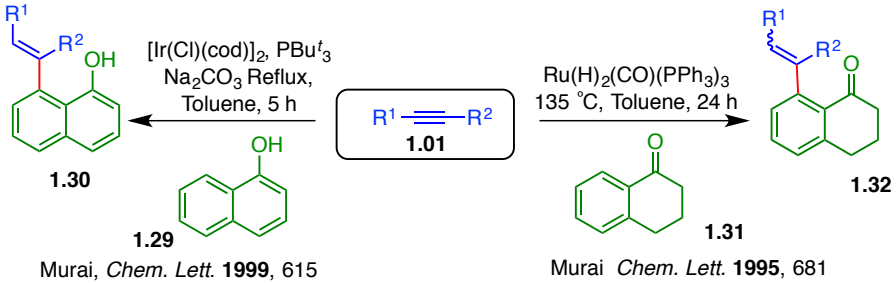
In 1993, Murai first reported aromatic ketone (**1.24**) as the directing group for hydroarylation of alkenes in the presence of ruthenium catalyst at 135 ºC.[13] In this reaction he proposed that aromatic ketone (**1.24**) directed C-H activation by ruthenium complexes to form a 5-membered hydrometallacycle intermediate (**1.27**). Later alkene insertion into Ru-hydride bond

forms ruthenium-alkyl intermediate (**1.28**) followed by C-C reductive elimination that forms hydroarylated product and regenerates the catalyst for another catalytic cycle (Scheme 1.11).



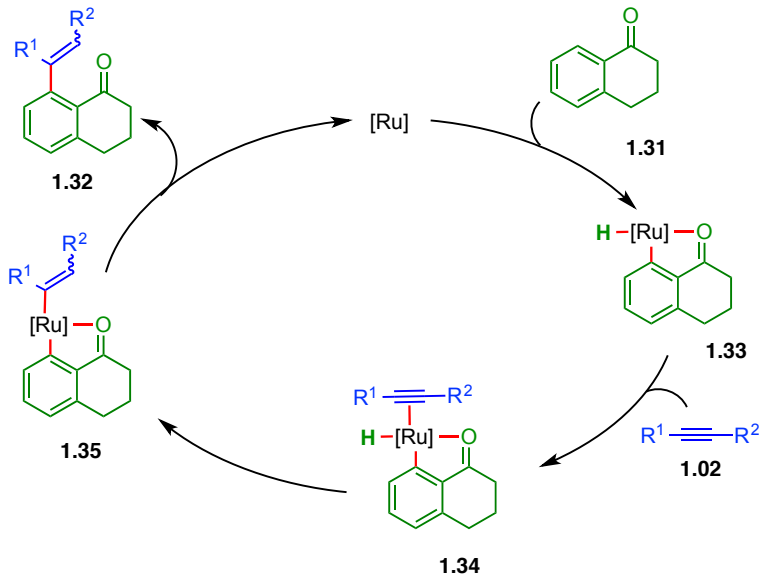
Scheme 1.11. Murai hydroarylation of olefins with aromatic ketones

Murai in the year 1995, reported hydroarylation of alkynes (**1.01**) by α-tetralones (**1.31**) in the presence of ruthenium catalyst at 135 ºC.[14] Due to combined steric and electronic effects a good stereoselectivity was not achieved. Later in the year 1999, he also reported hydroarylation of α-naphthols (**1.29**) in the presence of iridium catalyst to give hydroarylated products (**1.30**) with high regio- and stereoselectivity[15] (Scheme 1.12). α-Naphthols (**1.29**) on reaction with alkynes (**1.01**) in the presence of Iridium and a bulky phosphine, tri-*tert*-butyl phosphine refluxed for 5 h forms hydroarylated products (**1.30**).



Scheme 1.12. Metal catalyzed hydroarylation of alkynes with aromatic alcohols and ketones

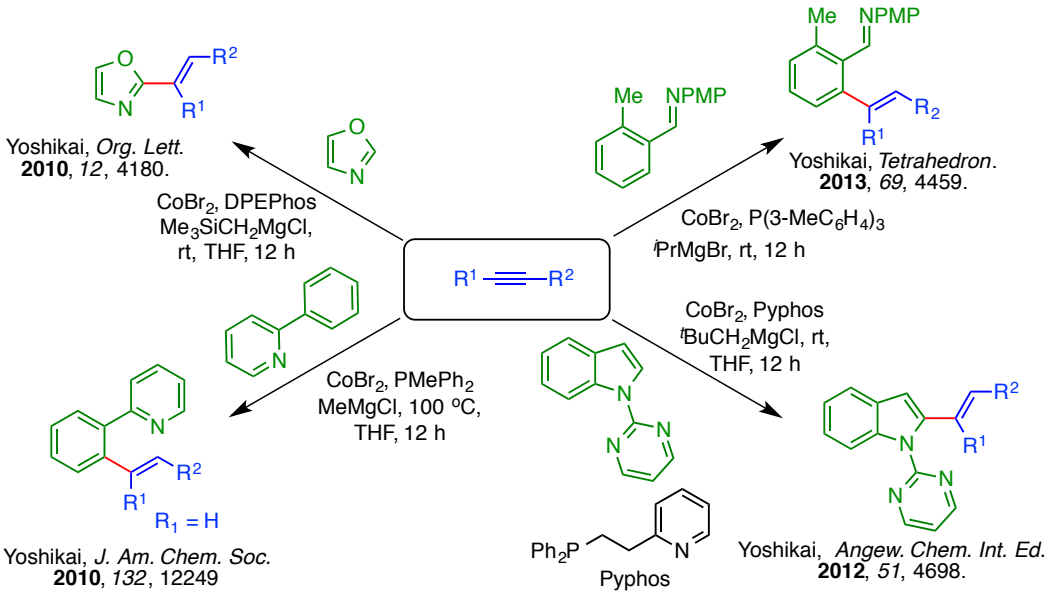
For the above two reactions Murai proposed that in the presence of metal the ketone group directs C-H activation by C-H oxidative addition pathway to give metal-hydride intermediate (**1.33**), followed by insertion of alkyne into ruthenium-hydride bond to give metal-alkenyl intermediate (**1.35**) subsequent C-C reductive elimination give hydroarylated product (**1.32**) and regenerates the active catalyst for another catalytic cycle[15] (Scheme 1.13). A similar pathway involving Ru(II) hydride intermediates was proposed for α-naphthol directed C-H alkenylation.



Scheme 1.13. Reaction mechanism of C-H activation by oxidative addition pathway

Very recently cobalt catalysis has gained significant interest in C-H activation because of the low price of cobalt and its abundant nature in earth's crust. Yoshikai reported several studies of alkyne hydroarylation using different directing groups. Directing groups such as oxazole,[16a] pyridine,[16b] piperazine,[16c] imines[16d] were used for alkyne hydroarylation for cobalt-mediated reactions. In all these reactions $CoBr_2$ is used as the catalyst and monophosphines as well as bisphosphines used as the ligands. Grignard reagent is used as the reducing agent in these

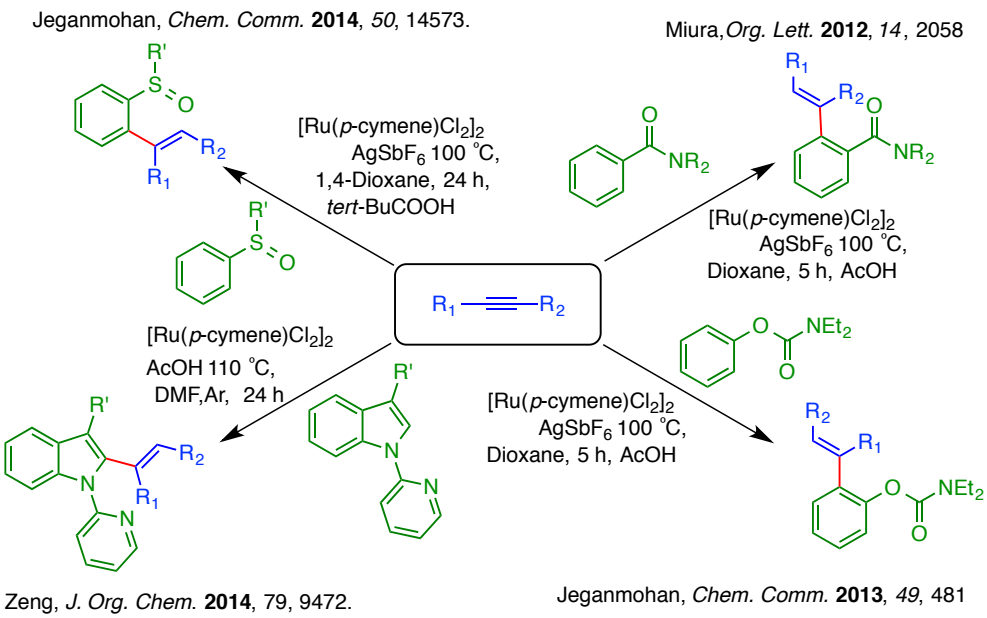
reactions. All these reactions are proposed to undergo directed C-H activation by oxidation addition to give Co(III)-hydride intermediate (Scheme 1.14).



Scheme 1.14. Cobalt catalyzed hydroarylation of alkynes

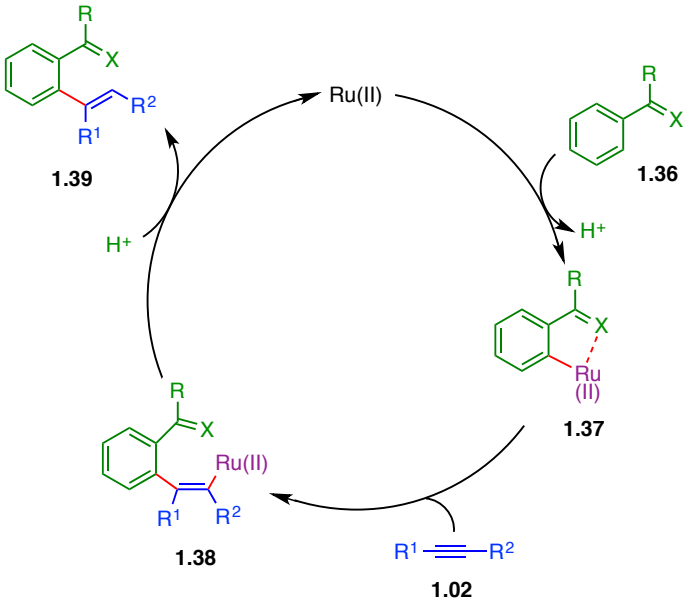
1.2.2.3. Directed C-H activation by deprotonation pathway

In order to achieve highly regioselective alkyne hydroarylation products chelation assistance by metal is a preferred method where heteroatom such as nitrogen- or oxygen-containing chelating group is required as an aromatic substituent to activate an *ortho*-C-H bond in a highly regioselective manner. In this deprotonation method, deprotonation occurs after metal coordinating to directing heteroatom without forming a metal-hydride bond. Generally a carbonate or acetate base is needed for deprotonating acidic C-H bond. After the seminal work by Murai, there are numerous reports reported by various groups in the field of directed C-H bond activation. Various directing groups such as amide[17], carbamates[18], sulfoxides[19] and pyridine[20] are used in the hydroarylation of alkynes by using ruthenium as the catalyst (Scheme 1.15).



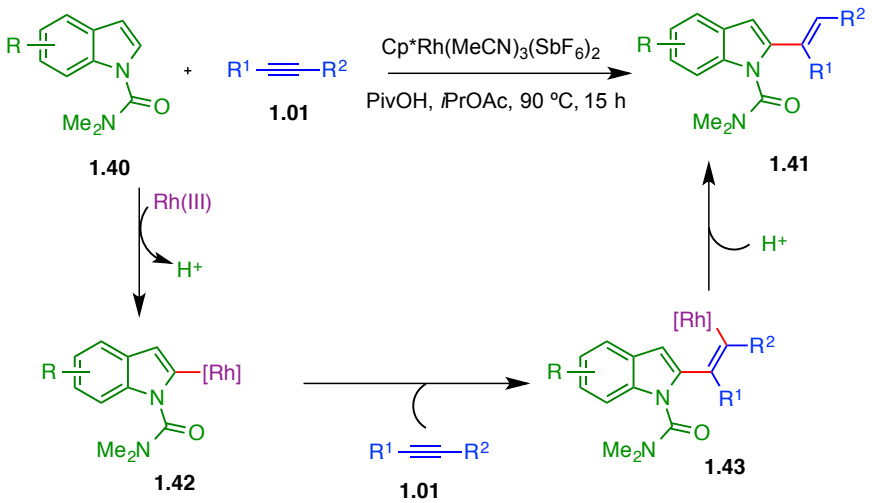
Scheme 1.15. Ruthenium catalyzed hydroarylation of alkynes by deprotonation pathway

These ruthenium-catalyzed reactions (Scheme 1.15) are proposed to proceed by C-H bond activation via deprotonation (Scheme 1.16). The generally accepted mechanism for the above transformations is C-H activation by deprotonation to give metallocycle intermediate (**1.37**) followed by 1,2-insertion of alkynes that gives metal-alkenyl intermediate (**1.38**) Subsequent protonation generates the hydroarylated product (**1.39**) and regenerate the active catalyst for another catalytic cycle.[20]



Scheme 1.16. Reaction mechanism of directed alkyne hydroarylation by deprotonation pathway

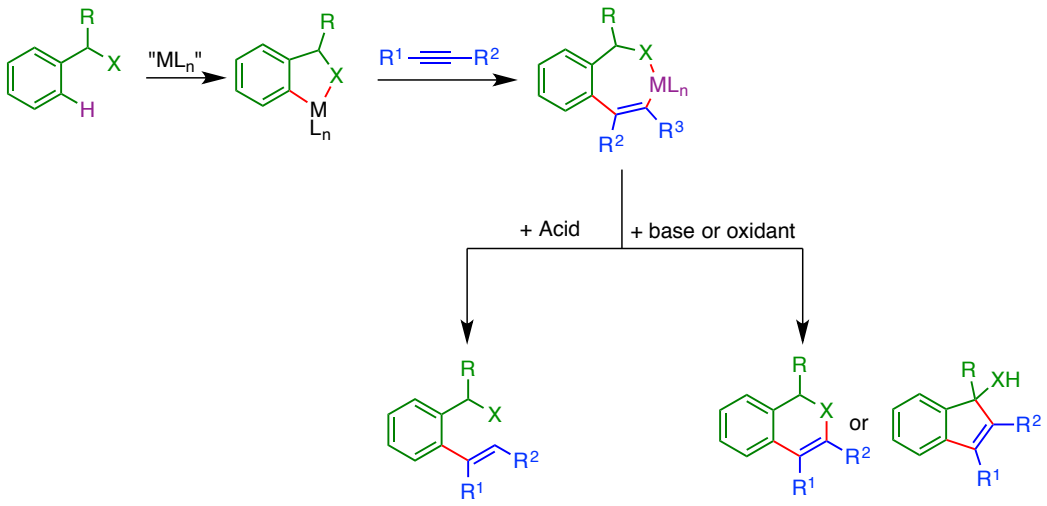
Fagnou in the year 2010, reported alkyne hydroarylation with indole derivatives (**1.40**) in the presence of cationic rhodium (III) and isopropyl acetate as the solvent to give C-2 hydroarylated products[21] (**1.41**). He proposed that pivalic acid initiates the C-H activation via proposed concerted metalation-deprotonation to form aryl rhodium complex (**1.42**). Subsequent alkyne insertion leads to the rhodium alkenyl intermediate (**1.43**), followed by protonolysis to yield the C-2 hydroarylated product (**1.41**) and regenarate the active catalyst[21] (Scheme 1.17).



Scheme 1.17. Rhodium catalyzed intermolecular alkyne hydroarylation with indoles

1.3. Annulation reactions of alkynes

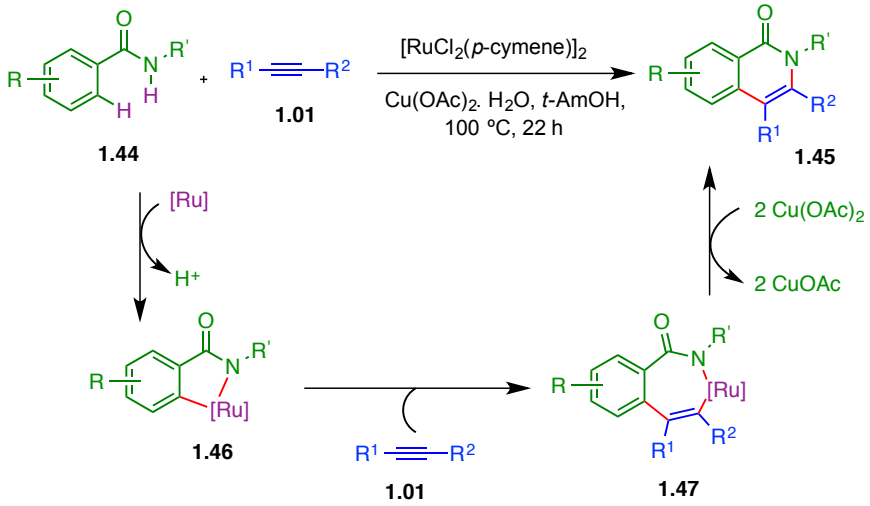
Directed *ortho* C-H bond activation by metal-mediated deprotonation pathway usually forms five-membered cyclometallated intermediate without forming a metal-hydride intermediate and upon 1,2-insertion of alkyne forms a seven-membered metal-alkenyl intermediate. This intermediate can undergo two types of reactions based upon the reaction conditions. If the reaction media is acidic, then it is quenched by proton to give hydroarylated product (uncyclised product). If the reaction media is basic or the reaction occurs in presence of oxidants it can undergo either [3+2] or [4+2] annulation (cyclized product) (Scheme 1.18). Therefore besides forming acyclic hydroarylation products, alkynes can also be used for annulation reactions after forming hydroarylated intermediates.



Scheme 1.18. Strategy towards hydroarylation vs annulation reactions

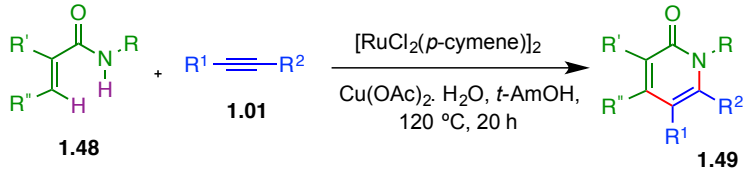
Ackermann in 2011 reported formal activation of both C-H and N-H bonds by oxidative [4+2] annulation of *N*-alkyl benzamides (**1.44**) with alkynes to synthesize isoquinolones (**1.45**). This reaction is promoted by ruthenium catalyst and $Cu(OAc)_2$ as both the oxidant and a base to deprotonate *ortho* C-H bond of amides[22] (Scheme 1.19). Based on mechanistic studies the

authors propose that the reaction procceds by an initial carboruthenation (**1.46**) via acetate-assisted C-H bond cleavage, followed by 1,2 insertion of alkyne to give ruthenium-alkenyl intermediate (**1.47**). Subsequent C-N reductive elimination released the annulation product followed by reoxidation of the ruthenium(0) intermediate for regeneration of the catalyst to complete the catalytic cycle[22] (Scheme 1.19).



Scheme 1.19. Ruthenium catalyzed oxidative annulation of amides and alkynes

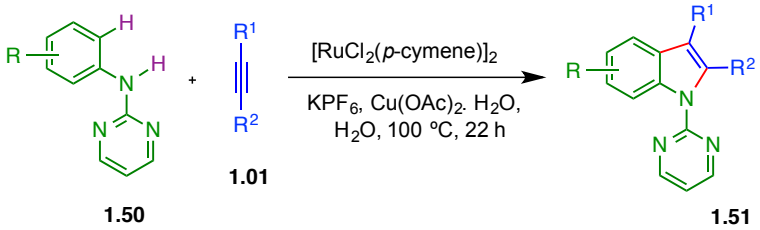
Later the same group has shown acrylamides (**1.48**) can also be used as the directing groups for alkenylic C-H bond activation in the presence of same ruthenium(II) catalyst precursor.[23] Acrylamide (**1.48**) upon reaction with alkynes (**1.02**) in the presence of ruthenium and $Cu(OAc)_2$ forms pyridone derivatives (**1.49**) (Scheme 1.20).



Scheme 1.20. Ruthenium catalyzed oxidative annulation of acrylamide and alkynes

For the electron-rich anilines, KPF_6 is also needed in addition to $Cu(OAc)_2$ to deprotonate as demonstrated in the example below.[24] 2-pyrimidyl aniline (**1.50**) derivatives on reaction with

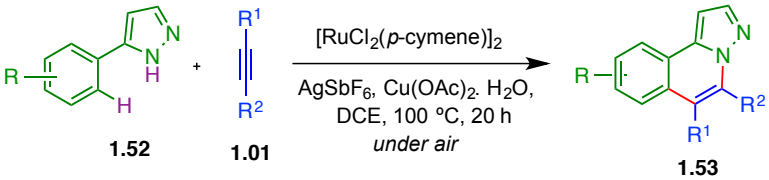
an alkyne in the presence of ruthenium (II) catalyst yielded N-protected indoles (**1.51**) (Scheme 1.21), which can be easily deprotected by NaOEt[24] to give N-H indoles.



1.50 **1.01** **1.51**

Scheme 1.21. Ruthenium catalyzed oxidative annulation of aniline and alkynes

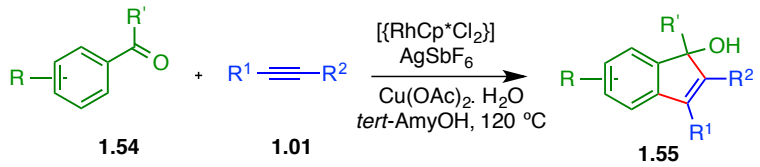
1H-Pyrazoles (**1.52**) can undergo oxidative annulation with alkynes (**1.01**) in the presence of cationic ruthenium (II) complexes, which was derived from $AgSbF_6$. This reaction takes place under aerobic conditions[25] (Scheme 1.22).



1.52 **1.01** **1.53**

Scheme 1.22. Ruthenium catalyzed oxidative annulation of 5-aryl-1H-pyrazoles and alkynes.

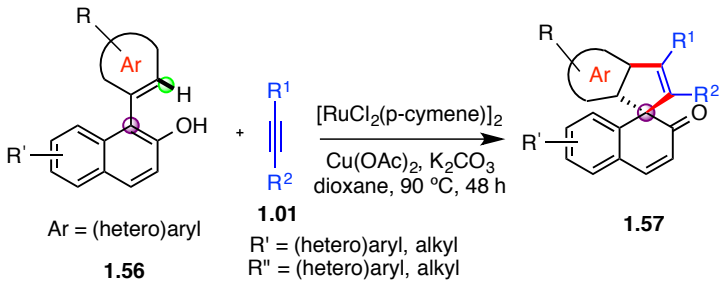
Not only can alkynes undergo [4+2] annulation reactions but they can also undergo [3+2] cycloadditions. For example, Glorius[26a] and Cheng[26b] independently reported [3+2] annulation of ketones (**1.54**) and alkynes (**1.01**) to synthesize indenol derivatives (**1.55**) using Rh (III) as a catalyst and Cu (II) as the oxidant (Scheme 1.23). Jeganmohan[26c] also reported the same reaction using the less expensive metal, ruthenium as catalyst.



1.54 **1.01** **1.55**

Scheme 1.23. Rh(III) catalyzed [3+2] annulation of ketone and alkynes

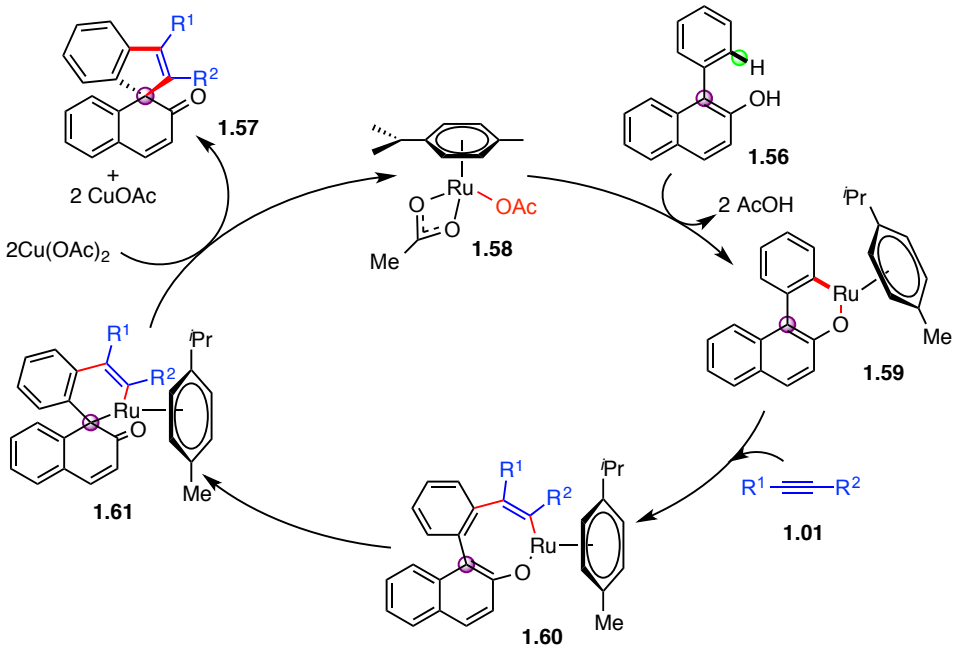
In 2013, Luan reported intermolecular annulation of 1-aryl-2-naphthols (**1.56**) with internal alkynes (**1.02**) in the presence of ruthenium catalyst to synthesize spirocyclic compounds[27a] (**1.57**) (Scheme 1.24).



Scheme 1.24. Ruthenium catalyzed annulation of 1-aryl-2-naphthols with alkynes

He proposed that the active catalyst, ruthenium acetate (**1.58**) promotes ortho C-H activation by deprotonation of 1-aryl-2-naphthol (**1.56**) to form six-memberered ruthenacycle intermediate (**1.59**) subsequent migratory insertion of alkyne forms 8-membered ruthenium-alkenyl intermediate (**1.60**). Next an important step of keto-enol tautomerism of the phenol ring takes place to give C-bound ruthenium enolate (**1.61**), followed by C-C reductive elimination to form the spiro product (**1.57**) and regenerate the catalyst to complete the catalytic cycle[27a] (Scheme 1.25).

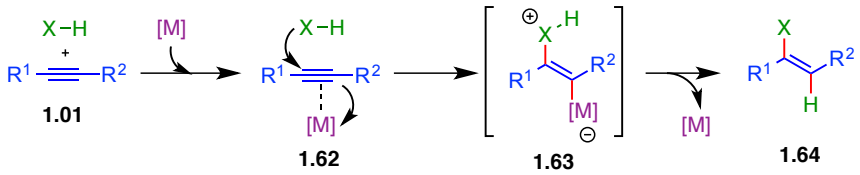
In the same year Lam also reported C-H functionalization of unsymmetrical 2-aryl cyclic, 1,3-dicarbonyl compounds by using Pd-NHC catalyst, which undergo oxidative annulation with alkynes to synthesize spiroindene compounds[27b].



Scheme 1.25. Proposed catalytic cycle for ruthenium catalyzed annulation of 1-aryl-2-naphthols with alkynes

1.4. Nucleophilic attack to metal-coordinated alkynes

The catalysis of adding nucleophilic atom oxygen and nitrogen to carbon-carbon triple bond is widely used to generate many highly useful transformations in organic synthesis. Once the metal coordinates to alkynes nucleophilic heteroatom atom will promote anti-nucleophilic attack to produce zwitter ions (**1.62**), followed by proton transfer that generates the final product from alkyne hydrofunctionalization (**1.64**) (Scheme 1.28).

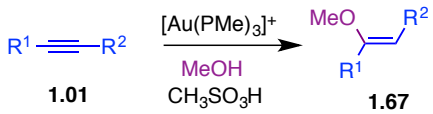


Scheme 1.26. Generalised nucleophilic addition to carbon-carbon triple bond

Based on the type of nucleophile, nucleophilic addition can be classified into different types, such as hydroalkoxylation or hydration, hydrocarboxylation, hydroamination.

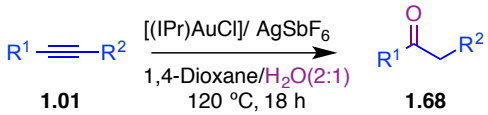
1.4.1. Hydroalkoxylation or hydration

If the nucleophile is an alcohol or water then it is termed as hydroalkoxylation or hydration respectively. Teles in the year 1998[28] first reported addition of alcohols to alkynes (**1.01**) in the presence of trimethylphosphine ligated gold(I) cationic catalyst (Scheme 1.27). The reactivity of alkyne increases as the electron density on triple bond increases and decreases with increasing steric hinderance.



Scheme 1.27. First gold catalyzed hydroalkoxylation of alkynes

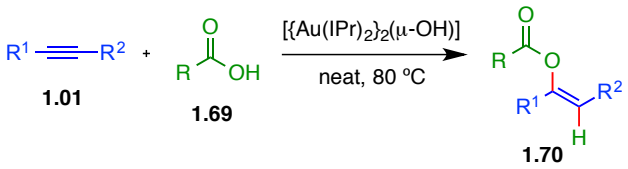
Later in the year 2002, Tanaka reported hydration of a wide range of alkynes (**1.02**) in aqueous methanol in the presence of gold(I) catalyst and CH_3SO_3H as the co-catalyst.[29] Later in 2008, Nolan also reported alkyne hydration reaction to synthesize carbonyl compounds (**1.68**) in the presence of Au(I)-NHC catalyst, $AgSbF_6$ as additive and also in the absence of acid[30] (Scheme 1.28).



Scheme 1.28. Nolan's gold catalyzed hydration of alkynes

1.4.2. Hydrocarboxylation

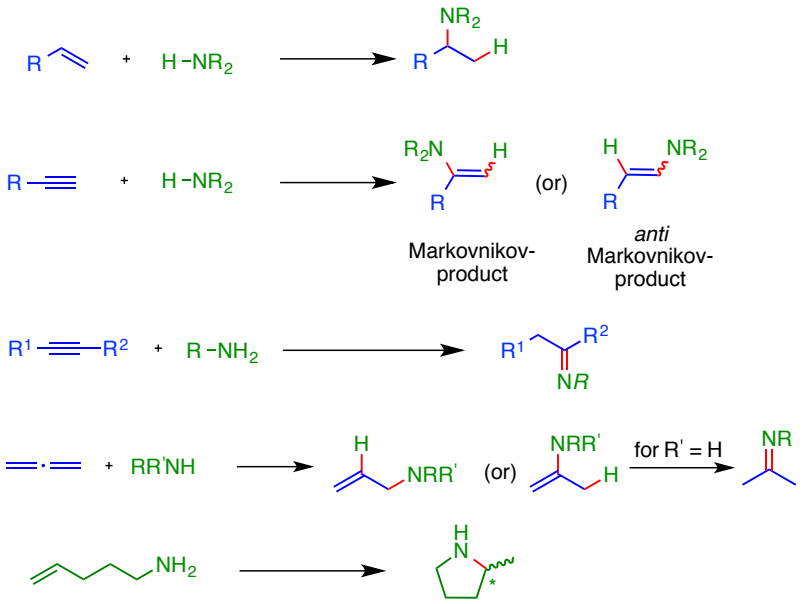
If the nucleophile attack to alkynes is from carboxylic acid then it is termed as hydrocarboxylation. Very recently Nolan reported a straightforward and highly efficient way for the preparation of enol esters (**1.70**) by reaction between carboxylic acids (**1.69**) and alkynes in the presence of a hydroxo gold(I)-carbene catalyst with superb regio-, chemo-, and stereoselectivity[31] (Scheme 1.31).



Scheme 1.29. Nolan's gold catalyzed hydrocarboxylation of alkynes

1.4.3. Hydroamination

Amines, enamines and imines are highly valuable parts of natural products and biological systems that attract significant research interests for their efficient synthesis.[32] The classical ways to synthesize amines[33] can be categorized into 4 ways: 1) reduction of nitro compounds, nitriles, azides, oximes and imines; 2) nucleophilic substitution of halogen or any other leaving group at sp^3- carbons by ammonia, primary and secondary amines; 3) reductive amination of ketones, aldehydes, hemiacetals that requires stoichiometric amounts of reducing agents; 4) Henry reaction (nitro aldol) followed by reduction. The major disadvantage of these methods is that they either produce byproducts or require stoichiometric amount of reducing agent. In comparison, hydroamination is the formal addition of N-H bond across a carbon-carbon multiple bond to synthesize amines and proceeds with 100% atom efficiency (Scheme 1.30).



Scheme 1.30. Various types of hydroamination reactions

Hydroamination of alkenes generates amine products, while hydroamination with alkynes affords imines and enamines. In the case of allene hydroamination, in general with early transition metals the amino group is added to the central carbon (thermodynamic product) where as with late transition metal the amino group is added to the terminal carbon atom (kinetic product). Intramolecular hydroamination of aminoalkenes forms pyrrolidines and piperidines.

If the alkene is activated by having electron-withdrawing groups such as keto, ester, nitrile, nitro or sulfoxide functionality then the addition will lead to anti-Markovnikov product. In case of aliphatic olefins and most aromatic olefins hydroamination often leads to Markovnikov products. Thermodynamically direct addition of amines to alkenes is feasible with ΔG^{θ} = -17 kJ/mol.[34] However the reaction is hampered by a high activation barrier, which is caused by unfavorable intermolecular electronic interactions, that arise during the approach of amine and alkene. A nucleophilic attack of the amine nitrogen bearing the lone pair on the electron rich non-activated alkenes leads to electrostatic repulsion. [2+2] Cycloaddition of N-H to the alkene is an orbital symmetry forbidden process and is unfavorable because of the high

energy-difference between π (C=C) and σ (N-H) orbitals. At higher temperature the reaction equilibrium is shifted towards the starting materials because of the highly negative reaction entropy.

Amines can undergo direct nucleophilic addition to a carbon-carbon triple bond if the π-system is electron-deficient or activated by neighboring functional groups. Since the discovery of metal-catalyzed hydroamination, reports on these reactions have been increasing drastically (figure 1.1).

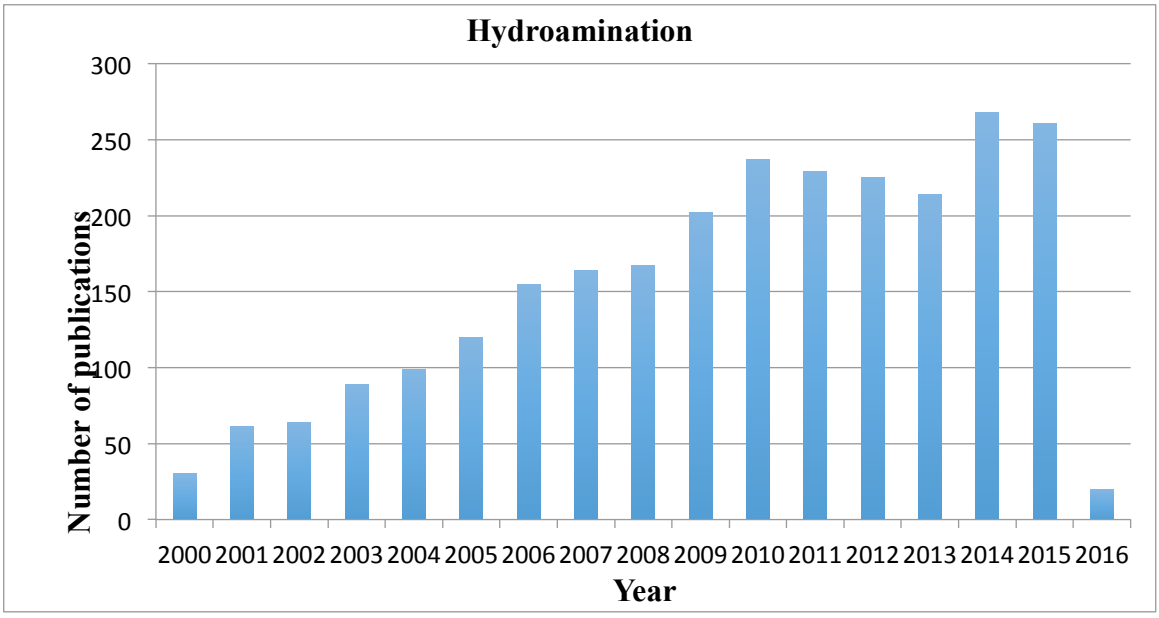


Figure 1.1. Number of publications on hydroamination in the year 2000-2016 (data collected from scifinder)

A general hydroamination reaction follows one out of three types of mechanism

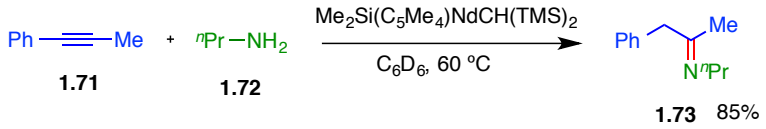
1) Amine activation by deprotonation

2) Amine activation by oxidative addition of N-H bond

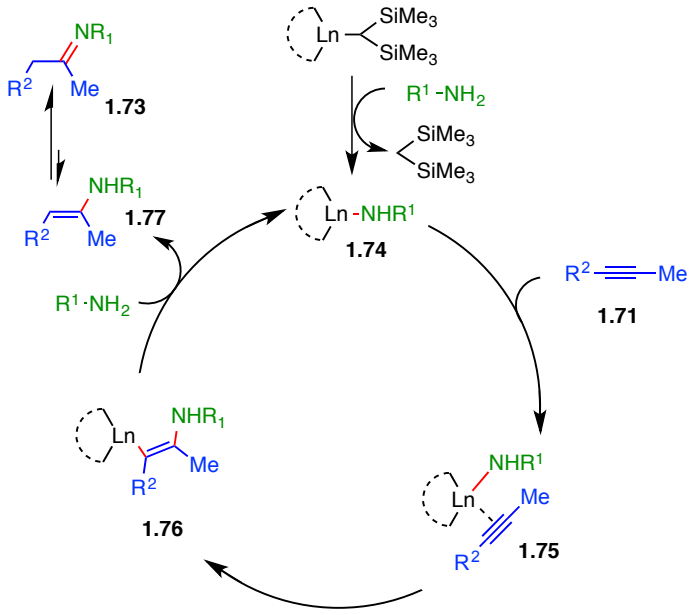
3) Olefin or alkyne activation by π- coordination followed by nucleophilic anti attack.

1.4.3.1. Amine activation by deprotonation

In this mechanism, deprotonation of N-H moeiety in amine is promoted by using alkali/alkaline earth metals and sometimes by early transition metals (for example lanthanides) to form amido complexes (M-NR_2). In year 1996, Tobin Marks and coworkers reported relatively mild reaction conditions for the hydroamination of internal alkynes (**1.71**) by aliphatic amines in the presence of lanthanide metallocenes (Scheme-1.31).[35] They proposed that Lanthanide metallocenes on reaction with amine forms a lanthanide amido complex, (**1.74**) followed by coordination to the internal alkyne (**1.71**) to form a π-coordinated lanthanide amido complex (**1.75**). In the turnover-limiting step (i.e., insertion of the alkyne into a Ln-N bond) a lanthanide alkenyl intermediate (**1.76**) is formed followed by protonolysis to form an enamine (**1.77**) product. The enamine isomerizes to give the corresponding imine (**1.73**) product (Scheme 1.32).



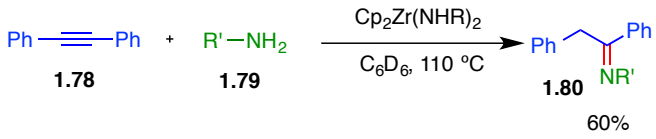
Scheme 1.31. Lanthanide based hydroamination of internal alkyne



Scheme 1.32. Lanthanide based hydroamination of internal alkyne-amido mechanism

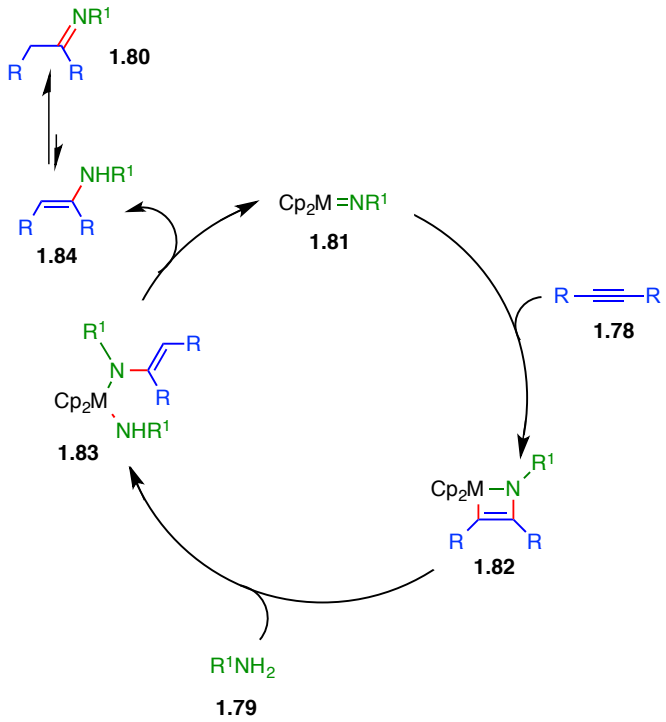
1.4.3.2. Amine activation by N-H oxidative addition

Generally group IV metals will undergo reversible oxidative addition reaction with primary amines to afford metal-imido species. These species can undergo [2+2] cycloaddition of alkyne to give azametallacyclobutenes. The metallocycles can be rapidly protonated with additional amine to form bisamide complex, which is the rate-determining step. Subsequent intramolecular proton transfer forms enamine and isomerization of enamine gives imine product. By using $Cp_2Zr(NHR)_2$ bisamide catalyst, Bergman reported hydroamination of alkynes (**1.78**) with amines (**1.79**) to give imines (**1.80**) as the products[36] (Scheme 1.33).



Scheme 1.33. Zirconium catalyzed hydroamination of alkynes

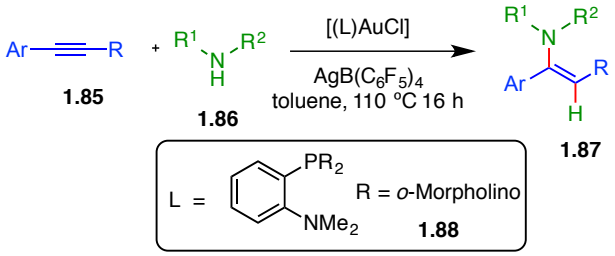
Bisamides precursors are activated to form metal-imido complexes (**1.81**), followed by alkyne insertion via [2+2] cycloaddition to give azametallocyclobutenes (**1.82**). Protonation with additional amine to give bisamide (**1.83**) and finally intramolecular proton transfer afforded enamines (**1.84**) (Scheme 1.34).



Scheme 1.34. Proposed catalytic cycle of zirconium catalyzed hydroamination of alkynes

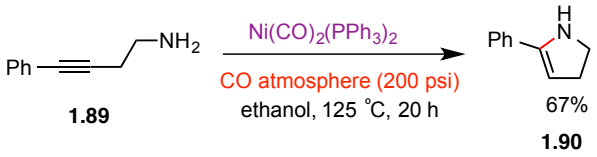
1.4.3.3. Olefin or alkyne activation by π- coordination followed by nucleophilic anti attack

Not only oxygen based nucleophiles but also nitrogen-based nucleophiles can undergo similar type of anti-addition to alkynes. For example Lingaiah reported silver catalyzed intermolecular hydroamination of aliphatic alkynes with amines in 2006.[37] In 2010 Stradiotto reported that by using P, N-ligands (**1.88**) a gold(I) catalyst was able to promote stereoselective hydroamination of internal alkynes (**1.02**) with diakylamines[38] (**1.85**) to afford *E*-enamine (**1.87**) with broad substrate scope (Scheme 1.35).



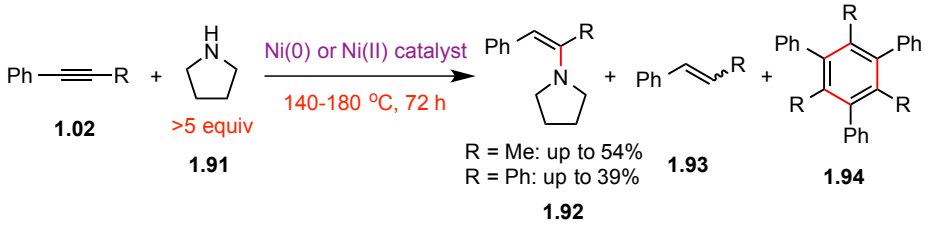
Scheme 1.35. Gold catalyzed hydroamination of alkynes

Nickel catalyzed hydroamination of alkynes are rare and so far only a few reports are known. For example an intramolecular hydroamination of alkynes (**1.89**) was reported by Jackson in 1996 by using nickel catalyst and in the presence of CO gas to synthesize pyrrolidines derivatives (**1.90**).[39] Because of high pressure of CO gas further investigation of this catalyst system is abandoned (Scheme 1.36).



Scheme 1.36. Nickel catalyzed intramolecular hydroamination of alkynes.

More recently Garcia[40] reported pyrrolidine hydroamination (**1.91**) of alkynes (**1.02**) by using pyrroles (**1.92**) in the presence of Ni (II) or Ni(0) catalyst but the reactions gave moderate yields because of the byproducts formation of alkyne semi-hydrogenation (**1.93**) and trimerization (**1.94**) (Scheme 1.37).



Scheme 1.37. Nickel catalyzed intermolecular hydroamination of alkyne

1.5. Conclusion

During the development of this thesis, a variety of catalyst systems derived from ruthenium, rhodium, iridium and palladium, have been reported for effective alkyne functionalization via C-H/N-H activation with different arenes/heteroarenes and other C/N-nucleophiles bearing different directing groups. Although the directing group allows precise regiocontrol of C-H functionalization in many cases, it typically remains intact on the product structure and its removal requires additional synthetic steps. Further, the utilization of high-cost precious metal catalysts is a discouraging step towards sustainable development, thus utilization of earth abundant transition metal based catalyst system is advocated. Moreover, the alkyne annulation via C-H/N-H functionalization generally proceeds in oxidative manner, where as relevant redox-neutral transformations are rare. Lastly, the precise control over stereoselectivity is still an unsolved problem in context of functionalization.

All these longstanding challenges have incited us to develop new catalytic methods for alkyne functionalization via C-H/N-H activation that involve rational catalyst and ligand design. The following chapters describe our research on the development of rhodium-based catalysts for the first time single metal-based catalyst system for the redox-neutral diastereoselective synthesis of dihydroisoquinolines via tandem C-H activation, alkyne coupling and intramolecular alkene hydroamination. In context of sustainable development under C-H functionalization, we discovered the first earth abundant nickel-catalyzed hydroimination of internal alkynes with N-H ketimines as N-nucleophiles. Further stereoselective alkyne hydrogenation to *E*/*Z*-selective olefins using simple alcohols as H-donor, by rational design of ligands under nickel catalysis was developed.

1.6. References

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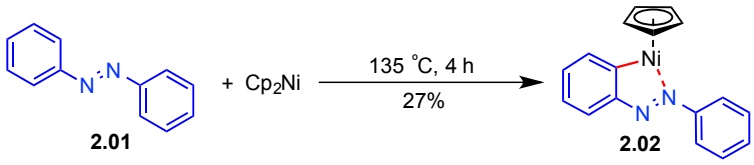
CHAPTER 2. MERGING RHODIUM-CATALYZED C-H ACTIVATION AND HYDROAMINATION IN A HIGHLY SELECTIVE [4+2] IMINE/ALKYNE ANNULATION

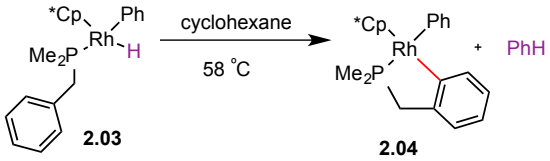
2.1. Introduction

Directing group assisted C-H bond functionalization/ C-H bond activation is an attractive strategy for the development of atom-efficient organic transformations. In fact the first reported method for transition metal-mediated C-H bond activation under homogenous conditions by Kleiman and Dubeck in 1963 utilize diazo moiety as a directing group for *ortho* C-H bond activation of diazobenzene (**2.01**) which reacted with a stoichiometric amount of dicyclopentadienylnickel (Cp_2Ni) to form a 5-membered nickelacycle (**2.02**) (Scheme 2.1).[1]



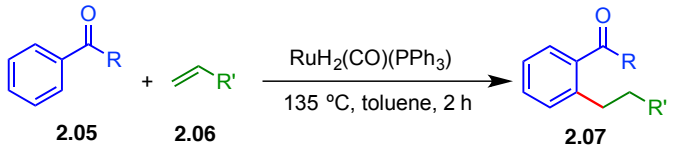
Scheme 2.1. Nickel mediated directed ortho C-H bond functionalization

After this pioneering work, various transition metals such as ruthenium, iridium, rhodium and palladium[2] were employed in stoichiometric quantities for demonstration of their ability to activate C-H bond. In particular, the first study on the use of rhodium complex for directed C-H bond functionalization was reported by Jones and Feher in 1985 (Scheme 2.2).[3] Upon heating, complex **2.03** undergoes phosphine directed C-H activation to generate benzene and a 5-membered rhodacycle (**2.04**).



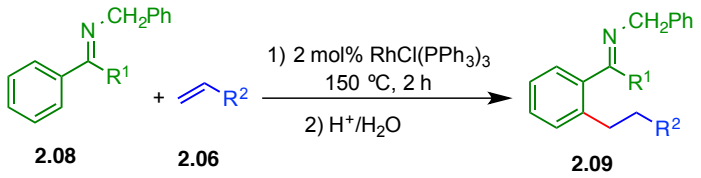
Scheme 2.2. Rhodium mediated directed C-H bond cleavage

Although the stoichiometric reactions have proven the mettle in transition metal mediated C-H activation reactions, similar strategies employing catalytic amounts of metal complexes led to various complications in terms of both selectivity and efficiency.[4] In the year 1993, Murai and co-workers reported the first breakthrough of employing catalytic transition metal complexes for C-H bond activation.[5] They employed ruthenium complexes for directed *ortho* C-H bond functionalization of aromatic ketones, coupling them with terminal olefins to form alkylated products (Scheme 2.3). The selectivity of these hydroarylation products was governed by the chelation assisted C-H bond cleavage at the *ortho*-position in aromatic ketones (**2.05**). This report highlighted the importance of chelation (or) directing group in the product regioselectivity.



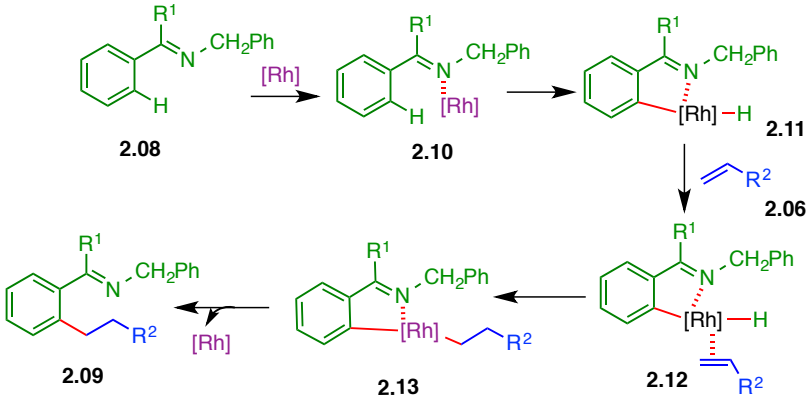
Scheme 2.3. Murai protocol for hydroarylation via ruthenium catalyzed directed C-H bond activation

Apart from carbonyl oxygen, nitrogen-containing functional groups can also act as directing groups for *ortho* C-H bond activation. In fact the functional group tolerance in rhodium catalyzed C-H bond functionalization was higher compared to ruthenium catalysts when nitrogen compounds are used as directing groups. In an early report, Jun and co-workers found that benzyl protected ketimine (**2.08**) acts as a good directing group in rhodium catalyzed C-H bond alkylation by coupling with olefin (**2.06**) substrates.[6] When they used Wilkinson's catalyst, both the terminal and internal alkenes reacted to provide *o*-alkylated aromatic imines that upon hydrolysis resulted in *o*-substituted aryl ketones (**2.07**), similar products as that of Murai protocol but with a broader alkene scope (Scheme 2.4).



Scheme 2.4. Rhodium catalyzed ortho-alkylation by directed C-H activation

The general mechanism for Murai-type *ortho*-alkylation via C-H bond activation is depicted in Scheme 2.5.[7] Coordination of transition metal to the chelating nitrogen facilitates cleavage of the C-H bond in the *ortho* position, providing a cyclometalated intermediate (**2.10**). It was proposed that C-H activation takes place by oxidative addition pathway to give cyclometalated rhodium (III) hydride intermediate (**2.11**). Subsequent olefin coordination and hydrometalation on the double bond give the metal-alkyl intermediate, (**2.13**) then C-C reductive elimination of complex (**2.13**) produces the final *ortho*-alkylated product (**2.09**) and completes the catalytic cycle (Scheme 2.5).

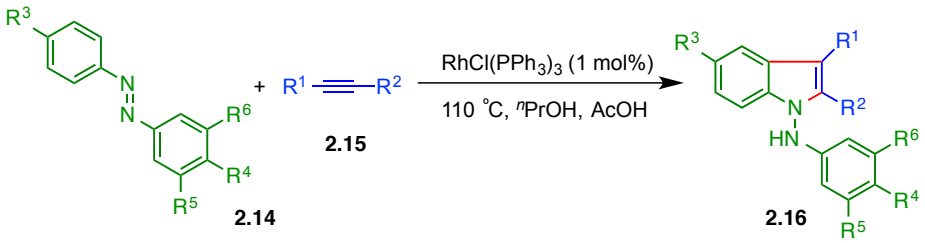


Scheme 2.5. General mechanism for hydroarylation by directed C-H activation

Since Murai's pioneering studies numerous examples of directed C-H activation catalyst have been reported in literature with various directing groups such as nitrogen-containing heterocycles including 2-pyridinyl, 1-pyrazolyl and 2-imidazolyl groups. In some cases carboxylic acids and amides are also effective as directing groups in rhodium catalyzed C-H

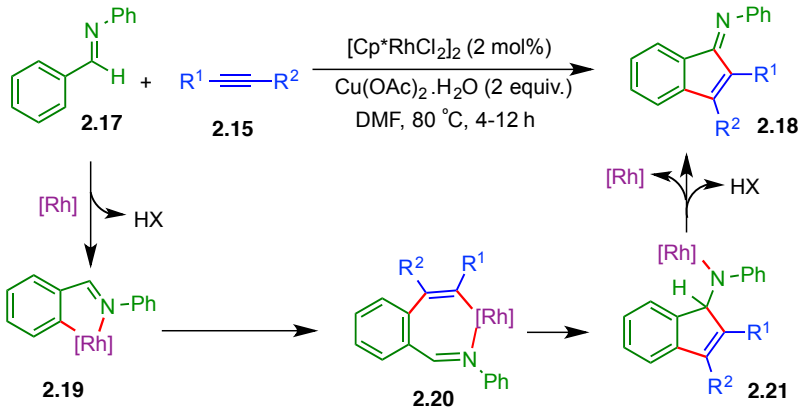
functionalizations. Although the directing group strategy is particularly useful for C-H bond activation and further coupling reactions, the directing functional group usually remains intact after the reaction, posing a problem of over functionalization and selectivity. Incorporating the directing group into the product backbone would provide an additional applicability and increase the efficiency of the C-H activation strategies.

Kisch and coworkers reported the first successful utilization of a functional group both as a directing group for C-H activation and as a component in product backbone.[8] N-substituted indoles were synthesized from the reaction between 1,2-diaryldiazenes and internal alkynes in the presence of catalytic amounts of Wilkinson's catalyst (Scheme 2.6).



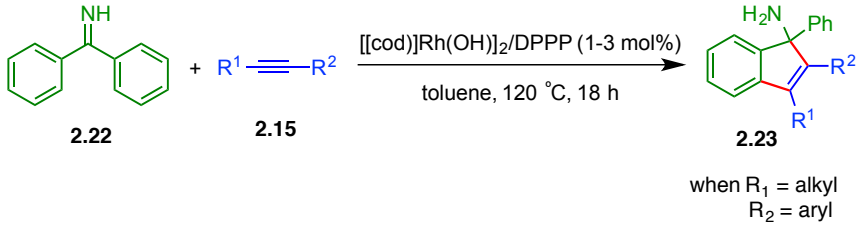
Scheme 2.6. Rhodium catalyzed directed C-H activation for indole synthesis

Aldimine and ketimine derivatives were utilized in rhodium catalyzed annulation reactions with alkynes, forming indenone imines. Satoh and Miura reported an example of such oxidative [3+2] annulation reaction of using Rh(III) catalyst (Scheme 2.7).[9] The proposed mechanism involves acetate assisted deprotonation and chelation by imine nitrogen to generate a cyclometalated rhodium(III) intermediate (**2.19**). A Rh(III) amido intermediate (**2.21**) is generated by alkyne insertion into the Rh-C bond of intermediate (**2.19**) and subsequent intramolecular insertion of imine moiety followed by β-hydride elimination yields indenone imines (**2.18**) (Scheme 2.7).



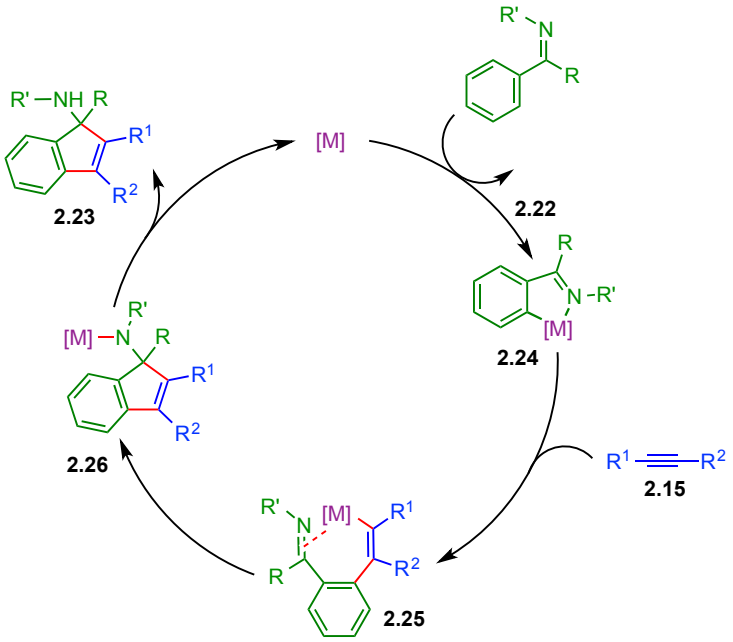
Scheme 2.7. Indenone imine synthesis by Rh(III)-catalyzed aldimines/alkyne annulation

With inspiration of the Takai group results we demonstrated that in the presence of catalytic amounts of $[Rh(cod)Cl]_2$ and DPPP, N-unprotected aromatic ketimines (**2.22**) reacted with internal alkynes (**2.15**) in toluene at 120 °C, generating carbinamine derivatives (**2.25**) in high yields with very good regioselectivity for addition with unsymmetrical aryl alkyl alkynes (Scheme 2.8).[10]



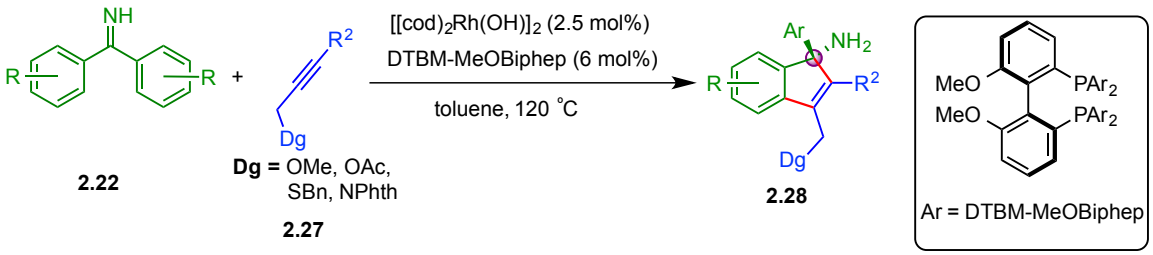
Scheme 2.8. Rh(l) catalyzed [3+2] carbocyclization with N-H ketimines and alkynes

We propose that in the presence of Re or Rh catalyst imine directed C-H activation proceeds via deprotonation pathway and forms a 5-membered metallocyclye intermediate (**2.24**). Then 1,2-insertion of alkyne takes place to generate nucleophilic transition metal-alkenyl intermediate (**2.25**) with a π-coordinated imine moiety. Ring-closure by intramolecular ketimine insertion takes place to form indene-based amido complex (**2.26**) and subsequent proton exchange would release the indenamine product[11] and regenerate the active catalyst for another catalytic cycle (Scheme 2.9).



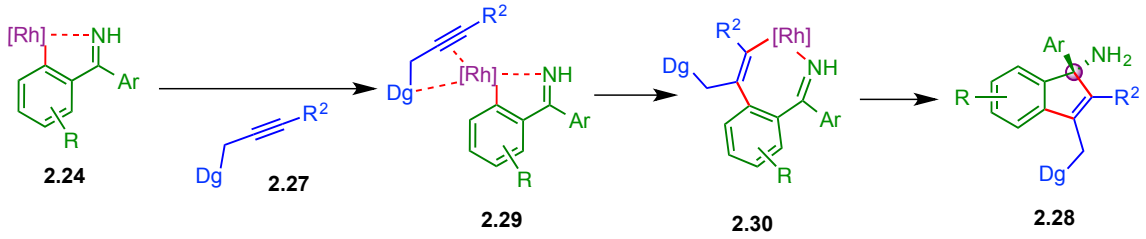
Scheme 2.9. A proposed catalytic cycle for the transition metal catalyzed [3+2] annulation of aromatic ketimines with alkynes

Cramer and co-workers have reported a chiral variant for *tert*-carbinamine synthesis under Rh(I) catalysis upon reaction of N-H ketimines with internal alkynes with enantioselectivities of up to 98% (Scheme 2.10).[12] The counter ions in Rh complexes have shown profound effect in catalyzing the reactions and hydroxide ion proved to be the best counter-ions with respect to reactivity and enantioselectivity. In order to get high ee% directing groups are required for alkyl-substituted alkynes; for diaryl alkynes lacking directing groups low to moderate ee% was observed.



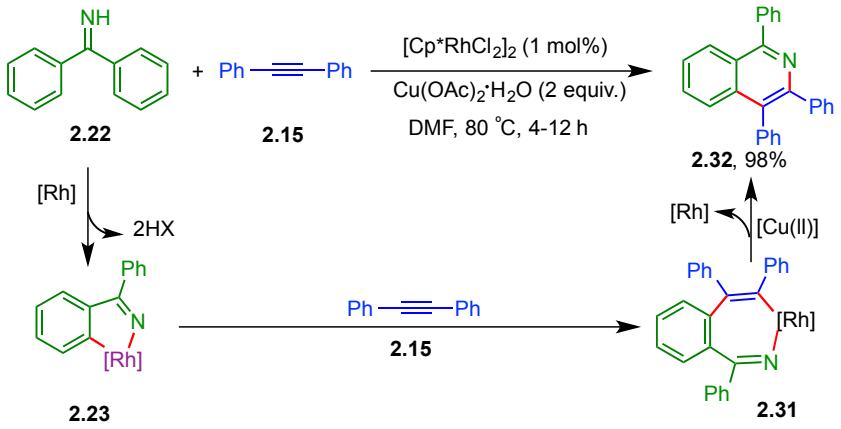
Scheme 2.10. Enantioselective [3+2] annulation of ketimines and internal alkynes

The regioselective for the unsymmetrically substituted dialkyl acetylenes is more challenging, and to control the regioselectivity a secondary directing group (Dg) on the alkyne was employed. The coordination of secondary directing group would form intermediate (**2.29**) orientating the alkyne for a selective migratory insertion to give vinyl rhodium (**2.30**) (Scheme 2.11).



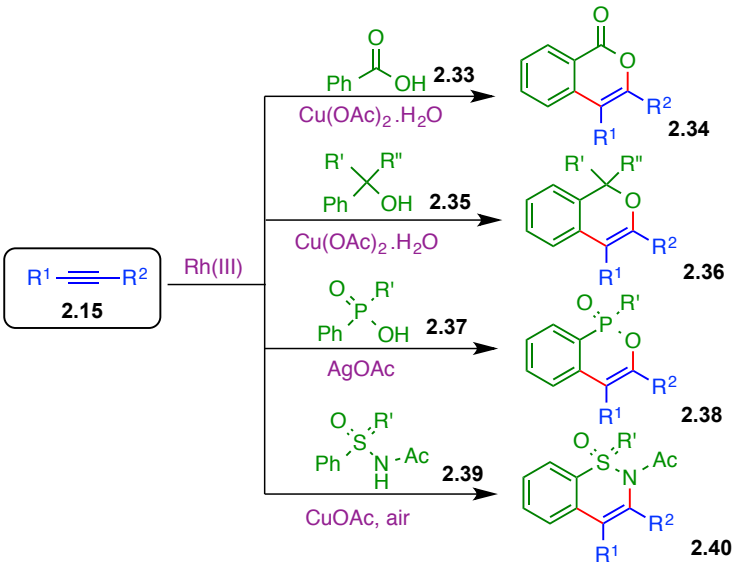
Scheme 2.11. Proposed mechanism of a secondary directing group on the dialkyl acetylenes

Ketimine directing groups are also suitable for a [4+2] cascade reaction yielding isoquinoline derivatives. The use of aldimines and ketimines was independently reported by Jun,[13] Fagnou,[14] Satoh and Miura[9] to produce highly substituted isoquinolines from rhodium-catalyzed oxidative coupling with internal alkynes. Miura and coworkers employed N-H ketimines as the starting annulation partners, [4+2] annulation occurred to form isoquinoline derivatives *via* imine nitrogen incorporation in the ring (Scheme 2.12). In these reactions, both N-H and C-H bonds were proposed to be deprotonated by acetate assisted Rh(III) catalysis forming rhodacycle intermediate. Subsequent alkyne insertion followed by ring-closure steps incorporated the directing groups into the isoquinoline product backbone.



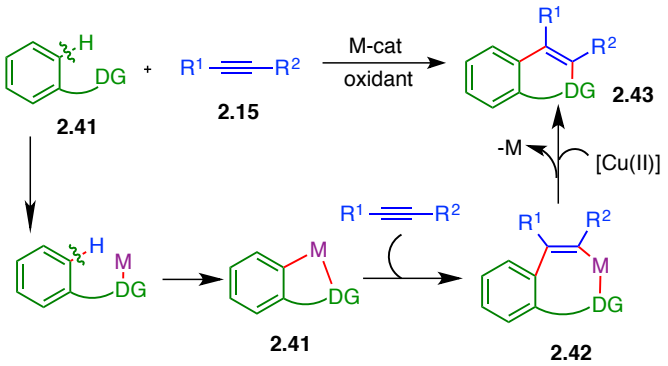
Scheme 2.12. Isoquinoline synthesis by ketimine directed Rh(III) catalyzed annulation

Utilizing a variety of heteroatom-based *ortho*-directing groups for aromatic C-H bond activation, various groups reported oxidative [4+2] annulations to synthesize different heterocyclic compounds[15] such as isocoumarins, isochromenes, phopshoisocoumarins, and arylsultams (Scheme 2.13). All these reactions require heteroatom-based directing groups with a N–H or O–H moiety and stoichiometric amounts of Ag(I) or Cu(II) oxidants are commonly used for oxidative [4+2] annulations. This need for external oxidants can be eliminated either by developing aerobic oxidation[16] or dehydrogenative coupling conditions,[17] or by using an "oxidizing directing group" as the internal oxidant that releases a small molecule byproduct such as water,[15j, 18] alcohol,[15k] or carboxylic acid.[19, 20]



Scheme 2.13. Rh(III) catalyzed heterocycle synthesis in the presence of oxidants

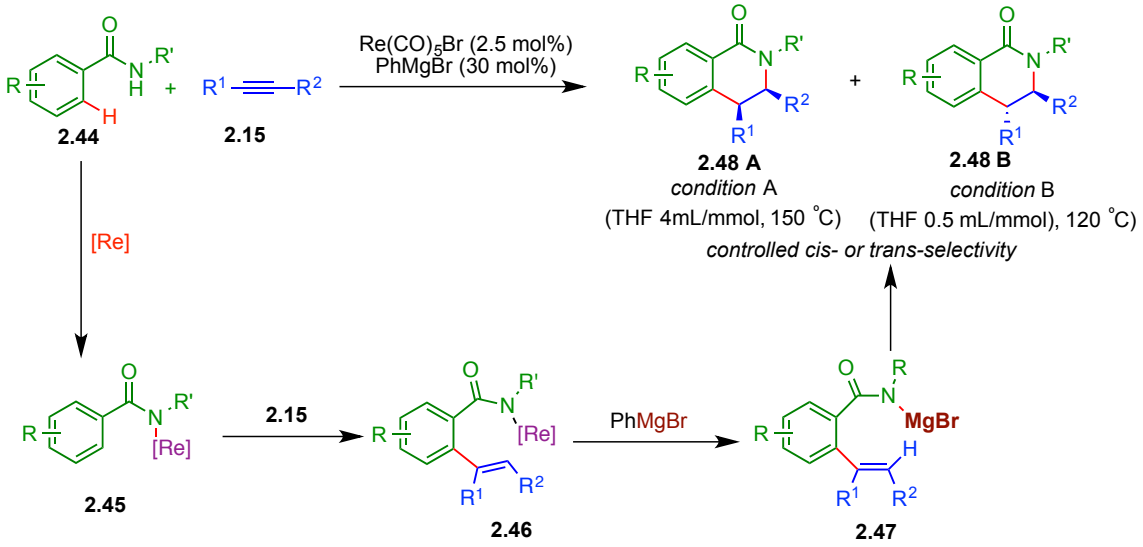
All these above reactions are proposed to undergo C-H activation by deprotonation pathway to give 5-membered metallacycle intermediate (**2.41**) followed by 1,2-insertion of alkynes that forms 7-membered metal-alkenyl intermediate (**2.42**) subsequent carbon-heteroatom reductive elimination forms desired heterocyclic products (**2.43**), and the resulting low-valence metal species is oxidized by oxidizing agent to turn over the catalytic cycle.



Scheme 2.14. Proposed mechanism for Rh(III) catalyzed variant heterocycles synthesis

In principle, redox-neutral [4+2] annulations with aromatic compounds with alkynes would provide direct access to partially saturated benzoheterocycles in 100% atom efficiency and forms up to two new chirality centres. However this strategy was only demonstrated

recently. In 2013, Sun, Wang and coworkers developed a Re(I)-Mg (II) bimetallic catalyst for benzamide/alkyne coupling to synthesize 3,4- dihydroisoquinolinones (**2.48**) with controlled *cis*- or *trans*-diastereoselectivity (Scheme 2.15).[21]



Scheme 2.15. Redox neutral [4+2] annulation of benzamide with alkyne by Re/Mg catalysis

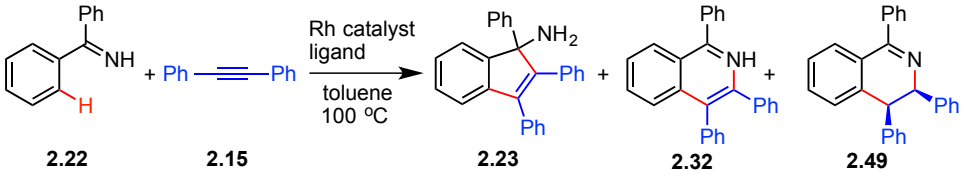
Mechanistically, rhenium catalyst promoted the directed *ortho* C-H activation. Subsequent alkyne insertion forms a hydroarylated amidorhenium intermediate (**2.46**). Transmetalation with PhMgBr regenerates active rhenium catalyst and a magnesium amide intermediate amido (**2.47**). The Mg amide underwent intramolecular nucleophilic addition/cyclization and subsequent protonation to form *cis* and *trans* isomers selectively depending on the concentration of the reaction mixture and reaction temperature. This redox-neutral [4+2] annulation featured a ring-closure step of Mg-catalyzed intramolecular alkene addition by the amide N–H bond, which represents an example of main group metal-catalyzed alkene hydroamination.[22]

We envisioned that redox-neutral [4+2] annulations for N-heterocycle synthesis might be promoted by a single transition metal catalyst via a domino sequence of C–H bond activation,

C–C bond formation by alkyne coupling, and C–N bond formation by intramolecular alkene hydroamination This "one catalyst does it all" approach for redox-neutral annulations would complement existing methods with operationally simple procedures and provide opportunities for ligand-enabled control over chemo- and stereoselectivity for hydroamination.

2.2. Initial observation

During our initial studies on Rh(I)-catalyzed coupling between benzophenone imine (**2.22**) and diphenylacetylene (**2.15**) leading to formation of [3+2] carbocyclization product[10,12] we also observed two other annulation products namely oxidative [4+2] N-heterocyclization product (**2.32**),[9,17] and the desired dihydroisoquinoline product (**2.49**) by redox-neutral [4+2] N-heterocyclization (Scheme 2.16). The overall yield and chemoselectivity depended significantly on the choices of Rh (I) catalyst precursor, ancillary ligand, and solvent for the reaction (*vide infra*). The major challenge for our catalyst development was to selectively promote formation of (**2.49**) over byproducts (**2.32**) and (**2.23**). In particular, we expected that formation of isoquinoline byproduct (**2.32**) would be highly competitive due to the strong thermodynamic driving force of aromatization.

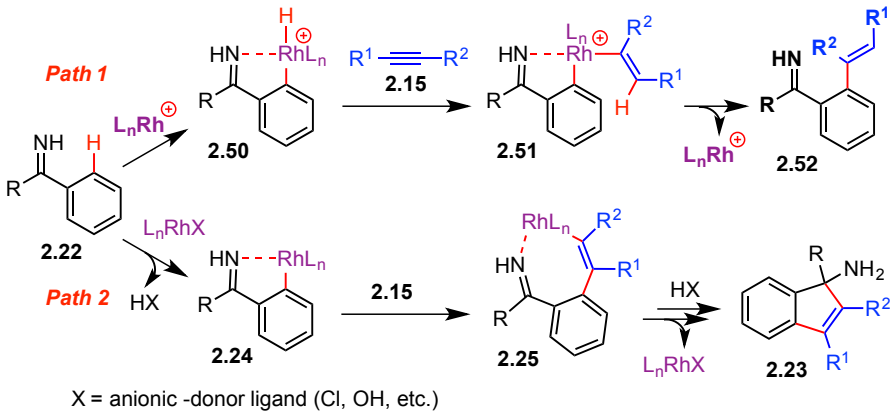


Scheme 2.16. Rh(I) catalyzed annulation of ketimines and alkynes

2.3. Mechanism-based catalyst design

Our effort for optimization of reaction conditions and catalyst system was guided by an early observation that cationic Rh (I) precursors with non-coordinating counteranions, e.g. $[Rh(cod)_2]BF_4$, appeared to promote higher chemoselectivity for (**2.49**) than neutral Rh(I) precursors with anionic ligands such as $[Rh(cod)_2(OH)]_2$. In addition, (**2.49**) was detected exclusively as the *cis*-3,4-diphenyl diastereomer by ^1H NMR spectroscopy with a relatively small H(3)-H(4) coupling in ^1H NMR ($^3J \sim 6.0$ Hz), which supported gauche *cis*- H(3)-H(4) and gauche *cis*-3,4-disubstitution relationships. These results led us to suggest two different pathways that could be operative in current reaction conditions.

1. An imine-directed C-H oxidative addition on cationic Rh(I)[23] to form a cyclometalated Rh(III) hydride **2.50** (Scheme 2.17, Path 1).[15b] Alkyne insertion into the Rh-H linkage and subsequent C–C reductive elimination gave an alkyne hydroarylation product (**2.52**), which we envisioned as a key intermediate for [4+2] annulation products (*vide infra*).[23]
2. Alternatively, a neutral Rh (I) catalyst precursor may promote a deprotonation-type C–H activation pathway, leading to a cyclometalated Rh(I) complex (**2.24**) (Path 2). Subsequent alkyne insertion into the Rh–C bond gave an imine-chelated Rh (I) alkenyl complex **2.25**,[15,d] which could lead to [3+2] carbocyclization product (**2.23**) by sequential intramolecular imine insertion into the Rh-alkenyl linkage and protonation of the resulting Rh(I) alkyl complex.[10,12]

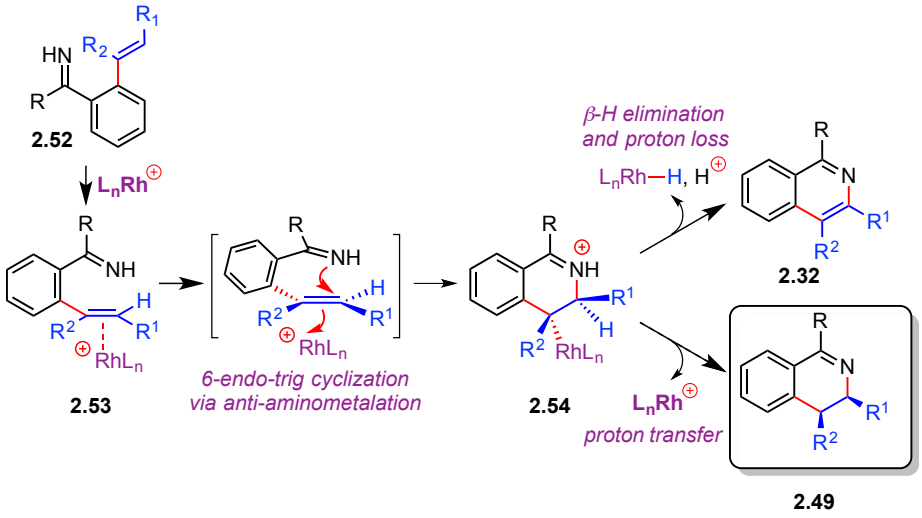


Scheme 2.17. Mechanistic pathways for hydroarylation vs [3+2] annulation

Aiming for a single catalyst-based domino procedure, we hypothesized that a cationic Rh (I) catalyst for the stage of C–H activation and alkyne coupling (Scheme 2.17, Path 1) could also promote subsequent ring-closure by intramolecular alkene hydroamination. As described in Scheme 2.18, alkene π-complexation between (**2.52**) and a Lewis acidic Rh (I) center (**2.53**) would promote intramolecular nucleophilic attack by the N-H imine moiety in stereospecific *6-endo-trig* fashion to give metal alkyl intermediate (**2.54**). With the stereochemistry of C-N bond formation determined by such *anti*-aminometalation,[22,24] (**2.54**) could undergo either *syn*-β-H elimination to give isoquinoline (**2.32**) or protonation of the Rh-alkyl linkage with stereospecific retention to give the *cis*-isomer of redox-neutral annulation product (**2.49**).

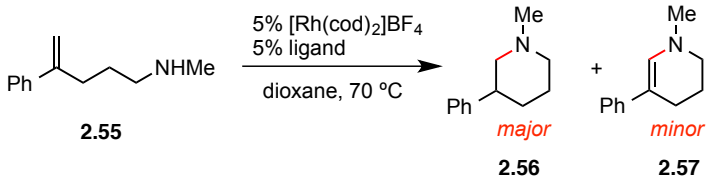
Although, we were not able to detect the proposed acyclic intermediate **2.52,** the involvement of similar alkyne hydroarylation intermediates was confirmed by Sun and Wang in their recent report on Re(I)-Mg(II) bimetallic catalyst for redox-neutral [4+2] benzamide/alkyne annulation.[21] In addition, Bergman, Ellman and coworkers have reported structurally analogous acyclic C–H alkenylation products in their reports on Rh(I)-catalyzed N-heterocyclization with α,β-unsaturated *N*-benzyl imines and alkynes, which undergoes non-catalytic 6π-electrocyclization to form dihydropyridines as reactive intermediates for several one-pot

procedures towards pyridine and tetrahydropyridine synthesis.[23b] Thus, we envisioned that an ideal catalyst system for selective synthesis of DHIQs should effectively promote a tandem sequence of C–H alkenylation (**2.22→2.52**), intramolecular alkene hydroamination (**2.52→2.54**), and selective protonation of a Rh-alkyl complex (**2.54→2.49**) over β-H elimination (Scheme 2.18).



Scheme 2.18. Mechanistic hypothesis for the formation of oxidative vs redox-neutral [4+2] annulation products

This catalysis design is inspired by cationic Rh(I) catalysts that have been successfully explored by the Hartwig group for inter- and intramolecular alkene (**2.55**) hydroamination.[25] For example, $[Rh(cod)_2]BF_4$ was demonstrated as an effective catalyst precursor for *anti*-Markovnikov intramolecular hydroamination of vinylarenes with secondary aliphatic amines (Scheme 2.19).[25b]



Scheme 2.19. Hartwig protocol for intramolecular alkene hydroamination

Notably, selective formation of desired hydroamination products vs. oxidative amination products in this report was significantly affected by the choice of chelating bis-phosphine ligands. Such ligand-controlled chemoselectivity can be attributed to the ligand bite angle effects on β-H elimination vs. protonation of metal alkyl intermediates in several catalytic processes including alkene hydroamination vs. oxidative amination, as well as Heck-Mizoroki olefinations vs. the corresponding alkylation processes.[26] It is also noteworthy that we have recently reported[27] a nickel-catalyzed intermolecular alkyne hydroamination with N-H aromatic ketimines that proceeded by a proposed imine nulcleophilic attack on Ni(0)-coordinated alkyne for stereospecific *anti*-addition. This result serves as an indirect evidence to support both the unconventional role of N-H imine moiety as a N-nucleophile for hydroamination and the proposed stereochemistry for C-N bond formation in current study.

2.4. Proposed catalytic cycle

To summarize the mechanistic details of the annulation reactions, there is a possibility of five different pathways for the formation of [3+2] carbocyclization product (**2.23**) (Scheme 2.20, path A), oxidative [4+2] N-heterocyclization product (**2.32**) (Scheme 2.20, Path B, C, and D) and the desired dihydroisoquinoline product (**2.49**) by redox-neutral [4+2] N-heterocyclization (Scheme 2.20, Path E).

Path A: formation of [3+2] annulation product (**2.23**) via intramolecular imine insertion into the Rh-alkenyl linkage in alkyne coupling intermediate (**2.30**), followed by protonation of Rh amide **2.24**.

Path B: formation of oxidative [4+2] annulation product (**2.32**) via N-H oxidative addition on Rh(I) center in intermediate (**2.30**), followed by C-N reductive elimination with the Rh(III) hydride intermediate (**2.59**).

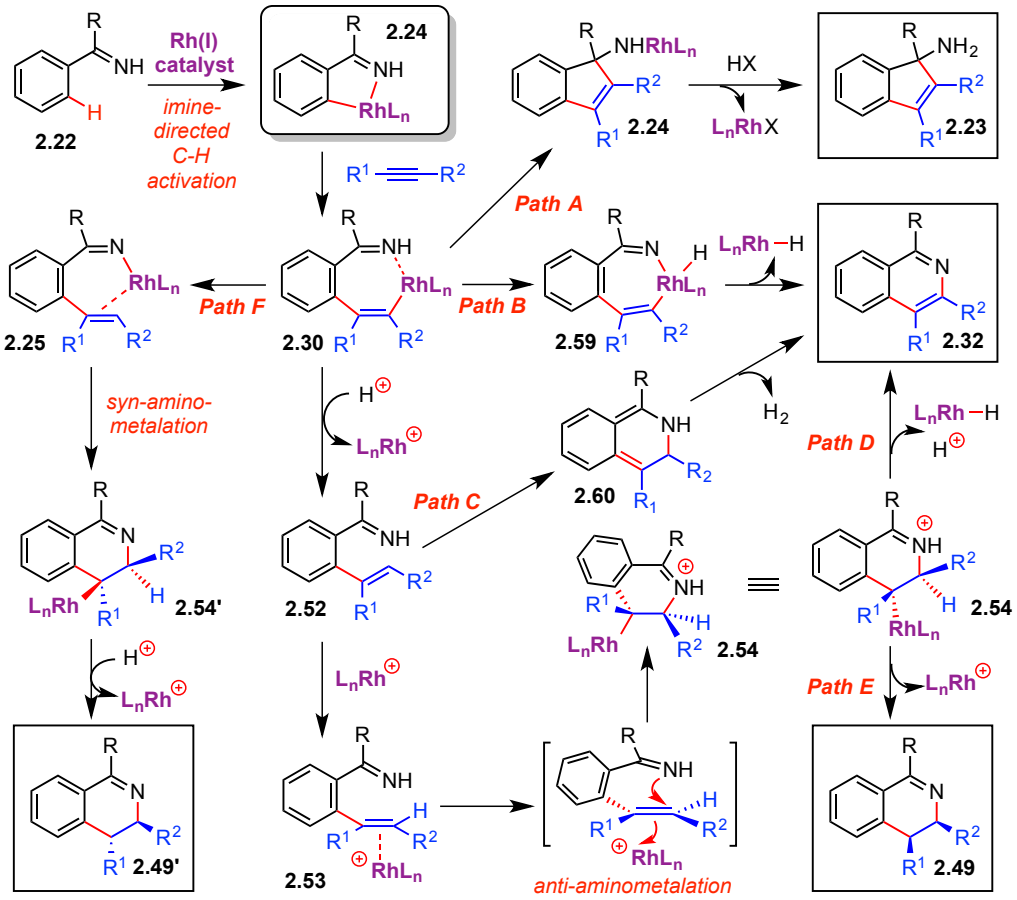
Path C: protonation of (**2.30)** to give *ortho*-alkenylation intermediate (**2.52**), followed by non-catalytic ring closure via 6π-electrocyclization, and aromatization-driven loss of H_2 to form product (**2.32**).

Path D: alkene activation by π-complexation between (**2.52**) and cationic Rh (I) center, followed by intramolecular alkene attack by the N-H imine nucleophile to give *anti*-aminometalation intermediate (**2.54**), and subsequent β-H elimination to form product (**2.32**).

Path E: formation of desired redox-neutral [4+2] annulation product (**2.49**) via protonation of Rh-alkyl bond in intermediate (**2.54**) that may involve intra- or intermolecular proton transfer with the iminium cation. The protonation process is assumed to occur in stereospecific retention to give the *cis*-4,5-disubstituted diastereomer.

Path F: formation of alkene-chelated Rh(I) iminyl intermediate (**2.25**) via proton exchange with (**2.30**), followed by *syn*-aminometalation by intramolecular alkene insertion into the Rh-iminyl linkage to form intermediate (**2.54'**) (an stereoisomer of **2.54**). Subsequent protonation of the Rh-alkyl bond occurred with stereospecific retention to afford the trans-isomer of 3,4-dihydroisoquinoline (**2.49'**) (not detected during our catalysis development).

Additional Note: In principle, reactive intermediate **(2.60)** may isomerize to give redox-neutral [4+2] annulation product **(2.49)**. However, the exclusive formation of the *cis*-isomers of **(2.49)**, which should be less stable than the corresponding *trans*-isomers, supports a *catalytic* pathway for C-N bond formation/ring-closure rather than electrocyclization.

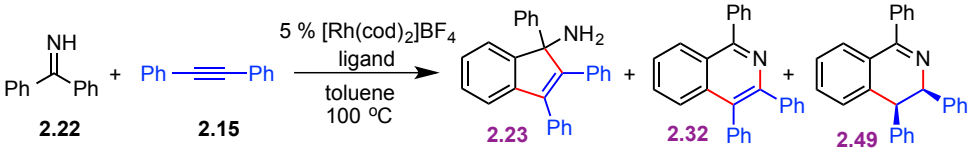


Scheme 2.20. Mechanistic details for the possible annulation products in Rh(I) catalyzed reaction between N-H ketimine and alkyne

With mechanistic insights described above, we have focused our attention on the combination of cationic Rh(I) precursors and chelating bis-phosphine ligands for catalyst development (Table 2.1). A particularly effective catalyst system was discovered using $[Rh(cod)_2]BF_4$ precursor (**2.61**) and DPEphos ligand (bis[(2-diphenylphosphino)phenyl] ether , **2.62**). It is noteworthy that DPEphos is a prominent example of bis-phosphine ligands with wide bite angles, whose significant ligand effects on chemo- and regioselectivity in metal-catalyzed coupling reactions including hydroamination are well documented. At 100 °C and in toluene solvent, a 1:1 coupling between **1a** and **2a** was promoted by 5 mol% $[Rh(cod)_2]BF_4$ (**2.61**) and 6 mol% DPEphos (**2.62**) to selectively form **2.49aa** in 93% yield over 24 hours. Under these

conditions, oxidative [4+2] annulation product **2.32** was formed in 3% yield, and the [3+2] carbocyclization product **2.23a** was not detected (entry 1). Significantly reduced reactivity and chemoselectivity was observed when replacing DPEphos with various bis- and mono-phosphines (entries 2-8).

Table 2.1. Optimization of reaction conditions – ligand screening

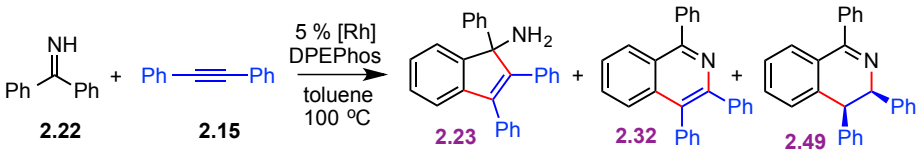


entry	Ligand	yield[b] **2.49** (%)	yield[b] **2.32** (%)	yield[b] **2.23** (%)
1	DPEPhos (**2.62**)	93	3	0
2	Diphos	0	5	0
3	DPPP	15	13	12
4	DPPPentane	0	8	4
5	DPPF	4	18	12
6	Xantphos	0	11	2
7[c]	PPh_3	0	11	2
8[c]	PCy_3	6	9	12

Conditions: **2.22** (0.17 mmol), **2.15** (0.18 mmol), Rh catalyst (5.0 mol%), ligand (6.0 mol%), solvent (1.0 mL), 100 °C, 24 h. [b] GC yields. [c] Using 11 mol% phosphine ligand.

Using DPEphos ligand as optimized ligand we screened different rhodium catalyst presursors and found triflate anion (entry 2) is unreactive towards DHIQ (**2.49**) product formation. Neutral rhodium(I) catalyst (entry 4-5) precursors were also found to be no DHIQ (**2.49**) product formation at all .

Table 2.2. Optimization of reaction conditions – catalyst precursor screening

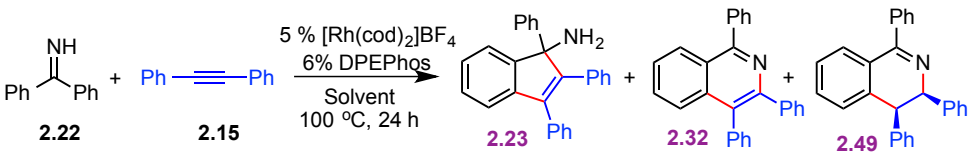


entry	Ligand	yield[b] **2.49** (%)	yield[b] **2.32** (%)	yield[b] **2.23** (%)
1	$[Rh(cod)_2]BF_4$	93	3	0
2	$[Rh(cod)_2]OTf$	5	35	2
3	$[Rh(nbd)_2]BF_4$	85	7	6
4	$[Rh(cod)(OH)]_2$	0	5	3
5	$[Rh(cod)(Cl)]_2$	3	13	7

Conditions: **2.22** (0.17 mmol), **2.15** (0.18 mmol), Rh catalyst (5.0 mol%), ligand (6.0 mol%), solvent (1.0 mL), 100 °C, 24 h. [b] GC yields.

With optimised $[Rh(cod)_2]BF_4$, as rhodium catalyst precursor and DPEPhos as the ligand we screened different solvents and found to be switching from toluene to THF solvent led to similar overall reactivity but slightly lower selectivity for **2.49aa** (entry 2), while much lower reactivity and chemoselectivity was observed in hexane (entry 3) and several solvents of higher polarity (entries 4-6). Lastly, using an increased amount of DPEphos ligand (entry 7) or reduced catalyst loading (entry 8) both led to lower combined yield of **2.49aa** and **2.23a** but higher yield for **2.32a** formation. This observation suggested that the oxidative [4+2] annulation may also proceed in different pathways that involve non-catalytic ring-closure steps such as 6π-electrocyclization.

Table 2.3. Optimization of reaction conditions – solvent screening



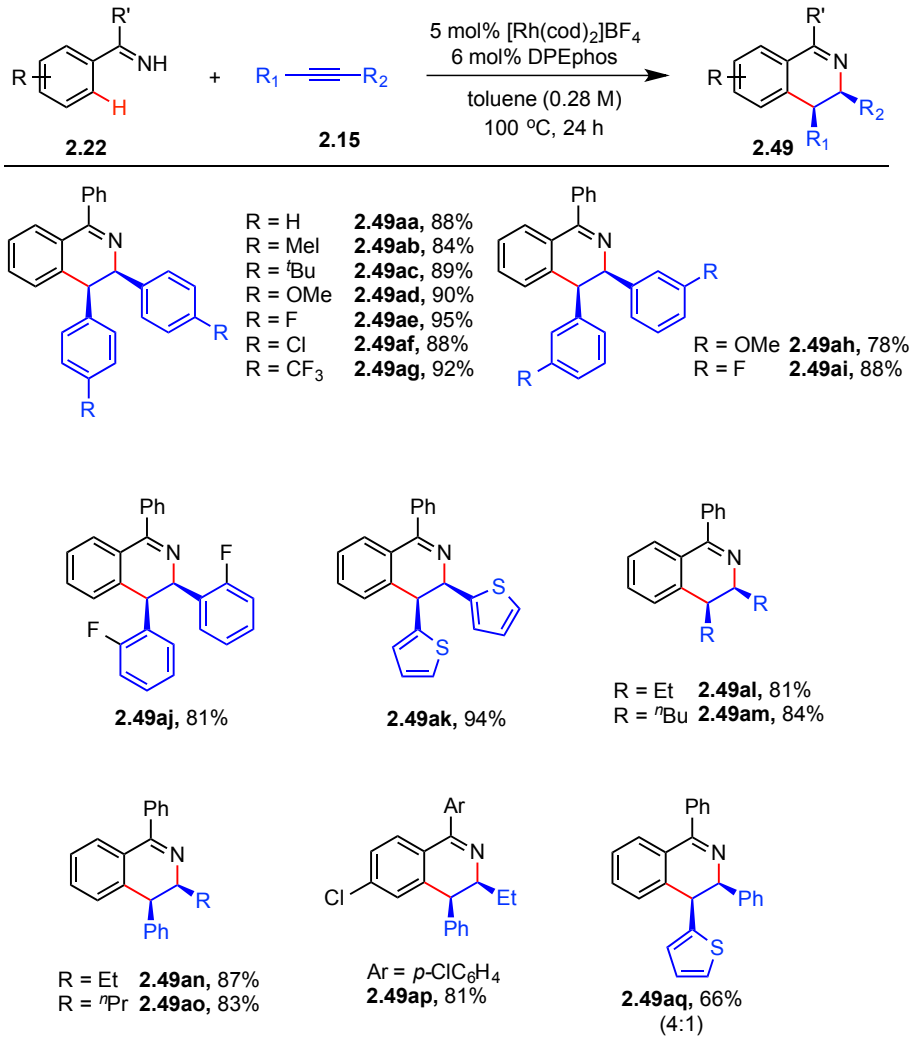
entry	Solvent	yield[b] **2.49** (%)	yield[b] **2.32** (%)	yield[b] **2.23** (%)
1	toluene	93	3	0
2	THF	89	8	2
3	hexane	8	5	3
4	dioxane	65	16	11
5	DMF	55	35	7
6	DCM	11	22	0
7[c]	toluene	13	22	0
8[d]	toluene	32	48	0

Conditions: **2.22** (0.17 mmol), **2.15** (0.18 mmol), Rh catalyst (5.0 mol%), ligand (6.0 mol%), solvent (1.0 mL), 100 °C, 24 h. [b] GC yields. [c] Using 11 mol% phosphine ligand. [d] Using 2.0 mol% [Rh] and 2.4 mol% DPEphos.

2.5. Alkyne substrate scope for redox-neutral [4+2] annulation of benzophenone imine and alkynes

With the standard reaction conditions established, various aromatic N-H ketimine (**2.22**) and internal alkyne (**2.15**) substrates were studied for Rh(I)-catalyzed redox-neutral [4+2] annulation (Scheme 2.21). In general, 1,3,4-trisubstiuted DHIQs (**2.49**) were formed in exclusive *cis*-3,4-diastereoselectivity and high chemoselectivity, with only trace amounts (0-5%) of isoquinoline byproducts (**2.32**) and no detection of indenamine byproducts (**2.23**) as evidenced by GC and ^{1}H NMR analysis of the unpurified reaction mixture. However, several DHIQ products appeared to undergo spontaneous dehydrogenation during the separation and purification procedures, which generated small amounts of isoquinoline byproducts **2.32** that

could not be fully removed from the isolated DHIQ products (*vide infra*). Scope of the alkyne substrates was studied with benzophenone imine as the reaction partner, and high coupling yields were achieved with various symmetrical alkynes having aryl, 2-thienyl, and alkyl substituents (products **2.49aa**-**2.49am**). However, no coupling products were detected for bis(2-pyridyl)acetylene or terminal alkynes such as phenylacetylene. Reactions with non-symmetrical phenyl alkyl alkynes led to the exclusive formation of *cis*-3-alkyl-4-phenyl products (**2.49an**-**2.49ao**). By sharp contrast, most reported methods of oxidative [4+2] heterocyclization with non-symmetrical aryl alkyl akynes displayed the opposite regioselectivity.[15] For instance, the Wang group recently reported regioselective formation of a 3-aryl-4-alkyl-substituted isoquinoline product by manganese-catalyzed dehydrogenative [4+2] annulation of N-H imines and alkynes.[17] The reaction with 1-(2-thienyl)-2-phenylacetylene generated a 4:1 mixture of regioisomers, and the major isomer of 3-phenyl-4-(2-thienyl)-substituted DHIQ product **2.49aq** was isolated in 66% yield. This modest regioselectivity was likely affected by potential coordination between sulfur center of the 2-thienyl moiety and the cationic Rh (I) center during the akyne coupling process.



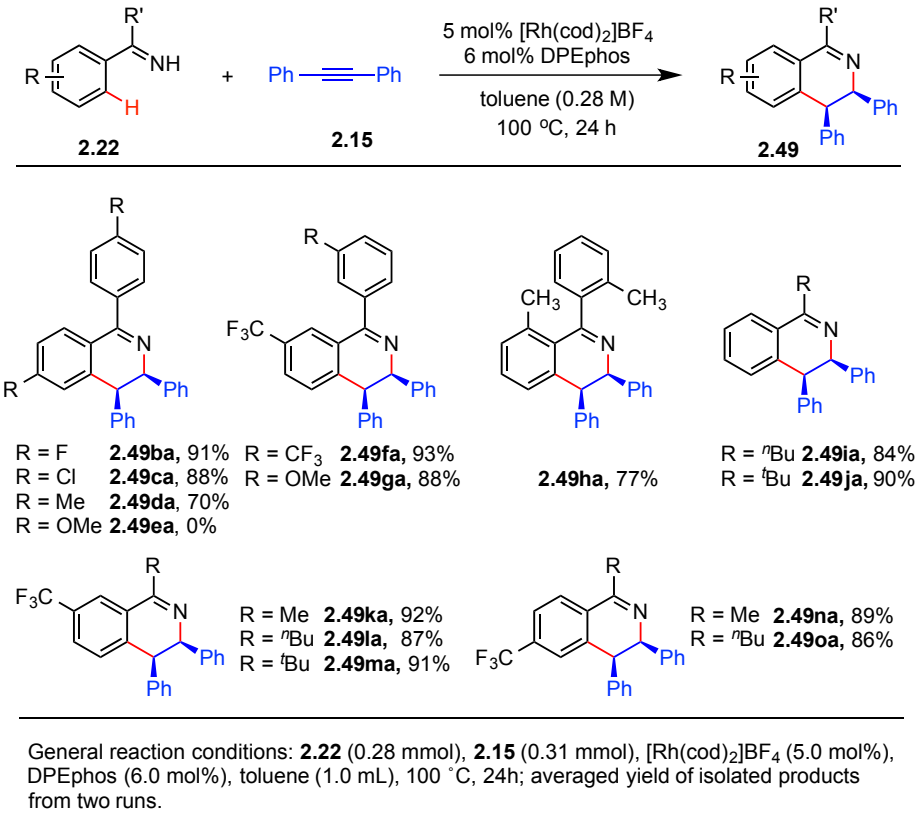
General reaction conditions: **2.22** (0.28 mmol), **2.15** (0.31 mmol), $[Rh(cod)_2]BF_4$ (5.0 mol%), DPEphos (6.0 mol%), toluene (1.0 mL), 100 ˚C, 24h; averaged yield of isolated products from two runs.

Scheme 2.21. Alkyne substrate scope in rhodium catalyzed [4+2] heterocyclization with diphenylketimine and internal alkynes

2.6. N-H ketimine substrate scope for redox-neutral [4+2] annulation of aryl ketimines with alkynes

Scope of the ketimine substrates was studied by coupling with diphenylacetylene (**2.15**), and high reactivity was observed for both diaryl and aryl alkyl ketimines with phenyl groups (**2.49ia** and **2.49ja**) or electron-poor aryl groups having F, Cl, and CF_3 groups at *para* or *meta*

positions (**2.49ba**, **2.49ca**, **2.49fa,** and **2.49ka-2.49oa**). Electron-rich di(*p*-tolyl) N-H ketimine gave product **2.49da** in 70% yield, while di(*p*-anisyl) N-H ketimine failed to react with (**2.49ea**) to give detectable coupling products. Such electronic effect on ketimine reactivity was further demonstrated with product **2.49ga**, which was formed with exclusive regioselectivity for C-H functionalization of the electron-poor aryl group with *meta*-CF_3 substituent over the electron-rich one with *meta*-methoxy substituent. Notably, the sterically hindered di(*o*-tolyl) N-H ketimine did react with (**2.49**) to give redox-neutral [4+2] adduct **2.49ha**. Product decomposition via dehydrogenation was also observed for **2.49ha**, and an isolated yield of 66% was calculated based on ^{1}H NMR analysis.

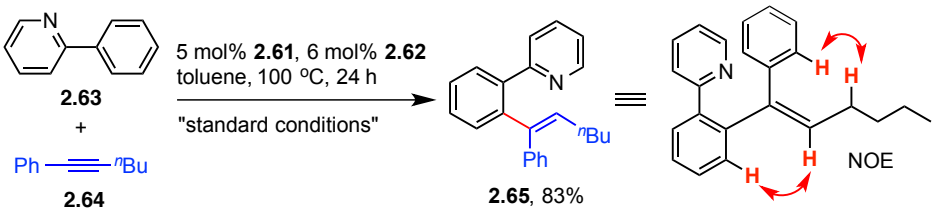


General reaction conditions: **2.22** (0.28 mmol), **2.15** (0.31 mmol), $[Rh(cod)_2]BF_4$ (5.0 mol%), DPEphos (6.0 mol%), toluene (1.0 mL), 100 °C, 24h; averaged yield of isolated products from two runs.

Scheme 2.22. Ketimine substrate scope in rhodium catalyzed [4+2] heterocyclization

2.7. Regioselective alkyne hydroarylation with 2-phenylpyridine

To further investigate regiochemistry of the proposed C–H alkenylation intermediate **2.52**, the current catalyst system was explored for a 1:1 coupling between 2-phenylpyridine (**2.63**) and *n*-butylphenylacetylene (**2.64**) that should not give an annulation product without oxidants (Scheme 2.23). Under the standard conditions for catalytic redox-neutral [4+2] annulations, a (*E*)-1,1-diarylhexene product **2.65** was acquired in 83% yield and with exclusive regio- and stereoselectivity. This result is consistent with our proposed C–H alkenylation pathway and represents a relatively rare example of high selectivity towards 1,1-diarylalkene regioisomers for catalytic hydroarylation with aryl alkyl alkynes by the directed C-H activation strategy. Lastly, the failure of produt formation for the highly electron-rich imine substrate di(p-anisyl) N-H ketimine (product **2.49ea**) suggested that C–H activation may be inhibited by strong σ-complexation between Rh(I) and imine ligands. A similar lack of reactivity for electron-rich N-H aromatic imines is observed in our previous study on Ni-catalyzed hydroimination of alkynes.[27]



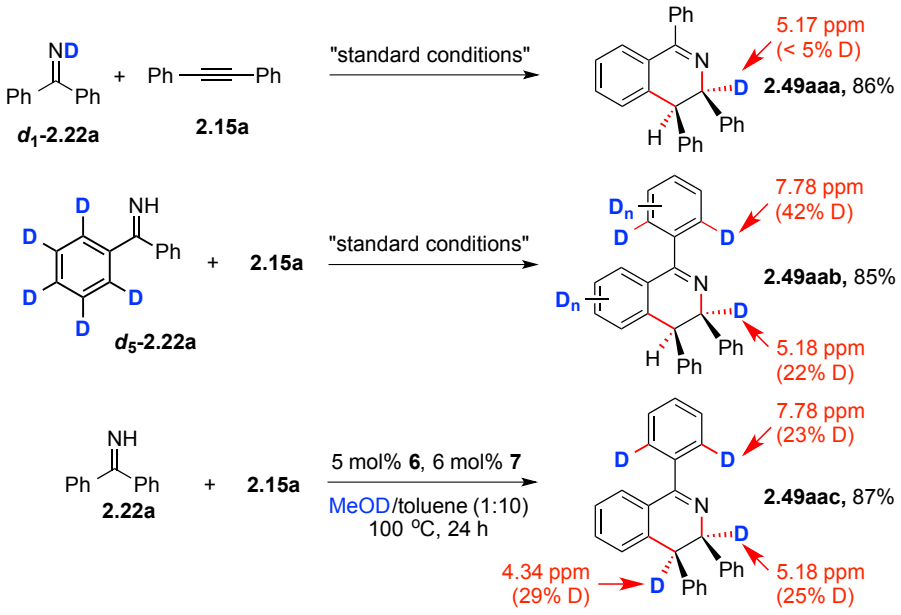
Scheme 2.23. Regioselective alkyne hydroarylation with 2-phenylpyridine

2.8. Deuterium labelling studies for better mechanism understanding

To better understand hydrogen atom transfer processes in the proposed mechanism for redox-neutral [4+2] annulation (Schemes 2.24 and 2.25), we carried out deuterium-labeling studies on the formation of **2.49aa** by coupling between **2.22a** and **2.15a** under standard catalytic conditions and with various deuterium sources (Scheme 2.24). Firstly, the reaction with

Ph_2C=ND (***d*$_1$-2.22a**) led to less than 5% D incorporation at C3 position of the product **2.49aaa**. The significant deuterium loss suggested a rapid H/D srambling between the imine moiety and the reaction media, presumably due to traces of moisture or acid impurities. The regioselective D-transfer to C3, albeit in low conversion, suggested an intramolecular H/D exchange between the imine N center and the *ortho* aromatic positions of ***d*$_1$-2.22a**. The resulting *ortho*-D atom would migrate to C3 position of **2.49aa** by the proposed pathways for C–H alkenylation (Scheme 2.24) and intramolecular alkene hydroamination (Scheme 2.24). Secondly, the reaction with (C_6D_5)PhC=NH (***d*$_5$-2.22a**) led to an inseparable mixture of products **2.49aab** and **2.49aab′** via imine-directed C–H or C–D activation. This mixture displayed 22% D incorporation at C3 position, while 42% D could be measured at each *ortho*-position of the 1-phenyl group. This result further supported the proposed H/D exchange between the N center and *ortho* aromatic positions of imine substrates. Thirdly, the reaction with non-deuterated **2.22a** and in a mixed solvent of 1:10 MeOD/toluene gave **2.49aac** with 25% D at C3, 29% D at C4, and 23% D at each *ortho* position of the 1-phenyl group. The partial deuterium incorporation at C4 suggested that the cleavage of Rh-alkyl linkage (Scheme 2.24, **2.54→2.49**) likely occurred by both intra- and intermolecular proton/deuterium transfer processes. Despite the complication by facile H/D scrambling, results from these deuterium labeling experiments allowed us to gain further evidence and additional details for proposed reaction pathways as described in Figure 4c. The proposed H/D exchange between the imine N atom and *ortho* aromatic positions likely occurs by reversible N–H(D) oxidative addition onto Rh(I) center of the catalyst to form a Rh(III) hydrido iminyl intermediate (***d*$_1$-2.22a→2.49**), which undergoes reversible 1,4-Rh migration to activate an *ortho* aromatic C–H bond and form the cyclometalated intermediate **2.50b** with a Rh–D linkage. Subsequent C–D reductive elimination generates *ortho*-deuterated imine (***d*$_1$-2.22a′**) and

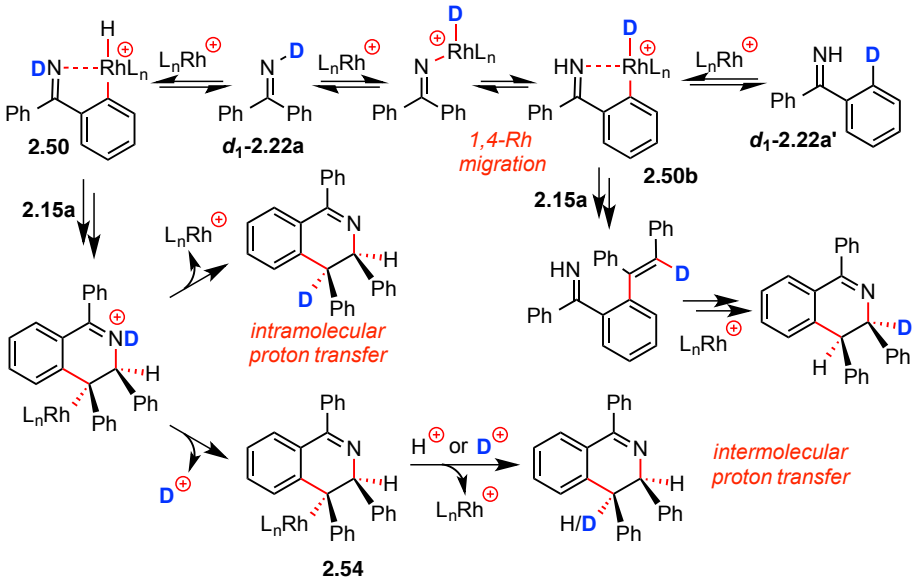
completes the proposed H/D exchange. Notably, the cyclometalated Rh(III) intermediate with a Rh–D linkage that is analogous to **2.50b** is also formed by imine-directed *ortho* C–D activation (*i.e.* microscopic reverse of C–D reductive elimination) with ***d*$_5$-2.22a** (Scheme 2.24). As described in Path 1 in Scheme 2.24, a tandem sequence of alkyne insertion with **2.50b** (or its analog from ***d*$_5$-2.22a**) and C–C reductive elimination leads to regioselective D-transfer onto the mono-substituted alkenyl position in alkyne hydroarylation product **2.52**, which followed the proposed hydroamination pathway (Scheme 2.24, **2.52→2.49**) to form the 3-deuterated compound **3-D-2.49aa** as observed in products **2.49aaa-2.49aac**.



Scheme 2.24. Results from deuterium-labelling studies

Besides the proposed intramolecular H/D exchange (***d*$_1$-2.22a→*d*$_1$-2.22a′**), imine-directed *ortho* C–H oxidative addition forms the cyclometalated intermediate **2.50a** that transforms into intermediate **2.54** after the proposed alkyne coupling and ring-closure steps. With the D atom retained on the iminium N center in **2.54**, cleavage of the Rh-alkyl linkage by intramolecular deuteron transfer in stereospecific retention forms the 4-deuterated compound **4-D-2.49aa** as

observed in product **2.49aac**. Alternatively, deuteron dissociation from **2.49** and subsequent cleavage of the Rh-alkyl linkage by intermolecular proton or deuteron transfer forms the non-deuterated **2.49aa** or **4-D-2.49aa** respectively. The observed facile H/D scrambling can be attributed to the Brønsted acid behaviors by several proposed reactive intermediates such as cationic Rh(III) hydride/deuteride complexes (**2.50a**, **2.50b** and **2.54**) and the iminium species (**2.54** and its protonated analog), which could undergo fast and reversible H/D transfer with external proton or deuteron sources such as trace moisture, acid, or added MeOD in the reaction environment (Scheme 2.25).

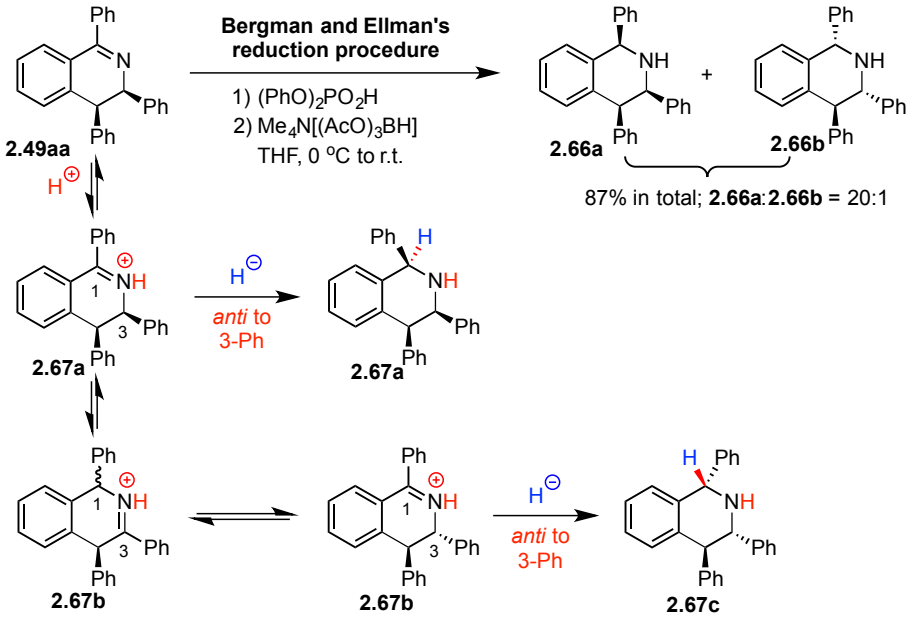


Scheme 2.25. Proposed pathway for regioselective deuterium transfer and equilibrium processes for H/D scrambling

2.9. Transformations of dihydroisoquinoline (DHIQ) compound

Product **2.49aa** was subjected to several stoichiometric and catalytic transformations to explore DHIQ products from the current study as valuable building blocks in chemical synthesis (Scheme 2.26 and 2.27). In particular, we expected that hydrogenation or nucleophilic addition of the imine moiety in these DHIQ products could lead to stereoselective formation of the corresponding 1,2,3,4-tetrahydroisoquinolines (THIQs), which are important structural motifs in

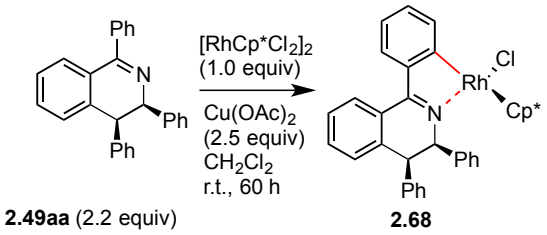
biologically active compounds including natural alkaloids and drug molecules.[28] Thus, we studied the hydride reduction of **2.49aa** using a procedure reported by Bergman and Ellman.[29] Upon acid-mediated activation, **2.49aa** underwent a borohydride reduction to give a 20:1 mixture of two diastereomers of the corresponding THIQ product in 87% overall yield. ^{1}H NMR and X-ray crystallography indicated that the major product was the all-*cis* diastereomer (**2.66a**), while the minor stereoisomer **2.66b** displayed *cis*-1,3 and *trans*-3,4 stereochemistry. The *cis*-1,3 relationship in both isomers should result from stereospecific, *anti* to 3-phenyl hydride transfer.[29] The formation of **2.67c** was likely due to acid-mediated epimerization at C3 via iminium intermediates.



Scheme 2.26. Diastereoselective hydride reduction of DHIQ

To further explore the synthetic utility of 1-aryl-substituted DHIQs as aromatic imine analogs for imine-directed C–H functionalization, a 1:1 reaction between **2.49aa** and a Cp*-ligated Rh(III) complex $[Cp^*RhCl_2]_2$ was carried out at room temperature with sodium acetate as an additive (Scheme 2.27). Although this transformation occurred with incomplete conversion,

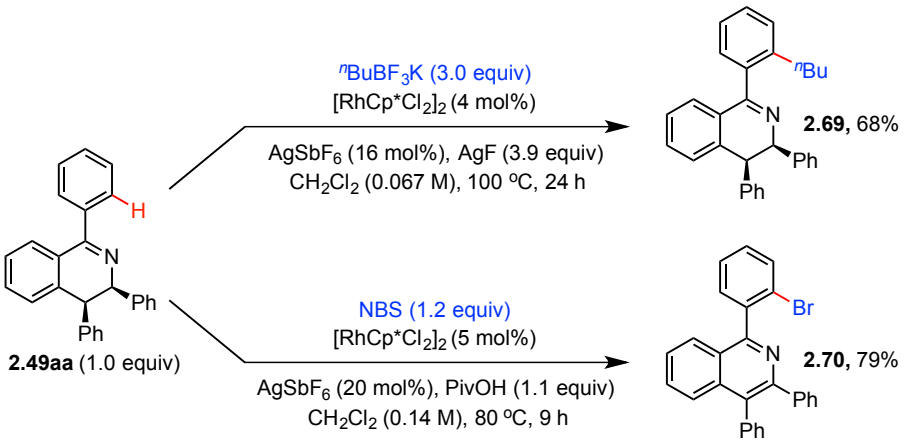
we were able to isolate a Rh(III) product with a cyclometalated DHIQ ligand (**2.68**) and characterized its solid-state structure by single-crystal X-ray diffraction. This {Cp*RhCl[η^2-(C,N)-DHIQ]} complex resulted from regioselective C-H activation of **2.49aa** at the *ortho* position of 1-phenyl instead of 3-phenyl substituent. Notably, a preliminary test reaction between the oxidative [4+2] annulation product **2.32** and $[Cp^*RhCl_2]_2$ under similar conditions failed to generate cyclometalation products. Such reactivity difference between **2.49aa** and **2.32** may result from the more rigid structure of isoquinoline than DHIQ, which led to more significant steric crowding by phenyl substituents and 1- and 3-positions that inhibits imine-directed aromatic C–H activation.



Scheme 2.27. Rh(III)-mediated regioselective cyclometalation

The Rh(III)-mediated regioselective C–H activation with **2.49aa** was further exploited in two catalytic transformations following reported procedures by Li[30] and Glorius,[31] both using $[Cp^*RhCl_2]_2$ as the catalyst precursor (Scheme 2.28). A coupling between **2.49aa** and the organoboron reagent ^{n}BuBF$_3$K gave alkylated DHIQ product **2.69** in 68% yield. Consistent with the stoichiometric cyclometalation result (Scheme 2.27), the *n*-butyl group was attached selectively at an *ortho*-position of the 1-phenyl group. By contrast, **2.49aa** underwent C–H bromination with the NBS reagent in same regioselectivity but dehydrogenated under the reaction conditions to give brominated isoquinoline product **2.70** in 74% yield. In another preliminary reactivity evaluation, we found that the isoquinoline compound **2.32** failed to

undergo C–H bromination under similar reaction conditions to form **2.70**, presumably due to the steric hindrance against cyclometalation as previously discussed. Thus, DHIQ products from current study could also be explored as isoquinoline precursors by tandem functionalization-dehydrogenation strategy.



Scheme 2.28. Rh(III)-catalyzed aromatic functionalizations via directed C-H activation

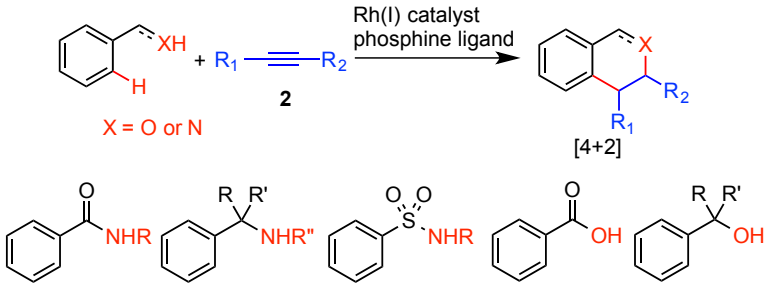
2.10. Conclusion

In summary, we have developed a single catalyst-based approach towards atom-efficient N-heterocycle construction by tandem C–H activation, alkyne coupling, and intramolecular alkene hydroamination. The mechanism-based catalyst development led to the combination of a cationic Rh(I) catalyst precursor and a bis(phosphine) ligand DPEphos, which promotes a redox-neutral [4+2] annulation between N-H aromatic ketimines and internal alkynes to form *cis*-3,4-disubstituted 3,4-dihydroisoquinolines (DHIQs) in high chemo-, regio- and stereoselectivity. With a proposed ligand-enabled intramolecular alkene hydroamination to introduce C3- and C4-chirality, this method can be potentially developed into an enantioselective version for asymmetric synthesis of poly-substituted chiral DHIQ building blocks towards highly valuable THIQ structures. The current strategy of combining metal-catalyzed C–H functionalization and alkene hydrofunctionalization represents a unified synthetic approach towards various 6-

membered benzoheterocycles by redox-neutral [4+2] annulation between aromatic compounds and alkynes.

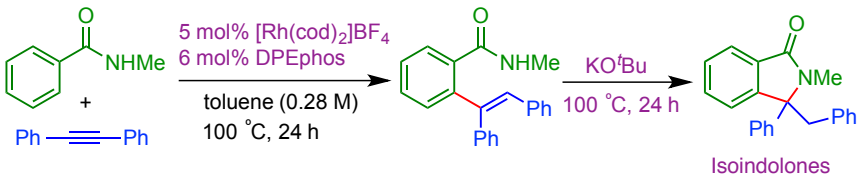
2.11. Future and ongoing studies

Acid or base-catalyzed isomerization of the *cis*-dihydroisoquinoline products is expected to promote formation of the more stable *trans*-dihydroisoquinolines. This transformation will be combined with the asymmetric catalysis strategy to develop separately enantioselective and diastereoselective reactions. Mean-while we also want to further investigate redox-neutral [4+2] annulations between various aromatic compounds containing functional groups such as amides, amines, sulfonamides, carboxylic acids and alcohols with alkynes for the controlled formation of each enantiomer of the N- or O- heterocycle products (Scheme 2.29).



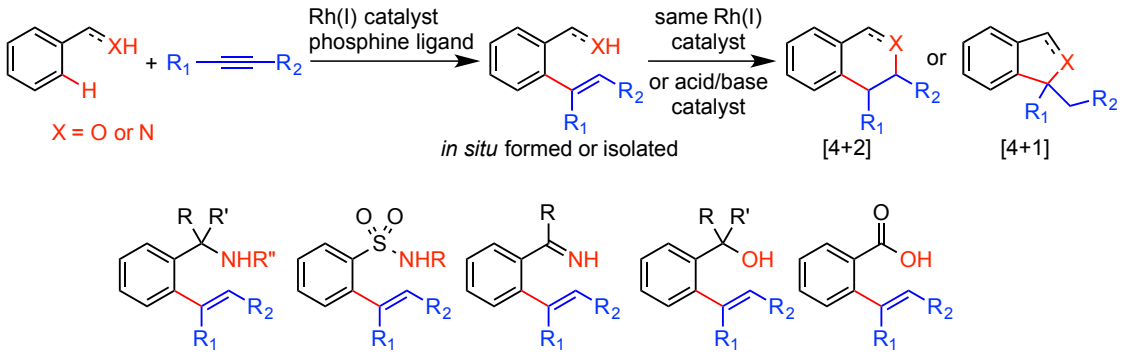
Scheme 2.29. Future directions for redox-neutral [4+2] annulation of various aromatic compounds and alkynes

We expanded our Rh(I) catalyst system for other aromatic compounds such as a N-methylbenzamide/alkyne coupling but to our surprise we got the acyclic hydroarylation product. A one-pot procedure is developed to transform this compound into an [4+1] annulation isoindolone product in the presence of NaO^{t}Bu as base additive (Scheme 2.30).



Scheme 2.30. Sequential one-pot [4+1] cyclization of amides and alkynes

Ongoing studies also include expansion of this hydroarylation product to its structural analogs to study their intramolecular alkene hydroamination reactivity for 5- or 6-membered N-heterocycle formation under Rh(I) or acid/base catalysis (Scheme 2.31).



Scheme 2.31. Other envisioned hydroarylation intermediate to be studied

2.12. Experimental procedures

2.12.1. General information

Unless otherwise noted, all manipulations were carried out under a nitrogen atmosphere using standard Schlenk-line or glovebox techniques. All glassware was oven-dried for at least 1 h prior to use. THF, toluene, ether, and hexane were degassed by purging with nitrogen for 45 min and dried with a solvent purification system (MBraun MB-SPS). DMF, dioxane, dimethoxyethane, dichloroethane, methanol, and ethanol were dried over activated 3 Å molecular sieves and degassed by purging with nitrogen. Other reagents and substrates were commercially available used as received, including unprotected forms of NHC ligands IPr, IMes, SIPr, and SIMes. TLC plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated by rotary evaporation at ~10 torr. Flash column chromatography was performed with 32–63 microns silica gel. GC analyses were performed on a Shimadzu GC-2010 with n-dodecane as the internal standard. ^{1}H NMR spectra were obtained on a 400 MHz spectrometer, and chemical shifts were recorded relative to residual protiated solvent. ^{13}C NMR

spectra were obtained at 100 MHz, and chemical shifts were recorded to the solvent resonance. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane (δ = 0 ppm). ^{19}F NMR spectra were obtained at 282.4 MHz, and all chemical shifts were reported in parts per million upfield of CF_3COOH (δ = -78.5 ppm). High-resolution mass spectra were obtained from a Bruker Daltronics BioTOF HRMS spectrometer.

2.12.2. General procedure for Rh(I)-catalyzed redox-neutral [4+2] annulation

2.12.2.1. Method A. for internal alkyne substrate scope

Into a 4 mL scintillation vial equipped with a magnetic stir bar was placed $[Rh(cod)_2]BF_4$ (5.6 mg, 0.014 mmol, 0.050 equiv), DPEphos (8.9 mg, 0.017 mmol, 0.060 equiv), and 1.0 mL of Toluene. Next, N-H ketimine **2.22** (0.28 mmol, 1.0 equiv) and internal alkyne **2.15** (0.31 mmol, 1.1 equiv) were transferred into the vial. The vial was sealed with a silicone-lined screw cap, transferred out of the glovebox, and stirred at 100 °C for 24 hours. After the reaction mixture was cooled to room temperature, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using neutral alumina. Isolated yields are based on the average of two runs under identical conditions.

2.12.2.2. Method B. for N-H Ketimine substrate scope

Into a 4 mL scintillation vial equipped with a magnetic stir bar was placed $[Rh(cod)_2]BF_4$ (5.7 mg, 0.014 mmol, 0.050 equiv), DPEphos (9.1 mg, 0.017 mmol, 0.060 equiv), and 1.0 mL of toluene. Next, N-H ketimine **2.22** (0.31 mmol, 1.1 equiv) and internal alkyne **2.15** (0.28 mmol, 1.0 equiv) were transferred into the vial. The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 100 °C for 24 hours. After the reaction mixture was cooled to room temperature, all volatile materials were removed under reduced pressure.

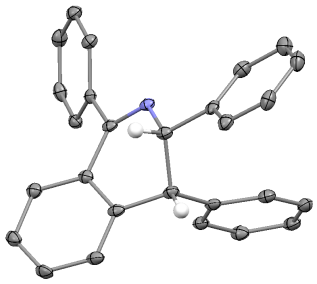
Further purification was achieved by flash-column chromatography using neutral alumina. Isolated yields are based on the average of two runs under identical conditions.

2.12.2.3. Method C. synthesis of cyclometalated Rh(III) complex 1.71

Into a 1 dram vial charged with a stir-bar was added $[Cp^*RhCl_2]_2$ (50 mg, 0.008 mmol), *cis*-1,3,4-triphenyl-3,4-dihydroisoquinoline (**2.49aa**, 0.18 mmol), and sodium acetate (0.20 mmol). Dichloromethane (2.0 mL) was added and the resulting solution was stirred at room temperature for 60 hrs. After Celite filtration, all volatiles were removed under reduced pressure to afford a dark red-colored powder that contains the mixture of complex **1.71** and remaining reactants. Further crystallization was carried out in a mixed solvent system of chloroform and layered with pentane to produce a small amount of single crystals suitable for X-ray diffraction .

2.12.3. Supplementary figures for ORTEP diagrams for 2.49aa, 2.49an, 2.49na and 2.66

ORTEP diagram (30% probability) of *cis*-1,3,4-triphenyl-3,4-dihydroisoquinoline (**2.49aa**), *cis*-3-ethyl-1,4-diphenyl-3,4-dihydroisoquinoline (**2.49an**) and *cis*-1-methyl-3,4-diphenyl-5-trifluoro…methyl-3,4-dihydroisoquinoline (**2.49na**).



2.49aa

Figure 2.1. ORTEP diagram of *cis*-1,3,4-triphenyl-3,4-dihydroisoquinoline (**2.49aa**)

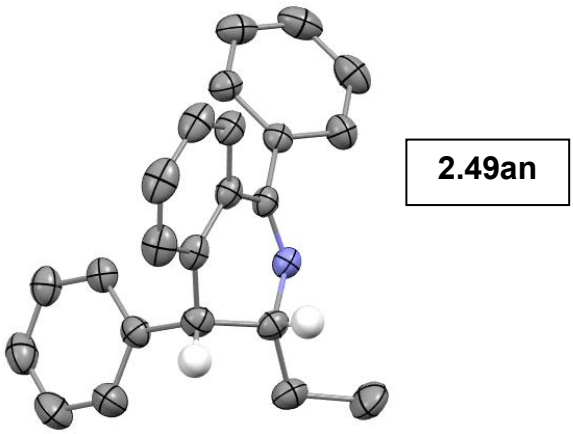


Figure 2.2. ORTEP diagram of *cis*-1-methyl-3,4-diphenyl-5-trifluoromethyl-3,4-dihydroisoquinoline (**2.49an**)

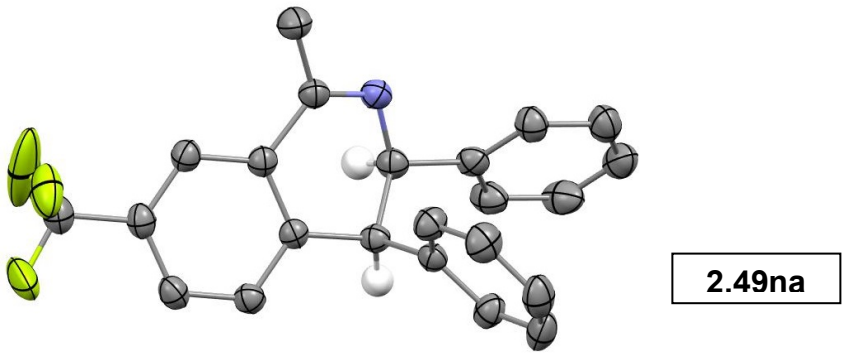


Figure 2.3. ORTEP diagram of *cis*-1-methyl-3,4-diphenyl-5-trifluoromethyl-3,4-dihydroisoquinoline (**2.49na**)

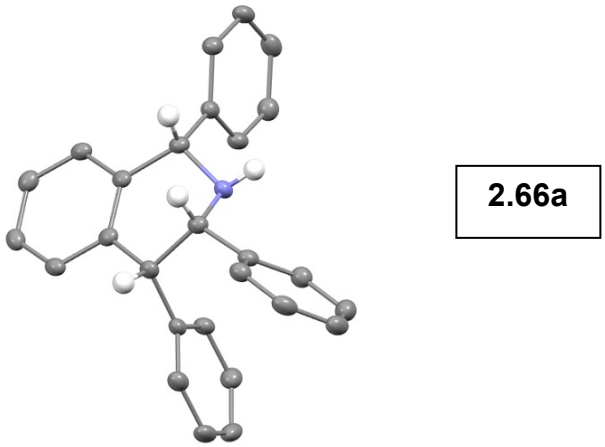


Figure 2.4. ORTEP diagram of all-*cis* diastereomer of 1,3,4-triphenyl-1,2,3,4-THIQ (**2.66a**)

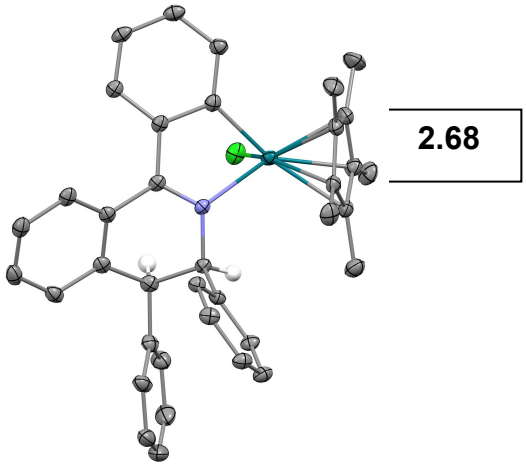
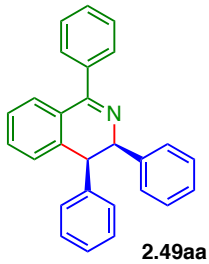


Figure 2.5. ORTEP diagram of cyclometalated Cp*Rh(III) complex (**2.68**)

Table 2.4. Summary of cell parameters, data collection and structural refinements for 2.49aa, 2.49an, 2.49na, 2.66a and 2.68.

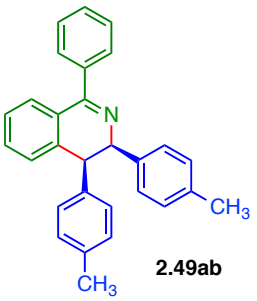
	2.49aa	**2.66a**	**2.49na**	**2.68**	**2.49an**
Formula	$C_{27}H_{21}N$	$C_{27}H_{23}N.1/2\ CHCl_3$	$C_{23}H_{18}F_3N$	$C_{38}H_{35}D_2Cl_3NRh$	$C_{23}H_{21}N$
FW	359.45	421.14	365.38	718.95	311.41
cryst. size_max [mm]	0.162	0.208	0.27	0.12	0.238
cryst. size_mid [mm]	0.095	0.2	0.2	0.09	0.191
cryst. size_min [mm]	0.045	0.075	0.12	0.02	0.161
cryst. system	monoclinic	triclinic	triclinic	triclinic	orthorhombic
Space Group, Z	$P2_1/n$, 4	P-1, 4	P-1, 2	P-1, 4	P 2ac 2ab
a [Å]	9.91151(4)	9.5479(4)	8.0095(2)	12.0885(6)	9.4007(3)
b [Å]	7.5788(3)	11.8989(5)	10.4347(2)	13.8960(6)	12.4572(4)
c [Å]	25.8148(13)	20.1528(9)	11.6372(3)	21.7793(11)	15.2327(6)
α [Å]	90.0	86.386(2)	76.4770(10)	72.428(3)	90.0
ß [Å]	95.699(4)	80.950(2)	86.8240	84.272(4)	90.0
γ [Å]	90.0	71.372(2)	76.469(2)	73.638(3)	90.0
V [$Å^3$]	1929.6(2)	2142.40(16)	919.39(4)	3346.1(3)	1783.85(11)
ρ_{calc} [g/cm^3]	1.237	1.306	1.320	1.427	1.160
μ [mm^{-1}]	0.542	2.244	0.815	6.531	0.506
F(000)	760	884	380	1472	664
no of measured refl.	10642	19642	11205	26949	6615
no of indep. refl.	3277	7379	3149	11084	2761
no of refl. (I ≥ 2σ)	2729	6556	2499	9133	2502
R1/wR2 (I ≥ 2σ)[a] [%]	8.89/21.5	3.42/8.70	3.88/10.1	6.65/17.5	3.30/8.18
R1/wR2 (all data) [%]	10.2/22.1	3.95/9.04	4.99/10.9	8.12/18.5	3.78/8.5

2.12.4. Analytical data of reported products



2.49aa

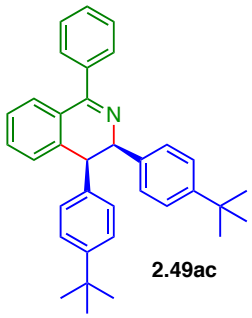
***cis*-1,3,4-Triphenyl-3,4-dihydroisoquinoline (2.49aa):** Prepared from benzophenone imine (**2.22a**) and 1,2-diphenylethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49aa** as a white solid (87 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.38 (d, 1H, *J* = 6.0 Hz), 5.21 (d, 1H, *J* = 6.0 Hz), 6.66 (d, 2H, *J* = 6.4 Hz), 7.02–7.09 (m, 3H),7.24-7.27 (m, 5H), 7.31 (d, 1H, J = 7.6 Hz), 7.38 (d, 1H, *J* = 7.6 Hz), 7.44 (d, 1H, *J* = 8.0 Hz), 7.52-7.53 (m, 4H), 7.81-7.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.9, 141.63, 141.60, 139.3, 137.8, 131.6, 129.8, 129.7, 129.34, 129.32, 128.6, 128.53, 128.50, 128.4, 128.1, 127.8, 127.5, 126.9, 126.7, 66.5, 49.2. HRMS: calcd for $C_{27}H_{22}N^{+}$ 360.1747, found 360.1758.



2.49ab

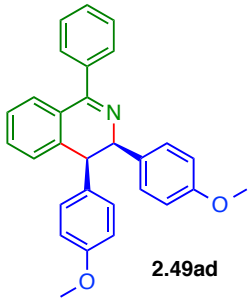
***cis*-1-Phenyl-3,4-di-*p*-tolyl-3,4-dihydroisoquinoline (2.49ab):** Prepared from benzophenone imine(**2.22a**) and 1,2-di-*p*-tolylethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ab** as a white solid (95 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.17, (s, 3H), 2.30 (s, 3H), 4.29 (d, 1H, *J* = 6.0 Hz), 5.09 (d, 1H, *J* = 6.0 Hz), 6.51 (d, 2H, *J* = 8.0 Hz), 6.79 (d, 2H, *J* = 8.0Hz), 7.00 (d, 2H, *J* = 8.0 Hz), 7.09 (d, 2H, *J* = 8.4 Hz), 7.24 (d, 1H, *J* = 10.0 Hz), 7.32 (d, 1H, *J* = 6.4 Hz) 7.38 (d, 1H, *J* = 6.0 Hz), 7.43-7.47 (m, 4H), 7.73 (d, 2H, *J* =

8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.6, 141.9, 139.3, 138.4, 138.2, 136.2, 136.1, 134.7, 131.4, 129.7, 129.6, 129.3, 128.7, 128.5, 128.4, 128.3, 128.29, 128.28, 127.2, 66.2, 48.7, 21.4, 21.1. HRMS: calcd for $C_{29}H_{26}N^+$ 388.2060, found 388.2045.



2.49ac

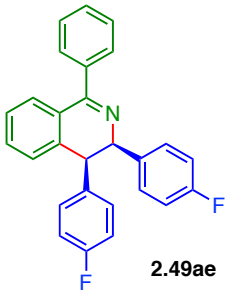
***cis*-3,4-bis(4-(*tert*-butyl)phenyl)-1-phenyl-3,4-dihydroisoquinoline (2.49ac):** Prepared from benzophenone imine(**2.22a**) and 1,2-bis(4-(*tert*-butyl)phenyl)ethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ac** as a yellow solid (109 mg, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23, (s, 9H), 1.33 (s, 9H), 4.33 (d, 1H, J = 5.6 Hz), 5.16 (d, 1H, J = 6.0 Hz), 6.55 (d, 2H, J = 8.4 Hz), 7.01 (d, 2H, J = 8.4Hz), 7.10 (d, 2H, J = 8.4 Hz), 7.23-7.25 (m, 2H), 7.29-7.39 (m, 2H), 7.46-7.53 (m, 5H), 7.80 (d, 2H, J = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.4, 149.5, 149.1, 141.6, 139.2, 138.2, 134.4, 131.2, 129.4, 129.2, 129.1, 128.4, 128.3, 128.2, 128.1, 128.0, 127.0, 124.5, 124.3, 66.1, 48.5, 34.4, 34.2, 31.5, 31.3. HRMS: calcd for $C_{35}H_{37}N^+$ 472.3004, found 472.3017.



2.49ad

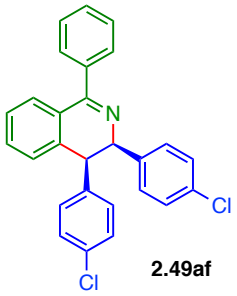
***cis*-3,4-Bis(4-methoxyphenyl)-1-phenyl-3,4-dihydro-isoquinoline (2.49ad):** Prepared from benzophenone imine (**2.22a**) and 1,2-bis(4-methoxyphenyl)ethyne by the general procedure A.

Chromatography (3% ethyl acetate in hexane) gave **2.49ad** as a light-yellow oil (104mg, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.78 (s, 3H), 4.28 (d, 1H, *J* = 6.0 Hz), 5.10 (d, 1H, *J* = 6.0 Hz), 6.58 (s, 4H), 6.78 (d, 2H, *J* = 8.4 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.26 (d, 1H, *J* = 7.2 Hz), 7.24 (d, 2H, *J* = 7.6 Hz), 7.41-7.43 (m, 2H), 7.47-7.76 (m, 5H), 7.77 (d, 2H, *J* = 9.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.7, 158.6, 158.4, 141.9, 139.4, 133.8, 131.5, 130.8, 130.6, 129.9, 129.70, 129.65, 129.3, 129.2, 128.5, 128.4, 127.3, 113.5, 113.3, 65.9, 55.5, 55.3, 48.5. HRMS: calcd for $C_{29}H_{26}NO_2^+$ 420.1958, found 428.1970.



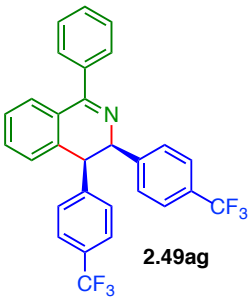
2.49ae

***cis*-3,4-Bis(4-fluorophenyl)-1-phenyl-3,4-dihydroisoquinoline (2.49ae):** Prepared from benzophenone imine (**2.22a**) and 1,2-bis(4-fluorophenyl)ethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ae** as a white solid (104 mg, 95%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.31 (d, 1H, *J* = 5.6 Hz), 5.16 (d, 1H, *J* = 6.0 Hz), 6.61 (t, 2H, *J* = 8.4 Hz), 6.72 (t, 2H, *J* = 8.8Hz), 6.96 (t, 2H, *J* = 8.8 Hz), 7.22-7.30 (m, 3H), 7.32 (s, 1H), 7.40 - 7.54 (m, 5H), 7.80 (d. 2H, *J* = 4.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.2, 163.3 (d, *J*(C,F) = 244.5 Hz), 163.1 (d, *J*(C,F) = 245.5 Hz), 141.3, 139.1, 137.5 (d, *J* = 3.0 Hz), 133.3 (d, *J* = 3.0 Hz), 131.9, 131.2 (d, *J* = 7.0 Hz), 130.1 (d, *J* = 8.0 Hz), 129.9, 129.3, 129.1, 128.7, 128.6, 128.5, 127.7, 115.1 (d, *J* = 21.1 Hz), 114.9 (d, *J* = 21.3 Hz), 65.6, 48.5. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -116.08, -116.09. HRMS: calcd for $C_{27}H_{20}F_2N^+$ 369.1558, found 369.1539.



2.49af

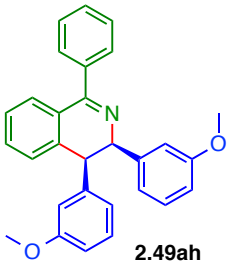
***cis*-3,4-Bis(4-chlorophenyl)-1-phenyl-3,4-dihydroisoquinoline (2.49af):** Prepared from benzophenone imine (**2.22a**) and 1,2-bis(4-chlorophenyl)ethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49af** as a white solid (104 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.28 (d, 1H, *J* = 6.0 Hz), 5.13 (d, 1H, *J* = 6.0 Hz), 6.56 (d, 2H, *J* = 8.4 Hz), 6.99 (d, 2H, *J* = 8.4 Hz), 7.24-7.29 (m, 5H), 7.38–7.49 (m, 2H), 7.44 (d, 1H, *J* = 8.8 Hz), 7.50–7.52 (m, 4H), 7.76 (d, 2H, *J* = 7.6 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 168.2, 140.9, 140.2, 138.9, 135.9, 132.8, 132.7, 131.9, 130.9, 129.99, 129.94, 129.3, 129.0, 128.7, 128.6, 128.44, 128.38, 128.2, 127.8, 65.5, 48.4. HRMS: calcd for $C_{27}H_{20}Cl_2N^+$ 428.0967, found 428.0952.



2.49ag

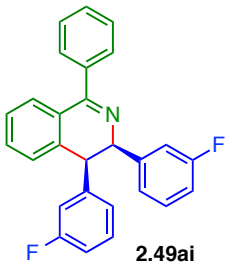
***cis*-1-Phenyl-3,4-bis(4-trifluoromethylphenyl)-3,4-dihydro-isoquinoline (2.49ag):** Prepared from benzophenone imine (**2.22a**) and 1,2-bis(4-triflormethylphenyl)ethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ag** as a white solid (126 mg, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.40 (d, 1H, *J* = 6.0 Hz), 5.25 (d, 1H, *J* = 6.0 Hz), 6.74 (d, 2H, *J* = 8.0 Hz), 7.26 – 7.28 (m, 3H), 7.42 – 7.48 (m, 3H), 7.49-7.56 (m, 7H), 7.78 (d,

2H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.3, 145.4, 141.2, 140.3, 138.5, 132.4 (q, J = 69.4 Hz), 131.82, 131.75, 130.8 (q, J = 57.3 Hz), 129.9, 129.4 (q, J = 22.1 Hz), 128.8, 128.7, 128.5 (q, J = 18.1 Hz), 127.9, 125.7 (q, J(C,F) = 271.6 Hz), 125.4 (q, J(C,F) = 252.5 Hz), 125.1 (q, J = 6.0 Hz), 124.8 (q, J = 3.0 Hz), 122.9, 122.7, 65.5, 48.5. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -15.3, -14.9. HRMS: $C_{29}H_{20}F_6N^+$ 496.1494, found 496.1474.



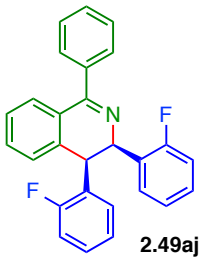
2.49ah

***cis*-3,4-Bis(3-methoxyphenyl)-1-phenyl-3,4-dihydro-isoquinoline (2.49ah):** Prepared from benzophenone imine (**2.22a**) and 1,2-bis(3-methoxyphenyl)ethyne by the general procedure A. Chromatography (3% ethyl acetate in hexane) gave **2.49ah** as a white solid (90 mg, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.50 (s, 3H), 3.61 (s, 3H), 4.31 (d, 1H, J = 6.0 Hz), 5.15 (d, 1H, J = 6.0 Hz), 6.18 (s, 1H), 6.25 (d, J = 7.6 Hz), 6.60 (d, 1H, J = 6.8 Hz), 6.77 (s, 2H), 6.89-6.95 (m, 2H), 7.16 -7.23 (m, 1H), 7.29-7.37 (m, 2H), 7.42- 7.50 (m, 5H), 7.78 (d, 2H, J = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.8, 159.7, 158.9, 143.4, 141.4, 139.3, 131.6, 129.7, 129.3, 129.23, 129.20, 128.9, 128.7, 128.5, 128.4, 127.4, 122.2, 120.9, 115.1, 114.0, 113.2, 112.8, 66.4, 55.4, 55.1, 49.1. HRMS: calcd for $C_{29}H_{26}NO_2^+$ 420.1958, found 420.1964.



2.49ai

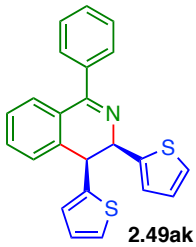
***cis*-3,4-bis(3-fluorophenyl)-1-phenyl-3,4-dihydroisoquinoline (2.49ai):** Prepared from benzophenone imine (**2.22a**) and 1,2-bis(3-fluorophenyl)ethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ai** as a white solid (96 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.35 (d, 1H, *J* = 6.0 Hz), 5.19 (d, 1H, *J* = 6.0 Hz), 6.61-6.47 (m, 2H), 6.76 (t, 1H, *J* = 8.4 Hz),6.93-7.01 (m, 2H), 7.08-7.16 (d, 2H), 7.24-7.29 (m, 1H), 7.32 (d, 1H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 7.6 Hz), 7.47-7.55 (m, 5H), 7.81-7.84 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.2, 164.4 (d, *J*(C,F) = 243.7 Hz), 161.9 (d, *J*(C,F) = 244.1 Hz), 144.5 (d, *J* = 7.8 Hz), 140.8, 140.2 (d, *J* = 7.2 Hz), 131.9,130.0, 129.7, 129.6, 129.4, 129.3, 129.1, 114.0 (d, *J* = 10.9 Hz), 113.8 (d, *J* = 10.7 Hz), 128.8, 128.61, 128.55, 127.9, 125.3 (d, *J* = 2.5 Hz), 116.6 (d, *J* = 22.2 Hz), 115.7 (d, *J* = 22.3 Hz), 114.0 (d, 10.9 Hz), 113.8 (d, 10.7 Hz), 65.6, 48.8. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -113.4, -113.6. HRMS: calcd for $C_{27}H_{22}N^{+}$ 396.1558, found 396.1565.



2.49aj

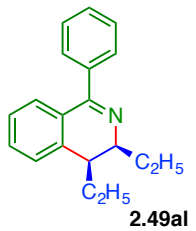
***cis*-3,4-bis(2-fluorophenyl)-1-phenyl-3,4-dihydroisoquinoline (2.49aj):** Prepared from benzophenone imine (**2.22a**) and 1,2-bis(2-fluorophenyl)ethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49aj** as a white solid (88 mg, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.08 (d, 1H, *J* = 6.4 Hz), 5.65 (d, 1H, *J* = 6.4 Hz), 6.78 (t, 1H, *J* = 8.4 Hz), 6.99-7.01 (m, 3H),7.07-7.18 (m, 2H), 7.24-7.31 (m, 2H), 7.42-7.47 (m, 2H), 7.42-7.47 (m, 2H), 7.52-7.57 (m, 1H), 7.59-7.69 (m, 4H), 7.89-7.93 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.4, 162.1 (d, *J*(C,F) = 243.5 Hz), 161.6 (d, *J*(C,F) = 244.6 Hz), 140.3, 139.1, 138.3 (d, J = 3.1 Hz), 137.7, 132.5, 131.8, 130.8 (d, *J* = 4.8 Hz), 130.6 (d, *J* = 3.6 Hz), 130.2, 129.7,

129.2, 129.1, 128.9, 128.5, 128.4, 127.6, 125.4, 115.1 (d, J = 23.4 Hz), 114.5 (d, J = 21.7 Hz), 59.2, 38.2. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -116.7, -120.1. HRMS: calcd for $C_{27}H_{22}N^+$ 396.1564, found 360.1577.



2.49ak

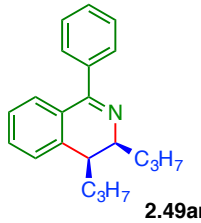
***cis*-1-Phenyl-3,4-di(thiophen-2-yl)-3,4-dihydroisoquinoline (2.49ak):** Prepared from benzophenone imine (**2.22a**) and 1,2-di(thiophen-2-yl)ethyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ak** as a white solid (92 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.76 (d, 1H, J = 5.2 Hz), 5.39 (d, 1H, J = 5.6 Hz), 6.53 (d, 1H, J = 3.2 Hz), 6.75 (t, 1H, J = 4.8Hz), 7.00–7.06 (m, 2H), 7.15–7.22 (m, 2H), 7.38–7.40 (m, 2H), 7.46-7.52 (m, 5H), 7.81 (d, 2H, J = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.9, 145.9, 141.7, 140.5, 138.7, 133.9, 135.2, 131.7, 129.9, 129.5, 128.8, 128.5, 128.1, 127.9, 126.9, 126.7, 126.4, 125.0, 124.7, 62.4, 45.2. HRMS: calcd for $C_{23}H_{18}NS_2^+$ 372.0875, found 372.0859.



2.49al

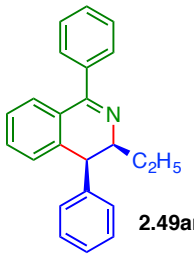
***cis*-3,4-Diethyl-1-phenyl-3,4-dihydroisoquinoline (2.49al):** Prepared from benzophenone imine (**2.22a**) and 3-hexyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49al** as a light yellow liquid (59 mg, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.83 (t, 3H, J = 7.2 Hz), 1.13 (t, 3H, J = 7.2 Hz), 1.35-1.43 (m, 1H), 1.64 (q, 1H, J = 7.2Hz), 1.83 (q, 1H, J = 6.8 Hz), 1.99-2.08 (m, 1H), 2.57 (sept, 1H, J = 10.0 Hz), 3.39 (d, 1H, J = 5.2 Hz), 7.20 (t, 3H, J

= 7.2 Hz), 7.34 (d, 1H, *J* = 6.8 Hz), 7.39 (d, 3H, *J* = 4.8 Hz), 7.59 (d, 2H, *J* = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.7, 143.7, 139.4, 130.2, 129.4, 129.1, 128.7, 128.5, 128.4, 128.2, 126.7, 62.8, 41.7, 26.1, 19.5, 12.4, 11.7. HRMS: calcd for $C_{19}H_{22}N^+$ 264.1747, found 264.1757.



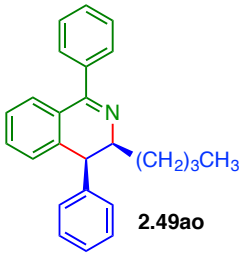
2.49am

***cis*-3,4-Dipropyl-1-phenyl-3,4-dihydroisoquinoline (2.49am):** Prepared from benzophenone imine (**2.22a**) and 4-octyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49am** as a light yellow liquid (68 mg). This product was contaminated with ~10% of the corresponding isoquinoline byproduct (generated by product decomposition during separation and purification), and the yield for **2.49am** was estimated to be 76% by ^{1}H NMR analysis. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 3H, *J* = 7.2 Hz), 1.01 (t, 3H, *J* = 7.2 Hz), 1.14 (t, 1H, *J* = 7.6 Hz), 1.21-1.32 (m, 2H), 1.38-1.44 (m, 2H), 1.49-1.60 (m, 2H), 1.72-1.77 (m, 1H), 2.66-2.69 (m, 1H), 3.39-3.54 (m, 1H), 7.20-7.22 (m, 2H), 7.34 (d, 1H, *J* = 7.2 Hz), 7.40 (d, 2H, *J* = 6.8 Hz), 7.47 (d, 1H, *J* = 8.0 Hz), 7.60 (m, 2H), 7.80 (d, 1H, *J* = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.7, 144.2, 139.4, 137.8, 132.6, 130.3, 129.4, 129.1, 128.4, 128.2, 126.6, 60.9, 40.1, 29.9, 28.9, 20.8, 20.3, 14.6, and 14.5. HRMS: calcd for $C_{21}H_{26}N^+$ 292.2060, found 292.2057.



2.49an

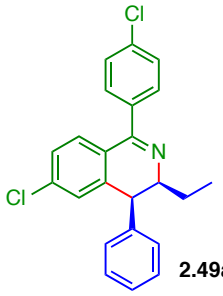
***cis*-3-Ethyl-1,4-diphenyl-3,4-dihydroisoquinoline (2.49an):** Prepared from benzophenone imine (**2.22a**) and 1-phenyl-1-butyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49an** as a light yellow liquid (75 mg). This product was contaminated with ~12% of the corresponding isoquinoline byproduct (generated by product decomposition during separation and purification), and the yield for **2.49an** was estimated to be 76% by ^{1}H NMR analysis. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, J = 7.6 Hz), 1.79 (qd, 2H, J_1 = 7.6 Hz, J_2 = 2.4 Hz), 3.78 (q, 1H, J = 6.0 Hz), 4.07 (d, 1H, J = 5.6Hz), 7.14-7.19 (m, 5H), 7.27–7.30 (m, 2H), 7.37–7.42 (m, 2H), 7.46-7.49 (m, 4H), 7.73–7.75 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.5, 142.7, 139.4, 131.4, 130.4, 129.6, 129.3, 129.2, 128.8, 128.52, 128.48, 128.4, 128.3, 127.1, 126.9, 63.5, 46.5, 26.9, 11.7. HRMS: calcd for $C_{23}H_{22}N^{+}$ 312.1747, found 312.1732.



2.49ao

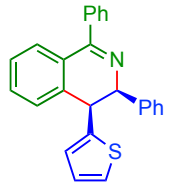
***cis*-3-Butyl-1,4-diphenyl-3,4-dihydroisoquinoline (2.49ao):** Prepared from benzophenone imine (**2.22a**) and 1-phenyl-1-hexyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ao** as a light yellow liquid (78 mg). This product was contaminated with ~10% of the corresponding isoquinoline byproduct (generated by product decomposition during separation and purification), and the yield for **2.49ao** was estimated to be 75% by ^{1}H NMR analysis. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, J = 7.6 Hz), 1.41-1.44 (m, 2H), 1.52-1.61 (m, 1H), 1.79 - 1.83 (m, 3H), 3.80 (dt, 1H, J_1 = 5.6 Hz, J_2 = 3.2 Hz), 4.07 (d, 1H, J = 6.0 Hz), 7.19-7.21 (m, 5H), 7.29 (d, 2H, J = 6.0 Hz), 7.37 (td, 2H, J_1 = 7.2 Hz, J_2 = 3.2 Hz), 7.48 (t,

3H, *J* = 6.0 Hz), 7.73-7.75 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.5, 142.8, 139.4, 139.3, 132.7, 131.4, 130.3, 129.7, 129.31, 129.25, 128.8, 128.5, 128.4, 127.1, 126.9, 61.8, 46.8, 33.7, 29.4, 23.1, 14.5. HRMS: calcd for $C_{25}H_{26}N^+$ 340.2060, found 340.2053.



2.49ap

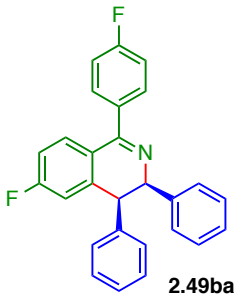
***cis*-6-chloro-1-(4-chlorophenyl)-3-ethyl-4-phenyl-3,4-dihydroisoquinoline (2.49ap):** Prepared from bis(4-chlorophenyl)methanimine and 1-phenyl-1-butyne by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49ap** as a white solid (92 mg, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.19 (t, 3H, *J* = 7.2 Hz), 1.79 (m, 2H), 3.67 (q, 1H, *J* = 7.6 Hz), 4.07 (d, 1H, *J* = 6.0 Hz), 7.13-7.16 (m, 2H), 7.21 -7.24 (m, 3H),7.29-7.33 (m, 3H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.67 (d, 2H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.4, 144.4, 138.1, 137.1, 137.0, 135.8, 131.4, 130.3, 129.3, 128.9, 128.7, 128.5, 127.3, 127.1, 126.6, 63.2, 46.2, 26.5, 11.5 HRMS: calcd for $C_{23}H_{20}Cl_2N^+$ 380.0973, found 380.0969.



2.49aq, 66% (4:1)

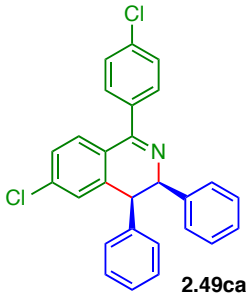
***cis*-1,3-diphenyl-4-(thiophen-2-yl)-3,4-dihydroisoquinoline (2.49aq):** Prepared from di-*p*-tolylmethanimine and 2-(phenylethynyl)thiophene by the general procedure A. Chromatography (1% ethyl acetate in hexane) gave **2.49aq** as a white solid (66 mg, 66%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.70 (d, 1H, *J* = 5.6 Hz), 5.22 (d, 1H, *J* = 5.6 Hz), 6.34 (d, 1H, *J* = 3.2 Hz), 6.75-6.77

(m, 1H), 7.01 (d, 1H, J = 5.2 Hz), 7.29 -7.46 (m, 6H),7.55-7.59 (m, 7H), 7.89-7.92 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.9, 141.9, 141.6, 140.6, 139.1, 131.4, 129.6, 129.3, 128.5, 128.31, 128.28, 128.1, 127.9, 127.7, 126.9, 126.2, 126.1, 124.5, 65.6, 45.0 HRMS: calcd for $C_{25}H_{19}NS^+$ 366.1317, found 366.1317.



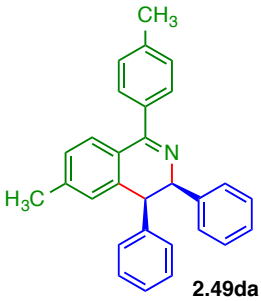
2.49ba

***cis*-6-Fluoro-1-(4-fluorophenyl)-3,4-diphenyl-3,4-dihydroisoquinoline (2.49ba):** Prepared from 4,4'-difluoro benzophenone imine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49ba** as a white solid (101 mg, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$): ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.30 (d, 1H, J = 6.0 Hz), 5.13 (d, 1H, J = 6.0 Hz), 6.57 (d, 2H, J = 8.8 Hz), 6.98-7.08 (m, 5H), 7.14-7.24 (m, 7H), 7.44-7.48 (m, 1H), 7.73-7.76 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.8, 165.5 (d, J(C,F) = 254.5 Hz), 165.2 (d, J(C,F) = 249.5 Hz), 144.7 (d, J = 8.1 Hz), 140.9, 136.9, 135.1 (d, J = 3.0 Hz), 131.2 (d, J = 9.1 Hz), 130.6 (d, J = 8.1 Hz), 129.6, 128.5, 128.1, 127.9, 127.1 (d, J = 7.0 Hz), 125.6 (d, J = 3.0 Hz), 115.7, 115.5, 114.5, 114.3, 66.1, 49.3. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -29.7 (s, 1F), -33.9 (s, 1F). HRMS: calcd for $C_{27}H_{20}F_2N^+$ 396.1558, found 396.1559.



2.49ca

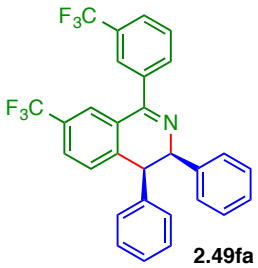
***cis*-6-Chloro-1-(4-chlorophenyl)-3,4-diphenyl-3,4-dihydroisoquinoline (2.49ca):** Prepared from 4,4'-dichlorobenzophenone imine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49ca** as a white solid (104 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.36 (d, 1H, *J* = 5.6 Hz), 5.17 (d, 1H, *J* = 6.0 Hz), 6.60 (d, 2H, *J* = 7.2 Hz), 7.04-7.11 (m, 3H), 7.21-7.29 (m, 5H), 7.33-7.45 (m, 3H), 7.49 (d, 2H, *J* = 8.4 Hz), 7.73 (d, 2H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.8, 143.3, 140.6, 137.3, 136.9, 136.6, 135.9, 130.4, 129.4, 129.3, 128.7, 128.6, 128.3, 127.9, 127.8, 127.6, 127.1, 126.9, 126.8, 66.1, 44.8. HRMS: calcd for $C_{27}H_{20}Cl_2N^+$ 428.0967, found 428.0973.



2.49da

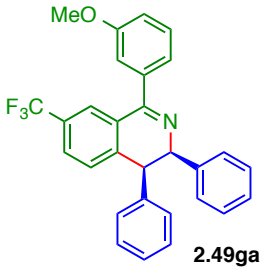
***cis*-6-methyl-3,4-diphenyl-1-(*p*-tolyl)-3,4-dihydroisoquinoline (2.49da):** Prepared from di-*p*-tolylmethanimine and diphenylacetylene by the general procedure A. Chromatography (0.5% ethyl acetate in hexane) gave **2.49da** as a white solid (75 mg, 70%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.49 (S, 3H), 2.59 (m, 3H), 3.67 (q, 1H, *J* = 7.6 Hz), 4.07 (d, 1H, *J* = 6.0 Hz), 7.13-7.16 (m, 2H), 7.21 -7.24 (m, 3H),7.29-7.33 (m, 3H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.67 (d, 2H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.4, 144.4, 138.1, 137.1, 137.0, 135.8, 131.4, 130.3,

129.3, 128.9, 128.7, 128.5, 127.3, 127.1, 126.6, 63.2, 46.2, 26.5, 11.5 HRMS: calcd for $C_{29}H_{25}N^+$ 388.2065, found 388.2073.



2.49fa

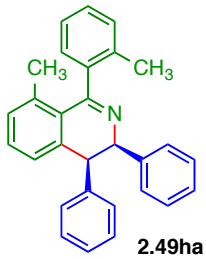
***cis*-3,4-Diphenyl-7-trifluoromethyl-1-(3-trifluoromethylphenyl)-3,4-dihydroisoquinoline (2.49fa):** Prepared from 3,3'-bis(trifluoro-methyl) benzophenone imine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49fa** as a white solid (129 mg, 93%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.45 (d, 1H, *J* = 6.4 Hz), 5.22 (d, 1H, *J* = 6.0 Hz), 6.60 (d, 2H, *J* = 5.6 Hz), 7.02-7.11 (m, 3H), 7.24-7.26 (m, 5H), 7.47 (d, 1H, *J* = 8.0 Hz), 7.66-7.83 (m, 4H), 7.96 (d, 1H, *J* = 8.0 Hz), 8.11 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.4, 148.9, 145.9, 145.3, 140.5 (q, J = 28.1 Hz), 139.9 (q, *J* = 29.2 Hz), 133.9, 132.1, 129.9(q, J = 10.9 Hz), 129.4, 129.3, 129.0, 128.3, 128.0, 127.9, 127.1 (q, *J* = 10.1 Hz), 125.9 (q, *J* = 3.0 Hz), 125.3 (q, *J*(C,F) = 272.6 Hz), 125.1 (q, *J*(C,F) = 272.6 Hz), 124.4 (q, *J* = 3.0 Hz), 119.9, 119.7, 66.1, 48.6. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -15.0 (s, 1F), -14.9 (s, 1F). HRMS: calcd for $C_{29}H_{19}F_6NNa^+$ 518.1314, found 518.1327.



2.49ga

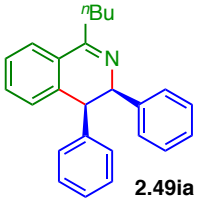
***cis*-1-(3-Methoxyphenyl)-3,4-diphenyl-7-trifluoromethyl-3,4-dihydroisoquinoline (2.49ga):** Prepared from 3-trifluoromethyl-3'-methoxy benzophenone imine and 1,2-diphenylethyne

(**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49ga** as a light yellow liquid (112 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 4.39 (d, 1H, *J* = 6.0 Hz), 5.17 (d, 1H, *J* = 6.0 Hz), 6.60 (d, 2H, *J* = 6.8 Hz), 7.00-7.10 (m, 4H), 7.22-7.24 (m, 5H), 7.31 (d, 2H, *J* = 4.8 Hz), 7.39 (t, 2H, *J* = 8.4 Hz), 7.67 (d, 1H, J = 8.0 Hz), 7.79 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.3, 159.9, 145.2, 140.5, 139.5, 136.5, 131.2, 131.1, 130.5, 130.3 (q, *J* = 14.1 Hz), 128.9, 128.6, 128.3, 128.5, 127.9, 127.7, 127.4 (q, *J* = 8.1 Hz), 124.9 (q, *J* = 4.0 Hz), 122.5 (q, *J*(C,F) = 271.6 Hz), 121.3, 116.0, 114.2, 65.9, 55.5, 48.8. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.4 (s, 1F). HRMS: calcd for $C_{29}H_{23}F_3NO^+$ 458.1726, found 458.1732.



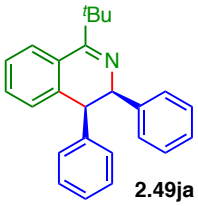
2.49ha

***cis*-8-Methyl-3,4-diphenyl-1-(*o*-tolyl)-3,4-dihydroisoquinoline (2.49ha):** Prepared from di-*o*-tolylmethyleneamine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49ha** as a white solid (83 mg). This product was contaminated with ~15% of the corresponding isoquinoline byproduct (generated via product decomposition during separation and purification), and the yield for **2.49ha** was estimated to be 66% by ^{1}H NMR analysis (see Figure 54). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 3H), 2.46 (s, 3H), 4.31 (d, 1H, *J* = 5.6 Hz), 5.14 (d, 1H, *J* = 5.6 Hz), 6.68 (d, 2H, *J* = 6.8 Hz), 6.97 (t, 4H, *J* = 7.6Hz), 7.11-7.14 (m, 2H), 7.21-7.23 (m, 5H), 7.27-7.29 (m, 2H), 7.33 (d, 2H, *J* = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.7, 143.3, 141.9, 141.8, 137.8, 136.8, 131.6, 131.4, 130.9, 130.4, 130.0, 129.7, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 126.8, 126.7, 126.2, 125.9, 65.4, 50.1, 22.4, 20.8. HRMS: calcd for $C_{29}H_{26}N^+$ 388.2060, found 388.2073.



2.49ia

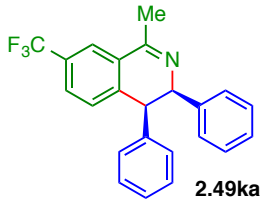
***cis*-1-Butyl-3,4-diphenyl-3,4-dihydroisoquinoline (2.49ia):** Prepared from 1-phenyl-pentylideneamine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49ia** as a light yellow liquid (80 mg, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.02 (t, 3H, *J* = 7.2 Hz), 1.53 (sext, 2H, *J* = 7.6 Hz), 1.78-1.93 (m, 2H), 2.91-3.05 (m, 2H), 4.26 (d, 1H, *J* = 6.4 Hz), 5.05 (d, 1H, *J* = 6.4 Hz), 6.48 (d, 2H, *J* = 7.2 Hz), 6.98-7.08 (m, 3H), 7.16-7.26 (m, 6H), 7.38-7.45 (m, 2H), 7.72 (d, 1H, *J* = 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.3, 141.9, 140.4, 138.1, 131.4, 129.8, 129.5, 128.9, 128.5, 128.0, 127.8, 127.6, 126.8, 126.6, 125.5, 65.3, 48.9, 36.0, 29.7, 23.1, 14.3. HRMS: calcd for $C_{25}H_{26}N^{+}$ 340.2060, found 340.2049.



2.49ja

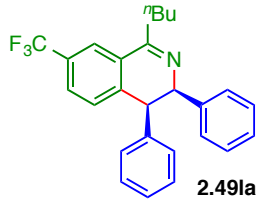
1-*tert*-Butyl-3,4-diphenyl-3,4-dihydroisoquinoline (2.49ja): Prepared from 2,2-dimethyl-1-phenyl-propylideneamineand 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49ja** as a yellow liquid (86 mg, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 9H), 4.20 (d, 1H, *J* = 6.0 Hz), 4.92 (d, 1H, *J* = 6.0 Hz), 6.43 (d, 2H, *J* = 7.2 Hz), 6.95 -7.06(m, 3H), 7.21-7.31 (m, 6H), 7.36-7.41 (m, 2H), 7.97 (d, 1H, *J* = 7.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.3, 142.6, 142.1, 137.5, 130.4, 129.9, 128.9, 128.5,

128.0, 127.4, 126.95, 126.85, 126.7, 126.4,64.8, 49.3, 40.2, 30.4. HRMS: calcd for $C_{25}H_{26}N^+$ 340.2060, found 340.2060.



2.49ka

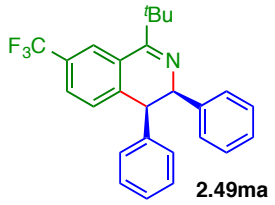
***cis*-1-Methyl-3,4-diphenyl-7-(trifluoromethyl)-3,4-dihydro-isoquinoline (2.49ka):** Prepared from 1-(3-trifluoromethyl-phenyl)-ethylideneamine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave 2**.49ka** as a yellow liquid (90 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.71 (s, 3H), 4.35 (d, 1H, *J* = 6.4 Hz), 5.09 (d, 1H, *J* = 6.4 Hz), 6.51 (d, 2H, *J* = 7.2 Hz), 7.06-7.17 (m, 5H), 7.24-7.26 (m, 3H), 7.35 (d, 1H, *J* = 7.6 Hz), 7.69 (d, 1H, *J* = 7.6 Hz), 7.99 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 164.1, 143.7, 140.6, 136.9, 130.6(q, *J* = 32.6 Hz), 129.9, 129.4, 129.1, 128.1, 127.93, 127.91, 127.87, 127.8, 126.9, 126.8, 125.3 (q, *J*(C, F) = 270.5 Hz), 123.6 (q, *J* = 5.0 Hz), 122.5 (q, *J* = 3.7 Hz), 65.1, 48.5, 23.4. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.4 (s, 1F). HRMS: calcd for $C_{23}H_{19}F_3N^+$ 366.1464, found 366.1457.



2.49la

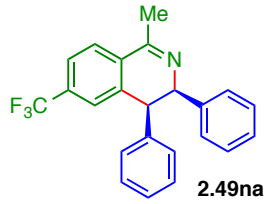
***cis*-1-Butyl-3,4-diphenyl-7-trifluoromethyl-3,4-dihydro-isoquinoline (2.49la):** Prepared from 1- (3-trifluoromethyl-phenyl)-butylideneamine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49la** as a yellow liquid (99 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.99 (t, 3H, *J* = 7.6 Hz), 1.47 (sext, 2H, *J* = 7.6 Hz), 1.78-1.84 (m, 2H), 2.94-2.98 (m, 2H), 4.29 (d, 1H, *J* = 6.4 Hz), 5.02 (d, 1H, *J* = 6.4 Hz), 6.42 (d,

2H, *J* = 7.2 Hz), 6.96-7.05 (m, 3H), 7.12-7.24 (m, 5H), 7.31 (d, 1H, J = 6.4 Hz), 7.63 (d, 1H, *J* = 6.4 Hz), 7.93 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.9, 144.2, 141.1, 137.1, 130.4, 130.0 (q, *J* = 32.2 Hz), 129.8, 129.7, 129.5, 128.3, 128.2, 127.8, 127.0, 126.9, 125.5 (q, *J*(C,F) = 272.6 Hz), 122.8, 122.1 (q, *J* = 4.0 Hz), 64.9, 48.6, 35.7, 29.2, 22.1, 14.2.^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -15.1 (s, 1F). HRMS: calcd for $C_{26}H_{25}F_3N^+$ 408.1934, found 408.1923.



2.49ma

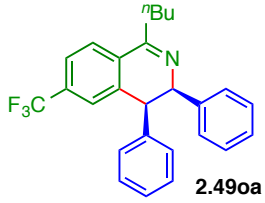
***cis*-1-*tert*-Butyl-3,4-diphenyl-7-trifluoromethyl-3,4-dihydro-isoquinoline (1.53ma):** Prepared from 2,2-dimethyl-1-(3-trifluoromethylphenyl)-propan-1-imine and 1,2-diphenylethyne (**1.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **1.53ma** as a yellow liquid (99 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 9H), 4.32 (d, 1H, *J* = 6.0 Hz), 4.97 (d, 1H, *J* = 6.0 Hz), 6.46 (d, 2H, *J* = 7.2 Hz), 7.02 (d, 2H, *J* = 6.8Hz), 7.09 (d, 1H, *J* = 6.0 Hz), 7.28 -7.31 (m, 5H), 7.36 (d, 1H, *J* = 7.6 Hz), 7.61 (d, 1H, *J* = 7.2 Hz), 8.18 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.1, 145.7, 141.6, 136.3, 131.4 (q, J = 32.7 Hz), 130.6, 129.5, 129.3, 128.9, 128.2, 127.9, 127.4, 126.6, 125.4 (q, *J*(C,F) = 270.7 Hz), 124.6 (q, *J* = 10.6 Hz), 123.3 (q, *J* = 3.0 Hz), 123.5 (q, *J* = 3.0 Hz), 64.3, 48.8, 39.9, 30.1. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.4 (s, 1F). HRMS: calcd for $C_{26}H_{25}F_3N^+$ 408.1934, found 408.1932.



2.49na

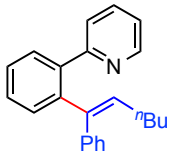
***cis*-1-Methyl-3,4-diphenyl-6-trifluoromethyl-3,4-dihydro-isoquinoline(2.49na):** Prepared from 1-(4-trifluoromethyl-phenyl)ethanimine and 1,2-diphenylethyne (**2.15a**) by the general

procedure B. Chromatography (1%) gave **2.49na** as a light yellow liquid (91 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H), 4.30 (d, 1H, *J* = 6.4 Hz), 5.02 (d, 1H, *J* = 6.4 Hz), 6.45 (d, 2H, *J* = 7.2 Hz), 6.99 (t, 2H, *J* = 6.8 Hz), 7.06-7.11 (m, 3H), 7.19-7.24 (m, 3H), 7.47 (s, 1H), 7.66 (d, 1H, *J* = 6.8 Hz), 7.78 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 164.4, 140.9, 137.0, 133.2(q, *J* = 32.5 Hz), 132.9, 132.3, 129.6, 128.3, 128.1, 127.9, 127.1, 126.9, 126.1, 125.6 (q, *J* = 3.0 Hz), 125.2 (q, *J*(C,F) = 272.6 Hz), 124.8 (q, *J* = 3.0 Hz), 65.4, 48.9, 23.6. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -63.3 (s, 1F). HRMS: calcd for $C_{23}H_{19}F_3N^+$ 366.1464, found 366.1458.



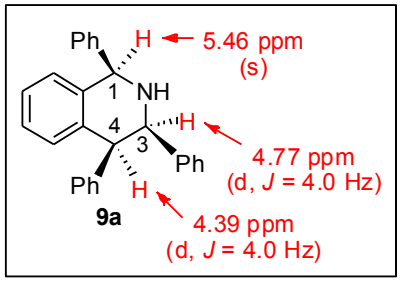
2.49oa

***cis*-1-tert-Butyl-3,4-diphenyl-6-(trifluoromethyl)-3,4-dihydro-isoquinoline (2.49oa):** Prepared from 2,2-dimethyl-1-(4-trifluoromethylphenyl)propan-1-imine and 1,2-diphenylethyne (**2.15a**) by the general procedure B. Chromatography (1% ethyl acetate in hexane) gave **2.49oa** as a light yellow liquid (98 mg, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.02 (t, 3H, *J* = 7.2 Hz), 1.50 (sext, 2H, *J* = 7.6 Hz), 1.76-1.94 (m, 2H), 2.90-3.08 (m, 2H), 4.33 (d, 1H, *J* = 6.4 Hz), 5.05 (d, 1H, *J* = 6.4 Hz), 6.46 (d, 2H, *J* = 7.6 Hz), 6.99 (t, 2H, *J* = 7.2 Hz) 7.07 (t, 1H, *J* = 7.6 Hz), 7.16-7.18 (m, 2H), 7.21 -7.27(m, 3H), 7.51 (s, 1H), 7.68 (d, 1H, *J* = 8.0 Hz), 7.81 (d, 1H, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.2, 141.3, 141.2, 137.0, 133.3, 132.9, 132.0 (q, *J* = 30.6 Hz), 129.7, 128.4, 128.1, 127.8, 126.9, 125.8 (q, *J* = 4.1 Hz), 124.8 (q, *J* = 4.2 Hz), 122.6, 119.8 (q, *J*(C,F) = 272.6 Hz), 65.1, 48.6, 35.7, 29.3, 23.0, 14.2.^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -14.7 (s, 1F). HRMS: calcd for $C_{26}H_{25}F_3N^+$ 408.1920, found 408.1934.



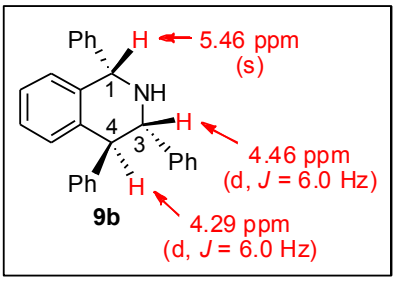
2.65

(*E*)-2-[2-(1-Phenylhex-1-enyl)-phenyl]-pyridine (2.65): Prepared from 2-phenylpyridine and 1-phenyl-1-hexyne by the general procedure A for redox-neutral [4+2] imine/alkyne annulation. Chromatography (1% ethyl acetate in hexane) gave **2.65** as a yellow liquid (84 mg, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.82 (t, 3H, J = 6.8 Hz), 1.24-1.30 (m, 4H), 2.16 (dt, 2H, J_1= J_2 = 7.2 Hz), 5.70 (t, 1H, J = 7.2 Hz), 6.97 (d, 2H, J = 6.4 Hz), 7.12-7.30 (m, 4H), 7.28 (d, 1H, J = 7.6 Hz), 7.37-7.40 (m, 3H), 7.47-7.51(m, 2H), 8.51 (d, 1H, J = 5.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 160.0, 148.9, 143.3, 140.6, 140.4, 140.3, 135.2, 134.1, 130.8, 130.0, 129.7, 127.9, 127.4, 127.1, 126.2, 124.4, 121.1, 31.9, 29.3, 22.3, 13.9. HRMS: calcd for $C_{23}H_{24}N^{+}$ 314.1903, found 314.1914.

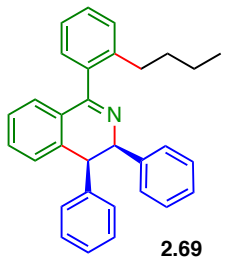


***cis*-1,3,4-Triphenyl-1,2,3,4-tetrahydroisoquinoline (2.66a):** Synthesized based on an analogous hydride reduction procedure reported by the groups of Bergman and Ellman.[29] Into a 20 mL scintillation vial equipped with a magnetic stir bar was placed *cis*-1,3,4-triphenyl-3,4-dihydroisoquinoline (**2.66a**, 0.28mmol, 1.00 equiv)**,** diphenylphosphate (0.58mmol, 2.10 equiv), and THF (4 mL). The mixture was stirred at room temperature for 16 h, transferred to a fume hood, and added to a suspension of tetramethylammoniumtriacetoxyborohydride (1.67 mmol, 6.00 equiv) in THF (10 mL) in a 50 mL round bottom flask immersed in a 0 ^{o}C bath. The mixture was stirred at 0 ^{o}C for 2 h before warming to room temperature and stirred for another 2 h. The reaction was quenched sequentially with water (1 mL) and saturated aqueous NH_4Cl (1 mL), and then was added

dropwise with 2 mL of 2.0 M NaOH until PH 11 was reached. The mixture was extracted with a mixed solution of Hexane:EtOAC:Et_3N (400:25:3, 3x30mL) and the organic layers were combined, filtered through Celite, and evaporated under reduced pressure to remove all volatiles. The crude product was further purified by flash column chromatography with neutral Alumina and 1% ethyl acetate in hexane to give a 20:1 inseparable mixture of **2.66a** and **2.66b** as a white solid (87.4 mg, 87% combined yield, diastereoselectivity determined by ^{1}H NMR analysis). ^{1}H-NMR for **2.66a** (400 MHz, $CDCl_3$): δ 4.39 (d, 1H, J = 4.0 Hz), 4.77 (d, 1H, J = 4.0 Hz), 5.46 (s, 1H), 7.01-7.06 (m, 5H), 7.19–7.23 (m, 9H),7.48 (d, 1H, J = 7.2 Hz), 7.53-7.56 (m, 2H), 7.71 (d, 2H, J = 6.8 Hz). ^{13}C-NMR for **2.66a** (100 MHz, $CDCl_3$): δ 144.3, 142.3, 141.9, 138.9, 138.7, 130.9, 130.8, 129.4, 128.7, 127.94, 127.88, 127.6, 127.14, 127.08, 126.9, 126.8, 126.3, 126.1, 65.0, 63.4, 52.0. HRMS: calcd for $C_{27}H_{24}N^+$ 362.1909, found 362.1910.



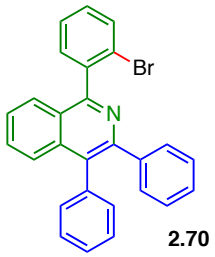
The following ^{1}H NMR signals could be identified for the aliphatic protons in **2.66b** (400 MHz, $CDCl_3$): δ 4.46 (d, 1H, J = 6.0 Hz), 5.29 (d, 1H, J = 6.0 Hz), 5.46 (s, 1H, overlapping with a singlet from **2.66a**). The relatively larger H(3)-H(4) coupling (compared to **2.66a**) is consistent with a *trans*-3,4-disubstitution stereochemistry.



2.69

***cis*-1-(2-butylphenyl)-3,4-diphenyl-3,4-dihydroisoquinoline (2.69):** In to a 4 dram vial *cis*-1,3,4-triphenyl-3,4-dihydroisoquinoline (**2.69aa**, 0.20 mmol), potassium butyltrifluoroborate (0.60 mmol), $[RhCp^*Cl_2]_2$ (0.008 mmol), $AgSbF_6$ (0.032 mmol), AgF (0.78 mmol) and DCE 3.0

mL were added and the vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 100 °C for 24 hours. After the reaction mixture was cooled to room temperature, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using neutral alumina. Chromatography (1% ethyl acetate in hexane) gave **2.69** as a colorless liquid (55 mg, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.83 (t, 3H, J = 7.6 Hz), 1.23 (q, 2H, J = 7.2 Hz), 1.54 (bs, 2H), 2.54 (bs, 2H), 4.38 (d, 1H, J = 10.0 Hz), 5.17 (bs, 1H), 7.01 (d, 2H, J = 7.6 Hz), 7.01 (d, 1H, J = 7.6 Hz),7.08 (d, 1H, J = 7.6 Hz), 7.17-7.26 (m, 9H), 7.29-7.34 (m, 4H), 7.34-7.41 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.6, 142.82, 142.81, 140.8, 139.2, 138.6, 131.4, 129.4, 129.3, 129.19, 129.18, 128.9, 128.8, 128.5, 128.3, 128.1, 127.8, 127.7, 127.2, 126.8, 125.8, 68.3, 49.9, 33.2, 29.7, 22.7, 13.9. HRMS: calcd for $C_{31}H_{29}N^{+}$ 416.2378, found 416.2391.



2.70

1-(2-bromophenyl)-3,4-diphenylisoquinoline (2.70): In to a 4 dram vial *cis*-1,3,4-triphenyl-3,4-dihydroisoquinoline (2**.49aa**, 0.28 mmol), NBS (0.33 mmol), $[RhCp^*Cl_2]_2$ (0.014 mmol), $AgSbF_6$ (0.056 mmol), PivOH (0.31 mmol) and DCE 2.0 mL were added and the vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 80 °C for 9 hours. After the reaction mixture was cooled to room temperature, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using neutral alumina. Chromatography (1% ethyl acetate in hexane) gave **2.70** as a colorless liquid (90 mg, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19-7.24 (m, 3H), 7.32-7.34 (m, 1H), 7.37

-7.46 (m, 7H),7.49-7.55 (m, 2H), 7.56-7.65 (m, 2H), 7.74–7.81 (m, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.1, 149.7, 140.7, 140.5, 137.3, 136.5, 132.9, 131.7, 131.4, 130.5, 130.2, 129.9, 128.4, 128.2, 127.6, 127.4, 127.3, 127.2, 127.0, 126.8, 126.0, 125.8, 123.4. HRMS: calcd for $C_{27}H_{18}NBr^+$ 436.0701, found 436.0719.

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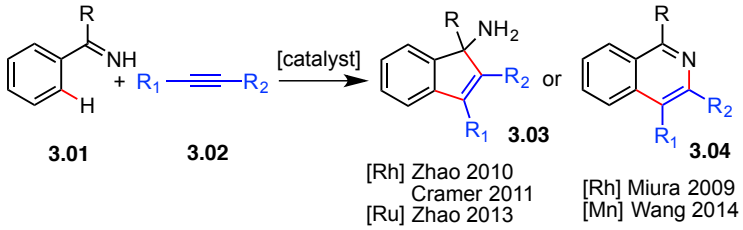
CHAPTER 3. NICKEL - CATALYZED HYDROIMINATION OF ALKYNES

3.1. Introduction

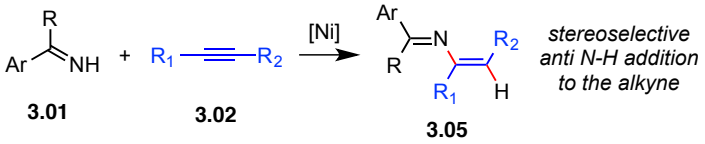
Nitrogen-substituted imines are ubiquitous substrates in transition metal-catalyzed transformations.[1,2] By contrast, catalytic transformations of N-unsubstituted imines (N-H imines) (**3.56**) are much less established. This is in large part because of concerns over their low stability, difficulty for synthesis, and potential complications by *E/Z* isomerism and imine-enamine tautomerization. These issues are less pronounced with aromatic N-H ketimines (ArRC=NH), which are readily accessible via organometallic addition to benzonitriles, usually exist and react as single isomers, and are relatively stable compared to N-H aldimines and aliphatic ketimines. Thus, aromatic N-H ketimines have been successfully explored in a number of catalytic processes such as Buchwald-Hartwig amination,[3] enantioselective imine hydrogenation,[4] and imine-directed aromatic C-H functionalization.[5-8] However, aromatic N-H ketimines are not known to undergo catalytic hydroamination, the formal addition of a N–H bond across an unactivated C–C π-bond.[9,10] Such "hydroimination" of alkene or alkyne substrates would provide convenient and atom-economical synthesis of N-substituted imine derivatives.

We report herein the development of a nickel-based catalyst system for intermolecular hydroimination of internal alkynes (**3.02**) with aromatic N-H ketimines (**3.01**).[11] To our best knowledge, this is the first example of catalytic hydroimination with unactivated alkynes.[10] Prior studies on catalytic coupling between these two classes of substrates have focused on annulation processes involving cyclometalated imine complexes via imine-directed C-H bond activation (Scheme 3.1). [12] Since the first report of such annulation strategy by Miura, Satoh and coworkers in 2009,[6a] several transition metal catalysts have been developed to promote oxidative [4+2] and

redox-neutral [3+2] N-H ketimine/alkyne annulations to form isoquinoline (**3.04**) and indenamine (**3.03**) products respectively.[2a,6,7] In comparison, the current catalyst system promotes alkyne hydroimination via a formal *anti* alkyne addition by the imine N-H bond, leading to the formation of (3*Z*)-2-aza-1,3-butadiene (**3.05**) products in high chemo- and stereoselectivity (Scheme 3.2). 2-Aza -1,3- dienes are important building blocks in amine and N-heterocycle synthesis due to their versatile reactivity towards a broad range of addition and cycloaddition reactions including the aza-Diels-Alder reaction.[13] Existing procedures for 2-aza-1,3-diene synthesis typically require multiple steps and often involve highly reactive intermediates such as phosphazenes and 2*H*-azirines.[13a] Thus, this work expands the scope of N-nucleophiles for metal-catalyzed hydroamination and provides rapid assembly of valuable 2-aza-1,3-diene structures from readily available starting materials.



Scheme 3.1. Previous reports on N-H aromatic imine/alkyne annulations



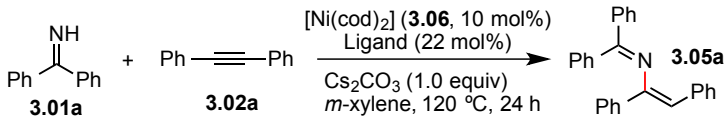
Scheme 3.2. Current study on N-H aromatic imine/alkyne hydroimination

3.2. Catalyst development

We began our catalyst development with the model reaction between benzophenone imine (**3.01a** in Table 3.1) and diphenylacetylene (**3.02a**). Results from an initial screening of various transition metal complexes led us to focus on Ni(0) complexes as catalyst precursors,

which appeared to selectively promote the formation of hydroimination product **3.05a** over byproducts from [3+2] (**3.03**) or [4+2] (**3.04**) annulations (Scheme 3.1). [6,7] Thus, we used $[Ni(cod)_2]$ (**3.06**) as a commercially available Ni(0) precursor to evaluate other reaction parameters such as the ligand, salt additive, and solvent (Table 3.1). In general, among different commercially available *N*-heterocyclic carbene (NHC) ligands (entries 1-4), IPr (**3.07a**) was found to be formed product **3.05a** in higher yields. Chelating bisphosphines (entries 7-8) and monophosphines (entries 9-10) were found to be unreactive towards this hydroimination reaction.

Table 3.1. Effects of ligand for nickel-catalyzed hydroimination of alkynes

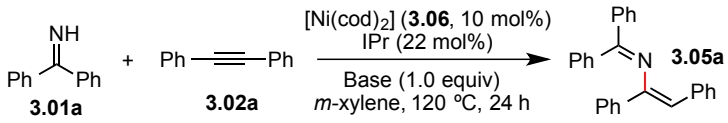


entry	Ligand	yield[b] (%)
1	IPr (**3.07a**)	90
2	SIPr (**3.08a**)	84
3	IMes (**3.07b**)	31
4	SIMes (**3.08b**)	28
5	DPPF	0
6	*t*Bu-Xantphos	0
7	Binap	0
8	DPEPhos	0
9[c]	PPh_3	0
10[c]	PCy_3	0

[a] General conditions: **3.01a** (0.28 mmol, 1.0 equiv), **3.02a** (1.20 equiv), Ni(0) catalyst (0.10 equiv), ligand (0.22 equiv), Cs_2CO_3 (1.00 equiv) *m*-Xylene (1.0 mL), 120 °C, 24 h. [b] GC yields. [c] Using 0.42 equiv phosphine ligand.

With IPr as optimized ligand we screened different base additives and found to be Cs_2CO_3 has good conversion compare to other bases. Strong bases like LiHMDS and KO*t*Bu were found to be unreactive and found to be lot of precipitation is formed in these solvents may be due to catalyst decomposition. In the absence of base additive it is found that the product is formed in moderate yields (Table 3.2).

Table 3.2. Effects of additives for nickel-catalyzed hydroimination of alkynes

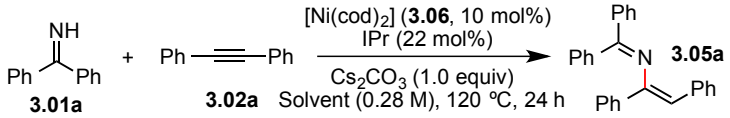


entry	Additive	yield[b] (%)
1	Cs_2CO_3	91
2	NaOEt	73
3	LiHMDS	0
4	Na_2CO_3	84
5	LiOH	83
6	*K*O*t*Bu	0
7	K_2CO_3	88
8	No Additive	56

[a] General conditions: **3.01a** (0.28 mmol, 1.0 equiv), **3.02a** (1.20 equiv), Ni(0) catalyst (0.10 equiv), IPr (0.22 equiv), additive (1.00 equiv) *m*-xylene (1.0 mL), 120 °C, 24 h. [b] GC yields.

With optimized IPr and Cs_2CO_3 as ligand and base additives respectively we screened different solvents. Among the non-polar aromatic (entries 1-2) and aliphatic solvents (entry 3) *m*-xylene is found to be have good conversion. Where as polar solvents (entries 4-8) 1,4-dioxane gave 87% conversion and CH_3CN is found to be have moderate yield where as DMF and DCE were found to be unreactive (Table 3.3).

Table 3.3. Effects of solvents for nickel-catalyzed hydroimination of alkynes



entry	Solvent	yield[b] (%)
1	Toluene	82
2	*m*-Xylene	90
3	Hexane	63
4	THF	56
5	1,4-Dioxane	87
6	CH_3CN	44
7	DMF	0
8	DCE	0

[a] General conditions: **3.01a** (0.28 mmol, 1.0 equiv), **3.02a** (1.20 equiv), Ni(0) catalyst (0.10 equiv), IPr (0.22 equiv), Cs_2CO_3 (1.00 equiv) solvent (1.0 mL), 120 °C, 24 h. [b] GC yields.

3.3. Substrate scope for nickel-catalyzed hydroimination of alkynes

Under the optimized conditions of 120 ºC and using *m*-xylene solvent, reaction between **3.01a** and **3.02a** (1.2 equiv) was promoted by 10 mol% **3.06**, 22 mol% **3.07a** and 1 equiv Cs_2CO_3 to selectively form **3.05a** in 91% yield over 24 hours (entry 1). **3.05a** was detected as a single isomer of (3*Z*)-2-aza-1,3-butadiene derivative by NMR spectroscopy and single crystal X-ray diffraction, suggesting a formal *anti* alkyne addition by the imine N-H bond. Traces of byproducts (<5 %) from alkyne oligomerization were also formed under these conditions,[11d,14] while none of the byproducts from [3+2] and [4+2] annulations (Scheme 3.1) was detected by GC analysis.

With the standard reaction conditions established, various aromatic N-H ketimines (**3.01**) and internal alkynes[15] (**3.02**) were studied for Ni(0)-catalyzed hydroimination (Scheme 3.2). In

general, 2-aza-1,3-butadienes (**3.05**) were formed in high chemo selectivity, with small amounts of byproducts from alkyne oligomerization. All of the azadiene products were detected and isolated as a single isomer of (*Z*)-enamine structures (*vide infra*). Scope of the alkyne substrates was studied with benzophenone imine (**3.01a**) as the reaction partner. For symmetrical diarylacetylenes, high product yields of 88-94% were achieved with those having electron-donating substituents at *para* or *meta* positions (**3.05b-e**, **3.05h**). In comparison, diarylacetylenes with *para* F/CF_3 or *meta* F groups led to slightly lower yields of 68-78% (**3.05f**, **3.05g**, **3.05i**). Diarylacetylenes with *ortho* OMe or F groups required a longer reaction time of 36 h to reach 60-79% yields (**3.05j**, **3.05k**). Di (2-thiphenyl) acetylene also reacted with **3.05a** to give product **3.05l** in 58% yield (Figure 3.1).

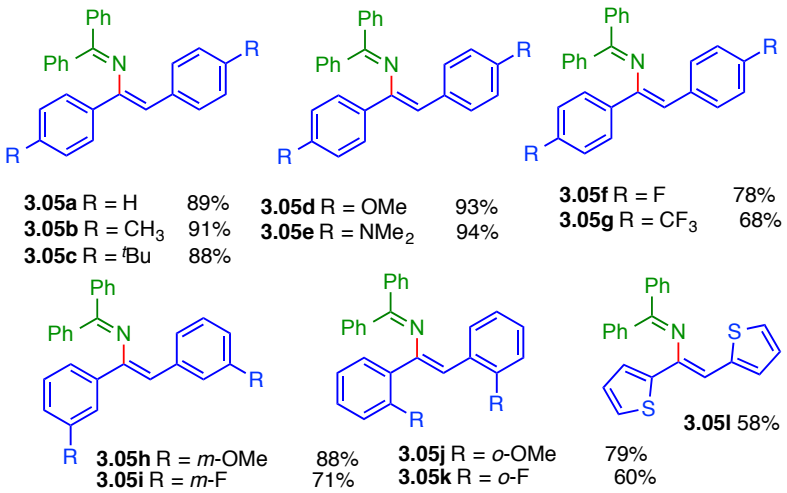
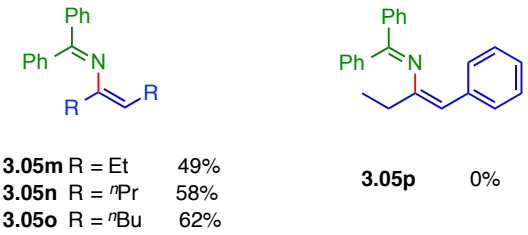


Figure 3.1. Substrate scope for nickel catalyzed hydroimination of aromatic alkynes

Symmetrical dialkyl acetylenes were significantly less reactive than diarylacetylenes under standard reaction conditions. Thus, 2 equiv of **3.05a** was required to promote complete conversion with dialkylacetylenes as the limiting reagents and gave products **3.05m-o** in 49-62% yields. Notably, 1-butynylbenzene failed to give the desired azadiene product **3.05p** but instead formed a mixture of alkyne oligomers (Figure 3.2).[11d,14]



3.05m R = Et 49%
3.05n R = ^{n}Pr 58%
3.05o R = ^{n}Bu 62%

3.05p 0%

Figure 3.2. Substrate scope for nickel catalyzed hydroimination of aliphatic and unsymmetrical aryl-alkyl alkynes

Scope of the ketimine substrates was studied by reactions with diphenylacetylene (**3.02a**), and high reactivity was observed for electron-poor diaryl N-H ketimines with *para* F or *meta* CF_3 groups (**3.05q**, **3.05r**). By contrast, the *electron-rich* di (*p*-anisyl) N-H ketimine failed to react with **3.01a** to give the desired product **3.05s**. Interestingly, the electron-rich *and* sterically hindered di(*o*-tolyl) N-H ketimine did react with **3.01a** to give azadiene **3.05t** in 71% yield. Alkyl-substituted (hetero) aromatic N-H imines with phenyl, electron-poor aryl, or 4-pyridyl groups showed slightly lower reactivity and required 1.5 equiv of **3.01a** to give products **3.05u-z** in 73-91% yields. As demonstrated with the solid-state structures of **3.05n** and **3.05x** by X-ray crystallography, the regio- and stereochemistry of the (3*Z*)-2-aza-1,3-diene structure from formal *anti* N-H addition was maintained for products with alkyl substituents at 1-, 3- or 4-positions. These results suggested that no E/Z isomerization or imine-enamine tautomerization occurred under current reaction conditions (figure 3.3).

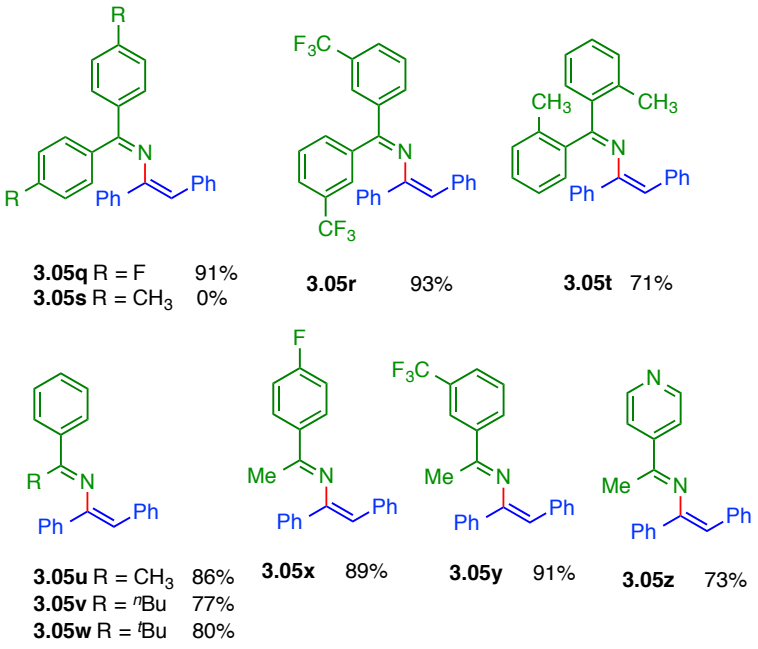
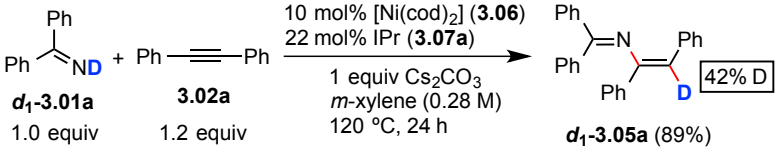


Figure 3.3. Substrate scope for nickel catalyzed hydroimination of N-H ketimines

3.4. Proposed catalytic cycle for hydroimination of alkynes

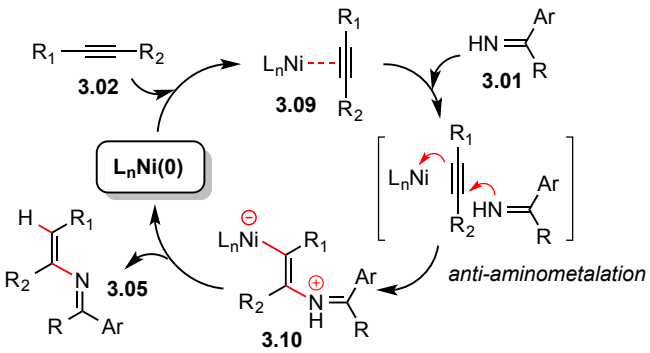
The reaction mechanism for Ni(0)-catalyzed alkyne hydroimination was investigated by several deuterium-labeling experiments and stoichiometric observations (Scheme 3.4). Under standard catalytic conditions, N-deuterated benzophenone imine (***d*$_1$-3.01a**) reacted with diphenylacetylene (**3.02a**) to give 2-aza-1,3-diene product **3.05a** in 87% yield and with only trace of deuterium incorporation (< 2%) at the 4-position. In comparison, reaction between non-deuterated **3.01a** and **3.02a** in the presence of 5 equiv D_2O additive led to 42% deuterium incorporation at the 4-position of the product (***d*$_1$-3.05a**, 89% yield) (Scheme 3.3).



Scheme 3.3. Deuterium-labeling experiment on N-H imine/alkyne hydroimination

These results suggested that the catalytic hydroimination pathway likely involved intermolecular proton transfer processes, which led to rapid H/D exchange between reactive

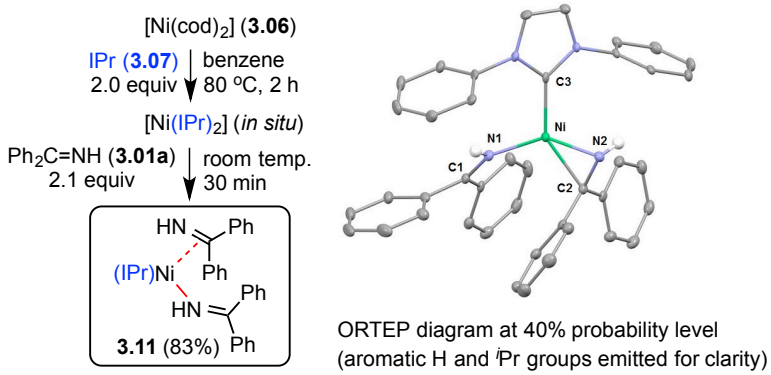
intermediates and the reaction media. Based on the deuterium-labeling and stereochemistry results, we proposed that Ni(0)-catalyzed alkyne hydroimination was initiated by formation of a Ni(0)-alkyne π-complex (**3.09** in **Scheme 3.4**), followed by stereospecific *anti*-attack by the N-H imine substrate (**3.01**) to form a zwitterionic alkenylnickel iminium intermediate **3.10**. Subsequent proton dissociation from iminium and protonation of the Ni-alkenyl linkage released the hydroimination product (**3.05**) and formed a coordinatively unsaturated Ni(0) intermediate, which was stabilized by π-complexation with an alkyne substrate (**3.02**) and regenerate intermediate **3.09** to complete the proposed catalytic cycle. The beneficial effects of inorganic base additives on catalytic reactivity (Table 1) suggested that the proposed proton transfer processes with intermediate **3.10** were likely assisted by external Brønsted bases and the corresponding conjugate acids, which also led to the observed H/D exchange during deuterium labeling studies. This proposed hydroimination mechanism was analogous to the well-established "alkyne activation" pathway for catalytic hydroamination with other transition metal catalysts that favored the formation of (*Z*)-enamine products via *anti*-aminometalation (scheme 3.4).[9,11]



Scheme 3.4. Proposed catalytic cycle for N-H aromatic imine/alkyne hydroimination

3.5. Synthesis of active catalyst Ni(0)-imine complex (3.11)

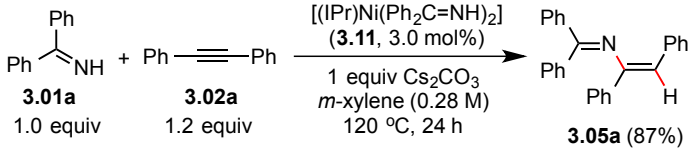
To gain further mechanistic insights, we sought to isolate or independently synthesize the proposed Ni(0)-π-alkyne intermediate (**3.09**) with attached IPr ligand and evaluate its catalytic activity. Unfortunately, our efforts were hindered by instability of the target Ni-alkyne complexes and formation of alkyne oligomers during attempted synthesis.[11d,14] Thus, we switched our synthetic target to IPr-ligated Ni(0)-imine complexes as a potential catalyst precursor (**Scheme 3.5**). Following the *in situ* formation of $[Ni(IPr)_2]$[16] by a 1:2 reaction between $[Ni(cod)_2]$ and IPr at 80 °C in benzene, 2.1 equiv of benzophenone imine (**3.01a**) was added and led to the formation of $[(IPr)Ni(Ph_2C{=}NH)_2]$ (**3.11**) in 83% yield. The solid-state structure of complex **3.11** was studied by single crystal X-ray diffraction to reveal a σ-imine as well as a π-imine ligand. This is a rare example of X-ray structures for late transition metal π-imine complexes.[17]



Scheme 3.5. Synthesis of active catalyst Ni(0)-imine complex (3.11)

3.6. Catalytic activity with Ni(0) imine complex (3.11) for N-H aromatic imine/alkyne hydroimination

Using complex **3.11** as a catalyst precursor to replace [Ni(cod)$_2$] and without added IPr ligand, a reaction between **3.01a** and **3.02a** was effectively promoted at a reduced catalyst loading of 3 mol% to give **3.01a** in 87% yield (**Scheme 3.6**).



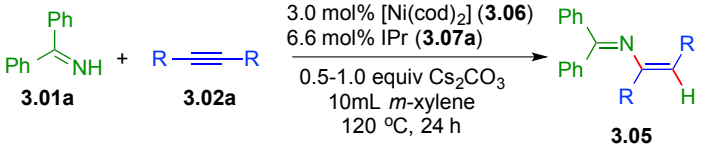
Scheme 3.6. Catalytic activity with Ni(0) imine complex (3.11) for N-H aromatic imine/alkyne hydroimination.

Thus, IPr-ligated Ni(0)-imine complexes were likely involved in the current catalyst system for alkyne hydroimination as IPr-activated catalyst precursors. In addition, we hypothesized that by having a relatively strong σ-imine ligand and a weak π-imine ligand, these Ni-imine intermediates may favor a single π-imine replacement by an alkyne substrate to form the proposed π-alkyne intermediate **3.09** while keeping the σ-imine ligand intact. In consequence, the desired alkyne hydroimination could be selectively promoted over alkyne oligomerization, which likely required two π-alkynes on a Ni(0) center for C-C bond formation via oxidative cyclization.[14] Several observations on structure-reactivity relationships with alkyne and imine substrates (Scheme 3.5) could be explained by the involvement of Ni(0)-imine complexes as a potential catalyst resting state and the imine/alkyne ligand replacement for catalyst activation: (1) Compared to alkyl-substituted alkynes, the relatively high reactivity of diary acetylenes for hydroimination was likely due to their higher steric hindrance, which inhibited alkyne oligomerization.[14] (2) The lack of hydroimination reactivity for 1-butynylbenzene probably resulted from a combination of its electronic and steric properties that

significantly favored alkyne oligomerization. (3) For electron-rich diaryl N-H ketimines such as di(*p*-anisyl) N-H ketimine, the Ni-imine complexation may be too strong to allow imine replacement by alkyne substrates, thus generating an unreactive nickel sink to shut down the catalysis.

3.7. Gram scale hydroimination reactions of N-H aromatic imine/alkyne

To demonstrate the potential of current method for practical synthesis, we carried out a preliminary study on gram-scale alkyne hydroimination with benzophenone imine (**3.01a**) (**Scheme 3.7**). With a reduced catalyst loading of 3 mol% [Ni(cod)$_2$] and 6.6 mol% IPr, reactions with diphenylacetylene (**3.02a**) and 4-octyne (**3.02b**) could be scaled up 15- to 20-fold to produce isolated products **3.05a** and **3.05n** in gram quantities, although the yield percentages were lower than those acquired under the standard catalytic conditions.



R = Ph (**3.02a**): 5.5 mmol **3.01a** (1.0 equiv), 1.2 equiv **3.02a** **3.05a** 64%
0.5 equiv Cs_2CO_3 (1.3 g isolated)

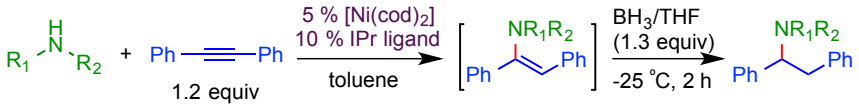
R = ^{n}Pr (**3.02b**): 9.1 mmol **3.02b** (1.0 equiv), 2.0 equiv **3.01a** **3.05n** 43%
0.5 equiv Cs_2CO_3 (1.1 g isolated)

Scheme 3.7. Gram scale hydroimination reactions for N-H aromatic imine/alkyne

In summary, we have developed a Ni(0)/NHC-based catalyst system for the first example of alkyne hydroimination with aromatic N–H ketimines. Stereochemistry and preliminary mechanistic results supported a proposed mechanism of alkyne activation via π-complexation with Ni(0) and subsequent nucleophilic attack by the N-H ketimine. Future studies will focus on mechanism-guided catalyst improvement for expanded substrate scopes and synthetic applications of the 2-aza-1,3-diene products

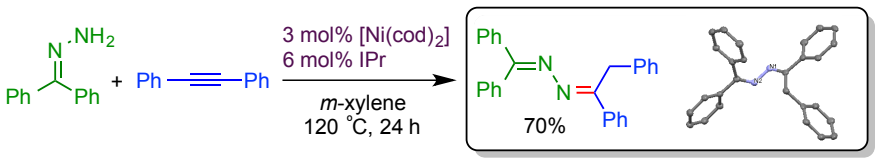
3.8. Future and ongoing studies

The Ni(0)/NHC catalyst for alkyne hydroimination was further explored for alkyne hydroamination with different *N*-nucleophiles. Encouraging preliminary results were obtained for hydroamination of diphenylacetylene with a number of aromatic and aliphatic amines. In comparision to imine products with aniline nucleophile, the reaction with morpholine, a secondary amine, generated the corresponding enamine product based on ^{1}H NMR analysis. The enamine and imine products have proven to be unstable for isolation so the products were subjected to borane reduction to afford the corresponding amine products that could be purified and measured for isolated yields (Scheme 3.8).



Scheme 3.8. Future directions for Ni(0)/NHC catalyzed hydroamination with primary and secondary amines followed by borane reduction

This catalyst system also promotes the unprecedented alkyne hydroamination with hydrazone nucleophiles (i.e. hydrohydrazonation). For example, coupling between benzophenone hydrazone and diphenylacetylene gave a 2,3-diazadiene product in 70% isolated yield, whose structure was established by X-ray crystallography (Scheme 3.9).



Scheme 3.9. Ni(0)/NHC catalyzed hydroamination with hydrazones as N-nucleophiles.

3.9. General experimental procedures and reagent availability

Unless otherwise noted, all manipulations were carried out under a nitrogen atmosphere using standard Schlenk-line or glovebox techniques. All glassware was oven-dried for at least 1 h prior to use. THF, toluene, and hexane were purified with a solvent purification system (MBraun MB-SPS). Anhydrous 1,4-dioxane and *m*-xylene was purchased from Sigma Aldrich and used as received. Except for commercially available benzophenone imine (**3.01a**), aromatic N-H ketimine substrates were prepared by following a reported general procedure of reactions between benzonitrile derivatives and organolithium reagents.[32,33] Among alkyne substrates, diphenylacetylene (**3.02a**), 3-hexyne, 4-octyne, and 5-decyne were purchased commercially and used without further purification; other diaryl alkyne substrates were prepared by following a reported general procedure of Sonogashira coupling.[34] N-Heterocyclic free carbenes and Cesium carbonate(99.9%) are purchased from sigma Aldrich and used as such. The rest of reagents and substrates were purchased from commercial vendors and were used as received. TLC plates were visualized by exposure to ultraviolet light or by exposure to I_2 sealed in a bottle at room temperature. Organic solutions were concentrated by rotary evaporation at ~10 torr. Flash column chromatography was performed with 58 Å pore size neutral alumina (Sigma Aldrich, Lot # BCBK5164V). GC analyses were performed on a Shimadzu GC-2010 with *n*-dodecane asthe internal standard. ^{1}H NMR spectra were obtained on a 400 MHz spectrometer, and chemical shifts were recorded relative to residual protiated solvent. ^{13}C NMR spectra were obtained at 100.6 MHz, and chemical shifts were recorded to the solvent resonance. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane (δ = 0). ^{19}F NMR spectra were obtained at 282.4 MHz, and all chemical shifts were reported in parts per

million upfield of CF_3COOH (δ = -78.5 ppm). High-resolution mass spectra were obtained at a Bruker Daltronics BioTOF HRMS spectrometer.

Single crystal X-ray diffraction data of compound **3.05a**, **3.05n**, **3.05x** and **3.05** were collected on a Bruker Apex Duo diffractometer with a Apex 2 CCD area detector at T = 100K. Cu radiation was used. All structures were process with Apex 2 v2010.9-1 software package (SAINT v. 7.68A, XSHELL v. 6.3.1). Direct method was used to solve the structures after multi-scan absorption corrections. Details of data collection and refinement are given in Table S4.

3.9.1. General procedure for nickel catalyzed alkyne hydroimination

Method A: For benzophenone imine and diarylacetylenes substrates. Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed [$Ni(cod)_2$] (**3.06**, 7.6mg, 0.028 mmol, 0.10 equiv), IPr (**3.07a**, 18.5 mg, 0.061 mmol, 0.22 equiv), and 1.0 mL of *m*-Xylene. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, benzophenone imine (**3.01a**, 0.28 mmol, 1.0 equiv) and internal alkyne (**3.02**, 0.33 mmol, 1.2 equiv) were added into the vial followed by Cs_2CO_3 (0.28 mmol, 1.00 equiv). The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 120 °C for 24 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using neutral alumina.

Method B: For diaryl N-H ketimine and dialkylacetylenes substrates. Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed [$Ni(cod)_2$] (**3.06**, 16.8mg, 0.061 mmol, 0.10 equiv), IPr (**3.07a**, 52.1 mg, 0.13 mmol, 0.22 equiv), and 1.0 mL of *m*-xylene. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, N-H ketimine (**3.01**, 1.22 mmol, 2.00 equiv) and dialkylacetylenes (**3.02**, 0.61

mmol, 1.00 equiv) were added into the vial followed by Cs_2CO_3 (0.61 mmol, 1.00 equiv). The vial was sealed with a silicone-lined screw cap, transferred out of the glovebox, and stirred at 120°C for 24 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using triethylamine-treated neutral alumina: after loading alumina, the column was basified with 3% triethylamine/hexane for two times, then washed with 100 mL hexanes for two times.

Method C: For aryl-alkyl N-H ketimine and diphenylacetylene substrates. Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed [Ni(cod)$_2$] (**3.06**, 7.7mg, 0.028 mmol, 0.10 equiv), IPr (**3.07a**, 27.3 mg, 0.062 mmol, 0.22 equiv), and 1.0 mL of *m*-Xylene. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, N-H ketimine (**3.01**, 0.28 mmol, 1.00 equiv) and internal alkyne (**3.02**, 0.42 mmol, 1.50 equiv) were added into the vial followed by Cs_2CO_3 (0.28 mmol, 1.00 equiv). The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 120 °C for 24 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using triethylamine-treated neutral alumina: after loading alumina, the column was basified with 3% triethylamine/hexane for two times, then washed with 100 mL hexanes for two times.

3.9.2. General procedure for deuterium labeling experiments

The deuterium labeling experiments followed the general hydroimination procedure (Method A) as described above. All reactions were carried out using diphenylacetylene (**3.02a**) as the internal alkyne substrate. The N-deuterated benzophenone imine substrate (Ph_2C=ND, ***d*$_1$-3.01a**) was prepared by a reported procedure of reaction between N-lithiated benzophenone imine (Ph_2C=NLi) and MeOD (99.8% deuterium-enriched), leading to greater than 95%

deuterium enrichment as determined by ^{1}H NMR.[35] No additional deuterium or proton sources were added for the reaction with ***d*$_1$-3.01a** as the N-H imine substrates. When using non-deuterated benzophenone imine (**3.01a**) as the N-H imine substrate, 5 equiv of D_2O (>99.9% deuterium-enriched) was added as the deuterium source. The products were further purified by flash-column chromatography (1% ethyl acetate in hexane) and the deuterium incorporation percentage was calculated based on ^{1}H and ^{2}H NMR. The reaction with ***d*$_1$-3.01a** gave hydroimination product **3.05a** in 87% yield and without only trace of deuterium incorporation (<2 %) at the vinyl C-H position. The reaction with **3.01a** and added D_2O led to 42% deuterium incorporation at the vinyl C-H position of hydroimination product (***d*$_1$-3.05a**) in 89% yield.

3.9.3. Synthesis of [(IPr)Ni(η^1-Ph_2C=NH)(η^2-Ph_2C=NH)] (3.11)

Into a 4 dram scintillation vial equipped with a magnetic stir bar was placed [Ni(cod)$_2$] (**3.06**, 50.0 mg, 0.18 mmol, 1.0 equiv), IPr (**3.07a**, 144.5 mg, 0.37 mmol, 2.05 equiv), and 2.0 mL of benzene. The mixture was stirred at 80 ^{o}C for 2 hrs. Next, benzophenone imine (**3.01a**, 0.38 mmol, 2.1 equiv) was added and the mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford a dark violet-colored powder (122 mg, 83% for crude product). Further crystallization was carried out in a mixed solvent system of benzene and layered heptane to produce single crystals suitable for X-ray diffraction analysis.

Figure S1. ORTEP diagrams of (*Z*)-*N*-(1,2-diphenylvinyl)-1,1-diphenylmethanimine (**3.05a**), (*Z*)-*N*-(hex-3-en-3-yl)-1,1-diphenylmethanimine (**3.05m**), (*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-1-(4-fluorophenyl)ethan-1-imine (**3.05x**), and [(IPr)Ni(η^1-Ph_2C=NH)(η^2-Ph_2C=NH)] (**3.11**) showing 40% probability ellipsoids; all aromatic and aliphatic H atoms, as well as the isopropyl groups in compound **3.11** are omitted for clarity.

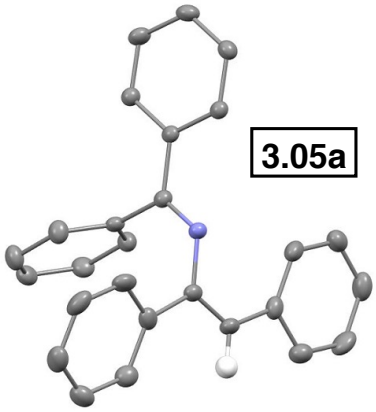


Figure 3.4. ORTEP diagram of (*Z*)-*N*-(1,2-diphenylvinyl)-1,1-diphenylmethanimine (**3.05a**)

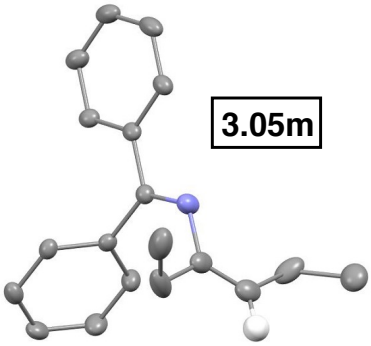


Figure 3.5. ORTEP diagram of (*Z*)-*N*-(hex-3-en-3-yl)-1,1-diphenylmethanimine (**3.05m**)

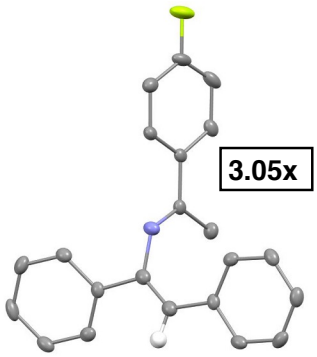


Figure 3.6. ORTEP diagram of (*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-1-(4-fluorophenyl)ethan-1-imine (**3.05x**)

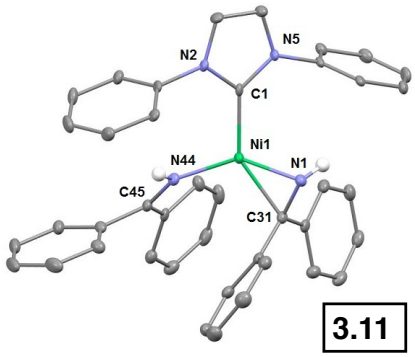
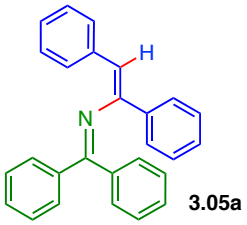


Figure 3.7. ORTEP diagram of [(IPr)Ni(η^1-Ph_2C=NH)(η^2-Ph_2C=NH)] (**3.05a**)

Table 3.4. Summary of cell parameters, data collection and structural refinements for compounds **3.05a, 3.05m**, **3.05x** and **3.11**.

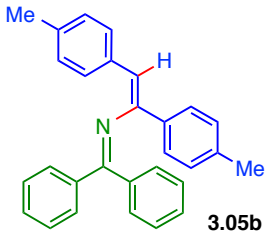
	3.60a	**3.60n**	**3.60x**	**3.66**
Formula	$C_{27}H_{21}N$	$C_{19}H_{21}N$	$C_{22}H_{18}NF$	$C_{53}H_{58}NiN_4$
FW	359.45	263.37	315.37	809.74
cryst. size_max [mm]	0.244	0.19	0.279	0.223
cryst. size_mid [mm]	0.208	0.18	0.244	0.203
cryst. size_min [mm]	0.157	0.06	0.081	0.07
cryst. system	Triclinic	orthorhombic	monoclinic	monoclinic
Space Group, Z	P-1	$Pna2_1$	C2/c	$P2_1/n$
a [Å]	9.910(8)	13.44765(7)	23.081(2)	12.539(3)
b [Å]	10.638(9)	7.6816(5)	5.6219(6)	18.204(4)
c [Å]	11.590(9)	29.8008(18)	27.44(4)	19.354(4)
α [Å]	66.662(14)	90	90	90
ß [Å]	68.065(13)	90	113.475(2)	92.174(5)
γ [Å]	63.042(12)	90	90	90
V [$Å^3$]	971.5(13)	3085.0(3)	3266.3(7)	4414.9(16)
ρ_{calc} [g/cm^3]	1.229	1.134	1.283	1.218
μ [mm^{-1}]	0.071	0.491	0.082	0.480
Radiation Type	Mo	Cu	Mo	Mo
F(000)	380	1136.0	1328.0	1728.0
no of measured refl.	14014	10172	25366	49184
no of indep. refl.	3957	4442	3772	8462
Resolution [Å]	1.06	0.84	1.06	1.06
R1/wR2 ($I \geq 2\sigma$)[a] [%]	4.42/10.46	3.85/10.05	5.59/11.71	4.26/9.69
R1/wR2 (all data) [%]	6.01/11.34	4.30/10.38	8.92/13.23	6.66/10.68

3.9.4. Preparation and analytical information for reported alkyne hydroimination products



3.05a

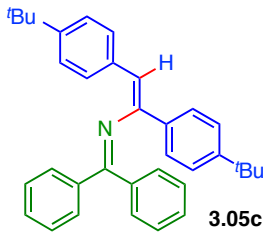
(*Z*)-*N*-(1,2-diphenylvinyl)-1,1-diphenylmethanimine (**3.05a**): Prepared from benzophenone imine (**3.01a**) and diphenylacetylene (**3.02a**) according to the general procedure (Method A). Chromatography (0.5% ethyl acetate in hexane) gave **3.05a** as a yellow solid (88 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.21 (s, 1H), 6.81 (d, 2H, *J* = 6.8 Hz), 7.10-7.19 (m, 3H), 7.22-7.28 (m, 4H), 7.28-7.32 (m, 2H), 7.41-7.44 (m, 2H), 7.49-7.55 (m, 5H), 7.95 (d, 2H, *J* = 6.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 111.8, 126.1, 126.2, 127.5, 127.69, 127.74, 128.4, 128.6, 128.7, 128.8, 129.1, 129.6, 131.3, 137.1, 137.8, 138.9, 140.5, 148.6, 169.4. HRMS: calcd for $C_{27}H_{22}N^{+}$ 360.1747, found 360.1749.



3.05b

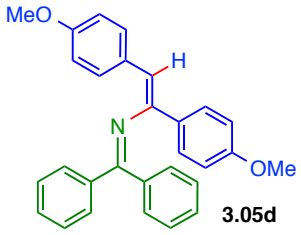
(*Z*)-*N*-(1,2-di-*p*-tolylvinyl)-1,1-diphenylmethanimine (**3.05b**): Prepared from benzophenone imine (**3.01a**) and 1,2-di-*p*-tolylethyne (**3.02b**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05b** as a yellow liquid (97 mg, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.38 (s, 3H), 6.18 (s, 1H), 6.71-6.79 (m, 2H), 6.85 (d, 2H, *J* = 7.2Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.13-7.17 (m, 4H), 7.32 (d, 2H, *J* = 8.0 Hz), 7.39 (d, 2H, *J* = 8.4 Hz), 7.49-7.58 (m, 3H), 7.96 (d, 2H, *J* = 7.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 21.2, 21.3, 110.7, 125.7, 127.3, 127.5, 128.4, 128.8, 128.9, 129.1, 129.4, 131.4, 134.1, 134.9,

135.3, 137.1, 137.4, 138.1, 140.4, 147.6, 168.9. HRMS: calcd for $C_{29}H_{26}N^+$ 388.2060, found 388.2079.



3.05c

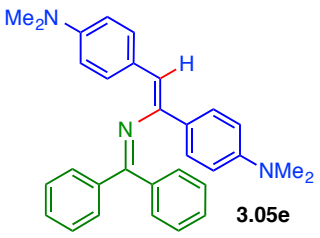
(Z)-N-(1,2-bis(4-(tert-butyl)phenyl)vinyl)-1,1-diphenylmethanimine (**3.05c**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(4-(*tert*-butyl)phenyl)ethyne (**3.02c**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05c** as a yellow liquid (115 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 1.36 (s, 9H), 6.17 (s, 1H), 6.85 (d, 2H, J = 6.8 Hz), 7.10-7.17 (m, 2H), 7.21-7.29 (m, 3H), 7.30-7.36 (m, 4H), 7.42 (d, 2H, J = 8.4 Hz), 7.50-7.59 (m, 3H), 7.95 (d, 2H, J = 6.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 31.36, 31.40, 3.5, 110.3, 124.9, 125.3, 125.7, 127.5, 128.3, 128.5, 129.4, 130.9, 134.8, 136.9, 137.01, 137.03, 137.7, 139.0, 147.7, 148.6, 150.2, 169.1. HRMS: calcd for $C_{35}H_{37}N^+$ 472.3004, found 472.3034.



3.05d

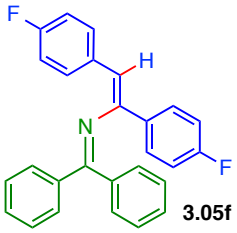
(*Z*)-*N*-(1,2-bis(4-methoxyphenyl)vinyl)-1,1-diphenyl-methanimine (**3.05d**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(4-methoxyphenyl)ethyne (**3.02d**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05d** as a light-yellow solid (108 mg, 93%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.81 (s, 3H), 6.05 (s, 1H), 6.76 (d, 2H, J =8.8 Hz), 6.83 (d, 4H, J = 7.2 Hz), 7.10-7.25 (m, 3H), 7.28 (d, 2H, J = 9.2

Hz), 7.37 (d, 2H, J = 8.4 Hz), 7.45-7.56 (m, 3H), 7.89 (d, 2H, J = 7.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ55.19, 55.24, 109.8, 113.5, 113.8, 126.9, 127.3, 127.5, 128.3, 128.5, 129.3, 129.9, 130.6, 130.9, 132.9, 136.9, 138.9, 146.3, 157.6, 158.9, 169.2. HRMS: calcd for $C_{29}H_{25}NO_2^+$ 420.1964, found 420.1960.



3.05e

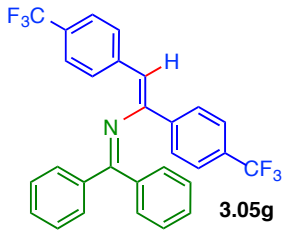
(*Z*)-4,4'-(1-((diphenylmethylene)amino)ethene-1,2-diyl)bis(*N*,*N*-dimethylaniline (**3.05e**): Prepared from benzophenone imine (**3.01a**) and 4,4'-(ethyne-1,2-diyl)bis(*N*,*N*-dimethylaniline) (**3.02e**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05e** as a maroon solid (116 mg, 94%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.963 (s, 6H), 2.966 (s, 6H), 6.06 (s, 1H), 6.62 (d, 2H, J = 6.8 Hz), 6.69 (d, 2H, J = 7.2 Hz), 6.91 (d, 2H, J = 7.2 Hz), 7.13-7.17 (m, 2H), 7.22-7.29 (m, 3H), 7.37 (d, 2H, J = 7.2 Hz), 7.48-7.56 (m,3H), 7.96 (d, 2H, J = 7.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ40.6, 40.7, 108.9, 112.1, 112.7, 126.4, 127.07, 127.14, 127.4, 127.5, 128.3, 128.8, 129.3, 129.6, 130.6, 137.1, 139.3, 145.3, 148.3, 149.6, 168.7. HRMS: calcd for $C_{31}H_{31}N_3^+$ 446.2596, found 446.2592.



3.05f

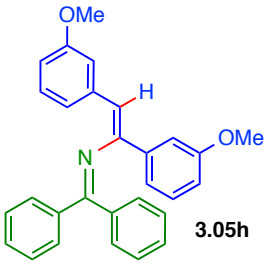
(*Z*)-*N*-(1,2-bis(4-fluorophenyl)vinyl)-1,1-diphenylmethanimine (**3.05f**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(4-fluorophenyl)ethyne (**3.02f**) according to the general procedure (Method A). Chromatography (0.5% ethyl acetate in hexane) gave **3.05f** as a yellow

liquid (85 mg, 78%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.07 (s, 1H), 6.79 (d, 2H, *J* =7.6 Hz), 6.91-7.03 (m, 4H), 7.14-7.18 (m, 2H), 7.25-7.28 (m, 1H), 7.32-7.38 (m, 2H), 7.41-7.46 (m, 2H), 7.48-7.59 (m, 3H), 7.91 (d, 2H, *J* = 7.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 110.5, 114.9 (d, *J* = 21.4 Hz), 115.2 (d, *J* = 21.2 Hz), 127.2, 127.5 (d, *J* = 7.9 Hz), 127.7, 128.5, 128.8, 129.4, 130.3 (d, *J* = 7.5 Hz), 131.3, 133.5 (d, *J* = 3.4 Hz), 136.5 (d, *J* = 3.1 Hz), 136.8, 138.5, 147.1, 159.9 (d, *J*(C,F) = 244.4 Hz), 161.0 (d, *J*(C,F) = 245.4 Hz), 169.8. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -114.4, -115.9. HRMS: calcd for $C_{27}H_{20}F_2N^+$ 396.1558, found 396.1557.



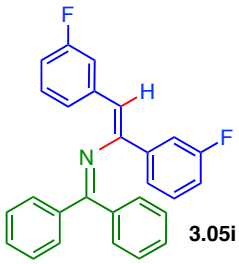
3.05g

(*Z*)-*N*-(1,2-bis(4-(trifluoromethyl)phenyl)vinyl)-1,1-diphenyl-methanimine (**3.05g**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(4-(trifluoromethyl)phenyl)ethyne (**3.02g**) according to the general procedure (Method A). Chromatography (0.5% ethyl acetate in hexane) gave **3.05g** as a yellow liquid (93 mg, 68%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.21 (s, 1H), 6.73-6.74 (m, 2H), 7.14 (s, 2H), 7.28 (s, 1H), 7.48-7.54 (m, 6H), 7.56-7.59 (m, 5H), 7.90-7.91 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 111.7, 120.1 (q, *J*(C,F) = 269.9 Hz), 120.3 (q, *J*(C,F) = 269.9 Hz), 125.1 (q, *J* = 3.6 Hz), 125.3 (q, *J* = 3.9 Hz), 126.3, 127.3 (q, *J* = 32.1 Hz), 127.8 (q, *J* = 14.5 Hz), 128.6 (q, *J* = 13.0 Hz), 128.9, 129.4, 129.2 (q, *J* = 32.6 Hz), 130.2,131.6, 137.9, 140.5, 143.4, 149.3, 170.2. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.4, -62.6. HRMS: $C_{29}H_{19}F_6NNa^+$ 518.1314, found 518.11322.



3.05h

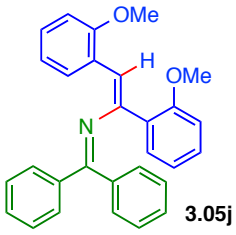
(*Z*)-*N*-(1,2-bis(3-methoxyphenyl)vinyl)-1,1-diphenyl-methanimine (**3.05h**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(3-methoxyphenyl)ethyne (**3.02h**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05h** as a light yellow liquid (102 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.81 (s, 3H), 6.22 (s, 1H), 6.79-6.83 (m, 2H), 6.89 (d, 2H, J = 5.6 Hz), 6.98-6.99 (m, 1H), 7.04-7.08 (m, 6H), 7.49-7.56 (m, 3H), 7.97 (d, 2H, J = 6.4 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 54.9, 55.3, 111.7, 111.8, 112.8, 113.0, 118.7, 121.9, 127.4, 127.59, 127.60, 128.4, 128.7, 129.1, 129.3, 129.4, 131.2, 136.8, 138.8, 141.5, 148.4, 159.4, 159.5, 169.1. HRMS: calcd for $C_{29}H_{25}NO_2Na^+$ 420.1964, found 420.1959.



3.05i

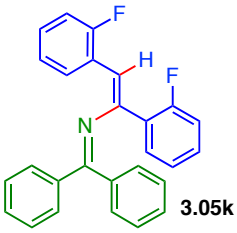
(*Z*)-*N*-(1,2-bis(3-fluorophenyl)vinyl)-1,1-diphenylmethanimine (**3.05i**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(3-fluorophenyl)ethyne (**3.02i**) according to the general procedure (Method A). Chromatography (0.5% ethyl acetate in hexane) gave **3.05i** as a yellow liquid (78 mg, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 1H), 6.79 (d, 2H, J = 5.6 Hz), 6.85-6.96 (m, 2H), 7.07-7.10 (m, 1H), 7.15-7.28 (m, 8H), 7.49-7.57 (m, 3H), 7.91 (d, 2H, J = 6.0 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 111.2 (d, J = 2.7 Hz), 112.3, 113.0, 114.4 (d, J = 21.1 Hz),

115.2 (d, J = 22.0 Hz), 121.6 (d, J = 2.8 Hz), 124.7 (d, J = 2.5 Hz), 127.2, 127.6, 128.5, 128.9, 129.4, 129.6, 129.66, 131.4, 136.6, 138.2, 139.3 (d, J = 8.1 Hz), 142.2 (d, J = 7.5 Hz), 148.3 (d, J = 2.5 Hz), 161.5 (d, J(C,F) = 243.5 Hz), 161.7 (d, J(C,F) = 242.6 Hz),170.0. ^{19}F-NMR (376.3 MHz, $CDCl_3$):δ -113.39, -113.42. HRMS: calcd for $C_{27}H_{20}F_2N^+$ 396.1558, found 396.1561.



3.05j

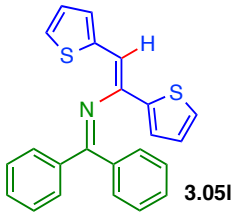
(*Z*)-*N*-(1,2-bis(2-methoxyphenyl)vinyl)-1,1-diphenylmethanimine (**3.05j**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(2-methoxyphenyl)ethyne (**3.02j**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05j** as a yellow liquid (91 mg, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 3H), 3.81 (s, 3H), 6.69 (s, 1H), 6.70-6.73 (m, 2H), 6.88-6.99 (m, 5H), 7.09-7.29 (m, 5H), 7.41-7.54 (m, 3H), 7.84-7.86 (m, 1H) 7.89 (d, 2H, J = 6.0 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 55.6, 55.7, 110.5, 110.85, 110.96, 120.1, 120.7, 126.8, 127.2, 127.6, 127.8, 128.0, 128.1, 128.3, 129.5, 130.1, 130.2, 130.5, 130.9, 137.9, 139.6, 145.4, 156.2, 157.1, 167.7.HRMS: calcd for $C_{29}H_{25}NO_2^+$ 420.1964, found 420.1968.



3.05k

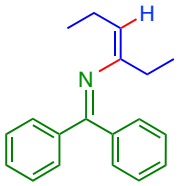
(*Z*)-*N*-(1,2-bis(2-fluorophenyl)vinyl)-1,1-diphenylmethanimine (**3.05k**): Prepared from benzophenone imine (**3.01a**) and 1,2-bis(2-fluorophenyl)ethyne (**3.02k**) according to the general procedure (Method A). Chromatography (0.5% ethyl acetate in hexane) gave **3.05k** as a yellow

liquid (66 mg, 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.47 (s, 1H), 6.86-6.95 (m, 4H), 7.03-7.20 (m, 7H), 7.23-7.29 (m, 1H), 7.45-7.56 (m, 3H), 7.85-7.90 (m, 3H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 108.8, 115.1 (d, J = 22.0 Hz), 115.8 (d, J = 23.1 Hz), 123.6 (d, J = 3.3 Hz), 124.0 (d, J = 3.4 Hz), 125.2 (d, J = 11.2 Hz), 127.6, 127.7, 127.8, 128.3, 128.7 (d, J = 12.9 Hz), 128.8, 128.9 (d, J = 3.4 Hz), 129.5, 129.7, 130.1, 131.1, 137.1, 138.7, 144.5, 160.4 (d, J(C,F) = 249.2 Hz), 161.6 (d, J(C,F) = 247.7 Hz), 169.5. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -117.2, -112.1. HRMS: calcd for $C_{27}H_{19}F_2N^+$ 396.1564, found 396.1563.



3.05l

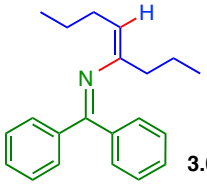
(*Z*)-*N*-(1,2-di(thiophen-2-yl)vinyl)-1,1-diphenylmethanimine (**3.05l**): Prepared from benzophenone imine (**3.01a**) and 1,2-di(thiophen-2-yl)ethyne (**3.02l**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05l** as a yellow solid (59 mg, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.86-6.88 (m, 1H), 6.93-6.94 (m, 1H), 7.01-7.09 (m, 4H), 7.18-7.22 (m, 2H), 7.27-7.32 (m, 1H), 7.48-7.56 (m, 3H), 7.58-7.64 (m, 1H), 7.95 (d, 2H, J = 7.6 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 106.2, 124.0, 124.3, 125.9, 126.1, 126.7, 127.1, 127.7, 128.2, 128.3, 128.4, 128.9, 129.8, 131.4, 132.4, 140.2, 140.5, 141.9, 172.3. HRMS: calcd for $C_{23}H_{17}NS_2Na^+$ 394.0695, found 394.0695.



3.05m

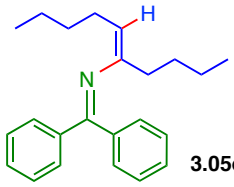
(*Z*)-*N*-(hex-3-en-3-yl)-1,1-diphenylmethanimine (**3.05m**): Prepared from benzophenone imine (**3.01a**) and 3-hexyne (**3.02m**) according to the general procedure (Method B). Chromatography

(0.1% ethyl acetate in hexane) gave **3.05m** as a white liquid (79 mg, 49%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.6 Hz), 1.07 (t, 3H, *J* = 7.6 Hz), 1.87-1.95 (m, 2H), 2.02-2.09 (m, 2H), 4.41 (t, 1H, *J* = 7.2 Hz), 7.28-7.29 (m, 2H), 7.39-7.48 (m, 6H), 7.73-7.76 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 12.1, 14.0, 20.6, 28.8, 109.6, 127.9, 128.1, 128.7, 128.9, 130.2, 137.2, 139.7, 148.5, 165.7. HRMS: calcd for $C_{19}H_{21}N^{+}$ 264.1752, found 264.1758.



3.05n

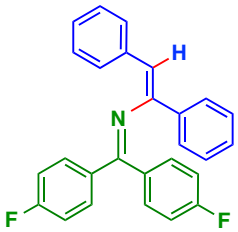
(*Z*)-*N*-(oct-4-en-4-yl)-1,1-diphenylmethanimine (**3.05n**): Prepared from benzophenone imine (**3.01a**) and 4-octyne (**3.02n**) according to the general procedure (Method B). Chromatography (0.1% ethyl acetate in hexane) gave **3.05n** as a white liquid (77 mg, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 7.2 Hz), 0.91 (t, 3H, *J* = 7.2 Hz), 1.23-1.33 (m, 2H), 1.48-1.59 (m, 2H), 1.81-1.83 (m, 2H), 1.90-1.97 (m, 2H), 4.42 (t, 1H, *J* = 6.8 Hz), 7.26-7.29 (m, 2H), 7.36-7.45 (m, 6H), 7.71 (d, 2H, *J* = 6.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.99, 14.02, 20.9, 22.7, 29.5, 38.5, 108.9, 127.8, 128.0, 128.1, 128.6, 128.9, 130.1, 137.3, 139.8, 147.4, 165.3. HRMS: calcd for $C_{21}H_{25}N^{+}$ 292.2065, found 292.2073.



3.05o

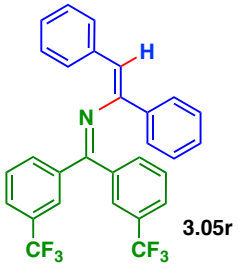
(*Z*)-*N*-(dec-5-en-5-yl)-1,1-diphenylmethanimine (**3.05o**): Prepared from benzophenone imine (**3.01a**) and 5-decyne (**3.02o**) according to the general procedure (Method B). Chromatography (0.1% ethyl acetate in hexane) gave **3.05o** as a white liquid (72mg, 62%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 3.2 Hz), 0.89 (t, 3H, *J* = 3.2 Hz), 1.21-1.37 (m, 2H), 1.46 (qt, 2H, *J* =

7.2 Hz), 1.82 (qt, 2H, J = 6.8 Hz), 1.94 (t, 2H, J = 8.0 Hz), 4.40 (t, 1H, J = 6.8 Hz), 7.25-7.31 (m, 2H), 7.37-7.47 (m, 6H), 7.71 (d, 2H, J = 8.0 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.98, 14.05, 22.6, 22.8, 27.0, 29.9, 31.8, 36.1, 108.8, 127.9, 128.0, 128.1, 128.6, 128.9, 130.1, 137.3, 139.8, 147.6, 165.3. HRMS: calcd for $C_{23}H_{29}N^+$ 320.2378, found 320.3276.



3.05q

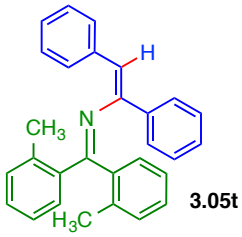
(*Z*)-*N*-(1,2-diphenylvinyl)-1,1-bis(4-fluorophenyl)methanimine (**3.05q**): Prepared from bis(4-fluorophenyl)methanimine (**3.01b**) and diphenyl-acetylene (**3.02a**) according to the general procedure (Method A). Chromatography (0.5% ethyl acetate in hexane) gave **3.05q** as a yellow liquid (83 mg, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.21 (s, 1H), 6.75-6.83 (m, 4H), 7.16-7.19 (m, 3H), 7.25-7.32 (m, 5H), 7.40-7.45 (m, 4H), 7.89-7.93 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 111.7, 114.5 (d, J = 21.6 Hz), 115.4 (d, J = 21.5 Hz), 125.9, 126.0, 127.7, 128.3, 128.4, 128.9, 129.3 (d, J = 8.1 Hz), 131.4 (d, J = 7.8 Hz),132.6, 134.8, 137.4, 139.9, 148.1, 161.5 (d, J(C,F) = 247.1 Hz), 163.6 (d, J(C,F) = 248.9 Hz), 167.0. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -108.9 (s, 1F), -111.6 (s, 1F). HRMS: calcd for $C_{27}H_{19}F_2N^+$ 396.1564, found 396.1561.



3.05r

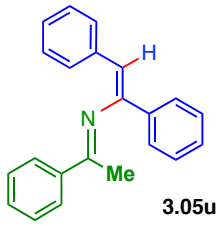
(*Z*)-*N*-(1,2-diphenylvinyl)-1,1-bis(3-(trifluoromethyl)phenyl)-methanimine (**3.05r**): Prepared from bis(3-(trifluoromethyl)phenyl)-methanimine (**3.01c**) and diphenylacetylene (**3.02a**)

according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05r** as a yellow liquid (73 mg, 93%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 1H), 6.97 (s, 1H), 7.03 (d, 1H, *J* = 8.0 Hz), 7.21-7.25 (m, 1H), 7.32-7.38 (m, 6H), 7.41-7.48 (m, 4H), 7.58 (d, 1H, *J* = 8.0 Hz), 7.63-7.67 (m, 1H), 7.63-7.67 (m,1H), 7.87 (d, 1H, *J* = 7.6 Hz), 8.02 (d, 1H, *J* = 7.6 Hz), 8.30 (s, 1H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 111.8, 119.6 (q, *J*(C, F) = 271.2 Hz), 119.9 (q, *J*(C, F) = 271.2), 124.2 (q, *J* = 3.7 Hz), 125.6 (q, *J* = 3.8 Hz), 125.8, 126.3, 126.7, 127.1 (q, *J* = 8.8 Hz), 127.9 (q, *J* = 3.0 Hz), 128.0, 128.45, 128.49, 128.9, 129.2, 129.9 (q, *J* = 22.7 Hz), 131.2 (q, *J* = 32.6 Hz), 132.4, 136.7, 136.9, 138.7, 139.5, 147.9, 166.1. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.6, -62.8. HRMS: calcd for $C_{29}H_{19}NF_6Na^+$ 518.1314, found 518.1314.



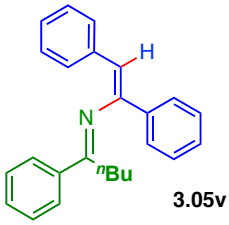
3.05t

(*Z*)-*N*-(1,2-diphenylvinyl)-1,1-di-*o*-tolylmethanimine (**3.05t**): Prepared from di-*o*-tolylmethanimine (**3.01e**) and diphenylacetylene (**3.02a**) according to the general procedure (Method A). Chromatography (1% ethyl acetate in hexane) gave **3.05t** as a yellow liquid (66 mg, 71%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.50 (s, 3H), 2.74 (s, 3H), 6.06 (s, 1H), 6.87-7.02 (m, 4H), 7.18-7.23 (m, 7H), 7.28-7.36 (m, 5H), 7.57 (d,2H, *J* = 7.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 19.4, 22.5, 113.7, 125.0, 125.8, 126.6, 127.2, 127.8, 128.4, 128.9, 129.7, 130.0, 131.0, 131.9, 134.8, 137.6, 138.1, 138.41, 138.44, 141.5, 149.2, 172.1. HRMS: calcd for $C_{29}H_{25}N^+$ 388.2065, found 388.2069.



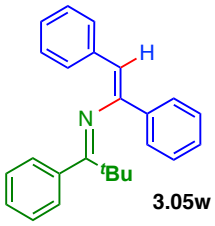
3.05u

(*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-1-phenylethan-1-imine (**3.05u**): Prepared from 1-phenylethan-1-imine (**3.01f**) and diphenylacetylene (**3.02a**) according to the general procedure (Method C). Chromatography (0.1% ethyl acetate in hexane) gave **3.05u** as a yellow liquid (107 mg, 86%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 6.47 (s, 1H), 6.92 (s, 1H), 7.15-7.19 (m, 1H), 7.28-7.30 (m, 2H), 7.36 (d, 1H, *J* = 7.2 Hz), 7.40-7.44 (m, 3H), 7.49 (d, 2H, *J* = 7.6 Hz), 7.55 (d, 2H, *J* = 7.2 Hz), 7.64 (d, 2H, *J* = 7.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 17.9, 109.9, 125.7, 125.9, 126.7, 127.4, 127.9, 128.4, 128.5, 128.6, 130.8, 131.5, 137.3, 138.6, 138.9, 147.6, 166.6. HRMS: calcd for $C_{22}H_{19}N^{+}$298.1596, found 298.1599.



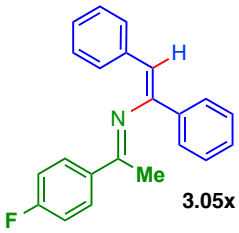
3.05v

(*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-1-phenylpentan-1-imine (**3.05v**): Prepared from 1-phenylpentan-1-imine (**3.01g**) and diphenylacetylene (**3.02a**) according to the general procedure (Method C). Chromatography (0.1% ethyl acetate in hexane) gave **3.05v** as a yellow liquid (81 mg, 77%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.77 (t, 3H), 1.20 (m, 4H), 2.66 (t, 2H), 6.52 (s, 1H), 7.19-7.23 (m, 1H), 7.34-7.41 (m, 3H), 7.44-7.48 (m, 2H), 7.55-7.61 (m, 5H), 7.71 (d, 2H, *J* = 7.6 Hz), 8.16 (d, 2H, *J* = 6.0 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ13.7, 23.0, 28.6, 31.3, 109.7, 125.9, 127.8, 127.9, 128.4, 128.6, 128.7, 128.8, 130.6, 137.5, 138.1, 139.5, 147.7, 170.5. HRMS: calcd for $C_{25}H_{25}N^{+}$ 340.2065, found 340.2061.



3.05w

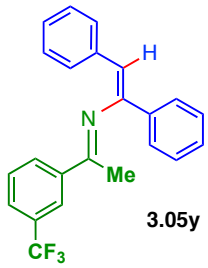
(*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-2,2-dimethyl-1-phenylpropan-1-imine (**3.05w**): Prepared from 2,2-dimethyl-1-phenylpropan-1-imine (**3.01h**) and diphenylacetylene (**3.02a**) according to the general procedure (Method C). Chromatography (0.1% ethyl acetate in hexane) gave **3.05w** as a yellow liquid (84 mg, 80%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9H), 6.00 (s, 1H), 6.42 (d, 2H, J = 7.2 Hz), 7.13-7.17 (m, 1H), 7.22-7.24 (m, 1H), 7.26-7.33 (m, 3H), 7.34-7.36 (m, 2H), 7.38-7.42 (m, 2H), 7.50 (d, 2H, *J* = 7.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 28.3, 40.6, 109.9, 125.7, 125.9, 126.8, 127.3, 127.37, 128.44, 128.1, 128.6, 129.1, 137.9, 140.5, 148.6, 179.8. HRMS: calcd for $C_{25}H_{25}N^{+}$ 340.2065, found 340.2072.



3.05x

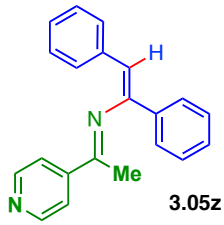
(*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-1-(4-fluorophenyl)ethan-1-imine (**3.05x**): Prepared from 1-(4-fluorophenyl)ethan-1-imine (**3.01i**) and diphenylacetylene (**3.02a**) according to the general procedure (Method C). Chromatography (0.1% ethyl acetate in hexane) gave **3.05x** as a yellow liquid (102 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3H), 6.95 (s, 1H), 6.96-7.17 (m, 1H), 7.17-7.26 (m, 2H), 7.28-7.32 (m, 2H), 7.37 (d,1H, *J* = 7.2 Hz), 7.40-7.45 (m, 2H), 7.49 (d, 2H, *J* = 7.6 Hz), 7.64 (d, 2H, *J* = 7.2 Hz), 8.16 (d, 2H, *J* = 5.6 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 17.9, 110.0, 115.6 (d, J = 21.5 Hz), 125.7, 125.9, 126.7, 128.4, 128.5, 128.6, 129.5 (d,

J = 8.7 Hz), 131.5, 135.0, 137.3, 138.5, 147.5, 165.2. 165.9 (d, *J*(C, F) = 249.5 Hz). ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -109.8. HRMS: calcd for $C_{22}H_{18}NF^+$ 316.1501, found 316.1499.



3.05y

(*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-1-(3-(trifluoromethyl)phenyl)ethan-1-imine (**3.05y**): Prepared from 1-(3-(trifluoromethyl)phenyl)ethan-1-imine (**3.01j**) and diphenylacetylene (**3.02a**) according to the general procedure (Method C). Chromatography (0.1% ethyl acetate in hexane) gave **3.05y** as a yellow liquid (89 mg, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.18 (s, 3H), 6.49 (s, 1H), 6.94 (s, 1H), 7.16 (d, 1H, *J* = 7.6 Hz), 7.28-7.38 (m, 1H), 7.38-7.40 (m, 1H), 7.42-7.49 (m, 4H), 7.62-7.69 (m, 3H), 7.83 (d, 1H, *J* = 7.6 Hz), 8.32 (d, 1H, *J* = 7.6 Hz), 8.39 (s, 1H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 17.9, 110.2, 120.1 (qt, *J*(C,F) = 270.9 Hz). 124.1 (qt, *J* = 3.7 Hz), 125.3, 125.5, 126.2, 126.6, 127.3 (qt, *J* = 3.7 Hz), 128.1, 128.47, 128.51, 128.7, 129.2, 130.6 (qt, J = 32.1 Hz), 137.1, 138.3, 139.5, 147.5, 165.2. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.5. HRMS: calcd for $C_{23}H_{18}NF_3^+$ 366.1470, found 366.1466.



3.05z

(*E*)-*N*-((*Z*)-1,2-diphenylvinyl)-1-phenylethan-1-imine (**3.05z**): Prepared from 1-phenylethan-1-imine (**3.01k**) and diphenylacetylene (**3.02a**) according to the general procedure (Method C). Chromatography (0.1% Methanol in DCM) gave **3.05z** as a yellow solid (91 mg, 73%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 6.44 (s, 1H), 7.13-7.17 (m, 1H), 7.25-7.29 (m, 2H), 7.33-7.42

(m, 5H), 7.56 (d, 2H, *J* = 7.2 Hz), 7.89 (d, 2H, *J* = 6.0 Hz), 8.80 (d, 2H, *J* = 4.4 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 17.6, 110.2, 121.1, 125.6, 126.2, 128.2, 128.45, 128.48, 128.7, 136.8, 137.9, 145.5, 147.0, 150.5, 165.2. HRMS: calcd for $C_{21}H_{18}N_2^+$ 299.1548, found 299.1549.

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16. Adding H_2O led to slightly improved yield for 3.60a compared to reactions without any additives (entries 11, 12) and generated only trace amount of benzophenone (<5%) by GC analysis. However, imine hydrolysis with added H_2O became much more significant with less stable N H ketimines. Thus, our catalyst development efforts focused on using base additives rather than added H_2O.

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18. Terminal alkynes such as phenylacetylene led to alkyne oligomerization instead of desired hydroimination; see ref 25c and 25d.

19. It is not clear to us why aryl alkyl alkyne substrates display such high chemoselectivity towards oligomerization (e.g. cyclotrimerization) over desired hydroimination. Alkyne reactivity for catalytic cyclotrimerization and hydroamination is known to depend on

both steric and electronic factors and can be difficult to predict. See ref 19d for an example of chemoselective alkyne hydroamination vs. cyclo trimerization using Ni(II) vs. Ni(0) catalyst precursors.

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21. Formation of the (*Z*) enamine product could also be explained by *E*/*Z* isomerization of an initial (*E*) enamine product from *syn* hydroamination pathways. Such a scenario cannot be ruled out at this point, but the lack of observation for any *syn* addition products suggested that it was unlikely to be the major reaction pathway.

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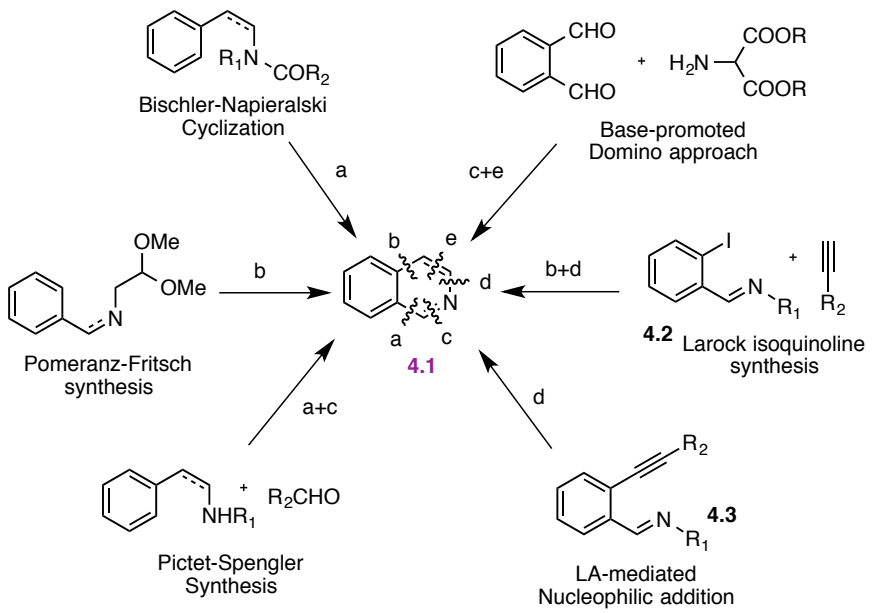
CHAPTER 4. DEHYDROGENATIVE [4+2] ANNULATION OF KETIMINE AND ALKYNE VIA MURAI-HYDRIDE PATHWAY

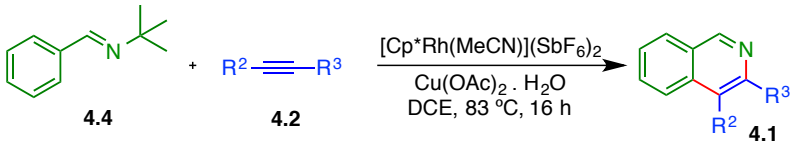
4.1. Introduction

Isoquinoline and its derivatives are found in natural products and pharmaceuticals that exhibit a variety of biological activities such as analgesic, antitumor and antihistaminic activities.[1] Isoquinolines are conventionally synthesized by Bischler-Napieralski[2], Pomeranz-Fritsch[3] and Pictet-Gams[4] reactions, which usually require preactivated substrates. In addition, the generally harsh reaction conditions lead to poor functional group tolerance. By using simple bases such as NaOEt, Bazureau developed a domino approach for reaction between phthaldehyde and α-aminomalonate to prepare isoquinoline derivatives.[5a] Recently Wang reported an alternative way leading to an isoquinoline skeleton by reaction between o-ethynyl benzacetals and sulfonyl azides.[5b] Larock and several other groups reported isoquinoline synthesis by intramolecular cyclization of *ortho*-alkynylated substrates. By using Pd and Ni catalysts people have reported [4+2] annulation of 2-halo benzaldimines and alkynes for isoquinoline synthesis[6] but these methods need pre-installation of *o*-alkynyl or *o*-halo groups into the substrates. An alternatively strategy is to activate unreactive C-H bonds to participate in such a reaction (scheme 4.1).[7]



Scheme 4.1. Different conventional approaches for isoquinoline synthesis

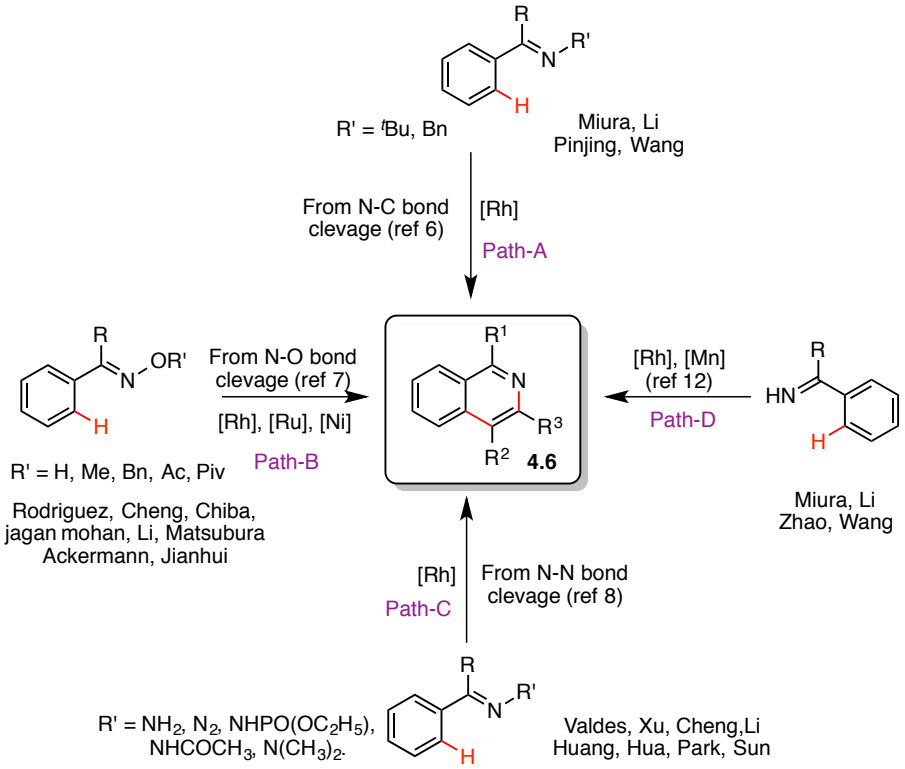
Fagnou and co-workers reported isoquinoline synthesis by coupling between aryl aldimines (**4.4**) and alkynes (**4.2**) using rhodium(III) catalyst.[8]



Scheme 4.2. Fagnou's isoquinoline synthesis

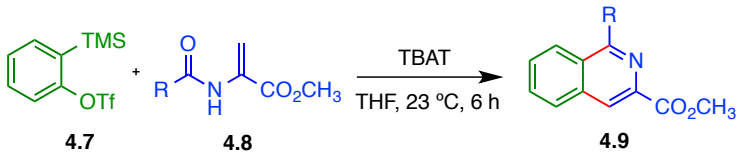
For isoquinoline synthesis different directing groups having N–H or O–H moiety and stoichiometric amounts of Ag(I) or Cu(II) oxidants have been used for oxidative [4+2] annulations. This need for external oxidants can be eliminated either by developing ways such as aerobic oxidation or dehydrogenative coupling conditions, or by internal oxidation through N-C bond cleavage (Path A)[9] in Scheme 4.3, N-O bond cleavage (Path B)[10] or N-N bond cleavage (Path C)[11] or N-H bond cleavage (oxidative/dehydrogenative) (Path D).[12] Miura reported rhodium(III) catalysed isoquinoline synthesis from ketimines and alkynes by C-H activation but in the presence of external oxidant to induce catalytic turn-over. Recently, a complimentary

method is reported by Wang using the less expensive metal, manganese as the catalyst (Path D) (Scheme 4.3).[12]



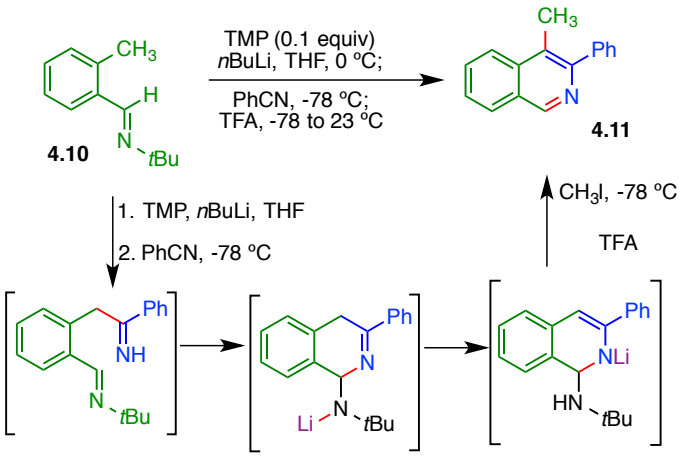
Scheme 4.3. Oxidative annulation by using different internal oxidants for isoquinoline synthesis

Stoltz developed an orthogonal strategy to synthesize isoquinoline derivatives from aryne annulation and ene carbamate respectively (Scheme 4.4).[13]



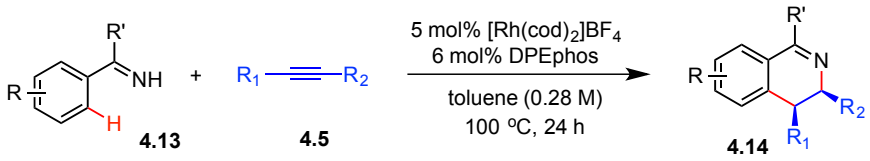
Scheme 4.4. Stoltz's orthogonal strategy for isoquinoline synthesis

Myers reported a direct route to 3-substituted isoquinolines by trapping metalated *o*-tolualdehyde tert-butylimines with nitriles in the presence of *n*-BuLi as a strong base (Scheme 4.5).[14]



Scheme 4.5. Myers's versatile synthesis for isoquinoline

Recently we and several other groups reported new applications of benzophenone imines in metal-catalyzed transformations including [3+2] cycloaddition[16], [4+2] cycloadditions, aza-Wittig[17] and hydroimination reactons[18]. Merging the strategies of late transition metal-catalyzed C-H activation and olefin hydroamination, we recently reported a Rh-catalyzed redox-neutral [4+2] benzophenone imine/alkyne annulations via a domino sequence of C-H bond activation, C-C bond formation by alkyne coupling, and C-N bond formation by intramolecular olefin hydroamination (Scheme 4.6).[19]



Scheme 4.6. Cationic rhodium catalyzed synthesis of dihydroisoquinoline

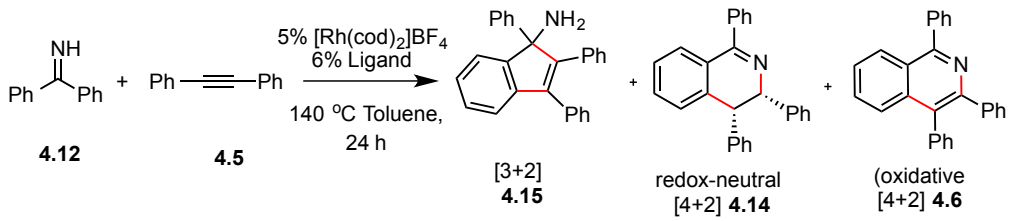
Our goal is to use this redox neutral [4+2] annulation of benzophenone imine/alkyne of dihydroisoquinoline synthesis to undergo dehydrogenation at higher temperature to to synthesize isoquinoline derivatives.

4.2. Initial observation

During our study on redox neutral [4+2] N-heterocyclization by on Rh(I)-catalyzed coupling between benzophenone imine (**4.12**) and diphenylacetylene (**4.5**) we also observed another annulation product by increasing the temperature, namely oxidative [4+2] N-heterocyclization product (**4.6**). The overall yield and chemoselectivity depended significantly on the choices of Rh (I) catalyst precursor.

From our previous studies, neutral Rh(I) precursors with anionic ligands such as $[Rh(cod)_2(OH)_2]$ were less effective so we began our study with cationic Rh(I) precursors with non- coordinating counteranions, e.g. $[Rh(cod)_2]BF_4$, which appeared to promote dehydrogenative [4+2] coupling. We began our catalyst development by screening the ligands with the detection of three different products from catalytic coupling between N-H aromatic ketimines and internal alkynes. Dihydroisoquinoline byproduct was also observed and the reaction conditions were screened to improve the yield and selectivity for Isoquinoline product. Monophosphines gave lower yield compare to the bisphosphines. Among the bisphosphines DPEPhos gave highest conversion. Monophosphines like triphenylphosphine and tricyclohexylphosphine were found to be ineffective. *N*-heterocyclic carbene ligands were also found to only give poor to moderate yileds of isoquinoline.

Table 4.1. Development of the catalytic reactions (ligand screening)

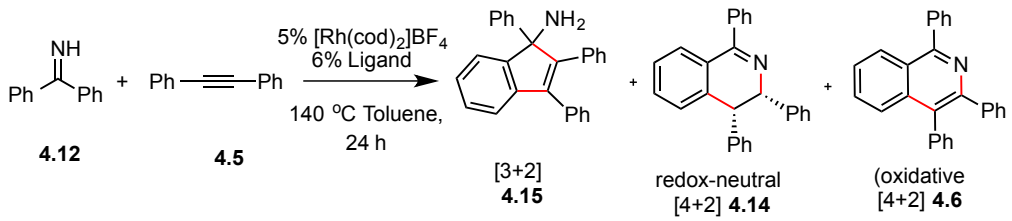


entry	Ligand	yield[b] **4.15** (%)	yield[b] **4.14** (%)	yield[b] **4.6** (%)
1	(*rac*)-BINAP	4	6	7
2	*Cis*-DPPPEthylene	3	13	24
3	BIPHEP	8	28	13
4	DPPF	11	13	17
5	DPEPhos	2	3	94
6	Xantphos	3	7	21
7[c]	PPh_3	0	12	15
8[c]	PCy_3	1	13	17
9	IPr	5	7	36
10	IMes	2	5	15

[a]General conditions: **4.12** (0.28 mmol, 1.0 equiv), **4.5** (1.05 equiv), Rh catalyst (0.050 equiv), ligand (0.060 equiv), solvent (1.0 mL), 140 °C, 24h. [b] GC yields. [c] Using 0.011 equiv phosphine ligand.

The overall yield and chemoselectivity influenced by various factors such as phosphine ligands and polarity of the solvent. With the optimized catalyst system of cationic Rh(I) pre-catalyst with BF_4 counteranion and DPEPhos as ligand optimized we screened different solvents. Polar solvents such as DMF, MeOH and 1,4-dioxane gave lower yields compared to aromatic non-polar solvents. Among aromatic non-polar solvents toluene gave the best conversion. Under the optimized conditions of 5 mol% of $[Rh(cod)_2]BF_4$ and 6 mol% of DPEPhos ligand in dry toluene at 140 ºC the reaction gave near quantitative yield of Isoquinoline product **4.6**.

Table 4.2. Development of the catalytic reactions (solvent screening)

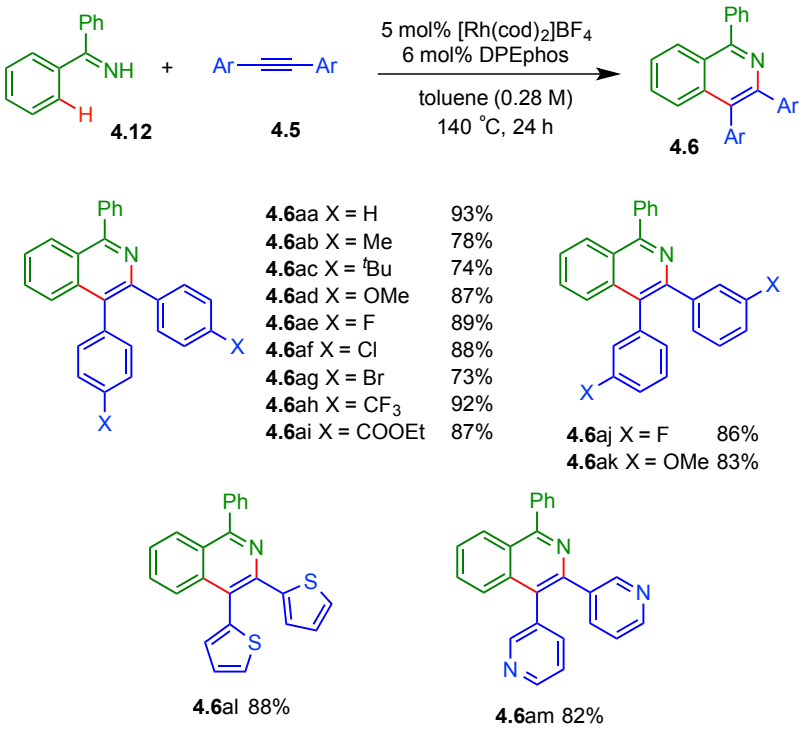


entry	Ligand	yield[b] **4.15** (%)	yield[b] **4.14** (%)	yield[b] **4.6** (%)
1	Toluene	1	4	94
2	1,4-Dioxane	6	5	63
3	DMF	1	24	55
4	Hexane	2	3	12
5	*m*-Xylene	4	12	71
6	Methanol	5	15	42
7	DME	4	33	40
8	DCE	3	12	11
9	PhCl	7	6	46

[a] General conditions: **4.12** (0.28 mmol, 1.0 equiv), **4.5** (1.05 equiv), Rh catalyst (0.050 equiv), ligand (0.060 equiv), solvent (1.0 mL), 140 °C, 24 h. [b] GC yields.

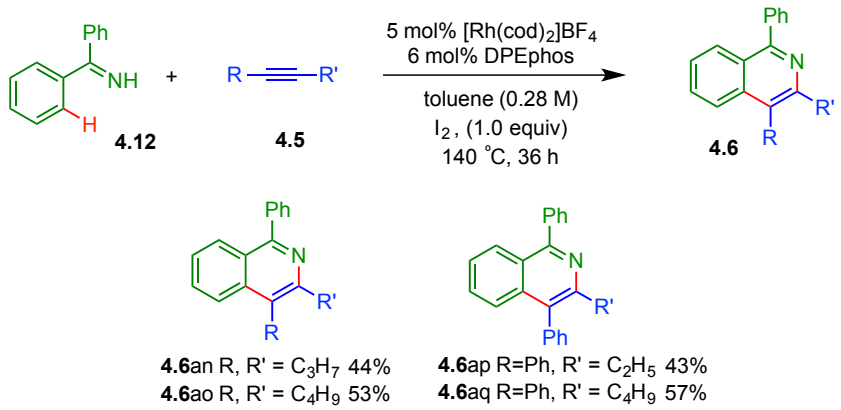
4.3. Alkyne substrate scope

With the standard reaction conditions established, various aromatic N-H ketimine (**4.12**) and internal alkyne (**4.5**) substrates were studied for Rh(I)-catalyzed dehydrogenative [4+2] annulation (Scheme 4.7). Scope of the alkyne substrate was studied with benzophenone imine as the reaction partner. Symmetrical aryl alkynes having electron donating or electron withdrawing showed high coupling yields. Even bromine containing aromatic alkynes were also tolerated with good yields. Alkynes with symmetrical heteroaryl substituents, such as 2-thienyl and 3-pyridyl also gave isoquinoline products in good yields (Scheme 4.7).



Scheme 4.7. Aromatic alkyne substrate scope for [4+2] imine-alkyne dehydrogenative annulation

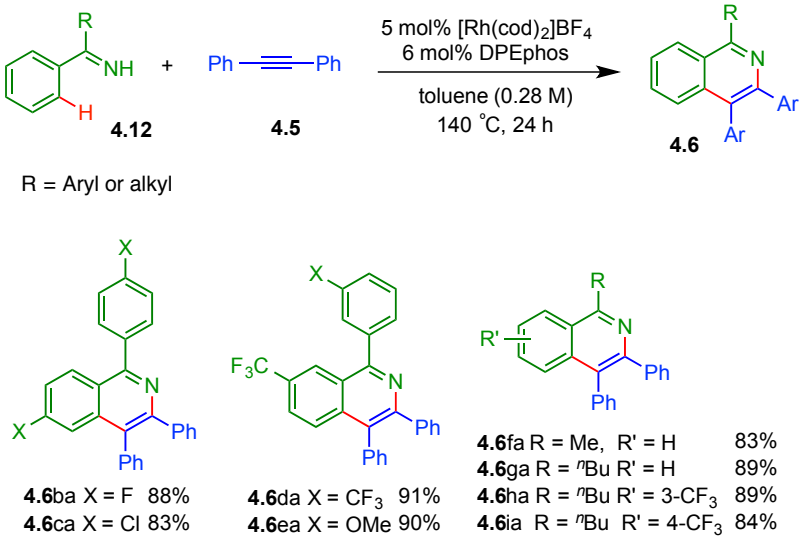
For Aliphatic alkynes and aryl-alkyl alkynes did not undergo dehydrogenation under standard conditions as shown above, However in the presence of stoichiometric amount of I_2 as oxidant they were reactive towards benzophenone imine to form desired isoquinoline products. Even though the yields are only moderate for the unsymmetrical alkynes the regioselectivity is different from other reported isoquinoline products by oxidative [4+2] annulations. This result supported a Murai-type alkyne hydroarylation pathway and a ring-closure step that is different from the proposed C-N reductive elimination in other oxidative [4+2] annulation for isoquinoline synthesis (*vide infra*) (Scheme 4.8).



Scheme 4.8. Aliphatic and unsymmetrical aryl-alkyl alkyne substrate scope for [4+2] imine-alkyne oxidative annulation

4.4. N-H ketimine substrate scope

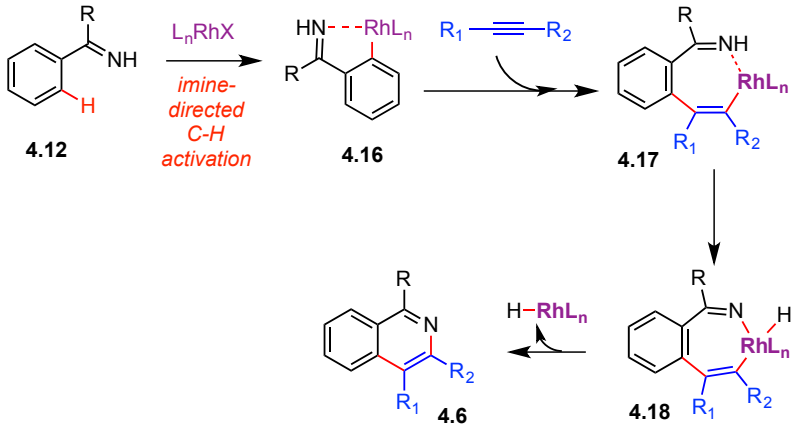
Ketimine substrate scope was studied by coupling with diphenylacetylene under optimized conditions as shown in Scheme 4.8. For both diaryl and aryl alkyl ketimines with phenyl groups or electron-poor aryl groups having F, Cl, and CF_3 groups at *para* or *meta* positions high reactivity was observed. Electron-rich di(*p*-anisyl) N-H ketimine failed to react whereas di(*p*-tolyl) N-H ketimines gave desired isoquinoline product in 70% yield. Such electronic effect is also observed in the unsymmetrical ketimines having both electron donating and withdrawing groups to the same ketimine and the product is formed with exclusive regioselectivity for C-H functionalization of the electron poor aryl group with *meta*-CF_3 substituent over the electron-rich one with *meta*-methoxy substituent (product **4.6ea**) (Scheme 4.9).



Scheme 4.9. Imine substrate scope for [4+2] imine-alkyne dehydrogenative annulation

4.5. Conventional proposed rhodium catalyzed C-N bond formation

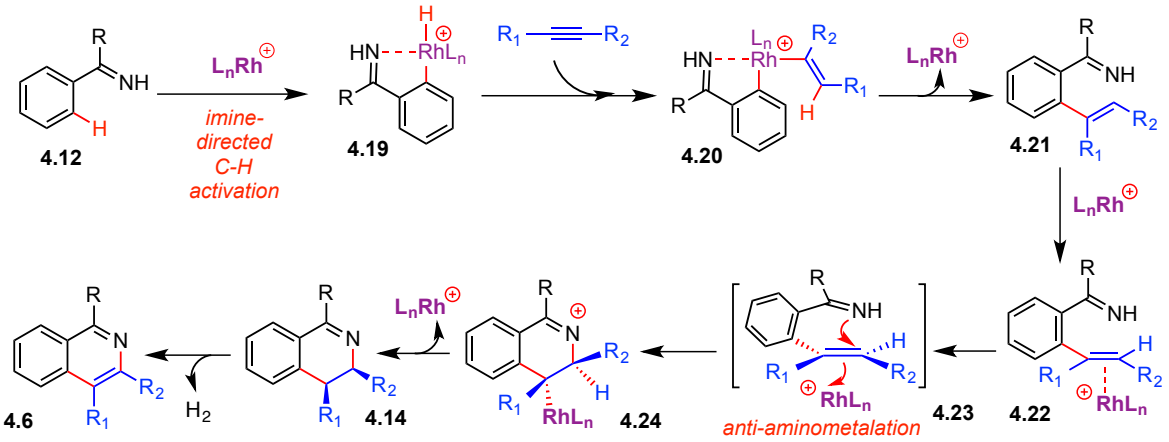
In reported oxidative [4+2] annulation for isoquinoline synthesis such as examples with Rh(I) catalyst, metal-mediated imine directed C-H activation gives Rh(I)-cyclometallated intermediate (**4.16**) followed by 1,2-insertion of the alkyne to give imine chelated metal-alkenyl intermediate (**4.17**). Subsequent N-H oxidative addition gives metal(III)-hydride intermediate (**4.18**) which upon C-N reductive elimination gives isoquinoline and regenarates the active catalyst for another catalytic cycle.



Scheme 4.10. Conventional pathway for isoquinoline synthesis

4.6. Murai-type of hydride pathway for C-N bond formation

In comparision, in our previously reported redox-neutral [4+2] annulation of N-H ketimine and alkyne we proposed Murai-type hydride pathway where a cationic Rh(I) catalyst promotes imine directed C-H activation via oxidative addition pathway to give Rh(III)-hydride (**4.19**). Subsequent alkyne insertion into Rh-hydride linkage gives Rh(III)-alkenyl intermediate (**4.20**) which upon C-C reductive elimination gives hydroarylation intermediate (**4.21**). Cationic Rh(I) will coordinate to olefin moiety in **4.21** and forms complex **4.22**. Such olefin activation by Lewis acidic metal species would promote intramolecular nucleophilic attack by the N-H imine moiety in stereospecific *6-endo-trig* fashion to give metal alkyl intermediate **4.24** followed by protonation of the Rh-alkyl linkage with retained configuration to give the *cis*-isomer of redox-neutral annulation product **4.6**. This dihydroisoquinoline product undergoes dehydrogenation *in situ* to give isoquinoline and regenerates the active catalyst (Scheme 4.11).

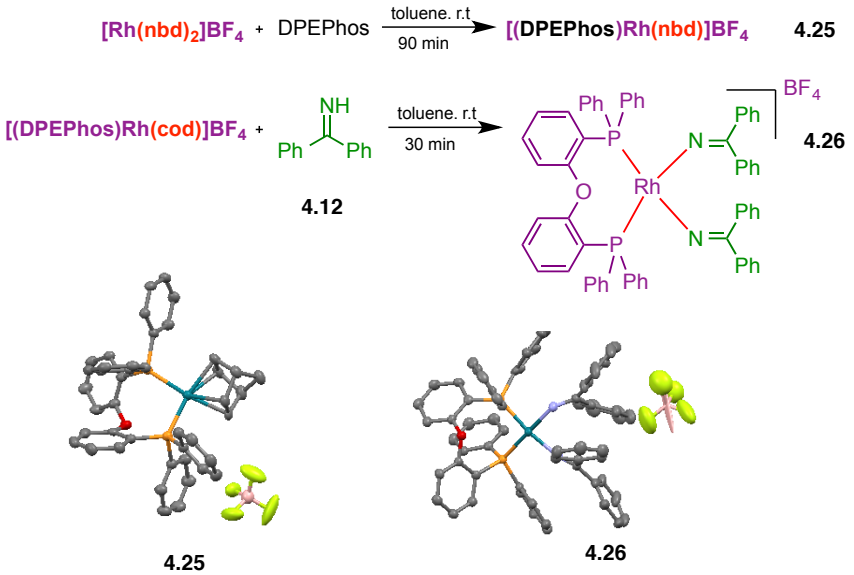


Scheme 4.11. Proposed Murai-hydride pathway for isoquinoline synthesis

4.7. Stoichiometrics attempts to isolate rhodium(III)-hydride intermediate

In order to gain further mechanistic insights, we sought to isolate Rh(III) hydride intermediate (**4.19**) with the attached DPEPhos ligand and evaluate its catalytic activity. Unfortunately, our efforts were hindered by the strong Rh-imine complexation that appears to

inhibit further transformations. Initially we did stoichiometric reaction by reacting $[Rh(nbd)_2]BF_4$ with DPEPhos ligand and were able to isolate $[Rh(nbd)DPEphos)]BF_4$ (**4.25**) in quantitative yield. Later we switched $[(DPEPhos)Rh(cod)]BF_4$ which was synthesized by reported literature[19] and then added 2.1 equiv of benzophenone imine to give a Rh(I) bis(imine) complex (**4.26**). Even after heating at higher temperature and also for prolonged time the compound is stable and did not undergo cyclometalation. We also tried by adding ancillary ligands such as pyridine so that one of the benzophenone imine can be replaced by pyridine to form a 4-coordinated square planar complex but our results were hampered due to strong coordination of benzophenone imine to rhodium(I) centre.



Scheme 4.12. Attempted stoichiometric studies to isolate Rh(III)-hydride intermediate

4.8. General experimental procedures and reagent availability

Unless otherwise noted, all manipulations were carried out under a nitrogen atmosphere using standard Schlenk-line or glovebox techniques. All glassware was oven-dried for at least 1 h prior to use. THF, toluene, and hexane were degassed by purging with nitrogen for 45 min and dried with a solvent purification system (MBraun MB-SPS). Dioxane was distilled over sodium

and freshly used. Other reagents and substrates were purchased from commercial vendors and were used as received. TLC plates were visualized by exposure to ultraviolet light or by exposure to I_2 sealed in a bottle at room temperature. Organic solutions were concentrated by rotary evaporation at ~10 torr. Flash column chromatography was performed with 32–63 microns silica gel.

GC analyses were performed on a Shimadzu GC-2010 with *n*-dodecane as the internal standard. ^{1}H NMR spectra were obtained on a 400 MHz spectrometer, and chemical shifts were recorded relative to residual protiated solvent. ^{13}C NMR spectra were obtained at 100 MHz, and chemical shifts were recorded to the solvent resonance. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane ($\delta = 0$). ^{19}F NMR spectra were obtained at 282.4 MHz, and all chemical shifts were reported in parts per million upfield of CF_3COOH (δ = -78.5P). High-resolution mass spectra were obtained at a Bruker Daltronics BioTOF HRMS spectrometer.

4.8.1. General procedure for dehydrogenative [4+2] annulation of imine and alkyne

Procedure-A (imine as limiting reagent): Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed $[Rh(cod)_2]BF_4$ (5.6 mg, 0.014 mmol, 0.050 equiv), DPEPhos (8.9 mg, 0.017 mmol, 0.060 equiv), and 1.0 mL of toluene. Next, N-H ketimine **1** (0.28 mmol, 1.00 equiv) and internal alkyne **2** (0.31 mmol, 1.10 equiv), were added into the vial. The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 140 °C for 24 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using 32–63 microns silica gel.

Procedure-B (alkyne as limiting reagent): Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed $[Rh(cod)_2]BF_4$ (5.6 mg, 0.014 mmol, 0.050 equiv), DPEPhos (8.9 mg, 0.017 mmol, 0.060 equiv), and 1.0 mL of toluene. Next, internal alkyne **1** (0.28 mmol, 1.00 equiv), N-H ketimine **2** (0.31 mmol, 1.10 equiv), were added into the vial. The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 140 °C for 24 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using 32–63 microns silica gel.

Procedure-C: Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed $[Rh(cod)_2]BF_4$ (5.6 mg, 0.014 mmol, 0.050 equiv), DPEPhos (8.9 mg, 0.017 mmol, 0.060 equiv), and 1.0 mL of toluene. Next, N-H ketimine **1** (0.28 mmol, 1.00 equiv), internal unsymmetrical alkyne **2** (0.41 mmol, 1.50 equiv), and I_2 (0.14 mmol, 0.50 equiv) were added into the vial. The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 140 °C for 36 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using 32–63 μ silica gel.

Supplementary Figures. ORTEP diagram of $[Rh(nbd)(DPEPhos)]BF_4$ (**4.25**), $[Rh(DPEPhos)(\eta^1\text{-}Ph_2C{=}NH)_2]BF_4$ (**4.26**) and 3-ethyl-1,4-diphenylisoquinoline (**4.6ap**). All aromatic hydrogen atoms and the ethyl hydrogen atoms in **4.6ap** are omitted for clarity.

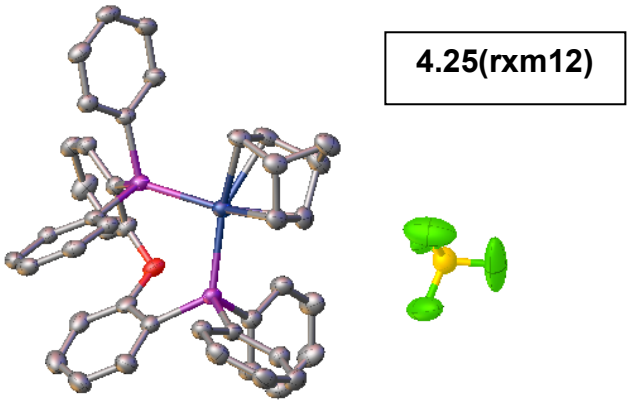


Figure 4.1. ORTEP diagram of complex [Rh(nbd)(DPEPhos)]BF_4 (**4.25**)

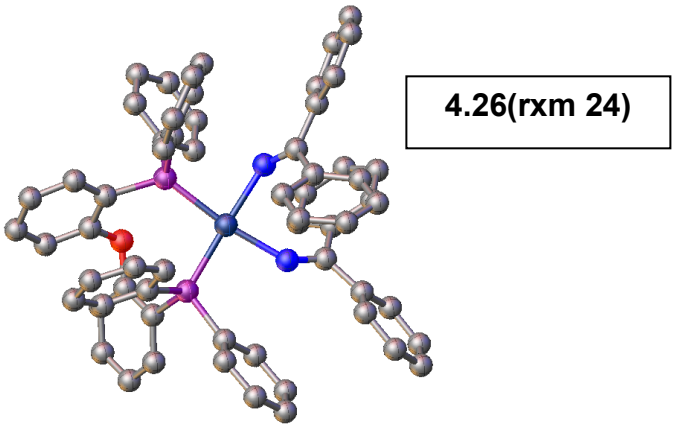


Figure 4.2. ORTEP diagram of complex [Rh(DPEPhos)(η^1-$Ph_2C{=}NH)_2$]BF_4 (**4.26**)

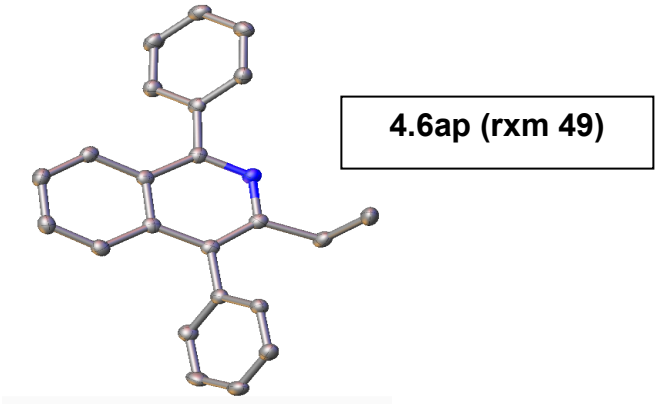
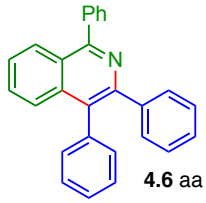


Figure 4.3. ORTEP diagram of 3-ethyl-1,4-diphenylisoquinoline (**4.6ap**)

Table 4.3. Summary of cell parameters, data collection and structural refinements for **4.25**, **4.26** and **4.6ap**.

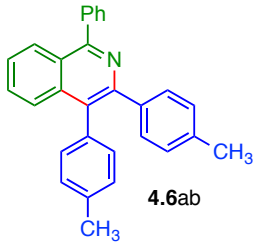
	4.25	**4.26a**	**4.6ap**
Formula	$C_{43}H_{35}OP_2RhBF_4$	$C_{64}H_{52}N_2OP_2Cl_2RhBF_4$	$C_{23}H_{19}N$
FW	984.57	1258.53	309.39
cryst. size_max [mm]	0.4	0.19	0.327
cryst. size_mid [mm]	0.264	0.15	0.113
cryst. size_min [mm]	0.046	0.11	0.120
cryst. system	monoclinic	triclinic	monoclinic
Space Group, Z	P 1 21/n, 1	P-1	P 1 21/c, 1
a [Å]	10.4182(4)	13.3628(5)	11.2345(7)
b [Å]	18.5694(6)	14.0839(5)	8.1436(5)
c [Å]	23.3372(8)	16.0363(5)	17.8594(10)
α [Å]	90.0	73.7520(10)	90.0
ß [Å]	99.287(2)	84.703(2)	92.166(3)
γ [Å]	90.0	77.180(2)	90.0
V [Å3]	4455.6(3)	2823.79(17)	1632.78(17)
ρcalc [g/cm3]	1.468	1.480	1.259
μ [mm-1]	4.295	5.205	0.552
F(000)	2022	1284	656
no of measured refl.	47238	33912	10277
no of indep. refl.	7870	9650	2823
no of refl. ($I \geq 2\sigma$)	6919	9024	2399
R1/wR2 ($I \geq 2\sigma$)a	3.96/10.20	6.33/17.44	4.11/10.45
R1/wR2 (all data)	4.66/10.67	6.62/11.12	4.92/11.17

4.8.2. Analytical data of reported products



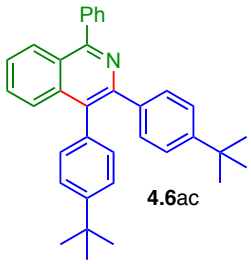
4.6 aa

1,3,4-Triphenylisoquinoline 4.6aa: Prepared from benzophenone imine (**4.13a**) and 1,2-diphenylethyne (**4.5a**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6aa** as a white solid (87 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21-7.24 (m, 3H), 7.34-7.43 (m, 5H), 7.49-7.61 (m, 7H), 7.76-7.79 (m, 1H), 7.86-7.89 (m, 2H), 8.22-8.25 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 125.7, 126.3, 126.9, 127.3, 127.6, 127.77, 127.83, 128.6, 128.8, 130.1, 130.2, 130.5, 130.8, 131.6, 137.3, 137.8, 140.1, 141.2, 149.7, 160.1. HRMS: calcd for $C_{27}H_{20}N^+$ 358.1590, found 358.1602.



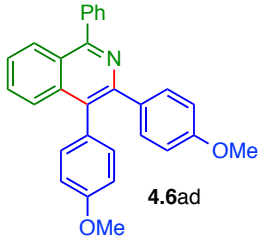
4.6ab

1-Phenyl-3,4-di-*p*-tolylisoquinoline 4.6ab: Prepared from benzophenone imine (**4.13a**) and 1,2-bis(4-methylphenyl)ethyne (**4.5b**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6ab** as a white solid (84 mg, 79%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.42 (s, 3H), 6.99 (d, 2H, J = 8.4 Hz), 7.18-7.24 (m, 4H), 7.35 (d, 2H, J = 8.0 Hz), 7.47-7.58 (m, 5H), 7.72 (d, 1H, J = 8.4 Hz), 7.82-7.84 (m, 2H), 8.16 (d, 1H, J = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4, 21.6, 125.5, 126.3, 126.5, 127.6, 128.46, 128.52, 128.7, 129.3, 129.7, 129.9, 130.5, 131.4, 134.9, 136.8, 137.0, 137.5, 138.4, 140.2, 141.8, 159.7. HRMS: calcd for $C_{29}H_{24}N^+$ 386.1830, found 386.1827.



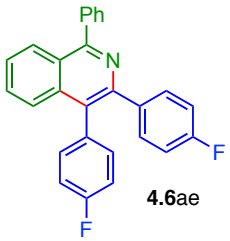
4.6ac

3,4-Bis(4-(*tert*-butyl)phenyl)-1-phenylisoquinoline 4.6ac: Prepared from benzophenone imine (**4.13a**) and 1,2-bis(4-(*tert*-butyl)phenyl)ethyne (**4.5c**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6ac** as a white solid (96 mg, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 1.42 (s, 9H), 7.21-7.29 (m, 4H), 7.41-7.46 (m, 4H), 7.51-7.60 (m, 5H), 7.81(d, 1H, *J* = 8.0 Hz), 7.86 (d, 2H, *J* = 6.8 Hz), 8.20 (d, 1H, J = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.3, 31.5, 34.4, 34.6, 124.4, 125.2, 125.3, 126.2, 126.4, 127.4, 128.3, 128.4, 129.6, 129.7, 130.1, 130.3, 130.4, 131.0, 134.6, 137.2, 138.1, 140.0, 149.7, 150.2, 159.5. HRMS: calcd for $C_{35}H_{36}N^+$ 470.2770, found 470.2763.



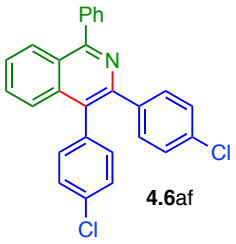
4.6ad

3,4-Bis(4-methoxyphenyl)-1-phenylisoquinoline 4.6ad: Prepared from benzophenone imine (**4.13a**) and 1,2-bis(4-methoxyphenyl)ethyne (**4.5d**) according to the general procedure **A**. Chromatography (3% ethyl acetate in hexane) gave **4.6ad** as a white solid (100 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.86 (s, 3H), 6.75 (d, 2H, *J* = 8.8 Hz), 6.96 (d, 2H, *J* = 8.8 Hz), 7.22 (d, 2H, *J* = 7.6 Hz), 7.42-7.59 (m, 7H), 7.74 (d, 1H, *J* = 9.2 Hz), 7.82 (d, 2H, *J* = 8.0 Hz), 8.16 (d, 1H, *J* = 9.2 Hz) . ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.4, 55.5, 113.3, 114.2, 125.5, 126.2, 126.5, 127.7, 128.5, 128.7, 129.1, 130.0, 130.2, 130.5, 131.9, 132.6, 133.8, 137.7, 140.2, 149.6, 158.8, 159.0, 159.7. HRMS: calcd for $C_{29}H_{24}NO_2^+$ 418.1802, found 418.1803.



4.6ae

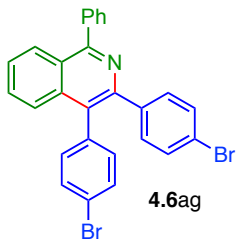
3,4-Bis(4-fluorophenyl)-1-phenylisoquinoline 4.6ae: Prepared from benzophenone imine (**4.13a**) and 1,2-bis(4-Fluorophenyl)ethyne (**4.5e**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6ae** as a white solid (97 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.88 (t, 2H, *J* = 8.4 Hz), 7.09 (t, 2H, *J* = 8.0 Hz), 7.24-7.27 (m, 2H), 7.37-7.41 (m, 2H), 7.49-7.57 (m, 4H), 7.59-7.63 (m, 1H), 7.68 (d, 1H, *J* = 7.6 Hz), 7.80 (d, 2H, J = 6.4 Hz), 8.18 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 114.7(d, *J* = 21.1 Hz), 115.7(d. *J* = 21.3 Hz), 125.7, 125.9, 127.0, 127.88, 127.91, 130.5, 132.3, 132.4, 132.3(d, *J* = 7.9 Hz), 133.1 (d, *J* = 7.9 Hz), 133.5(d, *J* = 3.2 Hz), 137.0, 137.2, 139.8, 149.1, 160.4, 161.0(d, *J* = 245.7 Hz), 161.2(d, *J* = 247.7 Hz) ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -115.0, -115.8. HRMS: calcd for $C_{27}H_{18}F_2N^+$ 394.1402, found 394.1408.



4.6af

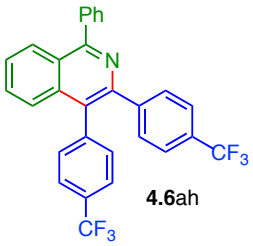
3,4-Bis(4-chlorophenyl)-1-phenyl-3,4-dihydroisoquinoline 4.6af: Prepared from benzophenone imine (**4.13a**) and 1,2-bis(4-Chlorophenyl)ethyne (**4.5f**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6af** as a white solid (103 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.18-7.25 (m, 4H), 7.36-7.41 (m, 4H), 7.52-7.64 (m, 5H), 7.68 (d, 1H, *J* = 8.8 Hz), 7.80 (d, 2H, *J* = 7.6 Hz), 8.20 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 125.8, 125.9, 127.2, 127.9, 128.2, 128.6, 128.8, 128.9, 129.1, 130.4, 130.6,

132.0, 132.9, 133.6, 136.1, 137.0, 139.3, 139.8, 148.7, 160.6. HRMS: calcd for $C_{27}H_{18}Cl_2N^+$ 426.0811, found 426.0807.



4.6ag

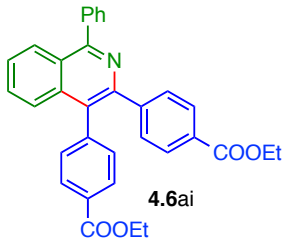
3,4-Bis(4-bromophenyl)-1-phenylisoquinoline 4.6ag: Prepared from benzophenone imine (**4.13a**) and 1,2-bis(4-bromophenyl)ethyne (**4.5g**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6ag** as a light-yellow oil (98 mg, 69%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.15 (d, 2H, *J* = 8.4 Hz), 7.24-7.35 (m, 4H), 7.48-7.56 (m, 6H), 7.59-7.63 (m, 1H), 7.65 (d, 1H, *J* = 8.0 Hz), 7.78 (d, 2H, *J* = 6.4 Hz), 8.17 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ121.9, 122.0, 125.7, 125.9, 127.2, 127.9, 128.6, 128.8, 128.9, 130.4, 130.6, 131.1, 132.1, 132.3, 133.1, 136.5, 136.9, 139.68, 139.74, 148.6, 160.6. HRMS: calcd for $C_{27}H_{18}NBr_2^+$ 513.9801, found 513.9818.



4.6ah

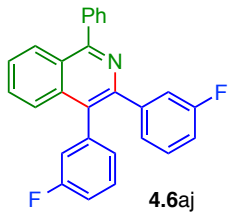
1-Phenyl-3,4-bis(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline 4.6ah: Prepared from benzophenone imine (**4.13a**) and 4,4'-trifluoromethyl diphenylacetylene (**4.5h**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6ah** as a white solid (125 mg, 92%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.47 (m, 4H), 7.51-7.61 (m, 6H), 7.65-7.70 (m, 4H), 7.81 (d, 2H, *J* = 6.4 Hz), 8.23 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.07 (q, *J*(C-F) = 270.4 Hz), 120.13 (q, *J*(C-F) = 270.4 Hz), 124.7(q, *J* = 3.7 Hz), 125.6(q, *J*

= 5.1 Hz), 127.4, 127.9, 129.2, 128.5, 128.9, 129.2, 129.5, 129.9, 130.0, 130.2, 130.71, 130.74, 131.8, 136.6, 139.3, 141.1, 144.0, 148.2, 160.9. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.53, -62.46. HRMS: $C_{29}H_{18}F_6N^+$ 494.1338, found 494.1328.



4.6ai

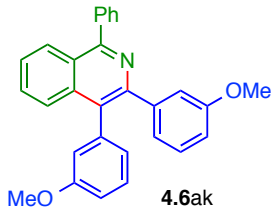
Diethyl 4,4'-(1-phenylisoquinoline-3,4-diyl)dibenzoate 4.6ai: Prepared from benzophenone imine (**4.13a**) and diethyl 4,4'-(ethyne-1,2-diyl)dibenzoate (**4.5i**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6ai** as a white solid (120 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J* = 7.2 Hz), 1.39 (t, 3H, *J* = 6.8 Hz), 4.29 (q, 2H, *J* = 7.2 Hz), 4.38 (q, 2H, *J* = 7.2 Hz), 7.36 (d, 2H, *J* = 8.0 Hz), 7.47-7.60 (m, 9H), 7.64 (d, 1H, *J* = 8.4 Hz), 7.79 (d, 2H, *J* = 6.4 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 8.07 (d, 2H, *J* = 8.0 Hz), 8.19 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.5, 14.6, 61.1, 61.4, 125.8, 125.9, 127.4, 127.7, 127.9, 128.6, 129.0, 129.2, 129.3, 129.6, 129.7, 129.9, 130.4, 130.6, 131.6, 136.7, 139.6, 142.3, 145.2, 148.8, 160.7, 166.5, 166.6. HRMS: calcd for $C_{33}H_{28}NO_4^+$ 502.2013, found 502.2008.



4.6aj

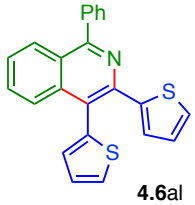
3,4-Bis(3-fluorophenyl)-1-phenylisoquinoline 4.6aj: Prepared from benzophenone imine (**4.13a**) and 3,3' difluoro diphenylacetylene (**4.5j**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6aj** as a white solid (86 mg, 93%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.89 (t, 1H, *J* = 9.2 Hz), 7.06-7.27 (m, 6H), 7.37-7.42 (m, 1H), 7.51-

7.66 (m, 5H), 7.72 (d, 1H, J = 8.4 Hz), 7.83 (d, 2H, J = 8.0 Hz), 8.22 (d, 1H, J = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 114.4 (d, J = 20.7 Hz), 114.8 (d, J = 21.0 Hz), 117.4 (d, J = 22.1 Hz), 118.4 (d, J = 21.4 Hz), 125.9, 126.0, 126.3, 127.3, 127.9, 128.6, 129.1, 129.3, 129.4, 130.3, 130.4, 130.7, 136.9, 139.6 (d, J = 3.9 Hz), 143.0 (d, J = 7.6 Hz), 160.7, 161.4 (d, J(C-F) = 243.4 Hz), 161.8 (d, J(C-F) = 245.8 Hz). ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -34.9, -36.3. HRMS: calcd for $C_{27}H_{18}F_2N^+$ 394.1402, found 394.1406.



4.6ak

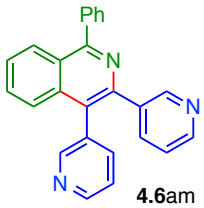
3,4-Bis(3-methoxyphenyl)-1-phenylisoquinoline 4.6ak: Prepared from benzophenone imine (**4.13a**) and 1,2-bis(3-methoxyphenyl)ethyne (**4.5k**) according to the general procedure **A**. Chromatography (3% ethyl acetate in hexane) gave **4.6ak** as a white solid (96 mg, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 3H), 3.72 (s, 3H), 6.72-6.75 (m, 1H), 6.85 (s, 1H), 6.89-6.94 (m, 2H), 7.00 (s, 1H), 7.09-7.14 (m, 2H), 7.30 (t, 1H, J = 7.6 Hz), 7.47-7.62 (m, 5H), 7.75 (d, 1H, J = 8.4 Hz), 7.81 (d, 2H, J = 6.8 Hz), 8.17 (d, 1H, J = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.4, 55.5, 113.4, 113.9, 115.6, 117.0, 123.3, 124.1, 125.7, 126.4, 126.9, 127.7, 128.6, 128.8, 129.6, 130.2, 130.5, 137.2, 139.3, 140.1, 142.4, 149.5, 159.1, 159.9, 160.1. HRMS: calcd for $C_{29}H_{24}NO_2^+$ 418.1802, found 418.1789.



4.6al

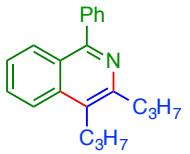
1-Phenyl-3,4-di(thiophen-2-yl)Isoquinoline 4.6al: Prepared from benzophenone imine (**4.13a**) and 1,2-di(thiophen-2-yl)ethyne (**4.5l**) according to the general procedure **A**. Chromatography

(1% ethyl acetate in hexane) gave **4.6al** as a white solid (90 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.89-6.90 (m, 1H), 6.96-6.98 (m, 1H), 7.21-7.22 (m, 1H), 7.34-7.36 (m, 2H), 7.51-7.55 (m, 2H), 7.59-7.69 (m, 5H), 7.74 (d, 1H, *J* = 8.0 Hz), 7.90-7.93 (m, 2H), 8.20 (d, 1H, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 119.4, 124.9, 125.9, 126.6, 127.5, 127.65, 127.71, 128.0, 128.4, 128.9, 128.9, 129.4, 130.4, 130.5, 137.9, 138.9, 139.4, 144.8, 145.1, 160.3. HRMS: calcd for $C_{23}H_{18}NS_2^+$ 372.0875, found 372.0859.



4.6am

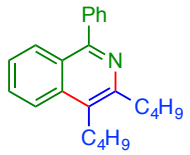
1-Phenyl-3,4-di(pyridin-3-yl)Isoquinoline 4.6am: Prepared from benzophenone imine (4.**13a**) and 1,2-di(pyridin-3-yl)ethyne (**4.5m**) according to the general procedure **A**. Chromatography (1% ethyl acetate in hexane) gave **4.6am** as a white solid (81 mg, 82%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09-7.14 (m, 1H), 7.31-7.34 (m, 1H), 7.41-7.43 (m, 1H), 7.48-7.57 (m, 4H), 7.61-7.66 (m, 3H), 7.68 (d, 1H, *J* = 7.6 Hz), 8.19 (d, 1H, *J* = 8.4 Hz), 8.38 (d, 1H, *J* = 4.4 Hz), 8.55-8.61 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 123.0, 123.6, 125.5, 127.0, 128.1, 128.7, 129.2, 130.3, 131.1, 132.2, 133.1, 136.3, 136.9, 137.8, 138.9, 139.4, 147.6, 148.5, 149.2, 151.4, 151.9, 161.3. HRMS: calcd for $C_{25}H_{18}N_3^+$ 360.1495, found 360.1493.



4.6an

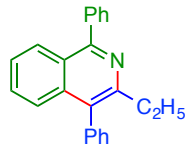
1-Phenyl-3,4-dipropylisoquinoline 4.6an: Prepared from benzophenone imine (**4.13a**) and 4-Octyne (**4.5n**) according to the general procedure **C**. Chromatography (1% ethyl acetate in hexane) gave **4.6an** as a white solid (35 mg, 44%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.09 (t, 3H, *J*

= 7.6 Hz), 1.18 (t, 3H, *J* = 7.6 Hz), 1.76 (sext, 2H, *J* = 7.6 Hz), 1.87 (sext, 2H, *J* = 7.2 Hz), 3.06-3.14 (m, 4H), 7.44-7.57 (m, 4H), 7.68-7.73 (m, 3H), 8.07 (d, 2H, *J* = 8.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.4, 14.8, 23.7, 24.2, 30.0, 37.5, 123.4, 125.3, 125.4, 127.2, 128.1, 128.2, 128.3, 129.5, 130.1, 136.2, 152.3, 158.1. HRMS: calcd for $C_{21}H_{24}N^+$ 290.1830, found 290.1826.



4.6ao

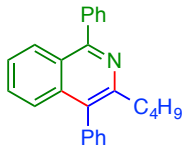
3,4-Dibutyl-1-phenylisoquinoline 4.6ao: Prepared from benzophenone imine (**4.13a**) and 5-Decyne (**4.5o**) according to the general procedure **C**. Chromatography (1% ethyl acetate in hexane) gave **4.6ao** as a white solid (46 mg, 53%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.00 (t, 3H, *J* = 7.6 Hz), 1.06 (t, 3H, *J* = 7.2 Hz), 1.48-1.59 (m, 2H), 1.60-1.66 (m, 2H), 1.71-1.78(m, 2H), 1.80-1.88 (m, 2H), 3.05-3.14(m, 4H), 7.43-7.57 (m, 4H), 7.67-7.72 (m, 4H), 7.67-7.72 (m, 3H), 8.04-8.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 23.1, 23.4, 32.7, 33.1, 35.3, 123.3, 125.28, 125.32, 127.2, 128.1, 128.2, 128.3, 129.5, 130.1, 136.1, 140.2, 152.4, 158.1. HRMS: calcd for $C_{23}H_{20}N^+$ 318.2143, found 318.2135.



4.6ap

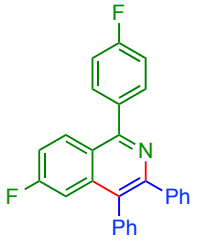
3-Ethyl-1,4-diphenylisoquinoline 4.6ap: Prepared from benzophenone imine (**4.13a**) and 1-phenyl-1-butyne (**4.5m**) according to the general procedure **C**. Chromatography (1% ethyl acetate in hexane) gave **4.6ap** as a white solid (37 mg, 43%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.28 (t, 3H, *J* = 7.6 Hz), 2.83 (q, 2H, J = 7.6 Hz), 7.40-7.43 (m, 2H), 7.47-7.49 (m, 2H), 7.54-7.60 (m, 7H), 7.80-7.82 (m, 2H), 8.11 (d, 1H, *J* = 8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.9, 29.2, 124.8, 125.6, 125.8, 127.4, 127.5, 127.9, 128.38, 128.45, 128.54, 129.4, 129.5, 129.6,

130.1, 130.3, 136.9, 137.9, 140.0, 153.4, 159.8. HRMS: calcd for $C_{23}H_{20}N^+$ 310.1517, found 310.1515.



4.6aq

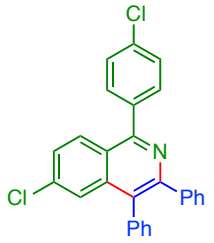
3-Butyl-1,4-diphenylisoquinoline 4.6am: Prepared from benzophenone imine (**4.13a**) and 1-phenyl-1-hexyne (**4.5m**) according to the general procedure **C**. Chromatography (1% ethyl acetate in hexane) gave **4.6am** as a white solid (48 mg, 52%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.83 (t, 3H, *J* = 7.6 Hz), 1.28 (sext, 2H, *J* = 7.2 Hz), 1.71-1.79 (m, 2H), 2.80 (t, 2H, *J* = 8.0 Hz), 7.39-7.41 (m, 2H), 7.41-7.48 (m, 2H), 7.51-7.61(m, 7H), 7.78-7.81 (m, 2H), 8.10 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 22.7, 32.5, 35.5, 124.8, 125.66, 125.74, 127.3, 127.5, 128.37, 128.43, 128.5, 129.6, 129.7, 130.1, 130.4, 132.4, 136.9, 137.9, 140.0, 152.3, 159.7. HRMS: calcd for $C_{25}H_{24}N^+$ 338.1830, found 338.1826.



4.6ba

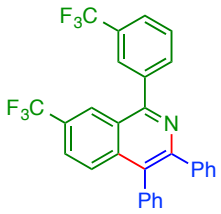
6-Fluoro-1-(4-fluorophenyl)-3,4-diphenylisoquinoline 4.6ba: Prepared from 4,4'-fluoro benzophenone imine (**4.13b**) and Diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.6ba** as a white solid (97 mg, 88%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22-7.24 (m, 3H), 7.26-7.32 (m, 5H), 7.41-7.46 (m, 5H), 7.81-7.87 (m, 2H), 8.18-8.22 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 109.7 (d, *J* = 22.2 Hz), 115.4, 115.6, 116.2 (d, *J* = 25.0 Hz), 122.7, 127.3, 127.7, 128.6, 129.6 (d, *J* = 5.2 Hz), 130.4, 130.5 (d, *J* = 9.5 Hz), 131.2, 132.0, 132.1, 132.5 (d, *J* = 8.9 Hz), 132.6 (d, *J* = 8.9 Hz), 137.1, 139.1 (d, *J* = 10.0

Hz), 140.5, 150.6, 158.6, 161.9 (d, *J*(C,F) = 250.2 Hz), 162.0 (d, *J*(C,F) = 246.5 Hz) . ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -112.9. (s, 1F), -106.9 (s, 1F). HRMS: calcd for $C_{27}H_{20}F_2N^+$ 394.1402, found 394.1405.



4.6ca

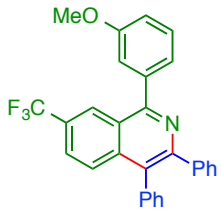
6-Chloro-1-(4-chlorophenyl)-3,4-diphenylisoquinoline 4.6ca: Prepared from 4,4'-chloro benzophenone imine (**4.13c**) and diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.13ca** as a white solid (99 mg, 83%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22-7.24 (d, 3H), 7.29-7.32 (m, 2H), 7.43-7.45 (m, 5H), 7.49-7.51 (m, 1H), 7.55-7.59 (m, 2H), 7.74-7.75 (m, 1H), 7.77-7.80 (m, 2H), 8.09 (d, 1H, *J* = 9.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 123.6, 125.1, 127.4, 127.7, 127.79, 127.80, 128.6, 128.7, 128.9, 129.3, 130., 131.2, 131.6, 135.1, 136.7, 137.8, 138.1, 140.4, 150.9, 158.5. HRMS: calcd for $C_{27}H_{18}Cl_2N^+$ 426.0811, found 426.0814.



4.6da

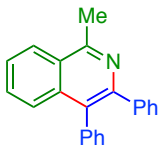
3,4-Diphenyl-7-(trifluoromethyl)-1-(3-(trifluoromethyl)phenyl)Isoquinoline 4.6da: Prepared from 3,3'-trifluoromethyl benzophenone imine (**4.13d**) and diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.6da** as a white solid (126 mg, 91%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21-7.24(m, 3H), 7.29-7.31(m, 2H), 7.40-7.46 (m, 5H), 7.89 (d, 1H, *J* = 8.8 Hz), 8.13 (s, 1H), 8.39 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$):

δ 122.7(q, *J*(C,F) = 271.0 Hz), 122.9(q, *J*(C,F) = 274.1 Hz), 124.4, 124.8(q, *J* = 4.9 Hz), 125.9 (q, *J* = 2.6 Hz), 126.1 (q, *J* = 3.9 Hz), 127.88, 127.93, 128.0, 128.1, 128.9 129.2, 129.3, 130.5, 130.6, 131.4, 131.7, 133.6, 138.8, 139.9, 140.2, 152.1, 159.2. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -15.0 (s, 1F), -14.9 (s, 1F) HRMS: calcd for $C_{29}H_{18}F_6N^+$ 494.1338, found 494.1331.



4.6ea

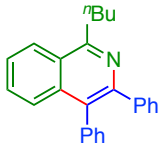
1-(3-Methoxyphenyl)-3,4-diphenyl-7-(trifluoromethyl)isoquinoline 4.6ea: Prepared from 3-trifluoromethyl 3'-methoxy benzophenone imine (**4.13e**) and diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.13ea** as a white solid (114 mg, 90%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 4.39 (d, 1H, *J* = 8.0 Hz), 5.17 (d, 1H, *J* = 8.0 Hz), 6.60 (d, 2H, *J* = 4.0 Hz), 7.00 (m, 5H), 7.22 (m, 5H), 7.31 (d, 2H, *J* = 8.0 Hz), 7.41 (t, 2H, *J* = 8.0Hz), 7.68 (d, 1H, *J* = 8.0 Hz) 7.79 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.6, 115.2, 115.8, 122.9, 124.6 (q, *J*(C,F) = 271.7 Hz), 125.6 (q, *J* = 6.5 Hz), 127.6 (q, *J* = 7.6 Hz), 127.89, 127.94, 128.8, 128.4, 128.7, 129.80, 129.82, 130.7, 131.5, 137.1, 138.7, 140.4, 151.9, 160.1, 160.7.. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -15.1 (s, 1F). HRMS: calcd for $C_{29}H_{21}F_3NO^+$ 456.1497, found 456.1492.



4.6fa

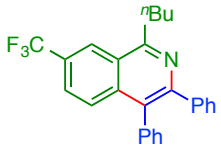
1-Methyl-3,4-diphenylisoquinoline 4.6fa: Prepared from 1-phenylethan-1-imine (**4.13f**) and Diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.6fa** as a light yellow oil (69 mg, 83%). ^{1}H-NMR (400 MHz, CDCl3):

δ 3.13 (s, 3H), 7.20-7.28 (m, 5H), 7.35-7.43(m, 5H), 7.61-7.65(m, 2H), 7.69-7.72 (m, 1H), 8.23-8.25(m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 22.7, 125.6, 126.2, 126.3, 126.6, 127.0, 127.1, 127.7, 128.2, 129.3, 130.0, 130.3, 131.5, 136.1, 137.6, 140.9, 149.4, 157.8. HRMS: calcd for $C_{22}H_{18}N^+$ 396.1361, found 396.1360.



4.6ga

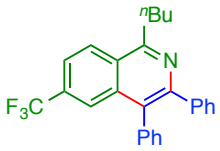
1-Butyl-3,4-diphenylisoquinoline 4.6ga: Prepared from 1-phenylpentan-1-imine (**4.13g**) and diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.13ga** as a light yellow oil (84 mg, 89%). ^{1}H-NMR (400 MHz, CDCl3): δ 1.08 (t, 3H, *J* = 7.6 Hz), 1.59 (sext, 2H, *J* = 7.2 Hz), 2.00 (pent, 2H, *J* = 7.6 Hz), 3.46 (t, 2H, *J* = 8.0 Hz), 6.91 (s, 1H), 7.22-7.30 (m, 5H), 7.37-7.46 (m, 5H), 7.60-7.64 (m, 2H), 7.71-7.74 (m, 1H), 8.29-8.31(m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.2, 23.2, 32.2, 35.6, 125.3, 125.6, 126.4, 126.7, 126.9, 127.2, 127.6, 128.3, 128.9, 129.7, 130.4, 131.4, 136.4, 137.8, 141.2, 149.4, 161.6. HRMS: calcd for $C_{25}H_{24}N^+$ 338.1830, found 338.1827.



4.6ha

1-Butyl-3,4-diphenyl-7-(trifluoromethyl)isoquinoline 4.6ha: Prepared from 1-(4-trifluoromethyl-phenyl)-butylideneamine (**4.13h**) and diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.6ha** as a yellow oil (98 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.08 (t, 3H, *J* = 7.6 Hz), 1.59 (sext, 2H, *J* =7.2 Hz), 1.99 (pent, 2H, *J* = 7.6 Hz), 3.48 (t, 2H, *J* = 8.0 Hz), 7.24-7.28 (m, 5H), 7.39-7.45 (m, 5H), 7.75-7.77 (m, 1H), 7.83 (d, 1H, 8.8 Hz) 8.57 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 23.0,

32.0, 35.3, 120.1 (q, *J*(C,F) = 270.7 Hz), 122.9 (q, *J* = 4.4 Hz), 12.5, 125.2 (q, *J* = 2.9 Hz), 125.5, 127.4, 127.5, 127.7, 127.8, 127.9, 128.2 (q, *J* = 9.7 Hz), 128.5, 128.8, 130.4, 131.3, 137.1, 137.9, 140.5, 151.3, 162. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.4 (s, 1F). HRMS: calcd for $C_{26}H_{23}F_3N^+$ 406.1777, found 406.1779.



4.6ia

1-Butyl-3,4-diphenyl-6-(trifluoromethyl)isoquinoline 4.6ia: Prepared from 1-(4-(trifluoromethyl)phenyl)pentan-1-imine (**4.13i**) and diphenylacetylene (**4.5a**) according to the general procedure **B**. Chromatography (1% ethyl acetate in hexane) gave **4.6ia** as a yellow oil (96 mg, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.05 (t, 3H, J = 7.2 Hz), 1.57 (sext, 2H, *J* = 7.2 Hz), 1.96 (pent, 2H, *J* = 8.0 hz), 3.45 (t, 2H, *J* = 8.0 Hz), 7.23-7.29 (m, 5H), 7.40-7.43 (m, 5H), 7.77-7.79 (m, 1H), 8.02 (s, 1H), 8.39 (d, 1H, *J* = 8.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 23.0, 32.0, 35.5, 119.8 (q, *J*(C,F) = 271.1 Hz), 122.0 (q, *J* = 3.1 Hz), 124.0 (q, *J* = 4.6 Hz), 126.4, 126.6, 127.3, 127.66, 127.68, 127.9, 128.5, 129.5, 130.3 (q, *J* = 31.9 Hz). 131.3, 135.8, 136.6, 140.5, 150.7, 161.6. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.9 (s, 1F). HRMS: calcd for $C_{26}H_{23}F_3N^+$ 406.1777, found 406.1775.

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CHAPTER 5. ACTIVATED NICKEL–NHC CATALYST FOR MILD TRANSFER SEMIHYDROGENATION OF ALKYNES

5.1. Introduction

The field of homogeneous nickel catalysis has made tremendous progress over the past decade[1,2]. Once viewed mainly as a low-cost replacement for palladium catalysis in cross-coupling reactions, nickel catalysis has gained increasing recognition as a powerful strategy in general organic synthesis. From the viewpoint of fundamental organometallic chemistry, the catalytic capacity of nickel is associated with several of its key properties such as high reactivity towards bond activation by oxidative addition and facile access to various oxidation states in the range of Ni(0) to Ni(IV). Reactivity and selectivity of nickel catalysts depend heavily on the choice of ancillary ligands, and N-heterocyclic carbene (NHC) ligands have played a prominent role in recent development of nickel catalysis[3-7]. Numerous examples of nickel-NHC complexes have been reported, and many of them have been successfully exploited in a broad scope of catalytic transformations[8].

Similar to other late transition metal catalysts with NHC ligands, the most common NHC ligands in nickel catalysis are imidazolylidene derivatives with bulky substituents on both nitrogen centers (Fig. 5.1)[5-8]. The leading examples of these bulky imidazolylidene NHCs are IPr (**5.1a**) and its less crowded structural analog IMes (**5.1b**), both featuring N,N'-diaryl substituents with alkyl groups blocking all four *ortho*-positions. Other important examples of NHC ligands in nickel catalysis include IPr analogs with further enhanced steric crowding such as IPr* (**5.1c**) and IPr*^{OMe} (**5.1d**)[9-12], as well as the imidazolinylidene NHC species such as SIPr (**5.2a**) and SIMes (**5.2b**). These NHCs are strong σ-electron donors that bind tightly to metal centers and stabilize low-coordinate complexes with steric protection.

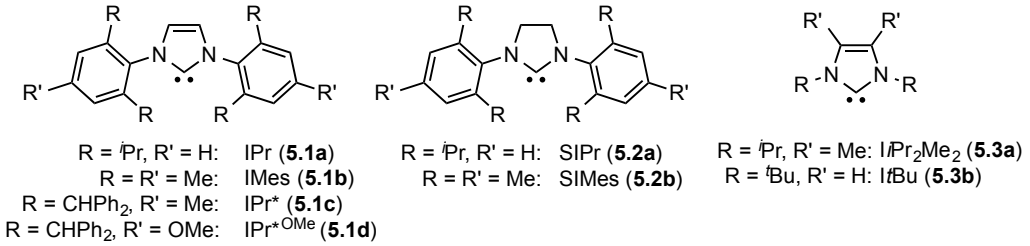


Figure 5.1. Representative common NHC ligands in organotransition metal catalysis

A vast majority of Ni(0)-NHC catalyst systems are established by combining the popular nickel(0) reagent $Ni(COD)_2$ (**5.4**) and the chosen NHC ligand as a free carbene or in a protected form such as imidazolium salt (NHC*HX) (Fig. 5.2). In addition, many NHC-ligated nickel(0) complexes have been synthesized and exploited in nickel catalysis, which include bis-carbene complexes $Ni(NHC)_2$ (**5.5**) and mono-NHC complexes with additional labile ligands such as π-olefins and π-arenes[8]. Comparing to relevant $Ni(COD)_2$/NHC systems, these NHC-ligated Ni(0) complexes have generally displayed similar or superior activity as catalyst precursors. For example, Louie and coworkers reported using $Ni(IPr)_2$ (**5.5a**) as an effective catalyst for [2+2+2] CO_2/diyne cycloaddition[13]. More recently, Hartwig and coworkers reported Ni-catalyzed linear-selective olefin hydroarylation using $Ni(IPr)_2$ and olefin hydroheteroarylation using $Ni(IPr^{*OMe})(\eta^6\text{-benzene})$[12,14]. Zimmerman, Montgomery and coworkers reported mild C–H functionalization processes using Ni(IMes)(η^4-1,4-hexadiene) as catalyst[15].

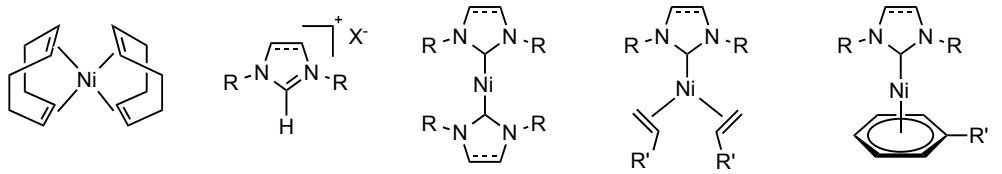


Figure 5.2. Common nickel(0) and NHC species in Ni-NHC catalyst systems

Results from mechanism studies on various nickel(0)-NHC catalyst systems support a common catalyst activation process, which involves formation of highly reactive, coordinatively unsaturated "[Ni(NHC)]" species upon dissociation of other ancillary ligands including a 2nd NHC (Fig. 5.3, **5.6→5.7**)[5-8]. It is noteworthy that intermediate **5.7** could be potentially stabilized by agnostic interactions involving alkyl or aryl groups on the NHC ligand; subsequent C-H bond cleavage by oxidative addition would generate nickel(II) hydride species with a cyclometalated NHC ligand (**5.7'→5.8**). Such cyclometalated NHC complexes are known for a broad scope of transition metals, and their impacts on catalytic processes via catalyst activation or deactivation have been documented[16,17]. For example, Whittlesey, Williams and coworkers reported a cyclometalated ruthenium(II) NHC complex as active catalyst for a tandem process of alcohol dehydrogenation and Wittig reaction, which was formed by methyl C–H activation of N-isopropyl groups on I*i*Pr$_2$Me$_2$ ligand (**5.3a**)[18]. By contrast, ruthenium-mediated C–H activation of the methyl groups on SIMes ligand (**5.2b**) is a major decomposition mode of the 2nd generation Grubb's catalyst for olefin metathesis[19-21].

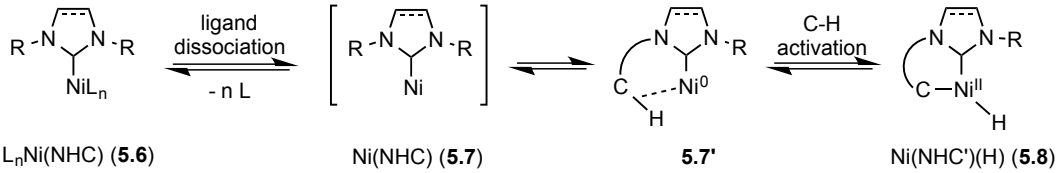
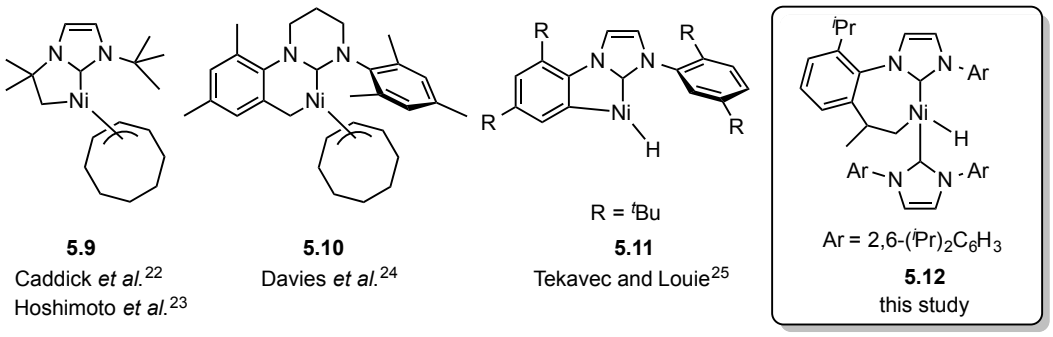


Figure 5.3. Nickel(0)-NHC catalyst activation and Nickel(0)-mediated cyclometalation of NHC ligands by C–H activation

Reports on C–H activated Ni-NHC complexes mainly focused on their structural features and stoichiometric transformations rather than catalytic activities (Fig. 5.4). For example, Caddick, Cloke and coworkers reported nickel(0)-mediated methyl C–H activation of N-*tert*-butyl groups on I*t*Bu ligand (**5.3b**), which was trapped by COD from Ni(COD)$_2$ precursor to

form an isolable π-allyl complex (**5.9a**)[22]. Formation of **5.9a** was also described by Ogoshi and coworkers on a Ni(COD)$_2$/I*t*Bu catalyst system for intramolecular alkene hydroacylation, although its catalytic activity was not discussed[23]. Whittlesey and coworkers reported an analogous Ni(II) π-allyl complex with a cyclometalated 6-membered ring NHC ligand as ring-expanded IMes analog (**5.10b**), whose facile decomposition by C–C reductive elimination led to its presumably low catalytic potential[24]. The only known example of catalytically active Ni-NHC metallacycles was reported by Tekavec and Louie in 2008, who proposed a cyclometalated Ni(II)-NHC hydride complex (**5.11**) as active catalyst for enyne cycloisomerization[25]. Although the formation of **5.11** by Ni(0)-mediated aromatic C–H activation of the NHC ligand was not directly observed, its involvement in the catalytic cycle was supported by deuterium labeling results. To our best knowledge, no reports were made on cyclometalated nickel-NHC complexes with IPr ligand – arguably the most important NHC ligand in homogeneous nickel catalysis – or its structural analogs exemplified in Fig. 5.1.



5.9
Caddick *et al.*[22]
Hoshimoto *et al.*[23]

5.10
Davies *et al.*[24]

5.11
Tekavec and Louie[25]

5.12
this study

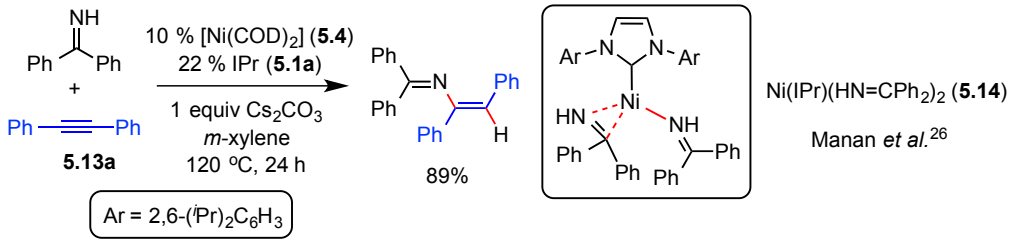
Figure 5.4. Examples of cyclometalated Ni-NHC complexes via C–H activation of NHC ligands

We report herein nickel(0)-mediated cyclometalation of IPr ligand that generates transient Ni(II) hydride species such as complex **5.12** (Fig. 5.4). The presence of **5.12** and its derivatives is evidenced by stoichiometric reactions with small molecules to form discrete Ni(0) and Ni(II) complexes, whose structures are established by X-ray crystallography. The generally

mild conditions for these transformations suggest that C–H activated Ni(II)-IPr complexes may readily form under catalytic conditions and affect catalyst activity. We evaluate this hypothesis by developing a Ni(0)/NHC catalyzed transfer semi-hydrogenation of internal alkynes that tolerates sensitive functional groups such as ketone, ester, nitrile, and trimethylsilyl functionality. The high catalyst activity with IPr or IMes ligand allows the use of simple alcohols such as isopropanol as the sole source of hydrogen. In addition, high stereoselectivity towards (*Z*)-alkene products is achieved by a room-temperature procedure using an activated catalyst system of crude $Ni(IPr)_2$ (**5.5a**) or pre-heated 1:2 mixture of $Ni(COD)_2$/IPr, which presumably lies in equilibrium with the cyclometalated Ni(II) hydride complex **5.12**.

5.2. Results and Discussion

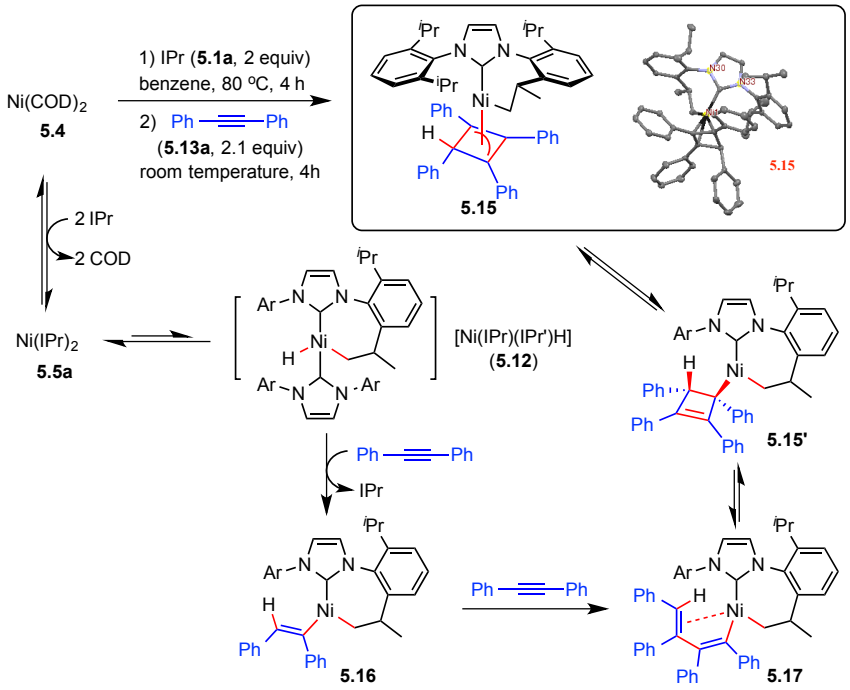
Our study on Ni/NHC catalysis started with the report on a Ni(0)/IPr catalyst for stereospecific *anti*-hydroimination of internal alkynes with N-H aromatic ketimines. For example, a catalyst system of 10 mol% $Ni(COD)_2$ (**5.4**) and 20 mol% IPr (**5.5a**) promotes a 1:1 reaction between benzophenone imine and diphenylacetylene (**5.13a**) to form a (*Z*)-2-aza-1,3-diene product in 89% yield (Scheme 5.1)[26]. A stoichiometric reaction between **5.4**, **5.5a** and benzophenone imine led to a discrete IPr-ligated Ni(0) bis(imine) complex **5.14**, which displayed significantly higher catalytic activity for desired alkyne hydroimination than the $Ni(COD)_2$/IPr system.



Scheme 5.1. A previous study on Ni-catalyzed alkyne hydroimination and a catalytically reactive bis(imine) complex (**5.14**)

By contrast, a similar stoichiometric reaction with diphenylacetylene (**5.13a**) instead of benzophenone imine did not generate the envisioned Ni(0) π-alkyne complex, but instead a C–H activated Ni(II) carbene complex (Scheme 5.2). In particular, a 1:2 reaction between **5.4** and **5.5a** in benzene at 80 °C for 4 hours, followed by adding 2 equivalents of **5.13a** and stirring at room temperature for another 4 hours generated complex **5.15**, whose solid-state structure was established by single crystal X-ray diffraction. Complex **5.15** has a η^2-[C,C]-cyclometalated IPr ligand (IPr') via Ni-methylene linkage, suggesting methyl C–H activation of an isopropyl group that has been demonstrated with iridium and ruthenium complexes with cyclometalated IPr ligand[27,28]. In addition, complex **5.15** features a 1,2,3,4-tetraphenylcyclobutenyl ligand in π-allyl coordination mode, with the Ni center and the allylic H atom on the same side of the cyclobutenyl ring. Ogoshi and coworkers have reported a π-allyl-type cyclobutenyl Ni(II) complex with tricyclohexylphosphine ligand, and its formation was proposed via double alkyne insertion into a Ni(II) hydride intermediate and subsequent ring-closure by [2+2] cyclization[29]. Thus, the observation of complex **5.15** provides indirect evidence for transient Ni(II) hydride species generated by Ni(0)-mediated C–H oxidative addition of methyl groups on IPr ligand. We hypothesize that such cyclometalation occurs with the bis(carbene) complex $Ni(IPr)_2$ (**5.5a**), which equilibrates with $Ni(COD)_2$ (**5.4**) via reversible COD/IPr ligand exchange under current reaction conditions[13,30]. The resulting cyclometalated Ni(II) hydride complex (**5.12**) is expected to be much less stable than **5.5a**, and we were not able to detect the presence of **5.12** by ^{1}H NMR analysis of an equilibrium mixture of **5.4** and **5.5a** in deuterated benzene (C_6D_6). Nevertheless, we propose that complex **5.12** is trapped by irreversible alkyne insertion into the Ni–H linkage (**5.12→5.16**), and the resulting Ni(II)-alkenyl intermediate undergoes a second alkyne insertion to form a butadienyl intermediate (**5.16→5.17**). Subsequent ring-closure via 4π-

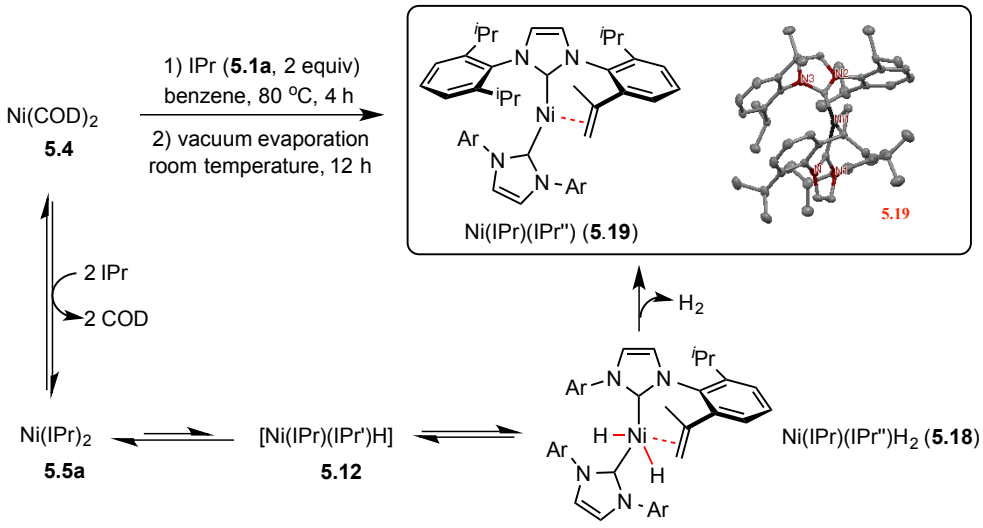
electrocyclization forms the cyclobutenyl intermediate **5.15'**, which is isolated in the more stable π-allyl form of complex **5.15**. Notably, the *cis*-H/Ni stereochemistry suggests a photochemical process for disrotatory 4π-electrocyclization, while the alternative thermal process of conrotatory cyclization is expected to be unlikely due to significant steric repulsion between the allylic phenyl and a nearby isopropyl group from cyclometalated IPr.



Scheme 5.2. Formation of a cyclometalated IPr-ligated Ni(II) η^3-cyclobutenyl complex (**5.15**)

To further demonstrate the presence of transient complex **5.12**, we repeated the procedure to establish an equilibrium mixture of **5.4** and **5.5a** and evaporated the solution *in vacuuo* for 12 hours at room temperature. Recrystallization of the resulting solid residue in toluene afforded a bis(carbene) Ni(0) complex **5.19**, whose solid-state structure was established by X-ray crystallography. Besides a normal IPr ligand, complex **5.19** is also ligated by a η^3-IPr derivative (IPr") via π-olefin complexation with a 2-propenyl group that results from apparent dehydrogenation of an isopropyl group[31,32]. We propose that complex **5.12** undergoes β-H

elimination to form a dihydride complex, Ni(IPr)(IPr")H_2 (**5.18**), which loses H_2 irreversibly *in vacuuo* to form complex **5.19** (Scheme 5.3).

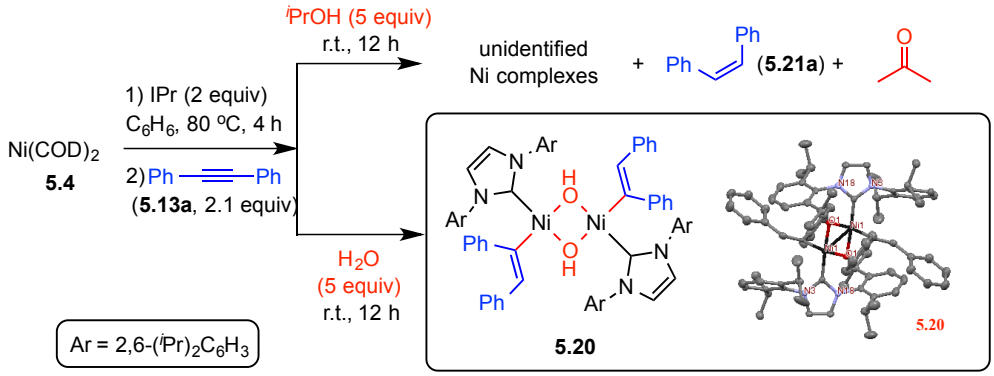


Scheme 5.3. Formation of a π-olefin Ni(0) complex (**5.19**) with a dehydrogenated IPr ligand

The facile formation of both complexes **5.15** and **5.19** under mild conditions suggests that Ni(0)-mediated C–H activation of IPr analog NHC ligands could be a common scenario for homogenous Ni/NHC catalysis. As demonstrated with other transition metal species[18-21,25], the resulting Ni-NHC metallacycles could positively or negatively affect catalyst activity. On the one hand, C–H activated Ni/NHC complexes may transform into low-activity species that lead to catalyst de-activation, which resonates with the studies on deactivation of 2nd generation Grubbs catalyst[19-21]. In fact, the cyclobutenyl complex **5.15** is highly stable and shows no catalytic activity for alkyne hydroimination as described in Scheme 5.1. Since complexes **5.15** readily forms from reaction between *in situ* generated Ni(IPr)$_2$ and diphenylacetylene at room temperature (Scheme 5.2), caution should be taken to avoid its formation when setting up Ni(0)/IPr catalyzed alkyne transformations. On the other hand, facile formation of proposed intermediate **5.12** and its apparently high activity towards reactions such as alkyne insertion provides a low-barrier access to NHC-ligated Ni(II) hydride species, which are considered

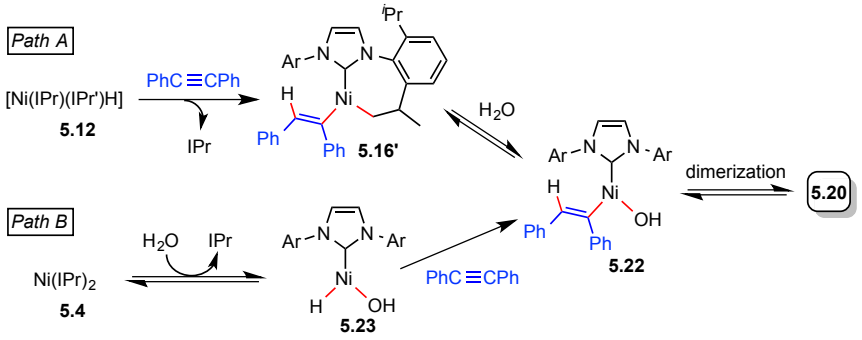
important intermediates in many catalytic transformations[11,34-38]. We seek to evaluate this hypothesis by developing a Ni(0)/IPr catalyst for alkyne transfer hydrogenation towards alkene products. Transition metal-catalyzed transfer hydrogenation (TH) is a fast-growing field and provides an attractive alternative to direct hydrogenation using H_2[39,40]. Simple alcohols are a common class of sacrificial hydrogen sources in catalytic TH of polar organic π-systems such as aldehydes, ketones and imines, with isopropanol (*i*-PrOH) as the most important reducing reagent due to its low cost and easy handling. By contrast, TH of olefins or alkynes generally requires more reactive hydrogen sources such as formic acid or its ammonium salt[39,40]. A notable exception is a 2009 report by Djukic and coworkers on cyclometalated phenylpyridine ruthenium(II) catalysts for stereoselective transfer semi-hydrogenation (TSH) of several alkynes using indenol or *i*-PrOH as the hydrogen source; the reactions were carried out at 90 °C and in the presence of Na_2CO_3 additive[41]. In the same year, Garcia and coworkers reported a phosphine-ligated nickel(I) catalyst for TSH of diaryl-substituted alkynes using MeOH as the hydrogen source; the reactions were proceeded at 180 °C and selectively generated (*E*)-alkene products[42]. More recently, the groups of Tsuji and Lalic independently reported copper-catalyzed mild and stereoselective TSH of alkynes using silane and alcohol as a two-reagent hydrogen source and Xantphos-type phosphine or IPr-type NHC ligand[43,44]. Both reducing reagents play key roles in the proposed catalytic cycle: silane as the hydride donor to generate Cu(I) hydride intermediate, and alcohol as the proton donor to protonate Cu(I)-alkenyl linkage and release alkene product. Thus, the main goals for our catalyst development are to enable the use of simple alcohols such as isopropanol as the sole hydrogen source and to allow control over *E*/*Z* stereoselectivity under mild reaction conditions.

Results of relevant studies described above indicate that a major challenge for alcohol-based alkyne TSH is to promote effective hydrogen atom transfer from alcohols to generate reactive metal hydride intermediates. In principle, this barrier can be bypassed with the envisioned facile formation of Ni(II) hydride complex **5.12** via IPr cyclometalation. However, complex **5.12** is not stable enough to be directly detected, and it appears to readily react with alkynes to generate inert cyclobutenyl complexes such as complex **5.15**. Thus, an important question for our alkyne TSH catalyst design is whether transient complex **5.12** could transform into catalytically active species in the presence of both alkyne substrate and alcohol reagent. We seek to answer this question by carrying out stoichiometric reactions with *in situ* generated $Ni(IPr)_2$ (**5.4**) from mixed $Ni(COD)_2$ and IPr, diphenylacetylene (**5.13a**) as a representative alkyne substrate, and either *i*-PrOH or H_2O as potential hydrogen sources (Scheme 5.4). A room-temperature reaction with *i*-PrOH generated a small amount of *cis*-stilbene (**5.21a**) and acetone as the expected products from alkyne TSH. However, the organometallic products were a mixture of unidentified nickel complexes based on NMR analysis. In comparison, a similar reaction with H_2O in place of *i*-PrOH generated a discrete Ni(II) μ-hydroxo dimer (**5.20**), whose solid-state structure is established by single-crystal X-ray diffraction. Complex **5.20** is the dimer form of a IPr-ligated alkenylnickel(II) hydroxide, and the alkenyl moiety is derived from *cis*-stilbene (**5.21a**).



Scheme 5.4. Formation of a IPr-ligated Ni(II) alkenyl μ-hydroxo dimer (**5.20**)

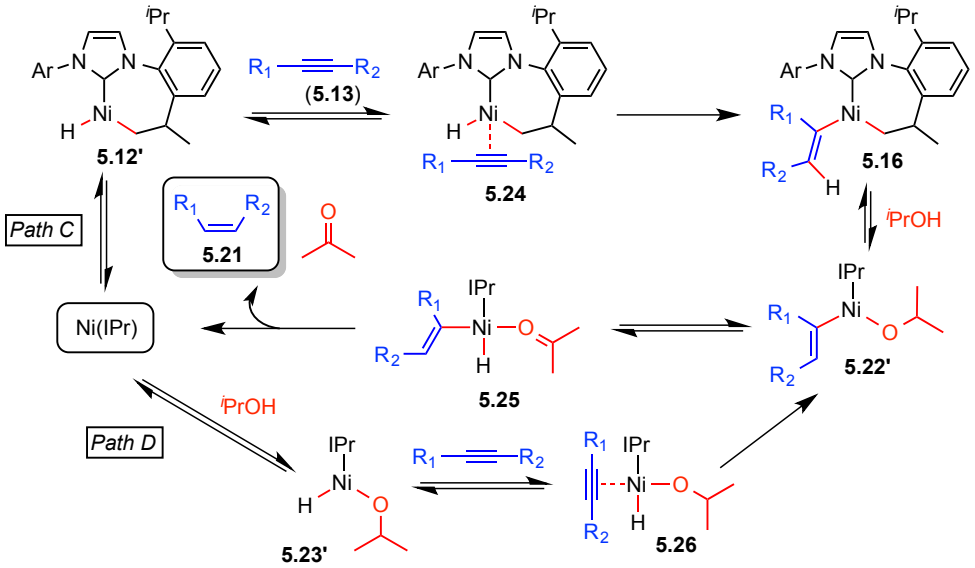
Comparing the formation of complex **5.20** with complex **5.15**, we propose that both involve alkyne insertion into the Ni–H linkage in C–H activated Ni-IPr complex **5.12** (Scheme 5.5, Path A). The resulting Ni(II) alkenyl intermediate **5.16'** reacts with H_2O to selectively protonate the Ni–alkyl linkage in Ni-IPr metallacycle over the Ni–alkenyl linkage to form IPr-ligated Ni(II) alkenyl hydroxide (**5.22**), which dimerizes to form **5.20**. In an alternative pathway without the involvement of Ni-IPr cyclometalation, $Ni(IPr)_2$ reacts with H_2O (presumably after dissociation of one IPr ligand) to form IPr-ligated hydroxonickel(II) hydride **5.23** (Path B); subsequent alkyne insertion into Ni–H linkage and dimerization generates complex **5.20**.



Scheme 5.5. Proposed pathway for the formation of a IPr-ligated Ni(II) alkenyl μ-hydroxo dimer

Based on these pathways towards hydroxo complexes **5.23** and **5.22**, analogous alkoxo complexes that are derived from *i*-PrOH and other alcohols are expected to be catalytically active

for alkyne TSH. Thus, we propose two possible catalytic cycles that both start with *in situ* generated mono-NHC intermediate [Ni(IPr)] to simplify the discussion (Scheme 5.6). In the pathway that involves Ni(0)-mediated cyclometalation of IPr (Path C), the resulting C–H activated Ni-IPr complex **5.12'** undergoes alkyne coordination to set the stage for alkyne insertion into the Ni–H linkage (**5.24→5.16**). Subsequent protonation with an alcohol such as *i*-PrOH selectively cleaves the Ni–alkyl linkage in Ni-IPr metallacycle to form IPr-ligated Ni(II) alkenyl alkoxide (**5.22'**), which resembles the formation of hydroxide complex **5.22** (Path A in Scheme 5.5). **5.22'** undergoes β-H elimination from the alkoxo ligand to form alkenylnickel(II) hydride intermediate **5.25**, which undergoes C–H reductive elimination and ligand dissociation to release (*Z*)-alkene product **5.21** and acetone as byproduct, completing the catalytic cycle. In an alternative pathway that does not involve IPr cyclometalation, [Ni(IPr)] activates *i*-PrOH to generate IPr-ligated alkoxonickel(II) hydride **5.23'** (Path D). **5.23'** undergoes alkyne coordination and subsequent insertion into the Ni–H linkage (**5.26→5.23'**), followed by the same steps of β-H elimination, C–H reductive elimination and ligand dissociation as shown in Path C to complete the catalytic cycle.



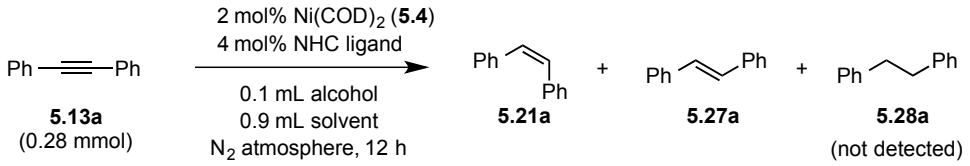
Scheme 5.6. Proposed catalytic cycles for Ni/IPr-catalyzed transfer semi-hydrogenation of alkynes

5.3. Catalyst optimization for *E* and *Z* selective transfer hydrogenation of internal alkynes

With mechanism understanding as described above, we have focused our attention on catalyst activation procedures in the development of Ni(0)/NHC catalyzed alkyne TSH using simple alcohol as the sole reducing agent. Optimization of various reaction parameters was carried out with the model substrate of diphenylacetylene (**5.13a**), and selected results are summarized in Table 5.1. The yields of (*Z*)- and (*E*)-selective alkene products, *cis*-stilbene (**5.21a**) and *trans*-stilbene (**5.27a**), were determined by GC analysis. Notably, the formation of alkane byproduct **5.28a** by over-reduction was not detected under all conditions reported here. When no pre-activation procedure was carried out (Method A), a catalyst system of 2 mol% $Ni(COD)_2$ (**5.4**) and 4 mol% IPr (**5.1a**) failed to promote room-temperature reaction between 1 equivalent of **5.13a** and ~5 equivalents of isopropanol to give any detectable alkene product (entry 1). However, we found that the catalyst system could be activated by a simple procedure of heating a 1:2 mixture of $Ni(COD)_2$/IPr in *m*-xylene at 80 °C for 30 minutes (Method B). After

cooling to room temperature, the mixture was charged with **5.13a** and isopropanol and stirred for 12 hours to form **5.21a** and **5.27a** in 77% and 9% yield respectively (entry 2). When the temperature was raised to 80 °C for reactions using non-activated or pre-activated $Ni(COD)_2$/IPr catalyst, **5.21a** and **5.27a** were detected in similar total yield of ~94% but with somewhat different *Z*/*E* stereoselectivity: 7:1 for Method A and 15:1 for Method B (entries 3,4). Further catalyst improvement towards higher reactivity and *Z*-stereoselectivity was attempted by a modified pre-activation procedure, which involved heating the 1:2 mixture of $Ni(COD)_2$/IPr in *m*-xylene at 80 °C for 2 hours before evaporation under reduced pressure to remove all volatiles (Method C). The resulting crude powder of $Ni(IPr)_2$ was tested as TSH catalyst without further purification and showed superior activity and *Z*/*E* stereoselectivity than the *in situ* generated $Ni(IPr)_2$ catalyst via Method A[13,30]. Thus, an optimized reaction for (*Z*)-selective TSH of **5.13a** was carried out using 2 mol% crude $Ni(IPr)_2$ via Method C and in a 1:9 mixture of isopropanol and *m*-xylene (~5 equiv of *i*-PrOH), which generated 96% **5.21a** and 2% **5.27a** upon stirring at room temperature for 12 hours (entry 5). Replacing isopropanol with methanol led to total loss of the reactivity at room temperature (entry 6), while using other simple alcohols such as ethanol, *n*-butanol and *s*-butanol led to significantly lower yields for **5.21a** (21-46%) and no detectable formation of **5.27a** (entries 7-9). When *m-xylene* was replaced with other non-polar solvents such as toluene and hexane, products **5.21a** and **5.27a** were generated in high overall yields of 95-96% but in reduced *Z*/*E* selectivity of 7:1 and 11:1, respectively (entries 10,11). Switching to more polar solvents such as THF, DME and DMF led to lower overall yields of 39-76% and good *Z*/*E* selectivity in the range of 5:1 to 22:1 (entries 12-14). Using isopropanol as both the reducing reagent and the solvent resulted in a low overall yield of 19% for **5.21a** and **5.27a** in 9:1 ratio (entry 15). To modify the catalyst system towards *E*-stereoselectivity, various reaction

parameters were evaluated at the elevated temperature of 80 °C to promote the formation of *trans*-stilbene (**5.27a**) as the thermodynamic alkene product[39,40]. An optimized catalyst system of 5 mol% $Ni(COD)_2$ and 11 mol% IMes ligand (**5.1b**) was found to promote (*E*)-selective TSH of **5.13a** in a 1:9 mixture of isopropanol and DME (~ 5 equiv. of *i*-PrOH), generating 1% **5.21a** and 98% **5.27a** over 12 hours at 80 °C and without catalyst pre-activation (Method A) (entry 16). When the catalyst loadings were reduced to 2 mol% $Ni(COD)_2$ and 4 mol% IMes, both Method A (no catalyst pre-activation) and Method B (*in situ* pre-activation without evaporation) led to high overall yields (92-94%) but low (*E*)-selectivity for stilbene products (entries 17,18). Replacing IMes with other structurally similar NHC ligands such as IPr (**5.1a**), SIPr (**5.2a**) and SIMes (**5.2b**) generated **5.21a** and **5.27a** in lower overall yields (55-61%) and low to moderate *E*/*Z* stereoselectivity (entries 19-21).



Method A: No catalyst pre-activation.

Method B: Heating $Ni(COD)_2$ and NHC ligand in solvent at 80 ^{o}C for 30 minutes.

Method C: Using crude "$Ni(NHC)_2$" powder by heating $Ni(COD)_2$ and NHC ligand in solvent at 80 ^{o}C for 2 hours, then removing all volatiles by evaporation.

Table 5.1. Optimisation table for *Z* and *E* selective transfer hydrogenation of internal alkynes.

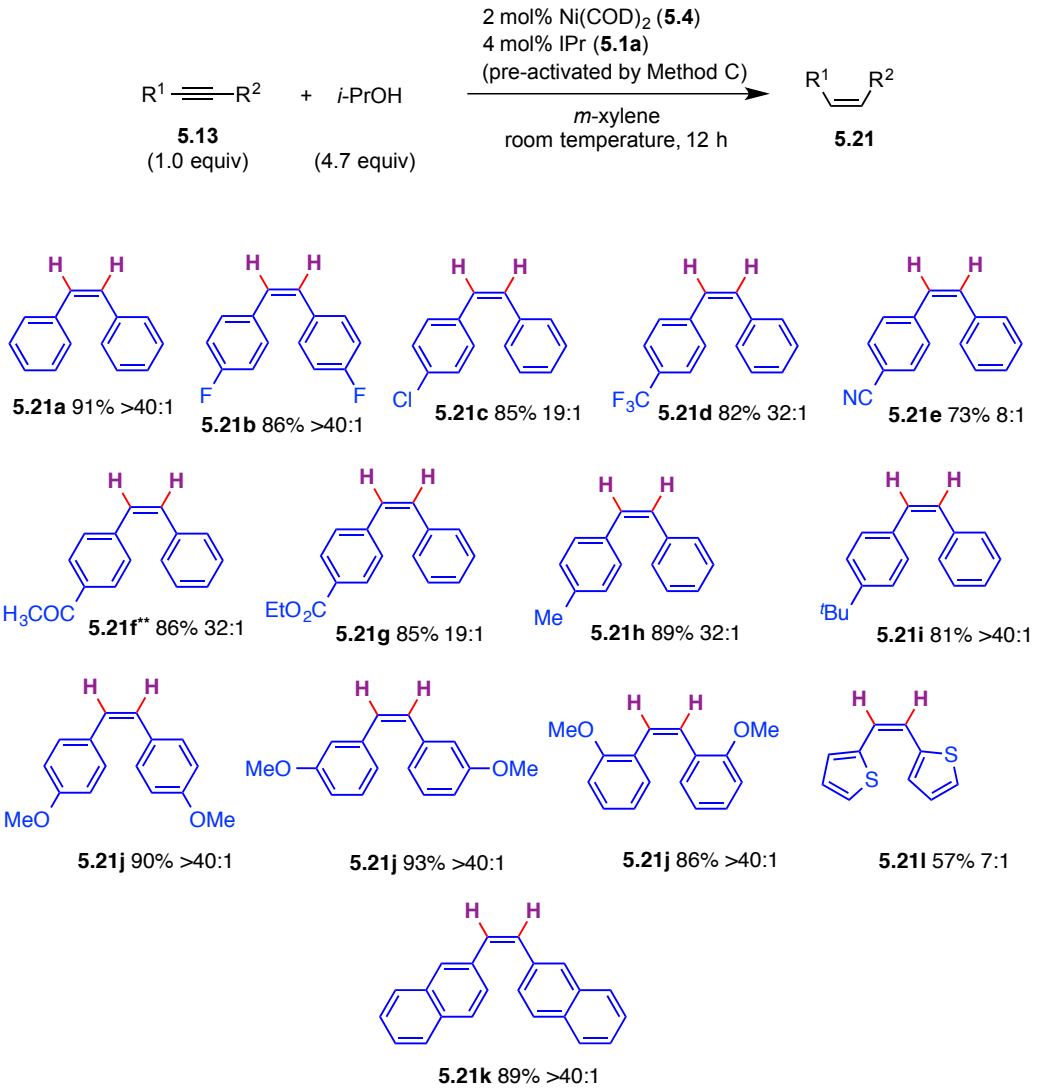
Entry	Ligand	Method	Alcohol	Solvent	Temperature	Yield (%)	
						5.21a	**5.27a**
1	IPr (**5.1a**)	A	*i*-PrOH	*m*-Xylene	room temp.	0	0
2	**5.1a**	B	*i*-PrOH	*m*-Xylene	room temp.	77	9
3	**5.1a**	A	*i*-PrOH	*m*-Xylene	80 °C	82	12
4	**5.1a**	B	*i*-PrOH	*m*-Xylene	80 °C	88	6
5	**5.1a**	C	*i*-PrOH	*m*-Xylene	room temp.	96	2
6	**5.1a**	C	*i*-PrOH	*m*-Xylene	room temp.	0	0
7	**5.1a**	C	EtOH	*m*-Xylene	room temp.	37	0
8	**5.1a**	C	*n*-BuOH	*m*-Xylene	room temp.	21	0
9	**5.1a**	C	*s*-BuOH	*m*-Xylene	room temp.	46	0
10	**5.1a**	C	*i*-PrOH	Toluene	room temp.	83	12
11	**5.1a**	C	*i*-PrOH	Hexane	room temp.	88	8
12	**5.1a**	C	*i*-PrOH	THF	room temp.	44	2
13	**5.1a**	C	*i*-PrOH	DME	room temp.	64	3
14	**5.1a**	C	*i*-PrOH	DMF	room temp.	32	7
15	**5.1a**	C	*i*-PrOH	*i*-PrOH	room temp.	17	2
16*	IMes (**5.1b**)	A	*i*-PrOH	DME	80 °C	1	98
17	IMes (**5.1b**)	A	*i*-PrOH	DME	80 °C	51	43
18	**5.1b**	B	*i*-PrOH	DME	80 °C	81	11
19*	**5.1a**	A	*i*-PrOH	DME	80 °C	8	53
20*	SIPr (**5.2a**)	A	*i*-PrOH	DME	80 °C	28	32
21*	SIMes (**5.2b**)	A	*i*-PrOH	DME	80 °C	4	51

Conditions: **5.13a** (0.28 mmol, 1.0 equiv), **5.4** (0.06 mmol, 2 mol%), NHC ligand (0.11 mmol, 4 mol%), alcohol (0.1 mL), solvent (0.9 mL), stirring at room temperature (20-22 °C) or 80 °C, 12h; yields determined by GC analysis. *Using 5 mol% **5.4** and 11 mol% NHC ligand.

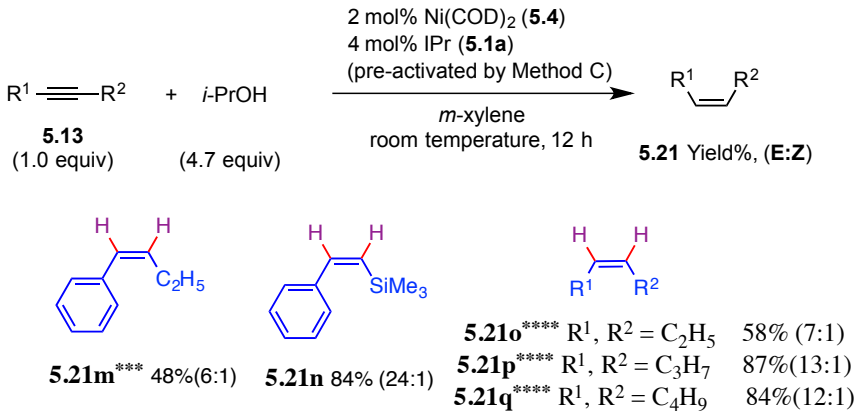
5.4. Substrate scope for Z-selective alkyne transfer hydrogenation with isopropanol

With the optimized conditions in hand, we studied various internal alkyne substrates for Ni/NHC catalyzed stereoselective transfer semi-hydrogenation with isopropanol. Scheme 5.7 and 5.8 summarize results on (*Z*)-selective alkyne TSH at room temperature using 2 mol% crude $Ni(IPr)_2$ as catalyst, which was generated via pre-activation of $Ni(COD)_2$/IPr mixture using Method C. In general, diaryl alkynes underwent smooth TSH to form *cis*-stilbene products in good isolated yields and high stereoselectivity. *Para*-substituted diaryl alkynes with electron-donating methyl, *tert*-butyl, and methoxy groups showed similar reactivity as those with electron-withdrawing fluoro, chloro, and CF_3 groups. Hydrogenation-sensitive *para*-substituents, such as acetyl, ester and cyano groups were also tolerated. A longer reaction time of 24 h was required to reach full conversion for 4-acetyl diphenylacetylene, while lower yield (73%) and Z/E stereoselectivity (8:1) was observed for 4-cyano *cis*-stilbene product **5.21j**. Methoxy substituents at *para*-, *meta*- or *ortho*-positions had little effect on catalytic reactivity or stereoselectivity. Among diphenylacetylene analogs with other aromatic systems, di-2-naphtyl-acetylene showed similar level of high reactivity and stereoselectivity. In comparison, reduced reactivity and stereoselectivity was observed with di-2-thienyl-acetylene. In contrast to clean TSH with diaryl alkynes under the standard conditions, aryl/alkyl and dialkyl alkynes underwent facile trimerization which is a known competitive process with nickel catalysts[45,46]. Thus, a slow-addition procedure was applied to reduce the formation of hexa-substituted benzene byproducts. For example, dropwise addition of a *m*-xylene solution of 1-phenyl-1-butyne by syring-pump

over 10 hours led to desired *cis*-alkene product **5.21o** in 48% yield and 6:1 Z/E stereoselectivity. In comparison, 1-phenyl-2-trimethylsilylacetylene did not undergo alkyne trimerization and generated *cis*-β-trimethylstyrene (**5.21p**) in 84% yield and 24:1 Z/E stereoselectivity. Notably, *cis*-alkene products **5.21q-s** from dialkyl alkyne substrates were difficult to separate due to high volatility. Therefore, their yields and stereochemistry were determined by ^{1}H NMR analysis after carrying out the TSH reactions in deuterated toluene solvent.



Scheme 5.7. Substrate scope of *Z*-alkenes for aromatic alkynes



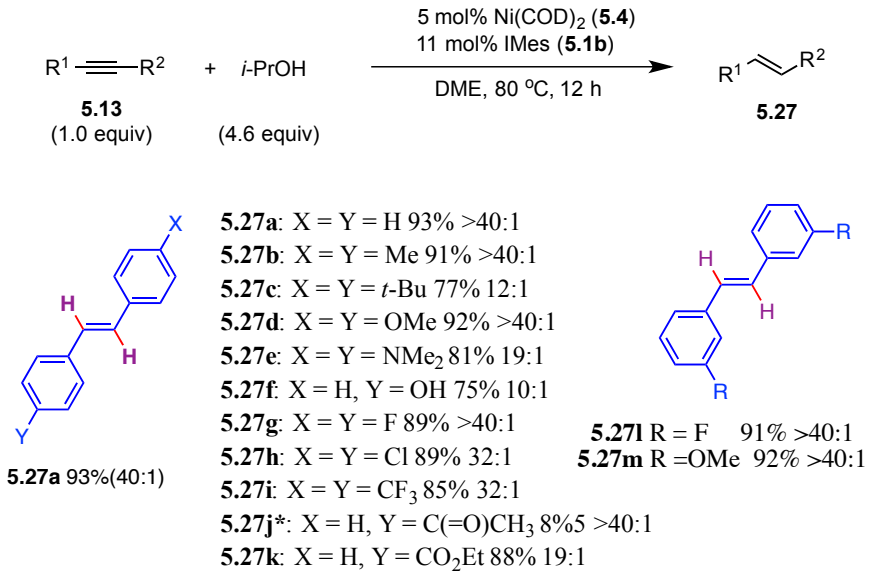
Scheme 5.8. Substrate scope of *Z*-alkenes for aliphatic and unsymmetrical aryl-alkyl alkynes

Conditions: **5.13** (0.28 mmol), **5.4** (0.006 mmol), **5.1a** (0.012 mmol), *i*-PrOH (0.1 mL), *m*-xylene (0.9 mL), room temperature (20-22 °C), 12h; average isolated yields of two runs; stereoselectivity determined by GC analysis of the crude product mixture. *Catalyst pre-activation was carried out by heating the 1:2 mixture of **5.4** and **5.1a** in *m*-xylene at 80 °C for 2 h, followed by evaporation in vacuuo to remove all volatiles (Method C); the resulting crude powder was used as catalyst without further purification. **24 h reaction time. ***Reaction carried out using 2.8 mmol alkyne, 0.056 mmol **5.4**, 0.11 mmol **5.1a**, 1.0 mL isopropanol and 19 mL hexane solvent; slow addition of alkyne by syringe pump over 10 hours. ****Reaction carried out using 0.9 mL d_8-toluene solvent; yield and stereoselectivity determined by ^{1}H NMR analysis.

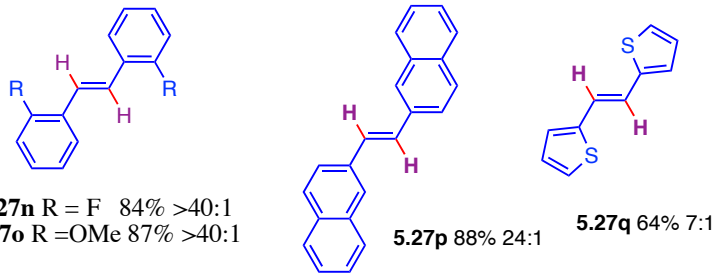
5.5. Substrate scope for *E*-selective alkyne transfer hydrogenation with isopropanol

In addition to the (*Z*)-selective alkyne TSH, a comparable scope of alkynes were studied for (*E*)-selective alkyne TSH at 80 °C using the catalyst system of 5 mol% Ni(COD)$_2$ precursor and 11 mol% IMes ligand in DME solvent Scheme 5.9-5.11. In general, similar results of reactivity trends, stereoselectivity and functional group tolerance were obtained when comparing (*Z*)- and (*E*)-selective TSH of internal alkynes. Competition by alkyne trimerization was also

observed with alkyl-substituted alkynes for (*E*)-selective TSH, and the slow-addition protocol was required to form desired E-alkene products in moderate to good yields and decent E/Z stereoselectivity. Notably, 4-hydroxy-dipehnylacetylene underwent (*E*)-selective TSH to form *trans*-stilbene product **5.27f**, whereas the *cis*-isomer failed to form as the major product under (*Z*)-selective TSH conditions at room temperature. On the other hand, the relatively high reaction temperature of 80 °C prevented successful (*E*)-selective TSH of 4-cyano-diphenylacetylene due to competitive nitrile reduction. A number of alkyne substrates failed to give desired alkene products in useful yields under either (*Z*)- or (*E*)-selective TSH conditions. For example, terminal alkynes such as phenylacetylene underwent rapid trimerization to form tri-substituted benzene byproducts[46]. In addition, reactions with diphenylacetylenes having *para*-bromo or –nitro group did not generate any detectable products. Lastly, diphenylacetylenes having *para*-formyl, -carboxyl, or –(pinacolato)boryl moiety did not undergo target TSH due to substrate decomposition.



Scheme 5.9. Substrate scope of *E*-alkenes for aromatic alkynes-1

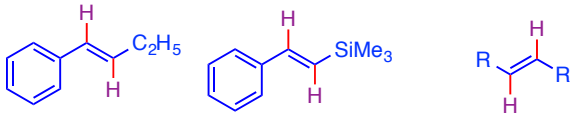


5.27n R = F 84% >40:1
5.27o R =OMe 87% >40:1

5.27p 88% 24:1

5.27q 64% 7:1

Scheme 5.10. Substrate scope of *E*-alkenes for aromatic alkynes-2



5.**27u** 56% 7:1

5.27v 87% 32:1

5.**27r** R = C_2H_5 60% 9:1
5.27s R = C_3H_7 79% 8:1
5.27t R = C_4H_9 60% 8:1

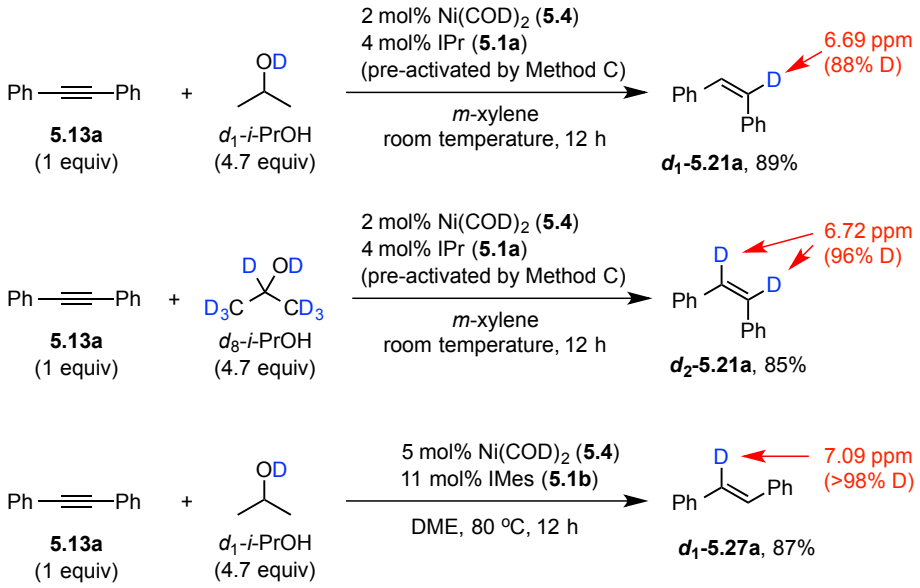
Scheme 5.11. Substrate scope of *E*-alkenes for aliphatic and unsymmetrical aryl-alkyl alkynes

Conditions: **5.13** (0.28 mmol), **5.4** (0.006 mmol), **5.1b** (0.012 mmol), *i*-PrOH (0.1 mL), DME (0.9 mL), 80 °C, 12h; average isolated yields of two runs; stereoselectivity determined by GC analysis of the crude product mixture. *9 h reaction time. **Reaction carried out using 2.8 mmol alkyne, 0.14 mmol **5.4**, 0.29 mmol **5.1b**, 1.0 mL isopropanol and 19 mL DME; slow addition of alkyne by syringe pump over 10 hours. ****Reaction carried out using 0.006 mmol **5.4** and 0.012 mmol **5.1a** in 0.9 mL d_8-toluene solvent; catalyst pre-activation carried out using Method C; yield and stereoselectivity determined by ^{1}H NMR analysis.

5.6. Deuterium-labeling studies for alkyne transfer hydrogenation with deuterated isopropanol

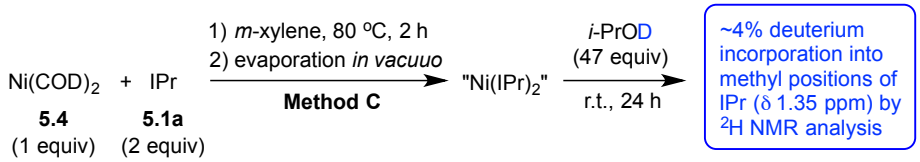
To better understand hydrogen atom transfer processes in Ni/NHC catalyzed alkyne TSH, we carried out deuterium-labeling studies using deuterated isopropanol reagents under otherwise standard catalytic conditions (Scheme 5.12). Diphenylacetylene underwent (*Z*)-selective TSH with d_1-isopropanol (*i*-PrOD) to form mono-deuterated *cis*-stilbene (***d*$_1$-5.21a**) in 89% yield and

with 88% D-incorporation at a vinyl position. A similar reaction with fully deuterated d_8-isopropanol led to di-deuterated *cis*-stilbene (***d*$_2$-5.21a**) in 85% yield and with an average of 96% D-incorporation at both vinyl positions. These results support the proposed dual-role of isopropanol in alkyne TSH, acting as both the proton donor via hydroxy functionality (Scheme 5.6, **5.16→5.22'** or **5.5a→5.23'**) and the hydride donor via β-H elimination from Ni(II) alkoxide intermediate (**5.22'→5.25**). The slightly lower value of D-incorporation percentage for ***d*$_1$-5.21a** than ***d*$_2$-5.21a** is consistent with the proposed TSH mechanism involving C–H activated Ni/IPr intermediates (Scheme 5.6, Path C), which leads to H/D exchange at the IPr methyl positions with *i*-PrOD as the external deuterium source. Consequently, both protium and deuterium atoms are incorporated onto *cis*-stilbene vinyl positions via alkyne insertion into the Ni–H or Ni–D linkage generated by IPr cyclometalation (**5.24→5.16**). Under (*E*)-selective TSH conditions with *i*-PrOD, mono-deuterated *trans*-stilbene (***d*$_1$-5.27a**) was formed in 87% yield and with 98% D-incorporation at the vinyl position. The lack of di-deuterated product formation suggests that the envisioned *Z*-to-*E* isomerization does not involve reactions between mono-deuterated stilbene and *i*-PrOD, which should have led to H/D exchange and further deuterium incorporation. Thus, the *Z*/*E* isomerization likely occurred by rapid alkene insertion/β-H elimination equilibrium catalyzed by Ni–H complexes generated under TSH conditions.



Scheme 5.12. (*Z*)- and (*E*)-selective TSH of diphenylacetylene using d_1- or d_7-isopropanol

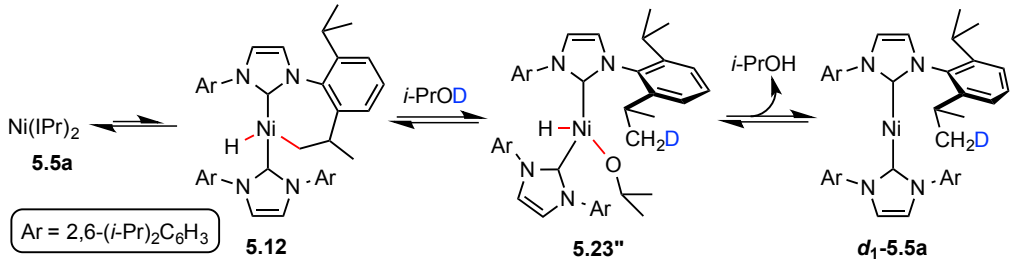
We further evaluated the potential intermediacy of C–H activated Ni/IPr complexes under catalytic conditions by carrying out a room-temperature reaction between *i*-PrOD and crude $Ni(IPr)_2$ (~2 mol%) that was generated via pre-activation of a $Ni(COD)_2$/IPr mixture by Method C (scheme 5.13). ^{2}H NMR analysis of the reaction mxiture indicated a slow process of selective D-incorporation onto the methyl positions of IPr (δ 1.35 ppm), although we were not able to distinguish between coordinated and non-coordinated IPr molecules due to rapid ligand exchange. The D-incorporation percentage was measured to be ~4% after 24 h, which is equivalent of mono-deuteration for each IPr molecule.



Scheme 5.13. Reaction between d_1-isopropanol and crude $Ni(IPr)_2$ via pre-activation of $Ni(COD)_2$/IPr mixture by Method C

This result suggests that in contrast to the facile and irreversible trapping of proposed cyclometalated Ni(II) hydride species (**5.12**) by diphenylacetylene (Scheme 5.2), complex **5.12**

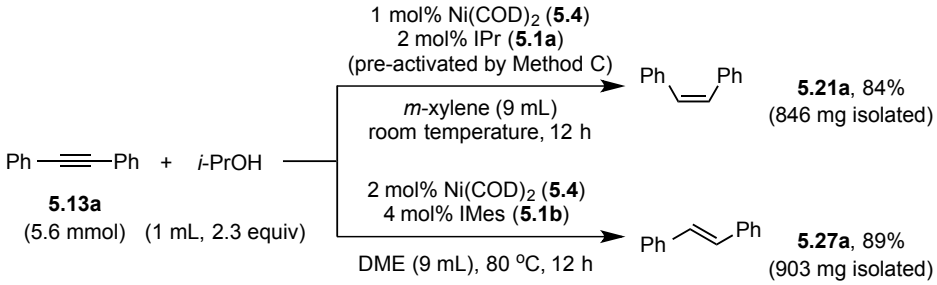
undergoes slow and reversible protonation of the Ni-alkyl linkage with isopropanol, which leads to H/D exchange at IPr methyl positions with *i*-PrOD (Scheme 5.14).



Scheme 5.14. A plausible pathway for H/D exchange between $Ni(IPr)_2$ and d_1-isopropanol.

5.7. Gram scale synthesis of *cis* and *trans*-stilbene products

To demonstrate the potential of Ni/NHC catalyzed alkyne TSH for practical synthesis, we carried out gram-scale synthesis of *cis*- and *trans*-stilbene products (Scheme 5.15). With reduced catalyst loadings of 1 mol% crude $Ni(IPr)_2$ or 2 mol% $Ni(COD)_2$ and 4 mol% IMes, (*Z*)- and (*E*)-selective TSH of diphenylacetylene could be scaled up 20-fold to selectively produce isolated products **5.21a** and **5.27a** in high yields and >40:1 stereoselectivity.

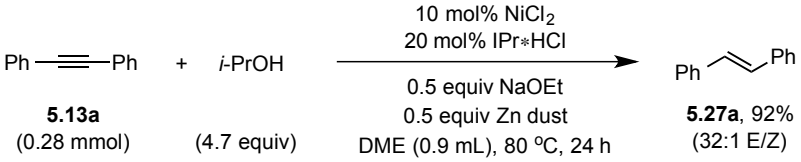


Scheme 5.15. Gram-scale synthesis of (*Z*)- and (*E*)-stilbene with reduced catalyst loadings

5.8. Bench top conditions for *E*-selective transfer hydrogenation

To modify the current catalyst systems towards simplified procedures that do not require glove-box or Schlenk techniques, we evaluated $NiCl_2$ and HCl salts of IPr/IMes as air-stable pre-catalyst and NHC ligands for alkyne TSH, using isopropanol as the hydrogen source and additional reducing reagents and inorganic bases for catalyst activation. In general, (*Z*)-selective

TSH was not successful due to low catalyst activity at room temperature and reduced *Z*/*E* stereoselectivity at higher temperatures. In comparison, diphenylacetylene (**5.13a**) underwent (*E*)-selective TSH using a catalyst system of 10 mol% $NiCl_2$, 20 mol% IPr-HCl salt, 0.5 equiv NaOEt, 0.5 equiv zinc dust and DME solvent (Scheme 5.16). Under these conditions, **5.13a** reacted with ~5 equiv isopropanol at 80 °C for 24 h to form *trans*-stilbene (**5.27a**) in 92% isolated yield and 32:1 *E*/*Z* stereoselectivity.



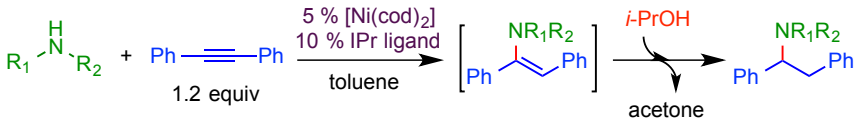
Scheme 5.16. (*E*)-Selective alkyne TSH under bench top conditions and without N_2 protection

In summary, we have shown that the commonly used IPr ligand in nickel catalysis undergoes Ni(0)-mediated cyclometalation by mild C–H activation at the methyl position. The resulting Ni(II) hydride complexes equilibrates with more stable Ni(0)/IPr complexes such as $Ni(IPr)_2$, and their presence is evidenced by further stoichiometric transformations to generate discrete organonickel products. To exploit Ni/IPr cyclometalation as a low-energy access to catalytically active Ni(II) hydride species, we developed a Ni(0)/NHC catalyzed stereoselective transfer semi-hydrogenation of a broad scope of internal alkynes using simple alcohols such as isopropanol as the only reducing reagent. In particular, room-temperature (*Z*)-selective alkyne TSH was effectively promoted by crude $Ni(IPr)_2$ as a convenient source of activated Ni(II) hydride catalyst. Results from this study call for a closer look at possible involvement of C–H activated Ni-NHC complexes in the prevalent catalyst system of Ni(0)/IPr and its analogs with other NHC ligands. In-depth structure and mechanism understanding of these Ni-NHC

metallacycles may advance the rational design and improvement of Ni/NHC catalyst systems towards broader applications in chemical synthesis.

5.9. Future and ongoing studies

Based on our study on Ni(0)/NHC-catalyzed transfer hydrogenation we aim to develop an one-pot procedure of tandem alkyne hydroamination and imine/enamine transfer hydrogenation by adding isopropanol upon completion of the hydroamination stage, followed by stirring the reaction mixture at 80-100 ºC. The results will be combined with our study on Ni(0)/NHC-catalyzed alkyne hydroamination to provide the target one-pot protocol towards α-branched amine synthesis that is operationally simple by using a single nickel catalyst, simple alcohol reagent, and without the need for separation or purification of the imine/enamine intermediates (Scheme 5.17).



Scheme 5.17. Proposed one-pot protocol for Ni/NHC-catalyzed alkyne hydroamination and transfer hydrogenation of imine/enamines with simple alcohols.

The long-term goal of this study is to explore cyclometalated Ni-NHC complexes as active catalyst precursors for broad-scope transformations that involve hydride transfer processes in reaction pathways such as hydrogenolysis of ethers etc.

5.10. General experimental procedures and reagent availability

Unless otherwise noted, all manipulations were carried out under a nitrogen atmosphere using standard Schlenk-line or glovebox techniques. All glassware was oven-dried for at least 1 h prior to use. THF, toluene, and hexane were purified with a solvent purification system (MBraun MB-SPS). Anhydrous 1,4-dioxane, Dimethoxy ethane and *m*-xylene was purchased from Sigma Aldrich and used as received. Except for commercially available alkyne substrates, diphenylacetylene, 3-hexyne, 4-octyne, and 5-decyne, 1-Phenyl-2-trimethylsilylacetylene were purchased from Sigma Aldrich commercially and used without further purification; other diaryl alkyne substrates were prepared by following a reported general procedure of Sonogashira coupling.[1] N-Heterocyclic free carbenes) are purchased from sigma Aldrich and used as such. Toluene-d_8 (99.5 atom %D) and 2-propanol-d_8 (99 atom %D) were purchased from Cambridge isotopes. 2-propanol-d1 (98 atom %D) is purchased from sigma aldrich. The rest of reagents and substrates were purchased from commercial vendors and were used as received. TLC plates were visualized by exposure to ultraviolet light or by exposure to I_2 sealed in a bottle at room temperature. Organic solutions were concentrated by rotary evaporation at ~10 torr. Flash column chromatography was performed with 58 Å pore size neutral alumina (Sigma Aldrich, Lot # BCBK5164V). GC analyses were performed on a Shimadzu GC-2010 with *n*-dodecane asthe internal standard. ^{1}H NMR spectra were obtained on a 400 MHz spectrometer, and chemical shifts were recorded relative to residual protiated solvent. ^{2}H NMR spectra were obtained on a 76.7 MHz spectrometer. ^{13}C NMR spectra were obtained at 100.6 MHz, and chemical shifts were recorded to the solvent resonance. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane (δ = 0). ^{19}F NMR spectra were obtained at 282.4 MHz, and all chemical shifts were reported in parts per million upfield of CF_3COOH (δ = -78.5

ppm). High-resolution mass spectra were obtained at a Bruker Daltronics BioTOF HRMS spectrometer.

Single crystal X-ray diffraction data of compound **5.15**, **5.19**, and **5.20** were collected on a Bruker Apex Duo diffractometer with a Apex 2 CCD area detector at T = 100K. Cu radiation was used. All structures were process with Apex 2 v2010.9-1 software package (SAINT v. 7.68A, XSHELL v. 6.3.1). Direct method was used to solve the structures after multi-scan absorption corrections. Details of data collection and refinement are given in Table S4.

5.10.1. General Procedure for Nickel Catalyzed transfer hydrogenation for *E* & *Z*-Selectivity

Method A: For aromatic alkynes substrates (*E*-Selectivity). Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed [Ni(cod)$_2$] (**5.4**, 3.9mg, 0.014 mmol, 0.05 equiv), IMes (**5.1b**, 9.0 mg, 0.029 mmol, 0.11 equiv), 0.9 mL of Dimethoxy ethane. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, internal alkyne (**5.13**, 0.28 mmol, 1.0 equiv) was added into the vial followed by 0.1 mL of Isopropanol. The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 80°C for 12 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using Silica.

Method C : For aromatic alkynes substrates (*Z*-selectivity). Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed crude Ni(IPr)$_2$ (**5.5a**, 4.7 mg, 0.006 mmol, 0.02 equiv), 0.9 mL of *m*-Xylene. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, internal alkyne (**5.13**, 0.28 mmol, 1.0 equiv) were added into the vial followed by 0.1 mL of Isopropanol. The vial was sealed with a silicone-lined

screw-cap, and stirred at room temperature for 12 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using Silica.

Method D: For dialkylacetylenes substrates (*E*-Selectivity). Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed [Ni(IPr)$_2$] (**5.5a**, 4.7 mg, 0.006 mmol, 0.02 equiv), 0.9 mL of Toluene-d$_8$. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, dialkylacetylenes (**5.13**, 0.28 mmol, 1.0 equiv) and 1,3,5-trimethoxy benzene (0.28 mmol, 1.0 equiv) were added into the vial followed by 0.1 mL of Isopropanol. The vial was sealed with a silicone-lined screw-cap, transferred out of the glovebox, and stirred at 80°C for 12 hours and calculated NMR Yield.

Method E: For dialkylacetylenes substrates. Into a 1 dram scintillation vial equipped with a magnetic stir bar was placed [Ni(IPr)$_2$] (**5.5a**, 4.7 mg, 0.006 mmol, 0.02 equiv), 0.9 mL of Toluene-d$_8$. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, dialkylacetylenes (**5.13**, 0.28 mmol, 1.0 equiv) and 1,3,5-trimethoxy benzene (0.28 mmol, 1.0 equiv) followed by 0.1 mL of Isopropanol. The vial was sealed with a silicone-lined screw-cap, and stirred at room temperature for 12 hours calculated NMR Yield.

Method F: For unsymmetrical aromatic aliphatic alkynes substrates (*E*-Selectivity). Into a 100 mL round bottom flask equipped with a magnetic stir bar was placed [Ni(cod)$_2$] (**5.4**, 39 mg, 0.14 mmol, 0.05 equiv), IMes (**5.1b**, 89.4 mg, 0.29 mmol, 0.11 equiv), 10 mL of Dimethoxy ethane. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, in to a 20 mL vial weighed 1-phenyl-1-butyne (364 mg, 2.8 mmol, 1.00 equiv) 9 mL dimethoxy ethane and 1 mL Isopropanol mixed thoroughly and added drop

wise in to the schlenk reaction tube (slowly for a period of 10 hrs with the help of syringe pump) at 80 °C for 12 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using Silica.

Method G: For aromatic aliphatic alkynes substrates (*Z*-Selectivity). Into a 50 mL schlenk reaction tube dram equipped with a magnetic stir bar was placed [Ni(IPr)$_2$] (**5.5**, 47 mg, 0.06 mmol, 0.02 equiv), 10 mL of Hexane. The mixture was stirred at room temperature for 2 minutes to form a dark brown homogeneous solution. Next, in to a 20 mL vial weighed 1-phenyl-1-butyne (364 mg, 2.8 mmol, 1.00 equiv) 9 mL Hexane and 1 mL Isopropanol mixed thoroughly and added drop wise in to the schlenk reaction tube (slowly for a period of 10 hrs with the help of syringe pump) room temperature for 12 hours. After the reaction mixture was cooled, all volatile materials were removed under reduced pressure. Further purification was achieved by flash-column chromatography using Silica.

5.10.2. General procedure for synthesis of [Ni(IPr)$_2$] (5.5a)

Into a 4 dram scintillation vial equipped with a magnetic stir bar was placed [Ni(cod)$_2$] (**5.4**, 50.0 mg, 0.18 mmol, 1.0 equiv), IPr (**5.1a**, 144.5 mg, 0.37 mmol, 2.05 equiv), and 1.0 mL of benzene. The mixture was stirred at 80 °C for 2 hrs. The solvent was removed under reduced pressure to afford a dark brown colored powder (138 mg, 89%).

5.10.3. General procedure for synthesis of cyclometalated IPr-ligated Ni(II) η^3-cyclobutenyl complex (5.15)

Into a 4 dram scintillation vial equipped with a magnetic stir bar was placed [Ni(cod)$_2$] (**5.4**, 50.0 mg, 0.18 mmol, 1.0 equiv), IPr (**5.1a**, 144.5 mg, 0.37 mmol, 2.05 equiv), and 1.0 mL of benzene. The mixture was stirred at 80 °C for 2 h. Next, diphenyl acetylene (**5.13a**, 0.37 mmol, 2.05 equiv) was added and the mixture was stirred at room temperature for 30 min. The

solvent was removed under reduced pressure to afford a dark violet-colored powder (132 mg, 86%). Further crystallization was carried out in a mixed solvent system of benzene and layered with hexane to produce single crystals suitable for X-ray analysis.

5.10.4. General procedure for synthesis of π-olefin Ni(0) complex (5.19) with a dehydrogenated IPr ligand

Into a 4 dram scintillation vial equipped with a magnetic stir bar was placed [$Ni(cod)_2$] (**5.4**, 50.0 mg, 0.18 mmol, 1.0 equiv), IPr (**5.1a**, 144.5 mg, 0.37 mmol, 2.05 equiv), and 1.0 mL of benzene. The mixture was stirred at 80 ^{o}C for 12 h. The solvent was removed under reduced pressure for over night to afford a dark green colored powder (129 mg, 85%).

5.10.5. General procedure for synthesis of IPr-ligated Ni(II) alkenyl μ-hydroxo dimer (5.20)

Into a 4 dram scintillation vial equipped with a magnetic stir bar was placed [$Ni(cod)_2$] (**5.4**, 50.0 mg, 0.18 mmol, 1.0 equiv), IPr (**5.1a**, 144.5 mg, 0.37 mmol, 2.05 equiv), and 1.0 mL of benzene. The mixture was stirred at 80 ^{o}C for 2 hrs. Next, diphenyl acetylene (**5.13a**, 0.37 mmol, 2.05 equiv) and water (16.4 mg, 0.91 mmol, 5.0 equiv) was added and the mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure to afford a dark violet-colored powder (129 mg, 86%). Further crystallization was carried out in a mixed solvent system of benzene and layered with hexane to produce single crystals suitable for X-ray diffraction.

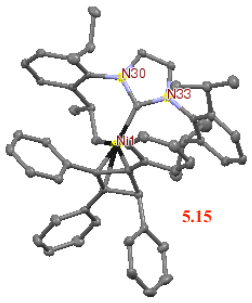


Figure 5.5. ORTEP diagrams of cyclometalated IPr-ligated Ni(II) η^3-cyclobutenyl complex **(5.15)**

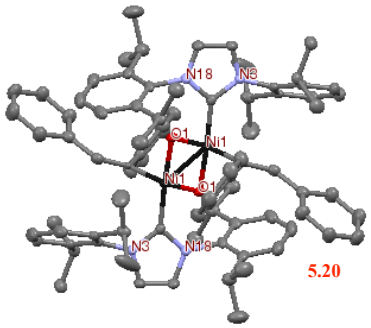


Figure 5.6. ORTEP diagrams of IPr-ligated Ni(II) alkenyl μ-hydroxo dimer (**5.20)**

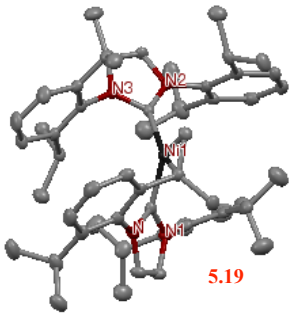
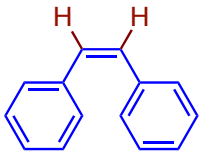


Figure 5.7. ORTEP diagrams of π-olefin Ni(0) complex (5.19) with a dehydrogenated IPr ligand **(5.19)**

Table 5.2. Summary of cell parameters, data collection and structural refinements for compounds **5.15**, **5.19**, and **5.20**

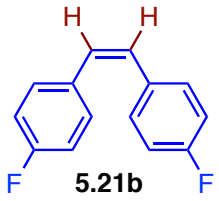
	5.15	**5.20**	**5.19**
Formula	$C_{55}H_{56}N_2Ni$	$C_{41}H_{48}N_2NiO$	$C_{54}H_{70}N_4Ni$
FW	842.3	646.8	825.8
cryst. size_max [mm]	0.172	0.172	0.19
cryst. size_mid [mm]	0.126	0.168	0.157
cryst. size_min [mm]	0.12	0.047	0.114
cryst. system	monoclinic	monoclinic	orthorhombic
Space Group, Z	P 2_1/n	P 2_1/n	P 2_1 2_1 2_1
a [Å]	10.5324(2)	14.7090(6)	12.0832(4)
b [Å]	17.4924(4)	16.5163(6)	19.1816(7)
c [Å]	24.8280(5)	14.7202(6)	20.8442(7)
α [Å]	90	90	90
ß [Å]	100.8110(10)	102.095	90
γ [Å]	90	90	90
V [Å^3]	4493.05	3496.72	4831.2(3)
ρ_{calc} [g/cm^3]	1.245	1.229	1.135
μ [mm^{-1}]	0.911	1.028	0.830
Radiation Type	Cu	Cu	Cu
F(000)	1795	1380	1784
# of measured refl.	28,877	12742	32077
no of indep. refl.	7757	5580	8417
no of refl. (I ≥ 2σ)	6906	4597	8065
R1/wR2 (I ≥ 2σ)[a]	3.67/9.38	4.47/12.20	3.88/11.22
R1/wR2 (all data)	4.20/9.75	5.35/12.83	4.06/13.41

5.10.6. Preparation and analytical information for reported alkyne transfer hydrogenation for *Z*-selectivity



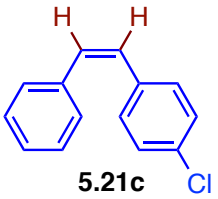
5.21a

(*Z*)-1,2-diphenylethene (**5.21a**): Prepared from diphenyl acetylene according to the general procedure (Method C). Chromatography (hexane) gave **5.21a** as a clear liquid (46 mg, 91%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 2H), 7.32-7.42 (m, 10H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 127.3, 128.4, 129.0, 130.4 and 137.4.



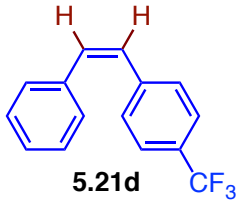
5.21b

(*Z*)-1,2-bis(4-fluorophenyl)ethene (**5.21b**): Prepared from 1,2-bis(4-fluorophenyl)ethyne according to the general procedure (Method C). Chromatography (hexane) gave **5.21b** as a clear liquid (52 mg, 86%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 2H), 6.93-6.99 (m, 4H), 7.20-7.25 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 115.2 (d, J = 21.3 Hz), 129.1, 130.5 (d, J = 7.9 Hz), 132.9 (d, J = 3.3 Hz), 160.7 (d, J(C,F) = 245.6). ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -114.4.



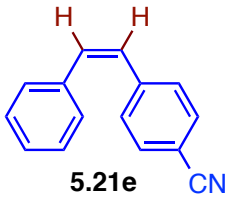
5.21c

(*Z*)-1-chloro-4-styrylbenzene (**5.21c**): Prepared from 1-chloro-4-(phenylethynyl)benzene according to the general procedure (Method C). Chromatography (hexane) gave **5.21c** as a clear liquid (70 mg, 85%, 19:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.56 (d, 1H, *J* = 12.4 Hz), 6.74 (d, 1H, *J* = 12.0 Hz), 7.18-7.20 (m, 4H), 7.23-7.29 (m, 5H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 127.4, 128.4, 128.5, 128.9, 129.0, 130.3, 131.0, 132.8, 135.7, and 136.9.



5.21d

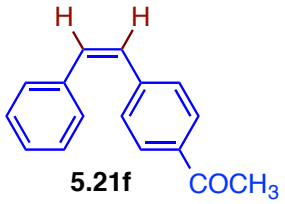
(*Z*)-1-styryl-4-(trifluoromethyl)benzene (**5.21d**): Prepared from 1-(phenylethynyl)-4-(trifluoromethyl)benzene according to the general procedure (Method C). Chromatography (hexane) gave **5.21d** as a clear liquid (73 mg, 82%, 32:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.61 (d, 1H, *J* = 12.4 Hz), 6.74 (d, 1H, *J* = 12.4 Hz), 7.24-7.29 (m, 5H), 7.36 (d, 2H, *J* = 8.4 Hz), 7.49 (d, 2H, *J* = 8.0 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 122.8 (q, *J* = 270.3 Hz), 125.1 (q, *J* = 3.7 Hz), 127.6, 128.4, 128.8 (q, *J* = 7.8 Hz), 132.3, 136.6, 140.9. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.6.



5.21e

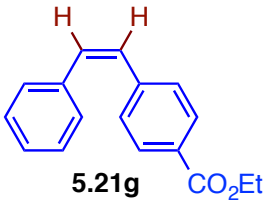
(*Z*)-4-styrylbenzonitrile (**5.21e**): Prepared from 4-(phenylethynyl)benzonitrile according to the general procedure (Method C). Chromatography (hexane and ethyl acetate) gave **5.21e** as a clear liquid (37 mg, 73%, 8:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10 (d, 1H, J = 16.4 Hz), 7.23 (d, 1H, J = 16.0 Hz), 7.33-7.37 (m, 1H), 7.40-7.44 (m, 1H), 7.55-7.57 (m, 2H), 7.60–7.62 (m, 2H), 7.65–

7.68 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 119.1, 126.8, 126.76, 126.88, 126.94, 128.7, 128.9, 132.4, 132.5, 136.3, 141.9.



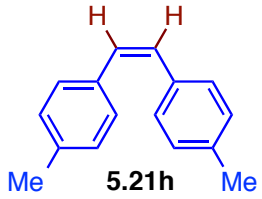
5.21f

(*Z*)-1-(4-styrylphenyl)ethan-1-one (**5.21f**): Prepared from 1-(4-(phenylethynyl)phenyl)ethan-1-one according to the general procedure (Method C). Chromatography (hexane and ethyl acetate) gave **5.21f** as a clear liquid (54 mg, 86%, 32:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.59 (s, 3H), 6.62 (d, 1H, *J* = 12.0 Hz), 6.74 (d, 1H, *J* = 12.0 Hz), 7.24-7.28 (m, 5H), 7.34 (d, 2H, *J* = 8.4 Hz), 7.83 (d, 2H, *J* = 8.4 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 26.6, 127.6, 128.3, 128.4, 128.9, 129.1, 129.2, 132.5, 135.6, 136.7, 142.3, 197.6.



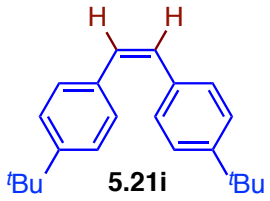
5.21g

ethyl (*Z*)-4-styrylbenzoate (**5.21g**): Prepared from ethyl 4-(phenylethynyl)benzoate according to the general procedure (Method C). Chromatography (hexane and ethyl acetate) gave **5.21g** as a clear liquid (60 mg, 85%, 19:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.40 (t, 3H), 4.42 (q, 2H), 6.63 (d, 1H, *J* = 12.4 Hz), 6.73 (d, 1H, *J* = 12.0 Hz), 7.24 - 7.29 (m, 5H), 7.33-7.35 (d, 2H, *J* = 8.4 Hz), 7.93 (d, 2H, *J* = 8.4 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.4, 60.9, 127.5, 128.4, 128.89, 128.98, 130.0 129.3, 129.5, 132.2, 136.7, 142.0, 166.4.



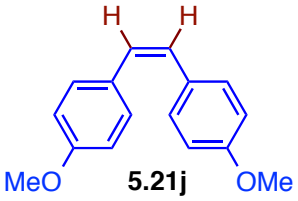
5.21h

(*Z*)-1,2-di-*p*-tolylethene (**5.21h**): Prepared from 1,2-di-*p*-tolylethyne according to the general procedure (Method C). Chromatography (hexane) gave **5.21h** as a clear liquid (52 mg, 89%, 32:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 6H), 6.68 (s, 2H), 7.18 (d, 4H, *J* = 7.6 Hz), 7.32-7.35 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 21.4, 128.9, 129.1, 129.7, 134.7, 136.8.



5.21i

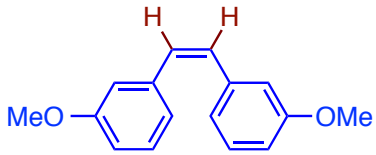
(*Z*)-1,2-bis(4-(*tert*-butyl)phenyl)ethene (**5.21i**): Prepared from 1,2-bis(4-(*tert*-butyl)phenyl)ethyne according to the general procedure (Method C). Chromatography (hexane) gave **5.21i** as a clear liquid (65 mg, 81%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 18H), 6.64 (s, 2H), 7.39 (s, 8H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 31.5, 34.7, 125.2, 128.7, 129.6, 134.7, 150.1.



5.21j

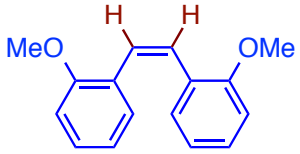
(*Z*)-1,2-bis(4-methoxyphenyl)ethene (**5.21j**): Prepared from 1,2-bis(4-methoxyphenyl)ethyne according to the general procedure (Method C). Chromatography (hexane and ethyl acetate) gave **5.21j** as a clear liquid (60 mg, 90%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 6H), 6.50 (s,

2H), 6.81 (d, 4H, *J* = 9.2 Hz), 7.25 (d, 4H, *J* = 8.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 55.2, 113.7, 128.4, 130.05, 130.11, 158.6.



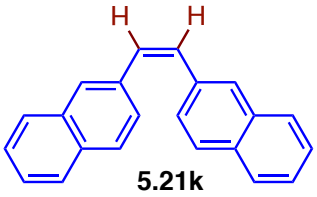
5.21j

(*Z*)-1,2-bis(3-methoxyphenyl)ethene (**5.21j**): Prepared from 1,2-bis(3-methoxyphenyl)ethyne according to the general procedure (Method C). Chromatography (hexane and ethyl acetate) gave **5.21j** as a clear liquid (62 mg, 93%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.74 (s, 6H), 6.68 (s, 2H), 6.84-6.86 (m, 2H), 6.94-6.98 (m, 4H), 7.23-7.27 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 55.1, 113.4, 113.9, 121.6, 129.3, 130.5, 138.7, 159.5.



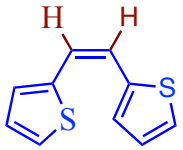
5.21j

(*Z*)-1,2-bis(2-methoxyphenyl)ethene (**5.21j**): Prepared from 1,2-bis(2-methoxyphenyl)ethyne according to the general procedure (Method C). Chromatography (hexane and ethyl acetate) gave **5.21j** as a clear liquid (57 mg, 86%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 6H), 6.77-6.81 (m, 2H), 6.88 (s, 2H), 6.93-6.95 (m, 2H), 7.22-7.26 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 55.5, 110.6, 120.2, 125.7, 126.5, 128.4, 130.1, 157.3.



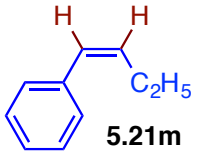
5.21k

(*Z*)-1,2-di(naphthalen-2-yl)ethene (**5.21k**): Prepared from 1,2-di(naphthalen-2-yl)ethyne according to the general procedure (Method C). Chromatography (hexane) gave **5.21k** as a clear liquid (70 mg, 89%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17-7.21 (m, 4H), 7.51 (s, 2H), 7.57-7.64 (m, 4H), 7.74-7.76 (m, 2H), 7.92–7.94 (m, 2H), 8.29-8.31 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 124.6, 125.5, 125.9, 126.1, 127.1, 127.5, 128.6, 130.3, 132.1, 133.7, 134.5.



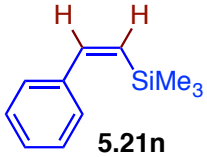
5.21l

(*Z*)-1,2-di(thiophen-2-yl)ethene (**5.21l**): Prepared from 1,2-di(thiophen-2-yl)ethyne according to the general procedure (Method C). Chromatography (hexane and ethyl acetate) gave **5.21l** as a clear liquid (31 mg, 57%, 7:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.65 (s, 2H), 7.02-7.04 (m, 2H), 7.15-7.16 (m, 2H), 7.28-7.29 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 122.9, 126.2, 126.9, 128.3, 139.1.



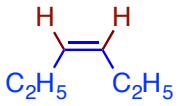
5.21m

(*Z*)-but-1-en-1-ylbenzene (**5.21m**): Prepared from but-1-yn-1-ylbenzene according to the general procedure (Method G). Chromatography (hexane) gave **5.21m** as a clear liquid (178 mg, 48%, 6:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13 (t, 3H), 2.39 (q, 2H), 5.70-5.77 (m, 1H), 6.46 (d, 1H, *J* = 11.6 Hz), 7.27-7.31 (m, 1H), 7.35-742 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.5, 22.0, 126.5, 128.2, 128.3, 128.8, 134.8, 137.8.



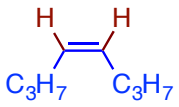
5.21n

(*Z*)-trimethyl(styryl)silane (**5.21n**): Prepared from trimethyl(phenylethynyl)silane according to the general procedure (Method E). Chromatography (hexane) gave **5.21n** as a clear liquid (NMR Yield, 84%, 24:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.33 (s, 9H), 6.62(d, 1H, J = 19.2 Hz), 7.02(d, 1H, J = 18.8 Hz), 7.38-7.40 (m, 1H), 7.46 -7.48(m, 2H), 7.58-7.59(m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ -1.6, 124.5, 127.2, 127.8, 128.6, 137.1, and 138.4.



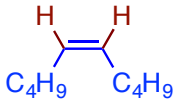
5.21o

(*Z*)-hex-3-ene (**5.21o**): Prepared from 3-Hexyne according to the general procedure (Method E). (NMR Yield, 58%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H), 1.67(m, 4H), 5.34(m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.1, 22.1, 130.7.



5.21p

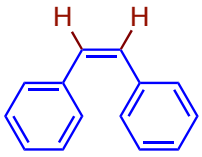
(*Z*)-oct-4-ene (**5.21p**): Prepared from 4-Octyne according to the general procedure (Method E). (NMR Yield 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 6H), 1.32(m, 4H), 1.98(m, 4H), 5.38 (t, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.5, 22.8, 29.6, 129.6.



5.21q

(*Z*)-dec-5-ene (**5.21q**): Prepared from 5-Decyne according to the general procedure (Method E). (NMR Yield 84%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 6H), 1.29(m, 4H), 1.67 (m, 4H), 2.02 (m, 4H), 5.39 (t, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.7, 22.7, 29.6, 54.4, 137.1.

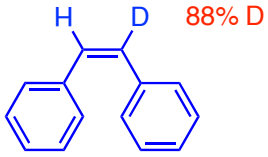
5.10.7 Gram scale synthesis for Z-selective transfer hydrogenation



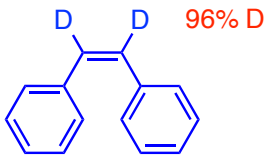
5.21a

(*Z*)-1,2-diphenylethene (**5.21a**): Prepared from diphenyl acetylene according to the general procedure (Method C). Chromatography (hexane) gave **5.21a** as a clear liquid (846 mg, 84%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.75 (s, 2H), 7.32-7.42 (m, 10H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 126.6, 127.7, 128.76, 128.78, 132.4.

5.10.8 Deuterium labelling for Z-selective transfer hydrogenation



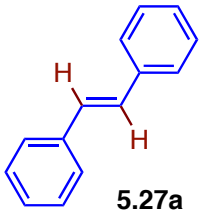
(*Z*)-(ethene-1,2-diyl-1-*d*)dibenzene (**5.21a**): Prepared from diphenyl acetylene according to the general procedure (Method C) and with 2-Propan(ol-d)(0.1 mL) instead of 2-propanol. Chromatography (hexane) gave **5.21a** as a clear liquid (45 mg, 89%). ^{1}H-NMR (400 MHz, CDCl3): δ 6.89 (s, 1H), 7.25-7.36 (m, 9H). ^{13}C-NMR (100.6 MHz, CDCl3): δ 127.3, 128.4, 129.1, 130.3, 130.4, 137.3, 137.4.



(Z)-1,2-diphenylethene-1,2-d2 (**5.21a**): Prepared from diphenyl acetylene according to the general procedure (Method C) and with 2-Propanol-d8(0.1 mL) instead of 2-propanol. Chromatography (hexane) gave 14a as a clear liquid (43 mg, 85%). 1H-NMR (400 MHz,

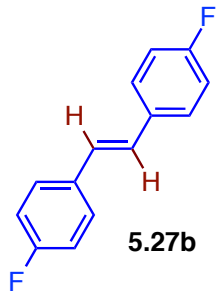
CDCl3): δ 6.75 (s, 2H), 7.32-7.42 (m, 10H). 13C-NMR (100.6 MHz, CDCl3): δ 126.6, 127.7, 128.76, 128.78, 132.4.

5.10.9. Preparation and analytical information for reported alkyne transfer hydrogenation for *E*-selectivity



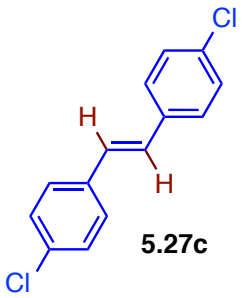
5.27a

(*E*)-1,2-diphenylethene (**5.27a**): Prepared from diphenyl acetylene according to the general procedure (Method A). Chromatography (hexane) gave **5.27a** as a white solid (47 mg, 93%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2H), 7.32-7.36 (m, 2H), 7.42-7.46 (m, 4H), 7.58-7.61 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 126.6, 127.7, 128.76, 128.78, 132.4.



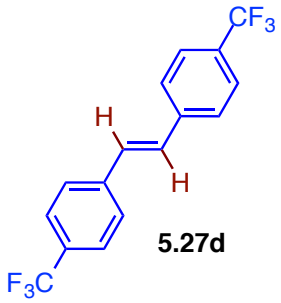
5.27b

(*E*)-1,2-bis(4-fluorophenyl)ethene (**5.27b**): Prepared from 1,2-bis(4-fluorophenyl)ethyne according to the general procedure (Method A). Chromatography (hexane) gave **5.27b** as a white solid (54 mg, 89%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.01 (s, 2H), 7.07-7.11 (m, 4H), 7.47-7.51 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 115.6 (d, J = 21.3 Hz), 127.3, 127.9 (d, J = 7.9 Hz), 133.4 (d, J = 3.2 Hz), 161.2 (d, J(C, F) = 245.8). ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -114.1



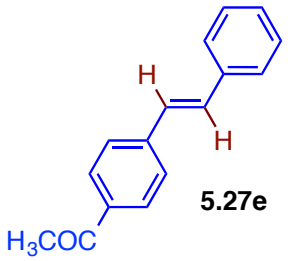
5.27c

(*E*)-1,2-bis(4-chlorophenyl)ethene (**5.27c**): Prepared from 1,2-bis(4-chlorophenyl)ethyne according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27c** as a white solid (61 mg, 86%, 32:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.59 (s, 2H), 7.18-7.20 (m, 4H), 7.23-7.29 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 128.6, 129.7, 130.2, 133.1, 135.3.



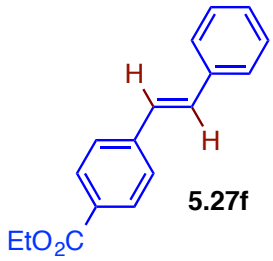
5.27d

(*E*)-1,2-bis(4-(trifluoromethyl)phenyl)ethane (**5.27d**): Prepared from 1,2-bis(4-(trifluoromethyl)phenyl)ethyne according to the general procedure (Method A). Chromatography (hexane) gave **5.27d** as a white solid (75 mg, 85%, 32:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (s, 2H), 7.63-7.68 (m, 8H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 122.8 (q, J = 270.0 Hz), 125.7 (q, J = 3.9 Hz), 126.9, 129.6 (q, J = 3.6 Hz), 130.1, 140.1. ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -62.6.



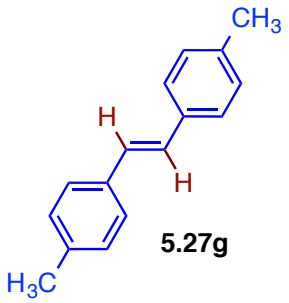
5.27e

(*E*)-1-(4-styrylphenyl)ethan-1-one (**5.27e**): Prepared from 1-(4-(phenylethynyl)phenyl)ethan-1-one according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27e** as a white solid (53 mg, 85%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.62 (S, 3H), 7.12-7.29 (m, 2H), 7.31-7.35 (m, 1H), 7.39-7.43 (m, 2H), 7.55-7.61 (m, 4H), 7.96 – 7.98 (d, 2H, J = 8.4 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 26.6, 126.5, 126.9, 127.5, 128.4, 128.8, 128.9, 131.5, 136.0, 136.7, 142.0, and 197.5.



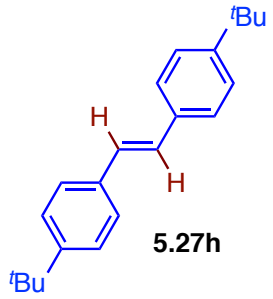
5.27f

ethyl (*E*)-4-styrylbenzoate (**5.27f**): Prepared from ethyl 4-(phenylethynyl)benzoate according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27f** as a white solid (62 mg, 88%, 19:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.62 (S, 3H), 7.12-7.29 (m, 2H), 7.31-7.33 (m, 1H), 7.35-7.43 (m, 2H), 7.56-7.61 (m, 4H), 7.96 – 7.98 (d, 2H, J = 8.4 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.4, 61.0, 126.3, 126.8, 127.6, 128.3, 128.8, 129.3, 130.0, 131.2, 136.8, 141.7, 166.4.



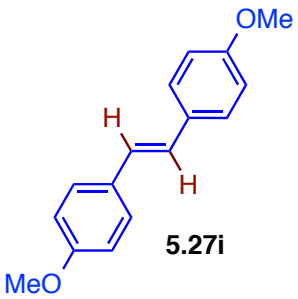
5.27g

(*E*)-1,2-di-*p*-tolylethene (**5.27g**): Prepared from 1,2-di-*p*-tolylethyne according to the general procedure (Method A). Chromatography (hexane) gave **5.27g** as a white solid (53 mg, 91%, >40:1).[1]H-NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 6H), 7.10 (s, 2H), 7.21 (d, 4H, J = 7.6 Hz), 7.46 (d, 4H, J = 8.0 Hz). [13]C-NMR (100.6 MHz, $CDCl_3$): δ 21.3, 126.4, 127.7, 129.4, 134.8, 137.3.



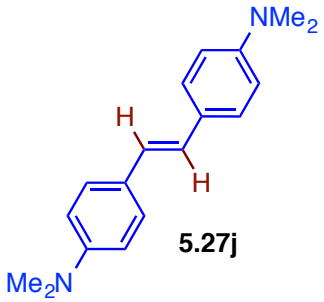
5.27h

(*E*)-1,2-bis(4-(*tert*-butyl)phenyl)ethene (**5.27h**): Prepared from 1,2-bis(4-(*tert*-butyl)phenyl)ethyne according to the general procedure (Method A). Chromatography (hexane) gave **5.27h** as a white solid (62 mg, 77%, 12:1). [1]H-NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 18H), 7.13-7.14 (s, 2H), 7.44-7.53 (m, 8H). [13]C-NMR (100.6 MHz, $CDCl_3$): δ 31.4, 34.7, 125.6, 126.2, 127.8, 134.8, 150.6.



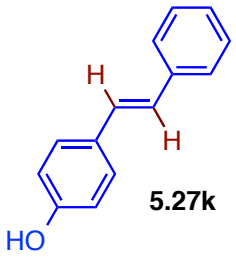
5.27i

(*E*)-1,2-bis(4-methoxyphenyl)ethene (**5.27i**): Prepared from 1,2-bis(4-methoxyphenyl)ethyne according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27i** as a white solid (61 mg, 92%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 6H), 6.91-6.96 (m, 6H), 7.44 (d, 4H, J = 8.4 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 55.3, 114.1, 126.2, 127.4, 130.5, 159.0.



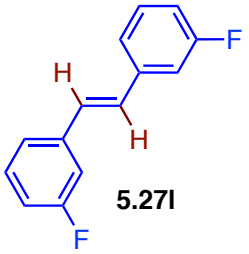
5.27j

(*E*)-4,4'-(ethene-1,2-diyl)bis(*N*,*N*-dimethylaniline) (**5.27j**): Prepared from 4,4'-(ethyne-1,2-diyl)bis(*N*,*N*-dimethylaniline) according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27j** as a white solid (60 mg, 81%, 19:1).^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.00 (s, 12H), 6.68-6.90 (m, 6H), 7.40-7.42 (d, 4H, J = 8.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 40.3, 112.0, 112.8, 127.1, 132.4, 149.7.



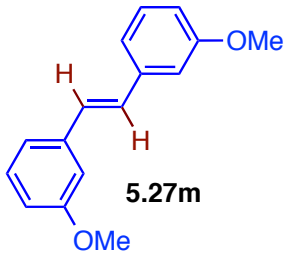
5.27k

(*E*)-4-styrylphenol (**5.27k**): Prepared from 4-(phenylethynyl)phenol according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27k** as a white solid (41 mg, 75%, 10:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.24 (bs, 1H), 6.83-6.87 (m, 2H), 6.98-7.11 (m, 1H), 7.29 (s, 1H), 7.34-7.39 (m, 3H), 7.43 – 7.47 (m, 2H), 7.51 – 7.56 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 115.6, 115.7, 126.3, 127.3, 127.9, 128.0, 128.3, 128.7, 131.5, 133.3.



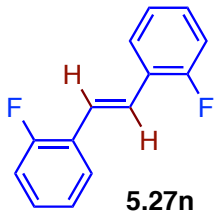
5.27l

(*E*)-1,2-bis(3-fluorophenyl)ethene (**5.27l**): Prepared from 1,2-bis(3-fluorophenyl)ethyne according to the general procedure (Method A). Chromatography (hexane) gave **5.27l** as a white solid (55 mg, 91%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.98-7.03 (m, 2H), 7.09 (s, 2H), 7.23-7.26 (m, 2H), 7.28-7.31 (m, 2H), 7.33 -7.38 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 112.8 (d, J = 21.9 Hz), 114.7 (d, J = 21.2 Hz), 122.6 (d, J = 2.6 Hz), 128.8, (d, J = 2.5 Hz), 130.2 (d, J = 8.2 Hz), 139.2 (d, J = 7.6 Hz), 161.9 (d, J = 243.8 Hz). ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -113.3.



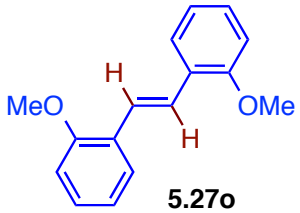
5.27m

(*E*)-1,2-bis(3-methoxyphenyl)ethene (**5.27m**): Prepared from 1,2-bis(3-methoxyphenyl)ethyne according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27m** as a white solid (61 mg, 92%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 6H), 6.87-6.90 (m, 2H), 7.10-7.18 (m, 6H), 7.31-7.35 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 111.8, 113.5, 119.3, 129.0, 129.7, 138.8, 160.0.



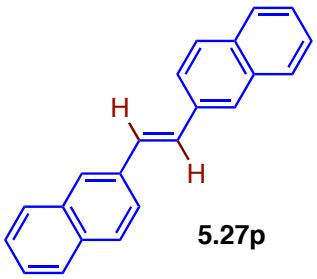
5.27n

(*E*)-1,2-bis(2-fluorophenyl)ethene (**5.27n**): Prepared from 1,2-bis(2-fluorophenyl)ethyne according to the general procedure (Method A). Chromatography (hexane) gave **5.27n** as a white solid (51 mg, 84%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09-7.12 (m, 2H), 7.14-7.21(m, 2H), 7.26–7.31 (m, 2H), 7.39 (s, 2H), 7.66-7.70 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 115.8 (d, J = 21.9 Hz), 123.0 (d, J = 3.7 Hz), 124.3 (d J = 3.4 Hz), 125.1(d, J = 12.1 Hz), 127.1 (d, J = 3.4 Hz), 129.1 (d, J = 8.3 Hz), 159.3 (d, J = 248.2 Hz). ^{19}F-NMR (376.3 MHz, $CDCl_3$): δ -117.9.



5.27o

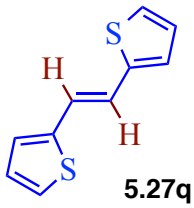
(*E*)-1,2-bis(2-methoxyphenyl)ethene (**5.27o**): Prepared from 1,2-bis(2-methoxyphenyl)ethyne according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27o** as a white solid (58 mg, 87%, >40:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 6H), 6.94-6.96 (m, 2H), 7.02-7.06 (m, 2H), 7.27-7.32 (m, 2H), 7.56 (s, 2H), 7.72-7.74 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 55.6, 111.0, 120.8, 123.7, 126.5, 127.2, 128.5, 156.9.



5.27p

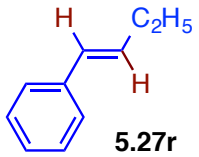
(*E*)-1,2-di(naphthalen-2-yl)ethene (**5.27p**): Prepared from 1,2-di(naphthalen-2-yl)ethyne according to the general procedure (Method A). Chromatography (hexane) gave **5.27p** as a white solid (69 mg, 88%, 24:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17-7.21 (m, 4H), 7.51 (s, 2H), 7.57-

7.64 (m, 4H), 7.74-7.76 (m, 2H), 7.92 – 7.94 (m, 2H), 8.29-8.31 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 124.6, 125.5, 125.9, 126.1, 127.2, 127.5, 128.6, 130.3, 132.1, 133.7, 134.5.



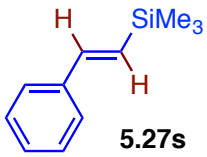
5.27q

(*E*)-1,2-di(thiophen-2-yl)ethene (**5.27q**): Prepared from 1,2-di(thiophen-2-yl)ethyne according to the general procedure (Method A). Chromatography (hexane and ethyl acetate) gave **5.27q** as a white solid (35 mg, 64%, 7:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.00-7.03 (m, 2H), 7.06-7.08 (m, 3H), 7.20-7.21 (m, 2H), 7.29 (s, 1H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 121.5, 124.3, 126.0, 127.7, 142.4.



5.27r

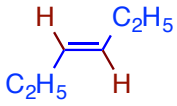
(*E*)-but-1-en-1-ylbenzene (**5.27r**): Prepared from but-1-yn-1-ylbenzene according to the general procedure (Method F). Chromatography (hexane) gave **5.27r** as a clear liquid (208 mg, 56%, 7:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23 (t, 3H), 2.36-2.39 (m, 2H), 6.37-6.44 (m, 1H), 6.51 (d, *J* = 16.0 Hz), 7.29-7.35 (m, 1H), 7.41-744 (m, 2H), 7.47–7.50 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.8, 26.2, 126.1, 126.9, 128.6, 128.9, 132.7, 138.1.



5.27s

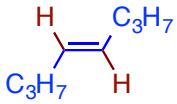
(E)-trimethyl(styryl)silane (**5.27s**): Prepared from trimethyl(phenylethynyl)silane according to the general procedure (Method A). Chromatography (hexane) gave **5.27s** as a white solid (42

mg, 87%, 32:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.33 (s, 9H), 6.62 (d, 1H, *J* = 19.2 Hz), 7.02 (d, 1H, *J* = 18.8 Hz), 7.38-7.40 (m, 1H), 7.45 -7.48(m, 2H), 7.57 - 7.60(m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 1.0, 126.5, 128.1, 128.6, 129.6, 138.5, 143.8.



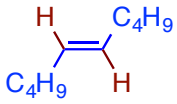
5.27t

(*E*)-hex-3-ene (**5.27t**): Prepared from 3-Hexyne according to the general procedure (Method D). (NMR Yield 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 6H), 1.97(m, 4H), 5.33(m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.1, 22.1, 130.7.



5.27u

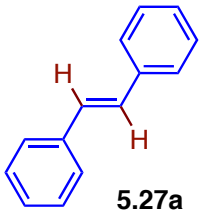
(*E*)-oct-4-ene (**5.27u**): Prepared from 4-Octyne according to the general procedure (Method D). (NMR Yield 79%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 6H), 1.265(m, 4H), 1.94(m, 4H), 5.33 (t, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.8, 22.7, 29.6, 129.6.



5.27v

(*E*)-dec-5-ene (**5.27v**): Prepared from 5-Decyne according to the general procedure (Method D). (NMR Yield 60%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.87 (t, 6H), 1.27(m, 4H), 1.40 (m, 4H), 1.96 (m, 4H), 5.38 (t, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.7, 22.7, 29.6, 54.4, 137.1.

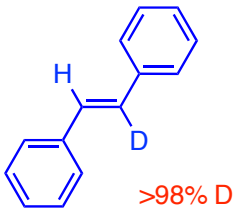
5.10.10 Gram scale for *E*-selective transfer hydrogenation



5.27a

(*E*)-1,2-diphenylethene (**5.27a**): Prepared from diphenyl acetylene according to the general procedure (Method A). Chromatography (hexane) gave **5.27a** as a white solid (903 mg, 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2H), 7.32-7.36 (m, 2H), 7.42-7.46 (m, 4H), 7.58-7.61 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 126.6, 127.7, 128.76, 128.78, 132.4.

5.10.11 Deuterium labelling for *E*-selective transfer hydrogenation



(*E*)-(ethene-1,2-diyl-1-*d*)dibenzene (**5.27**): Prepared from diphenyl acetylene according to the general procedure (Method A) and with 2-Propan(ol-d)(0.1 mL) instead of 2-propanol. Chromatography (hexane) gave **3a** as a white solid (44 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 1H), 7.23-7.25 (m, 2H), 7.32-7.36 (m, 4H), 7.48-7.51 (m, 4H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 126.58, 126.61, 127.7, 128.7, 128.8, 137.45, 137.42.

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