Transition-metal catalysed C-H bond alkynylation

Thesis Submitted to AcSIR

For the Award of the Degree of

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in

CHEMICAL SCIENCES

by

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This dissertation is dedicated to all those people who have always given me the love, trust, and support to come to this stage of my life

-To My Mother-

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CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled **"Transition-metal catalysed C-H bond alkynylation"** submitted by **Mr. Vinod Gokulkrishna Landge** (AcSIR Registration Number 10CC15J26004) to the Academy of Science and Innovation Research (AcSIR) in the fulfillment of the requirements for the award of the Degree of the Doctor of Philosophy, embodies original research work under my supervision at Organic Chemistry Division, CSIR-National Chemical Laboratory (CSIR-NCL), Pune, India. I further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table, etc., used in the thesis from other source have been duly cited and acknowledged.

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DECLARATION

I hereby declare that the original research work embodied in this thesis entitled **"Transition-metal catalysed C-H bond alkynylation"** submitted to the Academy of Scientific and Innovative Research (AcSIR), New Delhi, for the award of degree of **Doctor of Philosophy** in **Chemical Sciences** is the outcome of experimental investigations carried out by me under the supervision of **Dr. E. Balaraman**, Senior Scientist, CSIR-National Chemical Laboratory (CSIR-NCL), Pune. I affirm that the work incorporated is in original and has not been submitted to any other academy, university or institution in part or full forthe award of any degree or diploma.

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Acknowledgment

Ph.D. is like a long journey; an experience that takes you through the untraversed path, the green lush meadows and the island of Cyclopes to conquer the final goal fixed in mind. Once you achieve the target and turn back, you realize that all your efforts and the pain were worth going through. The small successes & the serendipitous discoveries, the frustrating failures & unexpected crystallizations, the imparted chemical wisdom & the laboratory camaraderie; they are all important parts of this beautiful voyage. But one can't succeed in this journey without the guidance and support of the research supervisor, friends, and well-wishers. I am taking this opportunity to express my deepest gratitude to everyone who has helped and supported me throughout the course of my research journey.

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My family is always a source of inspiration and a great moral support for me in pursuing my education. I owe a lot to my beloved parents who encouraged and helped me at every stage of my personal and academic life and longed to see this achievement come true. My sincere thanks to my beloved family members my father ‘Gokulkrishna Vishnu Landge, mother ‘Alka Gokulkrishna Landge’, other family members Krupali, Trupti, Varad, Tushar, Rahul for their endless love, support, and sacrifice. I am very much indebted to my whole family who supported me in every possible way to see the completion of this research work. I especially thank my brother Pramod Landge for their kind support and valuable suggestions.

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Vinod Gokulkrishna Landge

Table of Contents

Chapter 2: C-H Nickel/Cobalt Catalyzed C(sp^2)-H Bond Alkynylation of Amides

Chapter 2A: Nickel Catalyzed C(sp^2)-H Bond Alkynylation of Amides

Chapter 2B: Cobalt Catalyzed Bis-Alkynylation of Amides *via* Double C-H Bond Activation

Chapter 3: Cobalt-Catalyzed C-H Alkynylation of Benzylamines

Chapter 5: Pd(II)-Catalyzed γ-C(sp^3)-H Alkynylation of Amines

Abbreviations

Units

°C	Degree centigrade
mg	Milligram
h	Hour
Hz	Hertz
µs	Microsecond
mL	Millilitre
min.	Minute
MHz	Megahertz
mmol	Millimole
nm	Nanometre
ppm	Parts per million
%	Percentage
V	Volt
W	Watt

Chemical Notations

Ac	Acetyl
AcOH	Acetic Acid
Ar	Aryl
MeCN	Acetonitrile

BHT	3,5-Di-*tert*-4-butylhydroxytoluene
bpy	2,2′-Bipyridyl
NBS	*N*-Bromosuccinimide
$CDCl_3$	Deuterated Chloroform
DMA	N, N'-Dimethylacetamide
DMAP	*N*,*N*-Dimethylaminopyridine
DMC	Dimethyl carbonate
DMF	N, N'-Dimethylformamide
DMSO	Dimethyl sulfoxide
DCE	1,2-Dichloroethane
DABCO	1,4-diazabicyclo[2.2.2]- octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl Acetate
MeOH	Methanol
Me	Methyl
py	Pyridine
THF	Tetrahydrofuran
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy

Other Notations

δ	Chemical shift
J	Coupling constant in NMR
equiv.	Equivalents
GC	Gas Chromatography
HRMS	High Resolution Mass Spectrometry
NMR	Nuclear Magnetic Resonance
PTFE	Polytetrafluoroethylene
rt	Room temperature
UV	Ultraviolet

General remarks

- All catalysts were purchased from commercial sources and used as received.
- All reactions were carried out under innert atmosphere folowing standard procedures using schlenk techniques.
- Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR analysis were obtained using a Bruker or JEOL 200 MHz, 400 MHz or 500 MHz spectrometers. Coupling constants were measured in Hertz. All chemical shifts are quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br =broad.
- HRMS spectra were recorded at UHPLC-MS (Q-exactive-Orbitrap Mass Spectrometer) using electron spray ionization [(ESI^{+}, +/− 5kV), solvent medium: water, acetonitrile, methanol and ammonium acetate] technique and mass values are expressed as *m/z*. GC-HRMS (EI) was recorded in Agilent 7200 Accurate-mass-Q-TOF.
- All reactions are monitored by Thinlayer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, Iodine adsorbed on silica gel or by immersion in ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde or $KMnO_4$ followed by heating with a heat gun for ~15 sec.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Chemical nomenclature (IUPAC) and structures were generated using ChemDraw Professional 15.1.

Preface

Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Chemistry	
Name of the Candidate	**Mr. Vinod Gokulkrishna Landge**
Degree Enrolment No. & Date	**PhD in Chemical Sciences (10CC15J26004); January2015**
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Research Supervisor	**Dr. E. Balaraman (CSIR-NCL, Pune)**

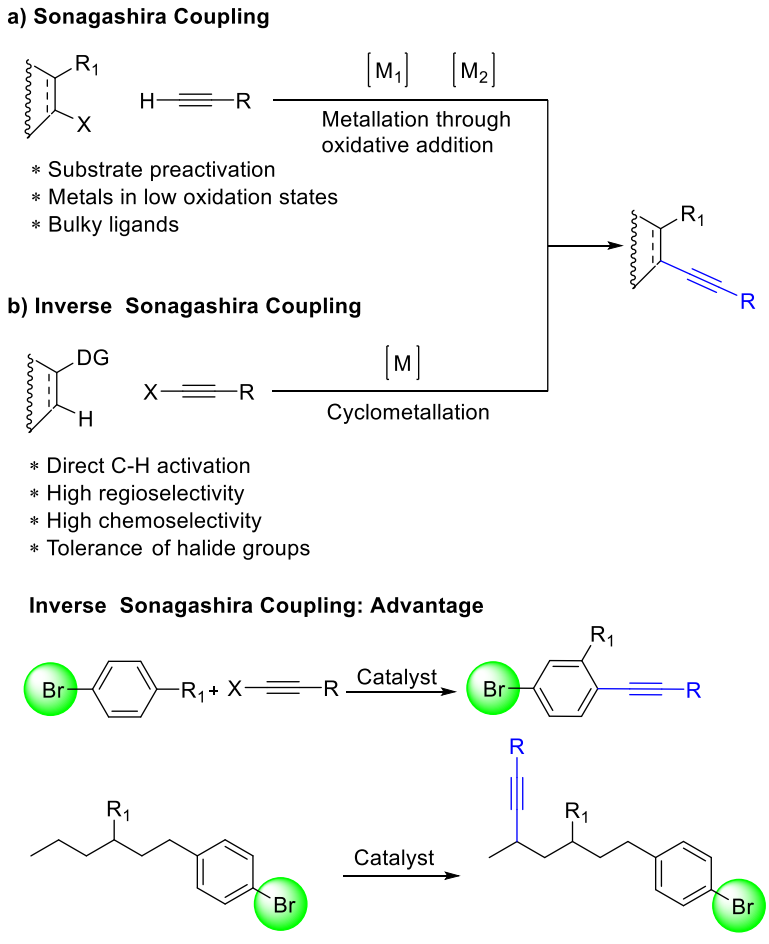
Keywords: *C-H Activation, Alkynylation, Acids/Amines, Auxiliary.*

This thesis deals with the transition-metal catalyzed C-H bond activation reactions, in particularly C(sp^2&sp^3)-H alkynylation. The thesis comprises of five chapters, out of which the first chapter is the introduction wherein strategy to C-H bond alkynylation (Inverse Songashira Coupling) and its importance in synthetic chemistry with recent literature precedents is described in details. From the second chapter to fifth chapters, all are working chapters which narrates our approaches to the transition metal-catalyzed C-H alkynylation. The second chapter describes earth-abundant and inexpensive nickel/cobalt-catalyzed alkynylation of amides. The C-H alkynylation of flexible benzyl amines was achieved by cobalt catalysis is discussed in chapter three. The first example of palladium-catalyzed ligand-enabled C(sp^3)-alkynylation of 8-methylquinoline derivatives is explained in chapter the four. The final chapter explores the development of Pd(II)-catalyzed *gamma* C(sp^3)-H alkynylation of amine substrate (linear, chain and amino acids), and various picolinamide-based auxiliaries.

Chapter I: "Inverse Sonogashira Strategy"-Conversion of C-H bond into C-alkynyl bond

Catalyst based direct activation of C–H bonds provides a sustainable and atom-economical synthetic strategy to diverse organic molecules from simple and prefunctionalized substrates. The development of catalytic systems for direct conversion of inert C–H bonds into the C-alkynyl bonds is very attractive, desirable and sustainable method, as the alkyne moiety is of significant importance in various synthetic transformations, including cycloaddition, metathesis, click reaction, etc. In addition, alkynes are excellent building blocks in synthetic chemistry and in materials science and they are also a common motif in drugs. The most prominent way to form C-alkynyl

bond is *via* the Sonogashira reaction, a palladium-catalyzed cross-coupling between aryl and alkenyl halides or triflates with metal acetylides. As in all the classical cross-coupling reactions, the activation of the carbon of interest is necessary for the initial oxidative addition to occur. This pre-activation is substantial in terms of reactivity and selectivity, since only one specific carbon should react in the cross-coupling reaction. However, to avoid this sometimes tedious or even impossible preactivation, the direct utilization of C-H bonds in such transformations has come into the focus of research. Considering these problems, the "inverse Sonogashira coupling" has been investigated recently as a complementary strategy to the classical cross-couplings i.e. sp-sp^2 bond formation (Scheme 1). In this strategy, the alkynylation occurs after an inert C-H bond activation or deprotonation step with an electrophilic alkyne source. Notably, many synthetically valuable groups such as halide (-Cl and-Br) could be reserved under reactions, which give chances for further modification of the products, wherein synthesis of such products using the traditional approach, "Sonogashira coupling" is very difficult and rather scare.



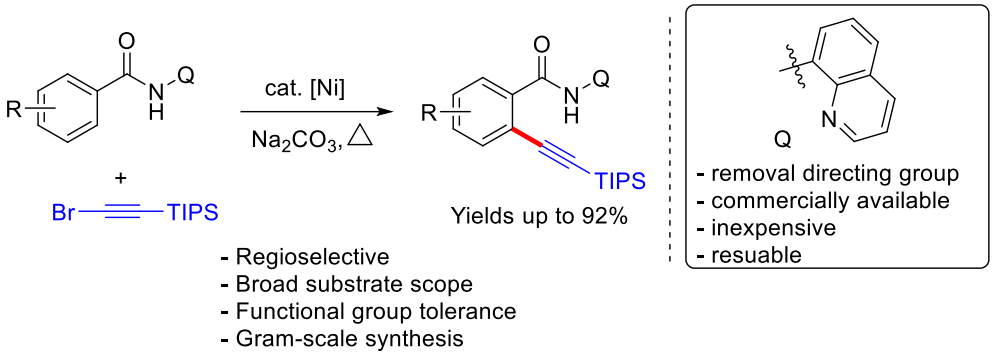
Scheme 1. Conversion of C-H bond into C-alkynyl bond.

Chapter II: Nickel/Cobalt catalyzed C(sp^2)-H bond alkynylation of amides

Transition-metal catalyzed direct functionalization of the inert C−H bond has emerged as a powerful strategy for the straightforward synthesis of value-added products with great step economy and low waste production. Over the past decades, considerable efforts have been dedicated toward catalysts based upon precious metals such as Pd, Ru, Rh, and Ir. The replacement of expensive noble metal catalysts by utilizing economical and environmentally benign first-row transition metal catalysts is an important paradigm in chemical synthesis. In this regard, earth-abundant first-row late transition metals have been intensely used in C−H bond activation strategy to emulate the selectivity and reactivity of precious-metal catalysts and thus broaden the scope and practical viability. However, their successful application in C−H bond functionalization remains at an early stage and can make it difficult to envisage and control catalytic reactivity, as they have a propensity to participate in one-electron chemistry as opposed to classical two-electron transformation ubiquitous in the second- and third-row transition metals. In the present chapter, we have replaced expensive noble metal catalysts with an inexpensive, benign, and sustainable Nickel/Cobalt catalyst for the C(sp^2)-H bond alkynylation of amides. This working chapter has been further divided into two parts.

Part 2A: Nickel catalyzed C(sp^2)-H bond alkynylation of amides.

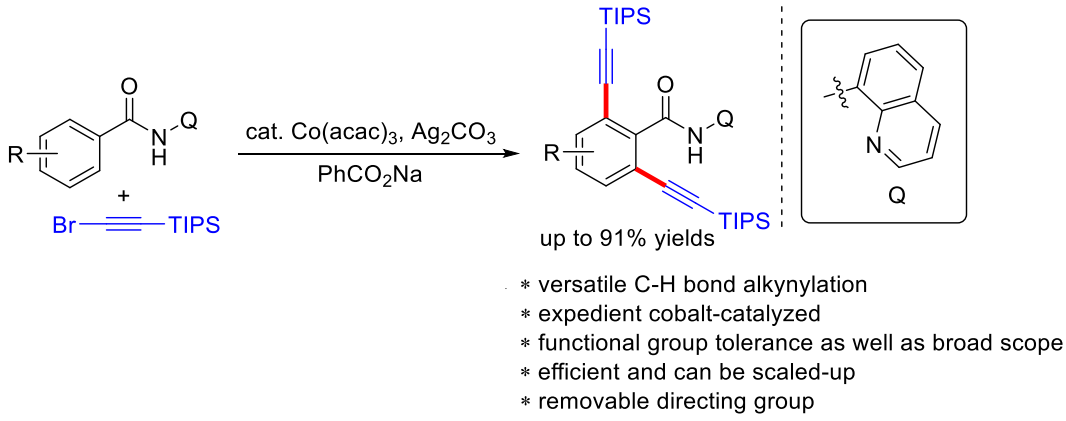
In this chapter, we disclose the first nickel(II)-catalyzed C(sp^2)-H alkynylation of benzamides using 8-aminoquinoline as a removable bidentate directing group to synthesize various *ortho*-alkynylbenzoic acids. The present nickel-catalyzed C(sp^2)-alkynylation has a broad substrate scope and functional group tolerance. Notably, many synthetically valuable groups such as halide (-Cl and -Br) could be reserved under our reaction reactions, which give chances for further modification of the products, wherein synthesis of such products using the traditional approach, “Sonogashira coupling” is very difficult and rather scare.A detailed mechanistic investigation has been carried out for this C(sp^2)-H alkynylation reaction.



Scheme 2. Nickel catalyzed C(sp^2)-H bond alkynylation of amides.

Part 2B: Cobalt-catalyzed bis-alkynylation of amides *via* double C−H bond activation.

A cobalt-catalyzed selective bis-alkynylation of amides *via* double C−H bond activation with the directing assistance of a removable bidentate auxiliary is reported in this chapter. The developed alkynylation strategy is simple, efficient, and tolerant of various functional groups includingether, amine, halides, and heterocyclic motifs. The reaction canbe scaled up (gram-scale synthesis) under mild conditions.

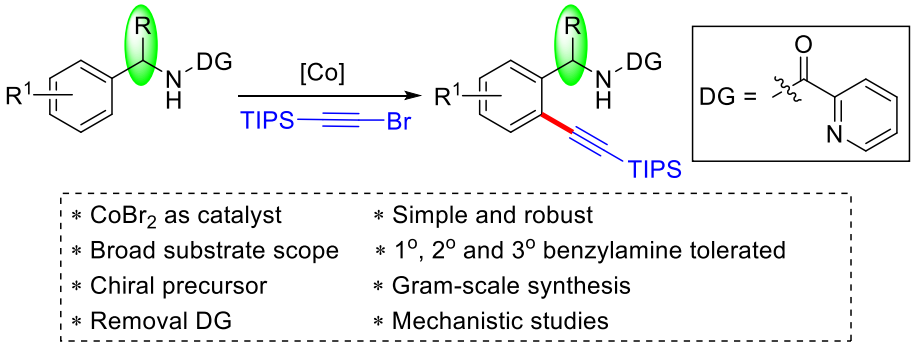


Scheme 3Cobalt-catalyzed bis-alkynylation of amides *via* double C−H bond activation.

Chapter III: **Cobalt-catalyzed C−H alkynylation of benzylamines**

Benzylamines constitute important synthetic precursors and are ubiquitous in agrochemical, peptide, pharmaceutical, and functional materials. Various effective, practical methods have been developed to access benzylamines. Indeed, the stereochemistry at the benzylic position of α-substituted benzylamines can also

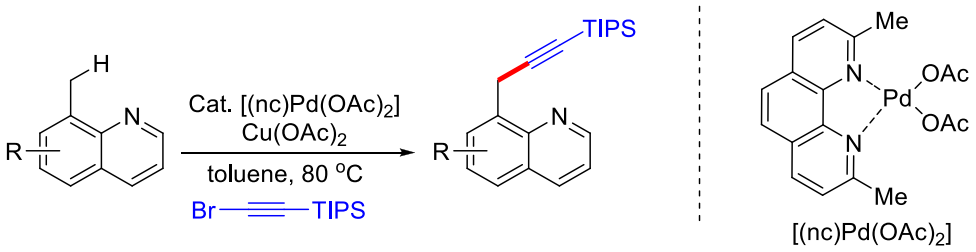
be readily introduced using well-explored asymmetric synthesis technologies.This chapter describes a versatile and efficient cobalt-catalyzed *ortho*-C(sp^2)–H alkynylation of the benzylamine precursor. The present cobalt-catalyzed alkynylation has a broad substrate scope and gram-scale synthesis can be performed under optimal conditions. Significantly, 1°, 2°, 3°, and enantiopure benzylamines were well tolerated. The mechanistic study shows that C–H bond cleavage is reversible, and the kinetic study illustrates that the rate of reaction depends solely on the catalyst.



Scheme 4. Cobalt-catalyzed C–H alkynylation of benzylamines.

Chapter IV: **Palladium-catalyzed C(sp^3)-H bond alkynylation of heterocycles**

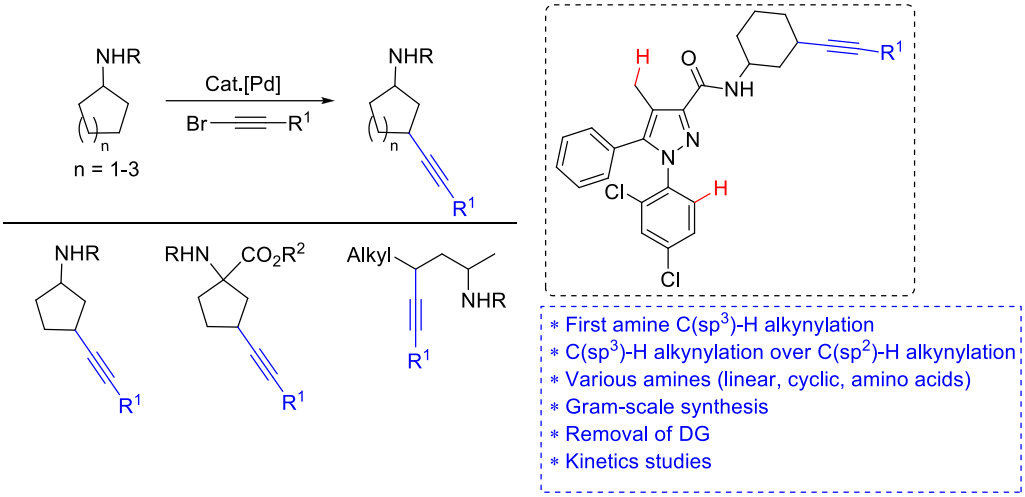
Ligands would alter the electronic and steric properties of the active catalyst and thus they could significantly accelerate C–H activation and successive bond forming reactions. In this chapter, the first example of ligand-enabled C(sp^3)-alkynylation of 8-methylquinoline is described. The reaction is catalyzed by well-defined Pd(II) complexes. The present C(sp^3)-alkynylation has a broad substrate scope as well as functional group tolerance and proceeds efficiently under mild conditions.



Scheme 5. Palladium catalyzed C(sp^3)-H bond alkynylation of 8-methyl quinolines.

***Chapter V*: Pd(II)-Catalyzed γ-C(sp^3)-H Alkynylation of Amines**

Amines constitute important synthetic precursors and are ubiquitous in agrochemical, peptide, pharmaceutical, and functional materials. We have developed the first example of *γ*-alkynylation of diverse alkyl amines. Easily removable picolinamide and its derivatives were identified as suitable auxiliaries for enabling palladium-catalyzed *γ*-alkynylation process. The substrate scope was successfully expanded applying carbocyclic and acyclic alkyl amines. Interestingly, the present protocol showed site-selective *γ*-alkynylation of C(sp^3)-H bond in the presence of an easily accessible Ar-C(sp^2)-H bond. The present alkynylation strategy is general and has a broad substrate scope. Remarkably, various ring size, α-quaternary, *N*-cyclic, and linear amines were alkynylated under our reaction conditions.



Scheme 6. Pd(II)-catalyzed γ-C(sp^3)-H alkynylation of amines.

Details of Publications:

1. **V. G. Landge**, C. H. Shewale, G. Jaiswal, M. K. Sahoo, S. P. Midya and E. Balaraman*. Nickel-catalyzed direct alkynylation of C(sp^2)–H bonds of amides: an "inverse Sonogashira strategy" to *ortho*-alkynylbenzoic acids. ***Catal. Sci. Technol***., 2016, 6, 1946.

2. **V. G. Landge**, G. Jaiswal and E. Balaraman*. Cobalt-catalyzed bis-alkynylation of amides *via* double C–H bond activation. ***Org. Lett***., 2016, 18, 812.

3. **V. G. Landge**, S. P. Midya, J. Rana, D. R. Shinde and E. Balaraman*. Expedient cobalt-catalyzed C–H alkynylation of (enantiopure) benzylamines. ***Org. Lett.***, 2016, 18, 5252.

4. **V. G. Landge**, M. K. Sahoo, S. P. Midya, G. Jaiswal and E. Balaraman*. Well-defined palladium(II) complexes for ligand-enabled C(sp^3)-alkynylation. ***Dalton Trans***., 2015, 44, 15382.

5. **V. G. Landge**, J. Rana, M. Subaramanian and E. Balaraman*. Nickel-catalyzed *N*-vinylation of heteroaromatic amines *via* C-H bond activation amines. ***Org. Biomol. Chem***., 2017, 15, 6896.

6. **V. G. Landge**, A.Parveen, A. Nandakumar and E. Balaraman*. Pd(II)-Catalyzed gamma-C(sp^3)–H alkynylation of amides: selective functionalization of R chains of amides $R^1C(O)NHR$. ***Chem. Commun***., 2018, 54, 7483.

Details of Patents:

1. Phenanthroline based pincer complexes useful as catalysts for the preparation of methanol from carbon dioxide. E. Balaraman, **V. G. Landge**, S. P. Midya, M. K. Sahoo, G. Jaiswal.International Application No.: PCT/IN2016/050050.

- 358/DEL/2015 (IN) and 417/DEL/2015 (IN)
- WO2016128997 (A1)
- US2018021766 (A1)
- EP3256250 (A1)

2. Direct C(sp^3)-H alkynylation of N-heterocyles: a chelation assisted Pd catalysis. E. Balaraman, **V. G. Landge.** US. Pat. 2014, Application No. 15/543714.

3.Catalytic process for the formation and/or hydrogenation of esters including lactones by phenanthroline based pincer complexes. E. Balaraman, S. P.Midya, **V. G. Landge**. US. Pat. 2015, Application No. 15/549827.

4. Novel phosphine free cobalt complexes acceptorless dehydrogenative annulation of aminoalcohols with alcohols. E. Balaraman, S. P. Midya, **V. G. Landge**. Ind. Pat.2017, Application No. 201711031330.

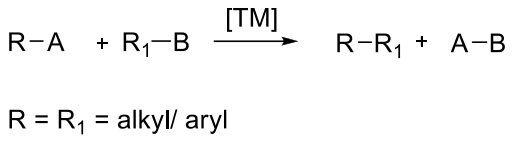
5. A Novel 2-pyraimidyl aniline derivatives, process for preparation and thereof. E. Balaraman, **V. G. Landge**, A. Mondal. Indian. Pat. 2017, Application No. 201711034640.

Chapter 1

“Inverse Sonogashira Strategy”- Conversion of C-H Bond into C-Alkynyl Bond

1.1 Cross-Coupling Reactions

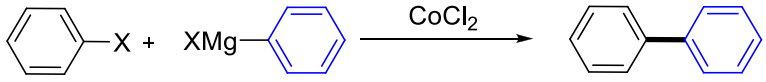
The reactions that form carbon-carbon (C-C) or carbon-heteroatom (C-Het) bonds are attractive tools for organic chemists, allowing for rapid diversification of advanced synthetic intermediates and complex target molecules. These strategies also provide new approaches to the synthesis of organic compounds that exhibit significant biological, pharmaceutical and material properties. The traditional methods for the construction of these bonds follow nucleophilic substitution/addition to polarized π-bonds, Friedel-Crafts type reactions, and "modern" strategies include catalytic cross-coupling and cross-metathesis reaction. In particular, metal-catalyzed cross-coupling reactions emerged as a viable strategy for the synthesis of natural products and other compounds of pharmaceutical importance, and are widely appreciated in the context of parallel synthesis and combinatorial chemistry (Scheme 1) .[1]



Scheme 1.1 General cross-coupling reaction (TM : transition metal)

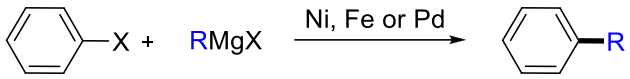
1.2 Background of Cross-Coupling Reactions

In 1941, Kharasch reported the synthesis of biaryl compounds from the reaction of aryl magnesium halides and aryl halides in presence of catalytic amount of cobalt (II) chloride (Scheme 2).[2] Subsequently, Kharasch reported the synthesis of cross-coupled aryl derivatives by using the Grignard reagents with vinyl halides catalyzed by cobalt or chromium salts.[3]



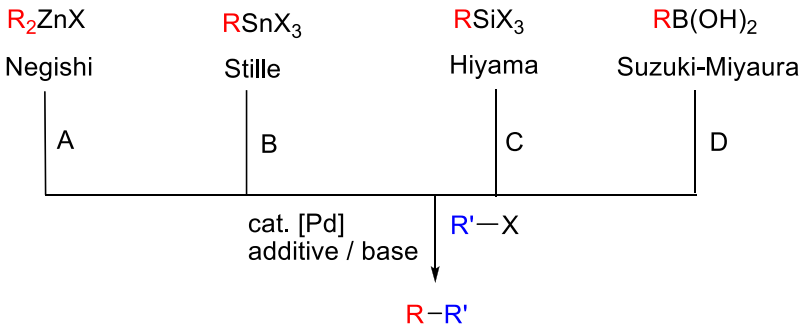
Scheme 1.2 The first example of a cross-coupling reaction.

In 1972, Kumada[4] and Corriu[5] independently developed the nickel-catalyzed cross-coupling reaction of aryl halides with the Grignard reagents (Scheme 3). Subsequently, Kochi reported the similar transformation by using iron complexes.[6] At the beginning of 1975, the value of palladium complexes had been soon discovered, and their applications in Kumada-Corriu reactions allow the coupling of a much broader array of Grignard reagents.[7]



Scheme 1.3 Kumada-Corriu reaction under different catalysis.

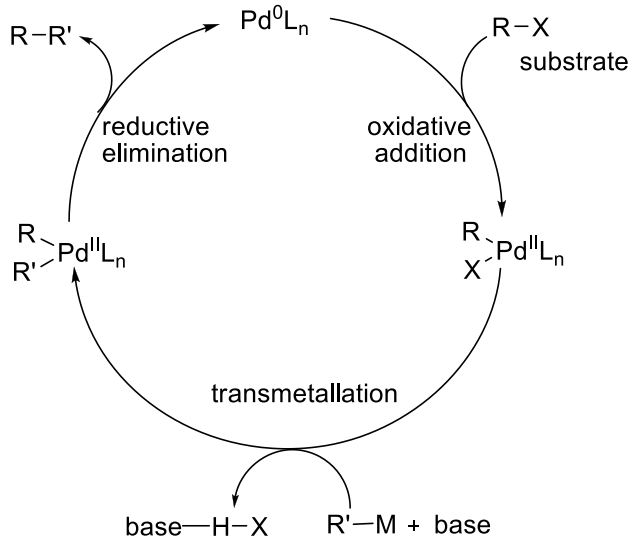
After the promising invention of Kumada-Corriu reaction, a lot of research efforts had been focused on transition metal-catalyzed C–C bond forming reactions of aryl and alkenyl halides and various organometallic reagents (Scheme 4). The use of Grignard reagents limits the synthetic utility of Kumada-Corrriu reaction, because of low functional group tolerance.



Scheme 1.4 Metal catalyzed cross-coupling reaction.

In order to retain the functional group in the Kumada-Corrriu coupling processes, other organometallic coupling partners containing less electropositive metals than lithium and magnesium were later employed in the transition metal-catalyzed coupling reactions. In the beginning of 1970s, Negishi and co-workers discovered the applications of organoaluminiums [8] and organozincs [9] in the cross-coupling reactions. Further extensive investigations showed that the best coupling reactions were obtained by employing organozinc compounds in the presence of palladium(0) catalysts (Scheme 4, A). The organostannanes in the palladium-catalyzed coupling reactions firstly used by Eaborn.[10] In the following several years, Stille investigated the use of organotin reagents emerged

as promising alternatives for the cross-couplings and significantly improved the yields under much milder reaction conditions (Scheme 4, B).[11] The advantages of organotin reagents are stable towards the water, and oxygen which makes the purification much easier than other main group organometallic reagents. However, the formation of stoichiometric tin halides is the main concern as a result their lack in practical application in chemical industries. The organosilanes are less toxic, but are also less reactive. Therefore, their use in coupling reactions normally requires an activating agent such as the fluoride ion or a base (Scheme 4, B).[12] In 1979, Suzuki and Miyaura reported the first palladium-catalyzed cross-coupling of aryl halides with alkenylboranes (Scheme 4, D).[13] Nowadays, Suzuki-Miyaura reaction has become one of the most powerful cross-coupling reactions because of its mild reaction conditions and high functional group tolerance. Notably, boronic acids are environmentally less toxic and safe than organostannanes, and the inorganic byproducts are easily removed from the reaction mixture, making the reaction suitable for industrial processes.



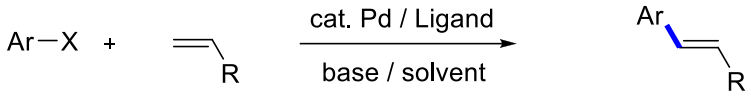
Scheme 1.5 General mechanism of palladium catalyzed cross-coupling reaction.

As depicted in Scheme 1.5, a typical palladium-catalyzed cross-coupling reaction of various organometallic reagents contains three stages: the catalytic cycle initiates with the reduction of the Pd(II) precursor to generate a catalytically active Pd(0) species (recent studies have revealed the formation of active Pd colloids or nanoparticles *via* precatalyst degradation). Oxidative addition of the Pd(0) active species into the organic electrophile (insertion into the C-X bond) generates a Pd(II) species, which subsequently

undergoes transmetallation, followed by the reductive elimination generate the final cross-coupled product while regenerating the Pd(0) catalyst.

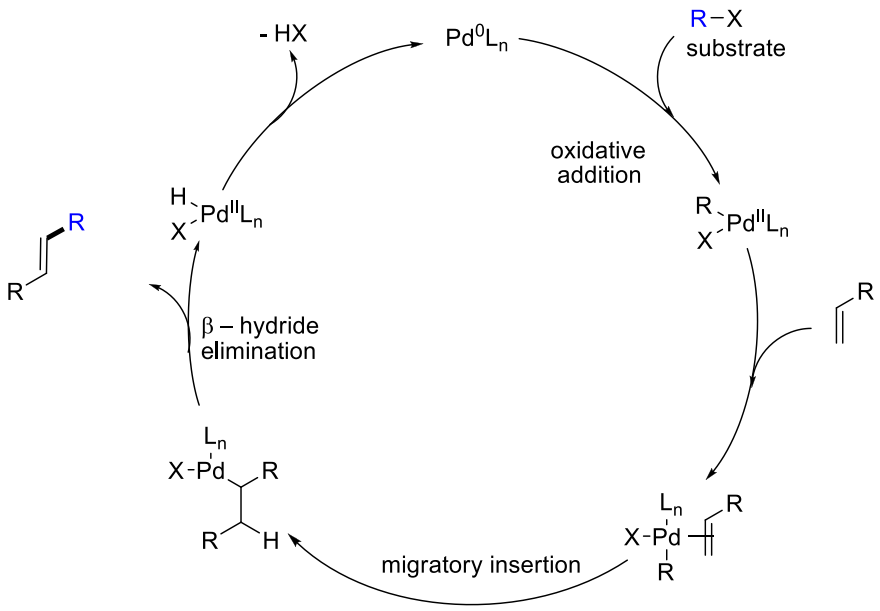
Heck coupling

This reaction was independently discovered by Mizoroki[14] and Heck[15] groups in 1972. This reaction is attractive from a synthetic point of view because of its high chemoselectivity and mild reaction conditions. The reaction of vinyl halides or aryl halides with activated alkenes in the presence of palladium catalyst and base affords the substituted alkenes (Scheme 1.6).



Scheme 1.6 Mizoroki-Heck coupling of aryl halides with alkenes.

The mechanism involves the oxidative addition of the aryl halide, insertion of the olefin, and β-hydride elimination to form the product. A base then regenerates the Pd(0) catalyst *via* reductive elimination and closes the catalytic cycle (Scheme 1.7).



Scheme 1.7 Generalmechanism of Heck reaction.

1.3 Limitations of Traditional Cross-Coupling Reactions

Though a plethora of methods have emerged in catalysts and methods for these pre-functionalizedcross-coupling reactions, still some drawbacks are associated with these methods. For example,

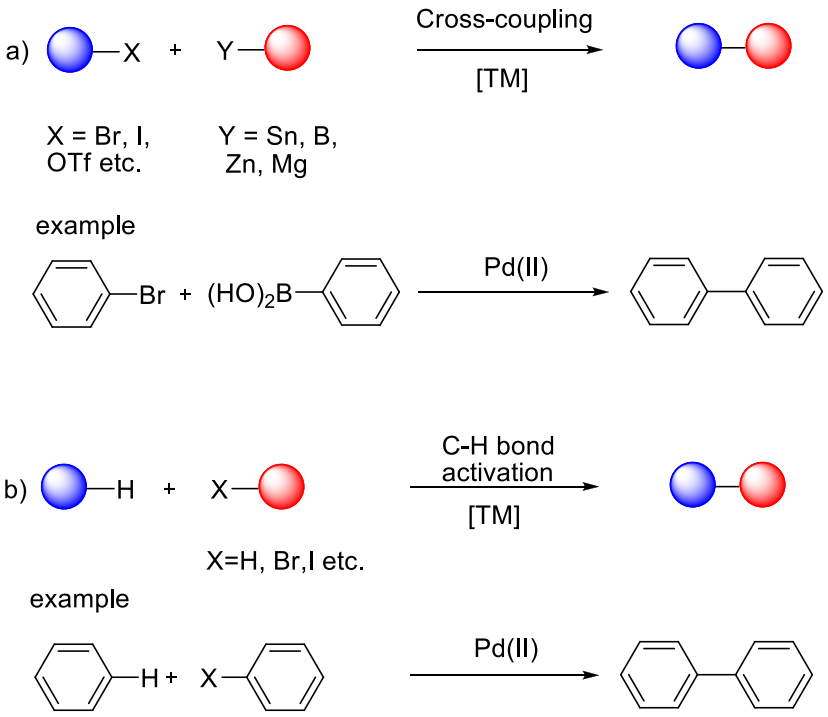
1) Required expensive palladium complexes, bulky and electron-rich ligands and special reaction conditions.

2) Rely on preactivated coupling partners such as organic halides and pseudohalides.

3) Some of these methods have employed a stoichiometric amount of coupling partners such as,organometalic reagents, organo boron, tin and silanes generating the stoichiometric amount of by-products at the end of the reaction.

1.4 Importance of C-HBond Activation/Functionalization Cross-Coupling

The C-H bond activation is a promising strategy to making unactivated C–H bonds into carbon–heteroatom and carbon-carbon (C–C) bonds. It has gained the momentum in last decades because C–H bonds are among the simplest and most common structural motifs in naturally occurring organic molecules, and they are ideal targets for chemical transformations. TheC-H activation could enable the conversion of cheap and abundant alkanes into valuable functionalized organic compounds and the efficient structural editing of already complex molecules.[16] However, the traditional making of C-C bond required preactivation of substrates, harsh conditions, and the formation of stoichiometric waste. On the other hand, this catalysis has proven to be valuable in natural products synthesis, where several distinct C–H functionalization strategies have been exploited. The C-H bond activation can reduce these procedures, thus making this reaction a cost-effective and step-economy system.[17]



Scheme 1.8 a) Cross-coupling strategy; b) C-H activation approach.

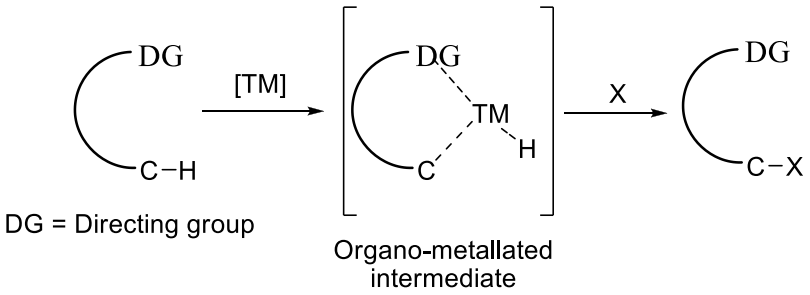
1.5 Types of DG (Directing Groups)

The challenges have associated with C-H activation are

1) Selection of directing group
2) Planarity
3) Site selectivity
4) Selection of ligand

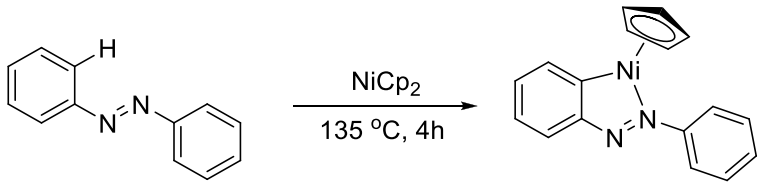
To realize the promise of transition metal-catalyzed C–H functionalization as a practical synthetic tool; however, two principal challenges must be overcome. The first challenge is the low reactivity of C–H bonds, which are generally considered to be chemically inert. The second challenge is controlling the site-selectivity. That is the reaction functionalizes only a single C–H bond in the presence of many accessible C–H bonds with a similar reactivity. Among various strategies employed to address these challenges, the use of directing groups has proven to be the most successful approach.[18] The most popular substrate control type strategy is based on the use of directing Lewis bases

covalently linked to the substrate, to induce approach of the metal in the vicinity of a specific, otherwise unactivated C-H position. Indeed, although C-H bonds do not form stable σ-adducts with transition-metals, metal to C-H-bond pre-organization is an obligatory step preceding the cleavage in the C-H activation process.[18c-d] Heteroatom-based groups are the most used directing groups, binding of the directing group promotes the formation of the agostic interaction through an increase in effective concentration between the metal and the C–H bond. Moreover, the directing group helps to arrange the geometry of the pre-transition state coordination structure in a favorable way for C–H cleavage.[18w] The directing group also serves to control the site selectivity of the reaction since it positions the catalyst in close proximity to a single C–H bond in the substrate, facilitating the formation of a complex intermediate *via* cyclometalation. In catalytic chemistry, directing groups have also played a major role in the development of the field.



Scheme 1.9 Importance of DG in C-H bond activation.

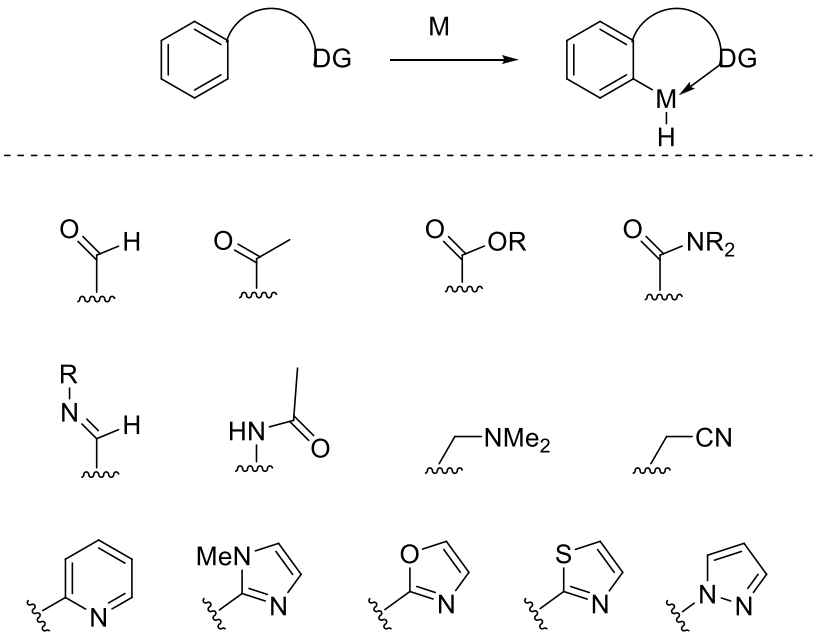
In 1963, Kleiman and Dubeck published the first characterization of a cyclometalated complex, thus highlighting the ability of some functional groups to promote the insertion



Scheme 1.10 Early examples of metal-promoted *ortho*-directed C-H activation.

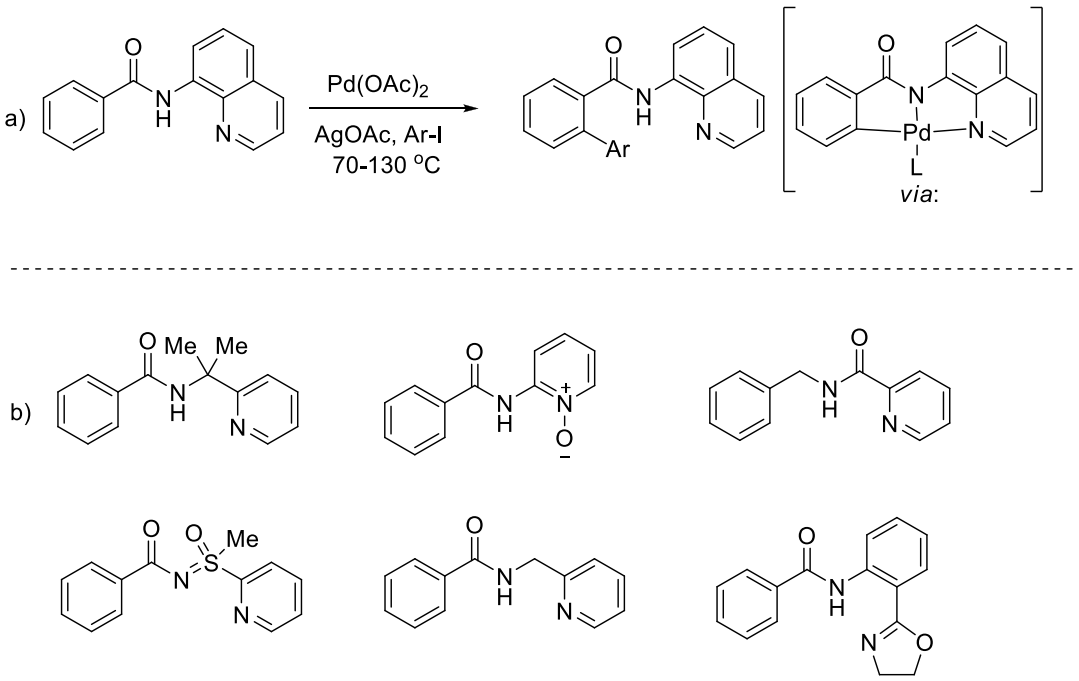
of a transition metal into an *ortho*-C(sp^2)-H bond. They found that a stoichiometric amount of [$NiCp_2$] ($Cp=C_5H_5$) reacts with azobenzene to form a five-membered *ortho*-nickelacycle (Scheme 1.10). Afterward, substantial progress was made in the field by

employing the monodentate directing groups for *ortho* C-H functionalization (Scheme 1.10).[19]



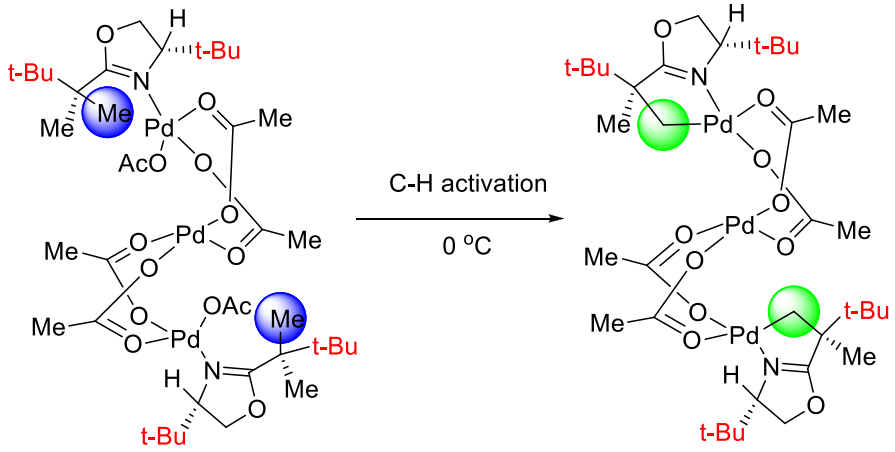
Scheme 1.10 A general depiction of directing group (DG) assisted C–H bond functionalization.

In 2005, Daugulis reported the arylation of C-H bonds by using 8-aminoquinoline and picolinamide as a bidentate directing groups, with $Pd(OAc)_2$ as the catalyst (Scheme 1.11, a).[20] Encouraged by these promising results, a number of transformation of C-H bonds have since been developed by using systems based on bidentate directing groups (Scheme 1.11, b). It is well recognized that the directing group coordinates to the metal center in a bidentate fashion and stabilized the transition metals in high oxidation states and can deliver the active catalytic site to a proximal C−H bond, typically *via* the formation of a five- or a six-membered metallacycle intermediate, and entails the C−H bond activation.[21] Encouraged by these promising results, some transformations of C-H bonds have been developed by using systems based on bidentate directing groups.



Scheme 1.11 Various bidentate directing groups have been employed in C-H activation.

Yu and coworkers isolated the sp^3 C-H bond activated palladacycle at 0 °C, it revealed that the conformation is the key role for the C-H bond activation (Scheme 1.12). [22]

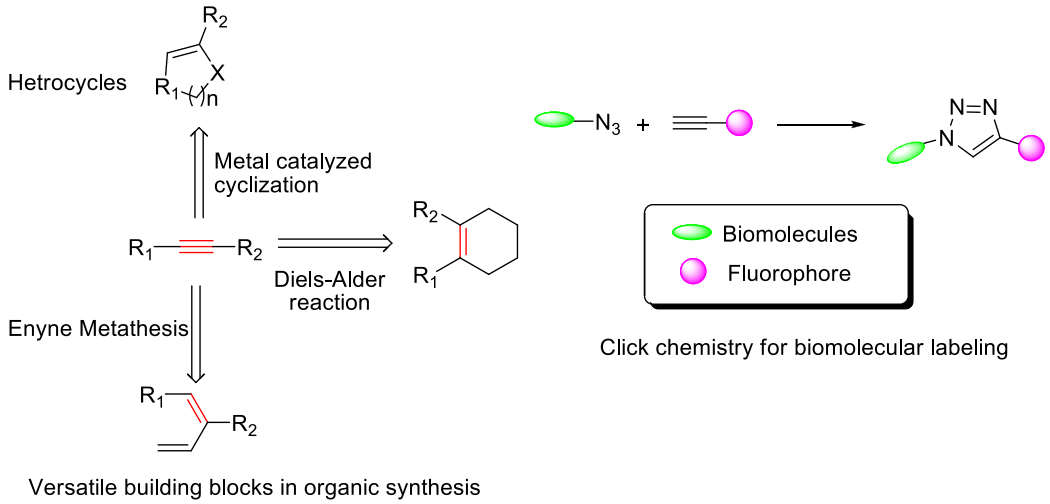


Scheme 1.12 Conformation induced sp^3 C-H bond activation.

1.6 Alkyne: Application/Importance

Transition-metal catalyzed direct functionalization of the inert C−H bond has emerged as a powerful strategy for the straightforward synthesis of value-added products with great

step economy and low waste production. Alkynes are among the most important structural motifs in a large number of natural products, pharmaceuticals, and materials. It has significant importance for various organic transformations including cycloaddition, metathesis, click reaction (Scheme 1.13).[23] Due to the impressive number of possible synthetic transformations, it is no surprise that C-C triple bonds can be introduced as C2-units with this strategy.

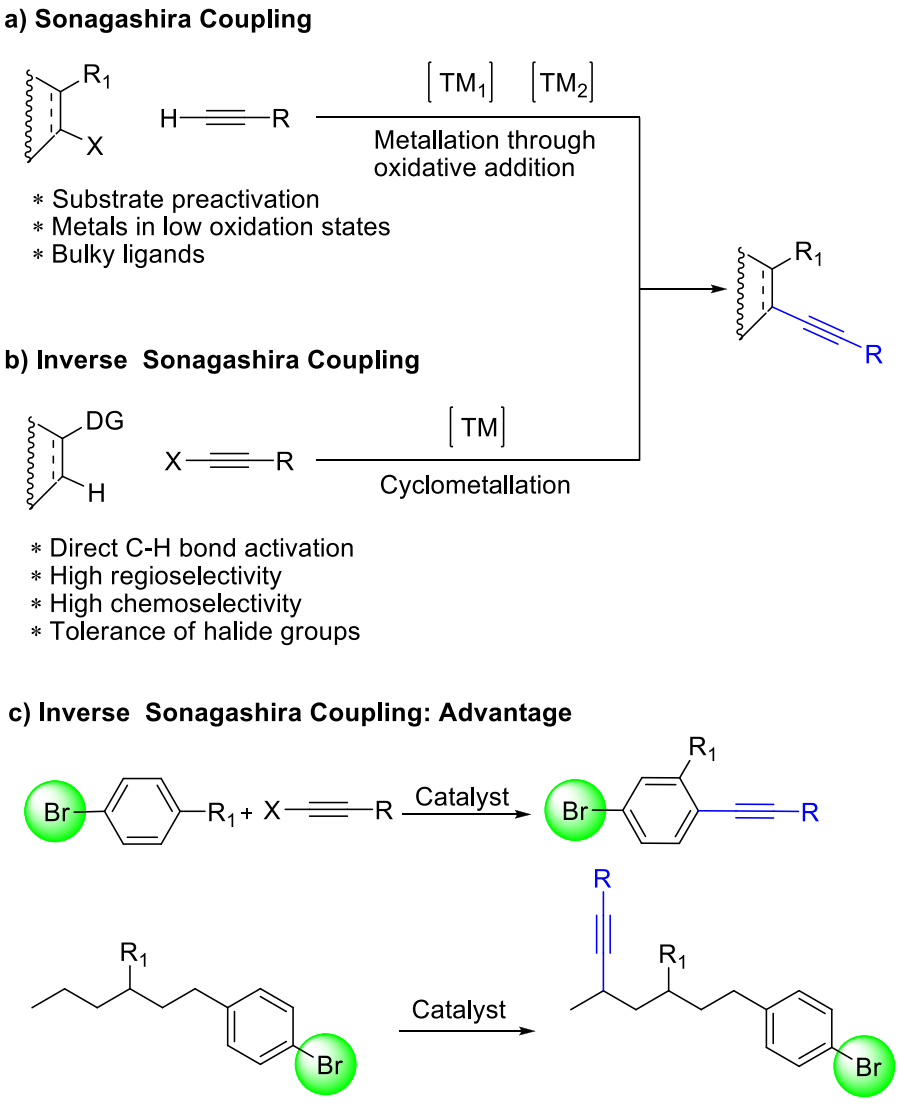


Scheme 1.13 Diversification of alkyne.

The most prominent example is the Sonogashira reaction, a Pd-catalyzed cross-coupling between aryl and alkenyl halides or triflates with metal acetylides. (Scheme 1.14, a). As in all "classical" cross-coupling reactions, activation of the carbon of interest is necessary for the initial oxidative addition to occur. This preactivation is substantial in terms of reactivity and selectivity since only one specific carbon should react in the cross-coupling reaction.[24] However, to avoid this sometimes tedious or even impossible preactivation, the direct utilization of C-H bonds in such transformations has come into the focus of research. Also, electron rich and bulky ligand has to employ to get the oxidative addition and reductive elimination.

Considering these problems, the "inverse" Sonogashira coupling has been investigated recently as a complemental strategy to classical cross-couplings (Scheme 1,14, b).[25] Herein, the alkynylation occurs after an initial C-H activation or deprotonation step with an electrophilic alkyne source.

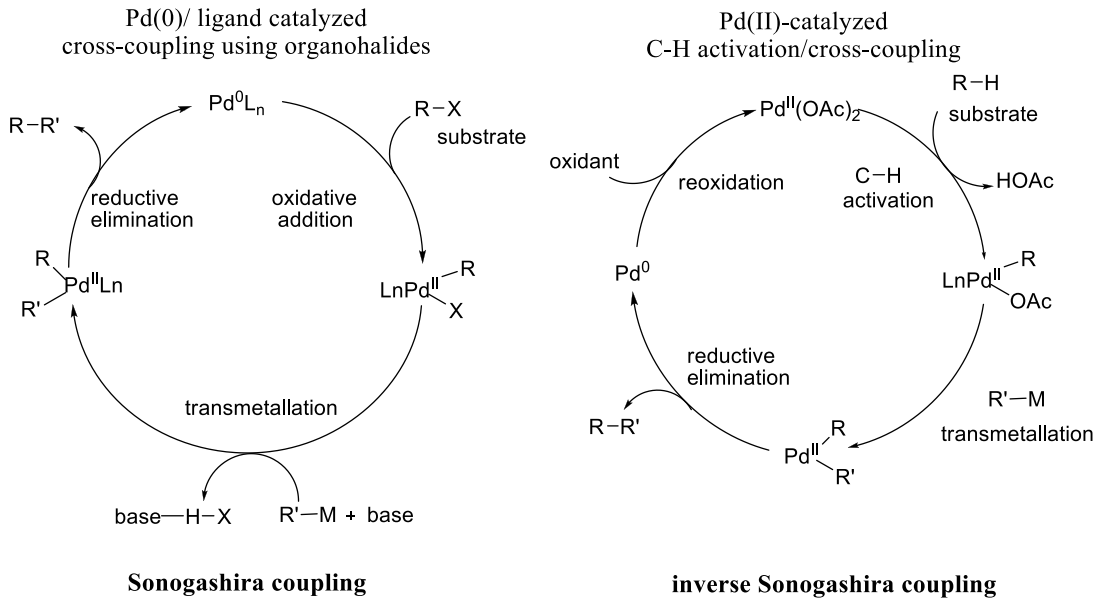
The advantages of "inverse" Sonogashira coupling: 1) A high regio and chemo-selectivity products in the presence of multiple C-H bonds. Here the directing groups (DGs) are necessary to guide the transition-metal exclusively to the desired bond to be activated. 2) Halide groups are retained, 3) Alkyne-homocouplings are avoided. Considering its superior step-economy and cost-effectiveness, it is no wonder that the direct C-H alkynylation has become a versatile alternative to reliable and approved Sonogashira approaches (Scheme 1.14, b). Notably, many synthetically valuable groups such as halide (-Cl and -Br) could be reserved under catalytic reactions, which give chances for further modification of the products, wherein synthesis of such products using the traditional approach, "Sonagashira coupling" is very difficult and rather scare (Scheme 1.14, c).



Scheme 1.14 Approaches to form sp^2-sp bond.

Mechanism:

In the mechanistic pathway both follow different mechanisms in case of Sonogashira coupling catalyzed by Pd(0) cross-coupling reactions rely upon bulky, electron-rich phosphine and *N*-heterocyclic carbene (NHC) ligands to promote the oxidative addition of the organohalides and subsequent reductive elimination while suppressing undesired side reactions. However, in inverse Sonagshira coupling these ligands have been incompatible in Pd(II)-catalyzed oxidative C-H activation reactions. It follows DGs assisted C-H bond activation, transmetallation, and reductive elimination to get the desired products. The Pd(0) is oxidized by oxidant to generate the Pd(II) active species to complete the cycle. The challenges associated with Pd(II) catalyzed cross-coupling reaction is transmetallation and *β*-hydride elimination is a competitive pathway (Scheme 1.15).



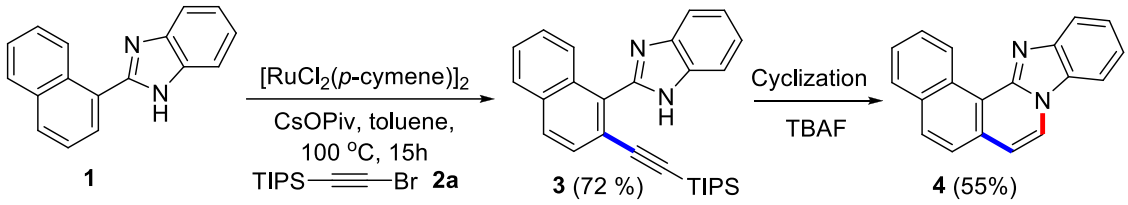
Scheme 1.15 Different mechanistic pathway for the Pd-catalyzed alkynylation.

The majority of catalyzed C−H functionalization was achieved employing precious second and third-row transition metals.[26] In contrast, naturally abundant base metal complexes have been thus far underutilized in C−H bond activation technology despite their prevalence in the active center of various enzymes. The development of catalysts based on the naturally more abundant and, a cost-efficient 3d transition metal complex represents an attractive alternative. As a result, the use of inexpensive first-row transition metal catalysts for C–C transformations has gained considerable recent momentum.[27] In this regard, earth-abundant first-row late transition metals have been intensely used in

C−H bond activation strategy to emulate the selectivity and reactivity of precious-metal catalysts and thus broaden the scope and practical viability. However, their successful application in C−H bond functionalizations still remains at an early stage and can make it difficult to envisage and control catalytic reactivity, as they have a propensity to participate in one-electron chemistry as opposed to classical two-electron transformation ubiquitous in the second- and third-row transition metals.

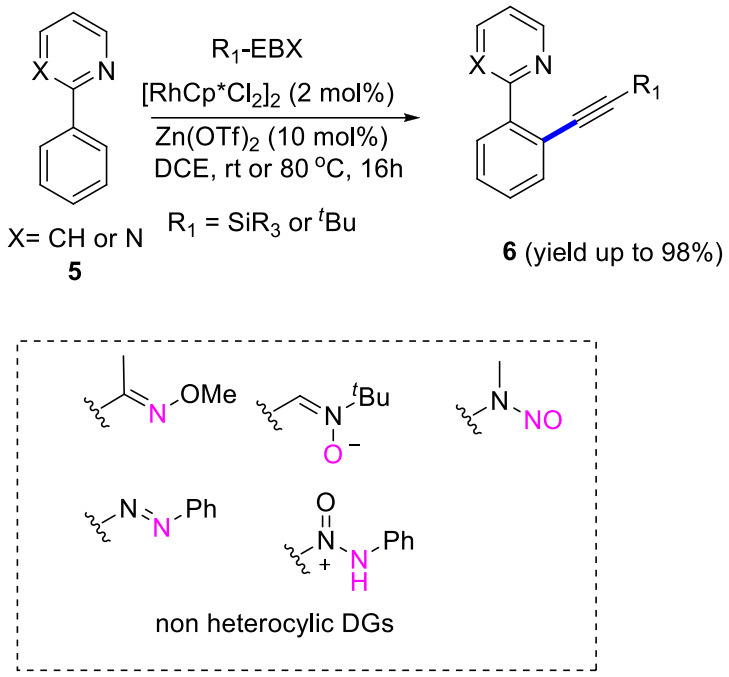
1.7 Alkynylations Directed by Heterocycles

A promising study by Chatani and Tobisu utilized a variety of the above mentioned *N*-heterocycles in a direct Ru-catalyzed *ortho*-alkynylation of arenes using TIPS-substituted bromoacetylene(**2a**).[28] When benzo[*d*]imidazole **1** were applied as DGs, the obtained products **3** could be applied in a fluoride-initiated 6-endo-dig cyclization to heteroarene **4** (Scheme 1.16). This initial article impressively shows the ambivalent function of *N*-heterocycles, initially as a DG for C-H activation and finally as a reacting group in a subsequent cyclization.



Scheme 1.16 Ru-catalyzed C-H alkynylation and cyclization.

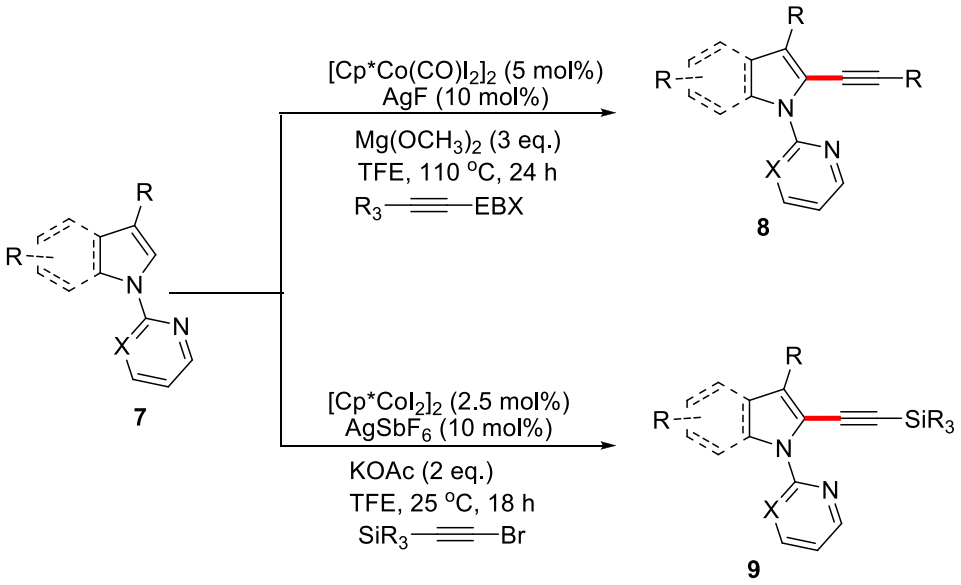
The prosperity of this field began in 2014, when the groups of Li,[29] Loh,[30] Glorius[31] and Chang[32] utilized benziodoxolones **1** in DG mediated transformations. Albeit those reagents have previously been employed in combination with various transition metal catalysts, this was the first time when Rh(III)- and Ir(III)-catalysts were utilized, enabling remarkably mild alkynylations of C(sp^2)-H bonds. In the extensive work of Li,[29] more than 80 (hetero)arenes **5** were alkynylated to **6** using 2-pyridines and 2-pyrimidines as DGs (Scheme 1.17). *N*-Pivaloyloxybenzamides, hydrazides, imine-*N*-oxides and a variety of other 5-membered heterocycles such as 1-pyrazoles, 2-oxazolines or cyclic azo, imine and, methines could be applied as well. Overall more than 15 *N*-containing cyclic and acyclic DGs were viable.



Scheme 1.17 Alkynylation of heteroarenes.

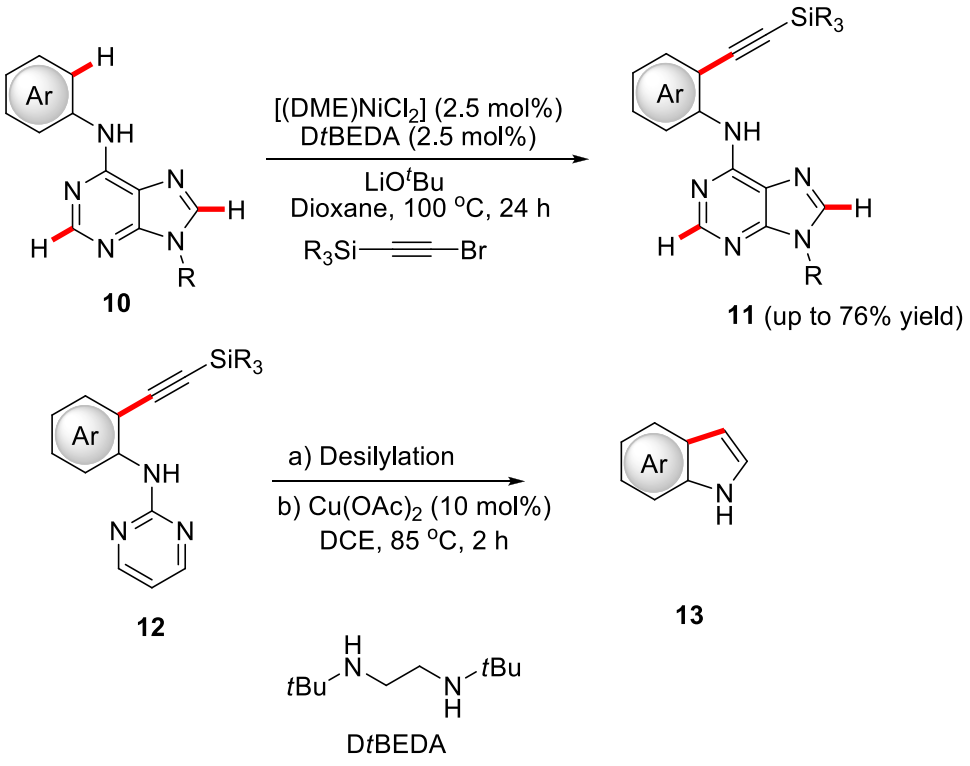
1.8 Alkynylations Directed by First Row Transition Metal

The indole and pyrroles substrates are basic structural units of many natural products, biologically active compounds and, agrochemicals. Shi[33]and Ackermann[34] were able to utilized cobalt-derived catalysts for C2-alkynylations of heterocycles, including indoles and, pyrroles efficiently coupled with an alkyne.



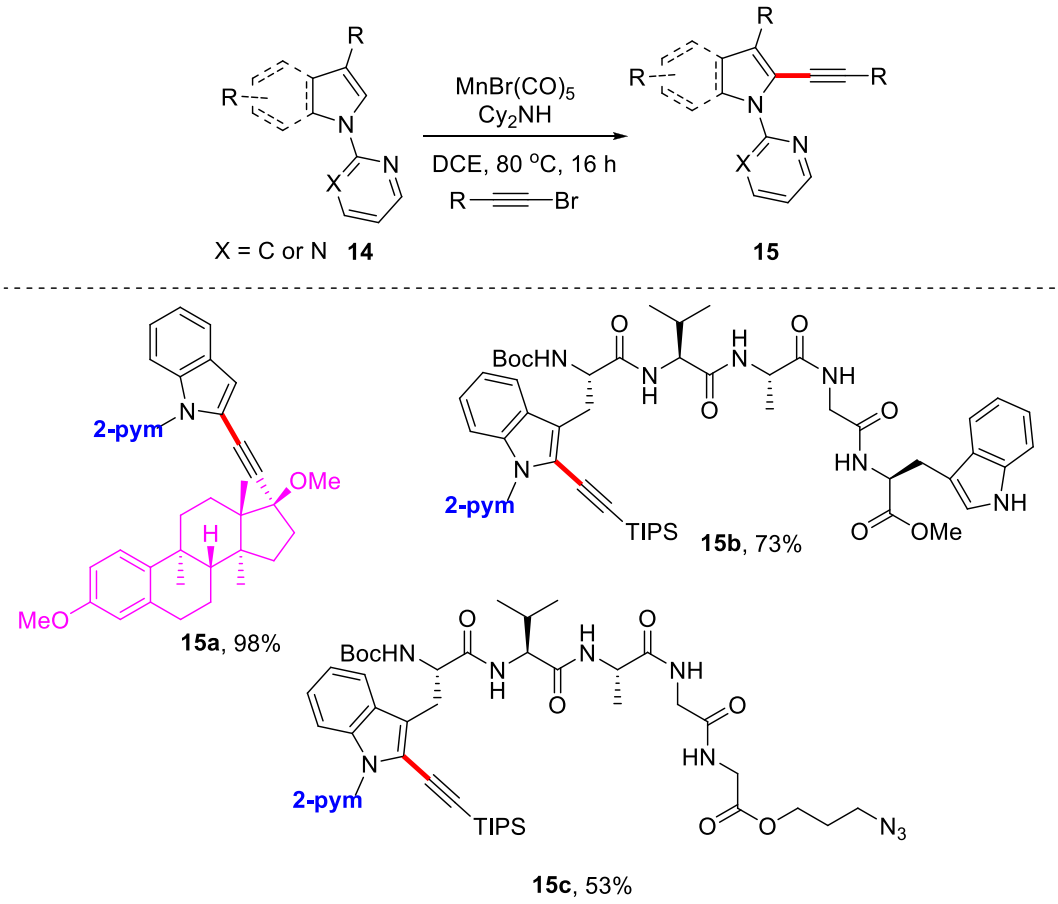
Scheme 1.18 Alkynylation of indoles.

For the first time with $MnBr(CO)_5$ as catalyst, pyri(mi)dine substituted indoles **14** were viable substrates yielding C2-alkynylated indoles **15** with enabled step-economical C-H functionalizations with silyl, aryl, alkenyl, and alkyl haloalkynes (Scheme 1.20).[37] This methods scope is remarkable since even fluorescent labels, steroids, and amino acids



Scheme 1.19 Nickel-catalyzed monodentate alkynylation.

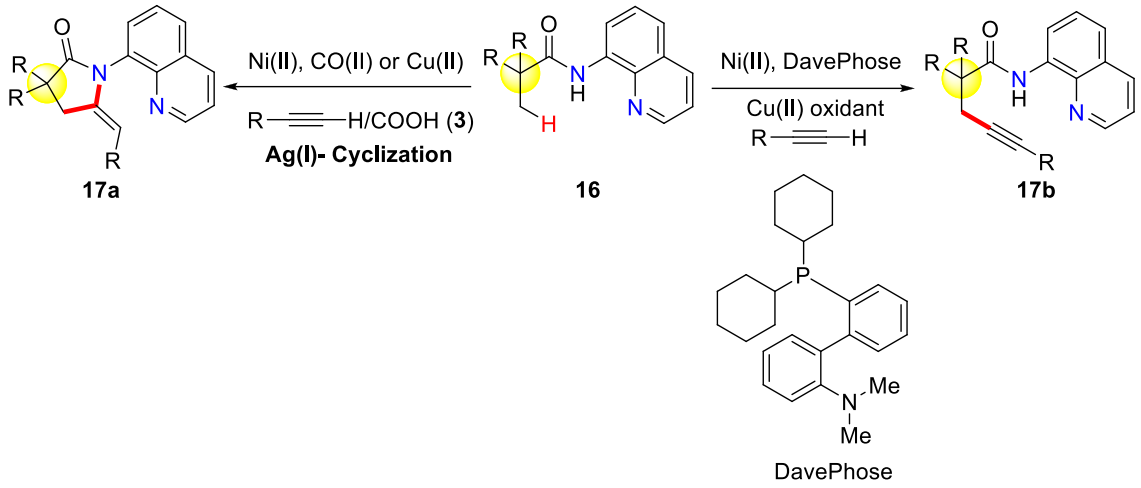
Based substrates could be alkynylated (**15a** – **15c**). The unique power of the versatile Mn(I) catalyzed C-H alkynylation approach set the stage for the efficient modification and assembly of cyclic and acyclic peptides under racemization-free conditions.



Scheme 1.20 Mn-catalyzed C2-alkynylation of *N*-(2-pyri(mi)dinyl)-indoles.

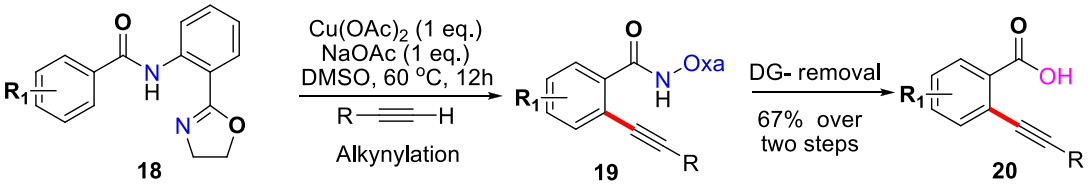
Zhang and co-worker[38-40] reported the C(sp^3)-H alkynylations of acid derivative by employing nickel, cobalt and copper as a catalyst, by using 8-aminoquinoline as a directing group. Notably, in C(sp^3)-H alkynylations of carboxylamides no other heterocycle has been utilized as DG so far. The isolation of free alkynes in oxidative alkynylations without further cyclization is difficult to achieve due to the necessity of metal-additives which strongly bind as π-acids to the emerging alkyne a subsequently induce a cyclization. Such oxidative alkynylation/cyclization cascades have been developed under various conditions.[38-40] While terminal alkynes **3** reacted under Co- and Ni-catalysis, a Cu-catalyzed variant in combination with stoichiometric amounts of Ag-oxidants enabled the use of alkyne carboxylic acids (Scheme 1.21). In every case, the

Ag(I)- additive caused immediate cyclization of the free alkyne giving direct access to vinylidenepyrrolidinones **17a**.



Scheme1. 21. Additive-dependent oxidative C(sp^3)-H alkynylations.

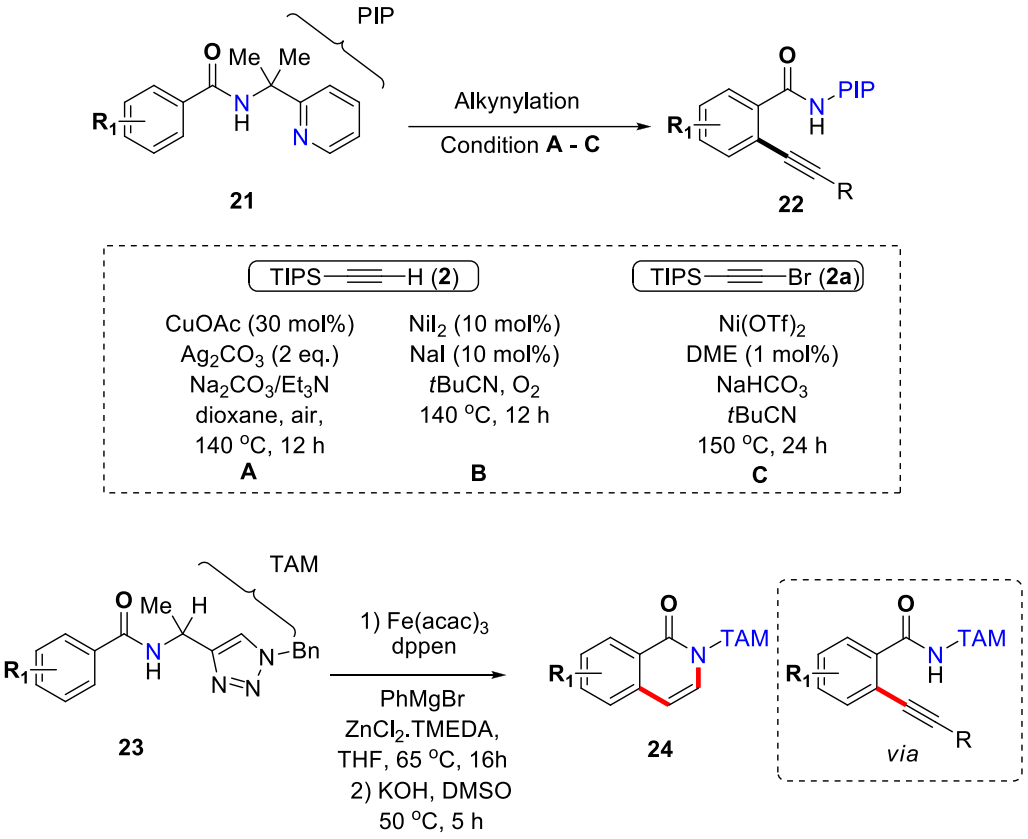
A similar reactivity has been observed in oxidative alkynylations of sp^2-bonds.[42,43] In the absence of Ag(I) no cyclization occurs and isolation of the free alkyne **17b** is possible, even under oxidative conditions (Scheme 1.21).[41] Apart from the additive, DG can influence the cyclization tendency as well. The stoichiometric Cu-mediated oxidative alkynylations of sp^2-carbons without cyclization have been achieved using 2-phenyloxazolines (Oxa) as DG (Scheme 1.22).[44] With stoichiometric amounts of $Cu(OAc)_2$ benzamides **18** gave *ortho*-alkynylated arenes **19** using terminal aryl- and alkylalkynes. Through *N*-Boc-protection and mild saponification with NaOEt the Oxa-DG could effectively be transformed to the free carboxylic acids **20**.



Scheme 1.22 Alkynylations directed by Oxa-DGs.

8-Aminoquinoline as well as the Oxa-DG contains a 1,4-dinitrogen motif. This bidentate binding motif is crucial for a proper coordination to the transition-metal and stabilized the metal in higher oxidation step. Other modified with bidentate 1,4- dinitrogen motifs are the PIP-groups (PIP = pyridine-2-ylisopropyl).[45-47]Shi[45a] and Liu[45b] were able to

utilize nickel catalysts for *ortho*-alkynylations of amides. PIP-benzamides **21** could be alkynylated to **22** under Cu(II)- or Ni(II)- catalysis using TIPS-acetylene (**2a**) under oxidative conditions (Scheme 23) or using **2** (C). The DG can easily undergo hydrolysis to the free carboxylic acid can be achieved in a short sequence consisting of *N*-nitrosylation and hydrolysis.



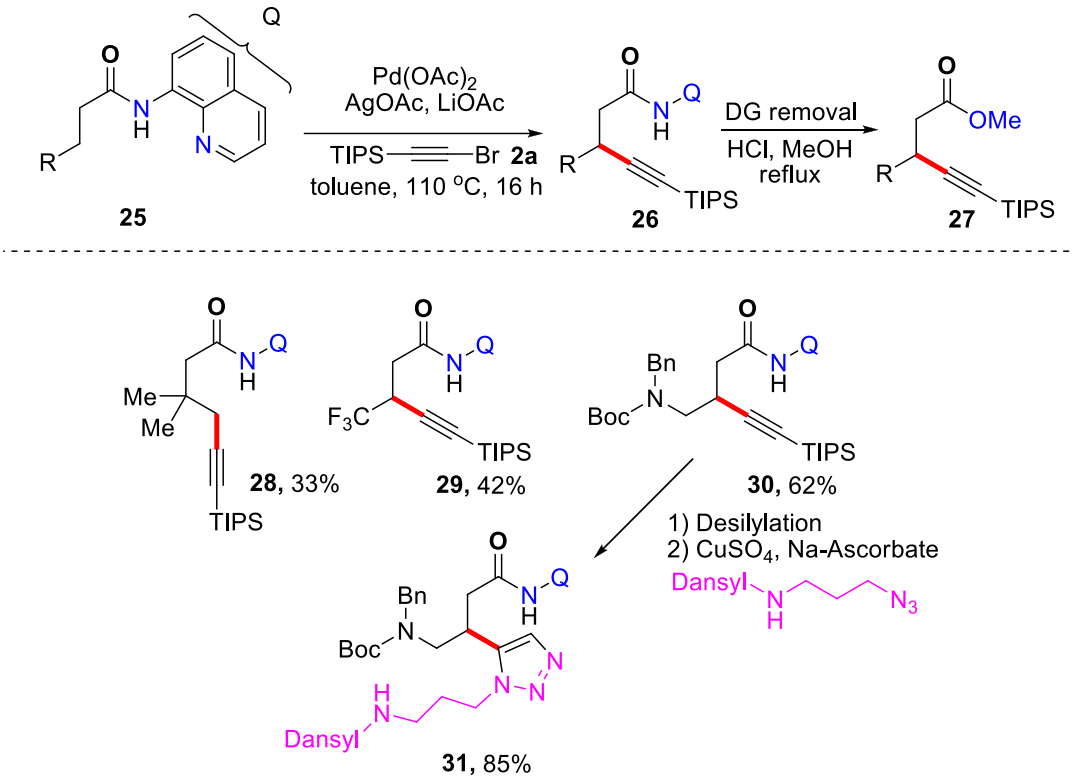
Scheme 1.23 C(sp^2)-H alkynylations using PIP- and TAM-DG.

The first iron-catalyzed C-H alkynylation of arenes, heteroarenes, and alkenes enabled by triazole assistance was achieved (Scheme 23).[48] The modular TAM (TAM = triazoleamine) directing group set the stage for a sequential C-H alkynylation/annulation strategy to synthesized of **24** from **23** *via* alkynylation under basic condition.

1.9 Palladium Catalyzed sp^3 C-H Alkynylation

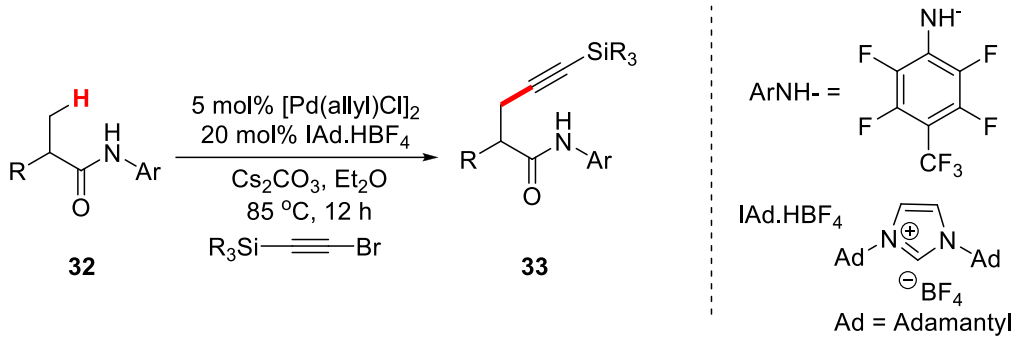
Among the examples shown, 8-quinolinylamides are utilized most frequently as DGs in C-H alkynylation reactions.. Promising work by Chatani and Tobisu installed 8-

quinoliny motify in arylbenzamides and alkylamides **25** derivatives for C-H alkynylation (Scheme 1.24).[49,50] Initially, activation of C(sp^3)-H bonds using $Pd(OAc)_2$ in combination with **2a** was achieved. The DG in the product **26** could be cleaved to methyl esters **27** under acidic conditions.[49] To demonstrate the synthetic importance of the products, an alkynylated γ-aminobutyric acid was desilylated and labeled with a fluorophore to give **31** *via* [3+2]-cycloaddition with Dansyl-azide. Other amino acids as well as cyclobutanes could be functionalized under similar conditions.[51, 52] The same DG could be applied for alkynylation of C(sp^3)-H-bonds under heterogeneous conditions using gold-supported palladium material (SAuPd) with palladium.[53] The catalyst can be recycled and reused 10 times for C(sp^3)-H bond functionalization.



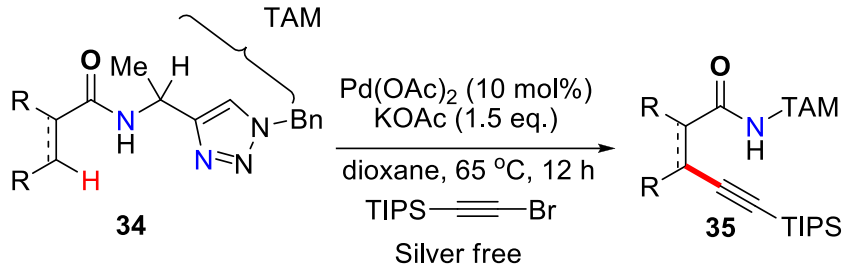
Scheme 1.24. The first example of Pd-catalyzed C(sp^3)-H alkynylations.

The alkynylation of *β*-C(sp^3)−H bonds in aliphatic amides with alkynyl halides has been enabled using Pd(0)/*N*-heterocyclic carbene (NHC) catalysts without the use of co-oxidants.[54] The alkynylation was achieved by utilizing [AlkynylPd(II)Ln] complexes to activate C(sp^3)-H bonds (Scheme 1.25).



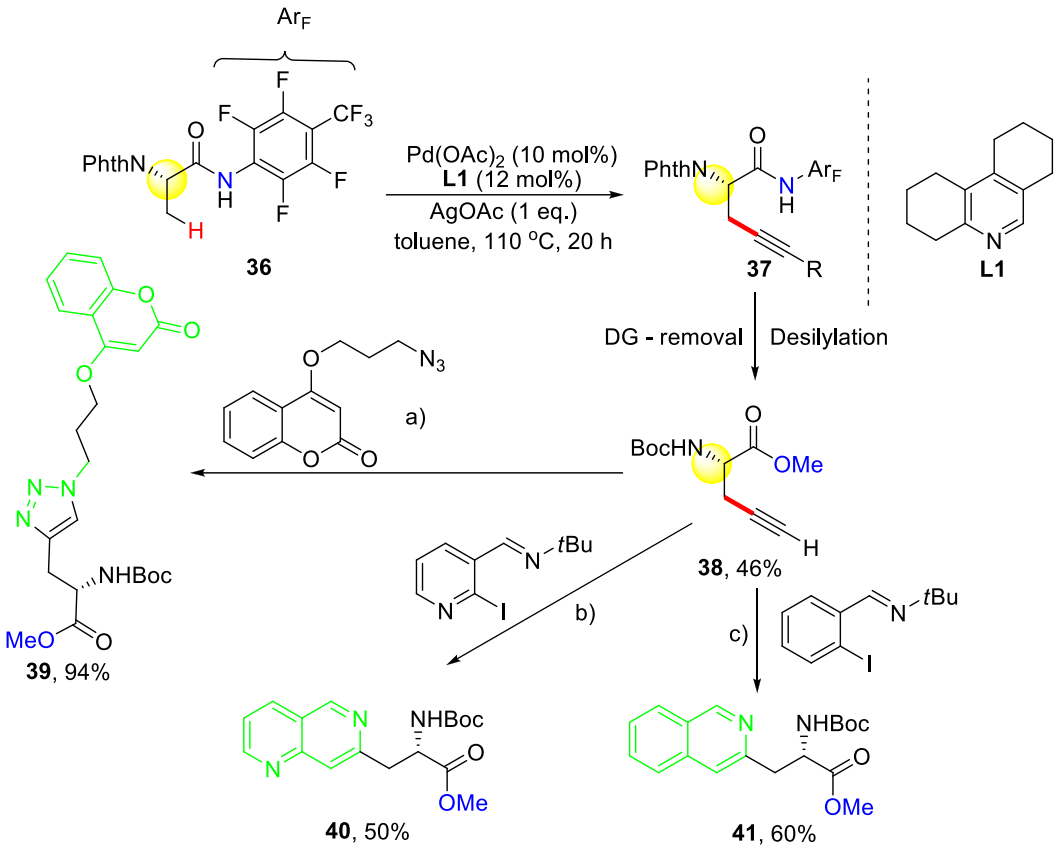
Scheme 1.25 Pd(0)-catalyzed C(sp^3)-H alkynylations of amide.

The silver-free approach was developed by using triazole amine as an effective directing group in promoting C–H alkynylation.[55] Interestingly, no other external oxidant was required, and the alkynylation products were received in good to excellent yields. (Scheme 1.26).



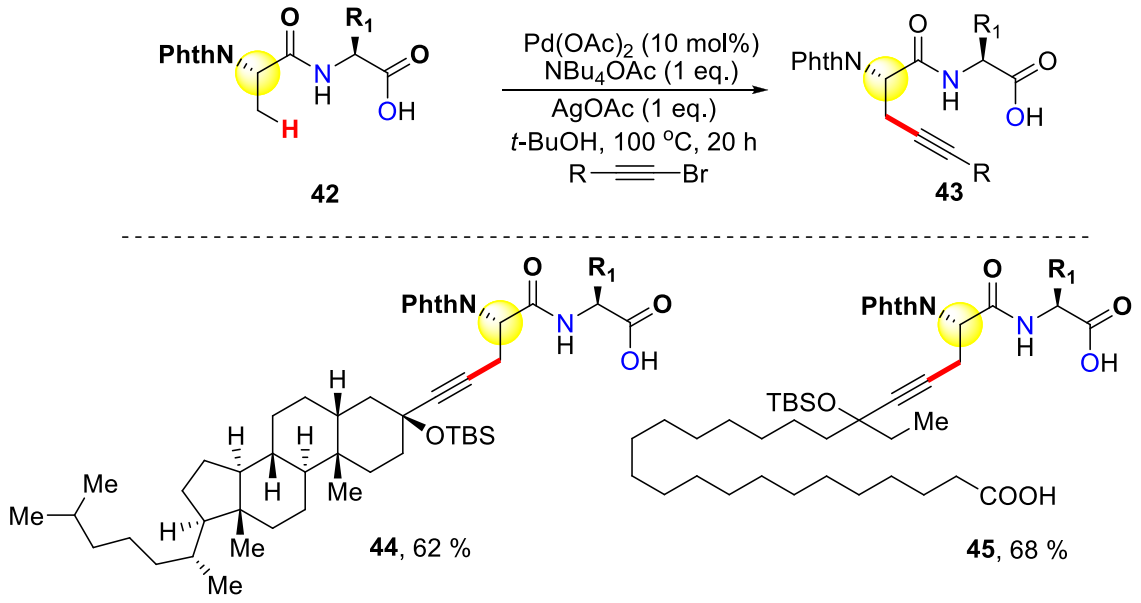
Scheme 1.26 Silver free Pd(II)-catalyzed C(sp^3)-H alkynylation using TAM-DG.

Outstanding achievements in C(sp^3)-H alkynylations using amide derived DGs have also been attained. For example, the pyridine ligand enabled Pd(II)-catalyzed could efficiently alkynylated perfluoroaryl substituted benzamides **36** (Scheme 1.27).[56] Even, α-quaternary amides and α-amino acids react in high yields. Further transformation of **37** into the *N*-Boc protected methyl ester **38** was achieved in 4 steps, giving fast access to a variety of unnatural amino acid derivatives **39** - **41**.



Scheme 1.27 Pyridine ligand enabled Pd(II) catalyzed C(sp^3)-H alkynylation of quaternary acids reaction condition : a) $CuSO_4 \cdot 5H_2O$(1.0 mol %), sodium ascorbate (5 mol %), H_2O/*t*-BuOH (2:1), RT, overnight; b) 1) $PdCl_2(PPh_3)_2$ (2.0 mol%), CuI (1.0 mol %), NEt_3,55 °C, 3h; 2) CuI (10 mol %), DMF, 100 °C; c) i) $PdCl_2(PPh_3)_2$ (2.0 mol %), CuI (1.0 mol %), NEt_3, 55 °C, 5h;ii) CuI (10 mol %), DMF, 100 °C.

The palladium(II)-catalyzed C(sp^3)-H alkynylation of oligopeptides was achieved with tetrabutylammoniumacetate as a key additive (Scheme 1.28). [57]A simple RNH-Ala-Val-OH dipeptides **42** can be alkynylated at the *β*-carbon to propargyl-substituted dipeptides **43**. This method gives direct access to dipeptide backbones wit steroid- (**44**) or arachidonic acid substituents (**45**).



Scheme 1.28 Pd(II) catalyzed C(sp^3)-H alkynylation of α-amino acids.

Nickel and cobalt catalyzed C−H functionalizations at thermodynamically more stable aryl or alkenyl C−H bonds are scarce and only scattered examples have recently been disclosed. In this perspective in this thesis, second and third chapters describe the sp^2 C-H alkynylation of acids and amines by employing the earth abundant nickel and cobalt catalyst. For quite some time it was believed that 3d metals such as iron, cobalt, and nickel, cannot compete with the 4d (Pd, Rh, Ru) and 5d (Ir) metals regarding their reactivity. However, sp^3 C-H alkynylation by employing earth-abundant metals are very limited and rarely reported. The first example of palladium-catalyzed ligand-enabled C(sp^3)-alkynylation of 8-methyl quinoline derivatives is explained in chapter four. The final chapter explores the development of Pd(II)-catalyzed *gamma* C(sp^3)-H alkynylation of amine substrate(linear, chain and amino acids), and various picolinamide-based auxiliaries.

Overview of the Thesis

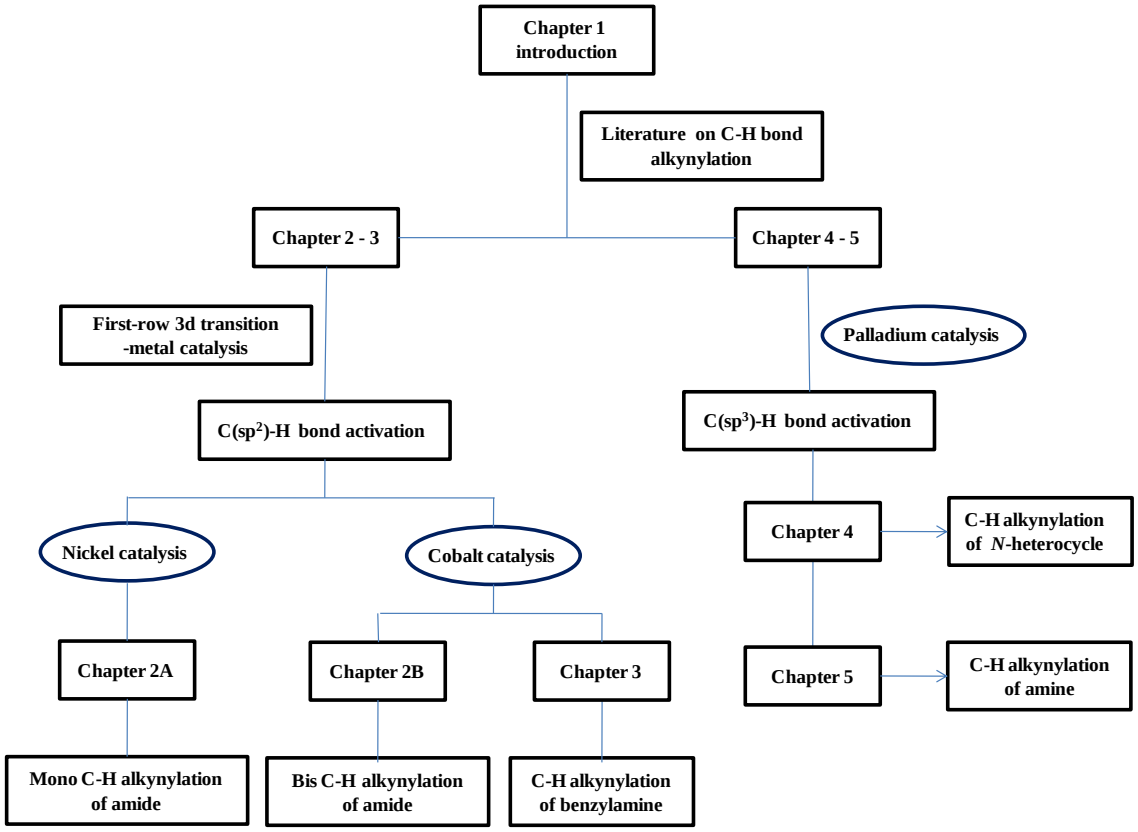


Figure 1 Arrangement of working chapters.

1.10 References

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Chapter 2

Nickel/Cobalt Catalyzed C(sp^2)-H Bond Alkynylation of Amides

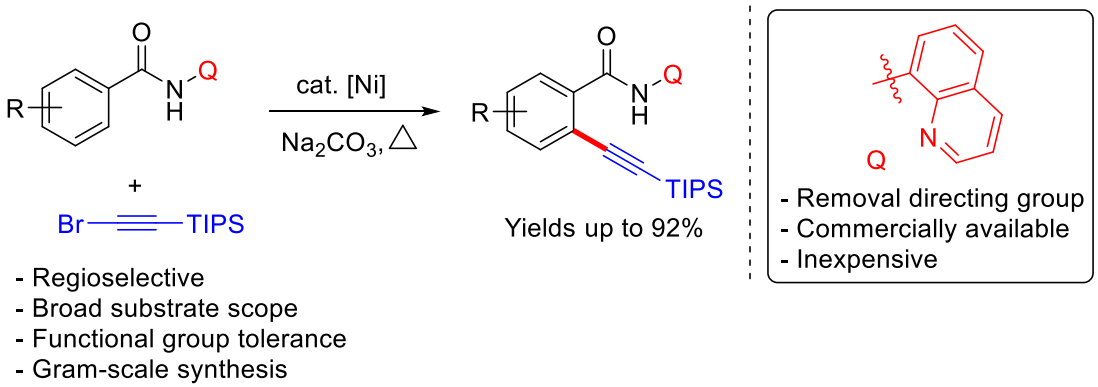
Section 2A: Nickel Catalyzed C(sp^2)-H Bond Alkynylation of Amides

Section 2B: Cobalt Catalyzed Bis-Alkynylation of Amides *via* Double C-H Bond Activation

Chapter 2A

Nickel Catalyzed C(sp^2)-H Bond Alkynylation of Amides

In this chapter, the nickel-catalyzed direct alkynylation of C(sp^2)-H bonds of amides using commercially available, inexpensive 8-aminoquinoline as a removable bidentate directing group is described. The present *ortho*-alkynylation has a broad substrate scope, functional group tolerance, and can be scaled up. The efficiency and regioselectivity of this strategy provides sustainable routes to a diverse array of *ortho*-alkynylbenzoic acids under Ni(II)-catalyzed conditions.



Vinod G. Landge *et al. Catal. Sci. Technol.*, 2016, *6*, 1946-1951

2A.1 Introducion

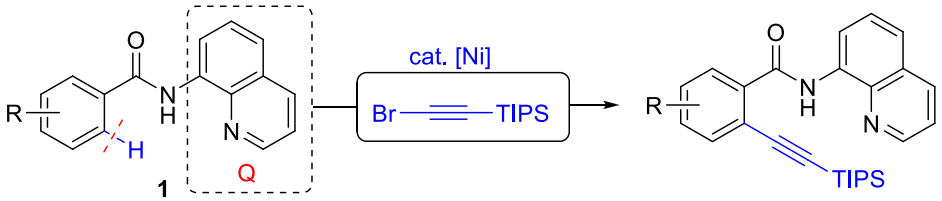
Functionalized alkynes occupy a privileged position in contemporary organic synthesis as they can be found in drugs, biomolecules, and material science.[1] In addition, alkyne moiety is of significant importance for various organic transformations including cycloaddition, metathesis, click reaction, *etc*. (see Chapter1, Scheme 1.13). Thus, the development of an efficient strategy for the construction of alkynyl scaffolds is a key motivation in organic synthesis and is usually achieved by the Sonogashira cross-coupling reaction between an aryl halide and a terminal alkyne.[2] However, there has been increasing interest in the development of a complementary approach, an "inverse Sonogashira coupling" involving the direct conversion of inert C-H bonds into C-alkynyl bonds with easily accessible alkynyl halides (see Chapter1 Scheme 1.14).[3-4]

The activation of a C-H bond is a highly challenging yet fundamentally important process in organic chemistry, since C-H bonds are known to be strong, lack polarity, and are generally unreactive. These features render C-H bond activation a demanding task. Considering that essentially all chemicals ultimately derive from fossil resources (contain mostly C-H and C-C bonds) the success of C-H activation can potentially revolutionize the industrial manufacture of fine chemicals and thus, more efficiently use these non-renewable resources. Hence, successful C-H bond activation can dramatically impact organic synthesis and natural product chemistry.[5]

Despite substantial growth in this active research area, unreactive C-H bond functionalization requires the assistance of a directing group embedded in the substrate that is able to coordinate to a metal center and deliver the active catalyst to a proximal C-H bond, typically *via* the formation of a five- or a six-membered metallacyclic intermediate.[6] After Daugulis's promising work[7] on the palladium-catalyzed chelation-assisted functionalization of C-H bonds using an 8-aminoquinoline as *N,N'*-bidentate directing group, many researchers started to use this chelating strategy for inert C-H bond activation (see Chapter 1, Scheme 1.11).[8]

The utilization of 8-aminoquinoline as a bidentate directing group has recently gained much attention in transition-metal catalyzed C-H bond functionalization reactions because of its commercial availability, economical, chelating ability, relatively acidic nature of N-H bond, and rigid backbone.[8b,8d-e]

Chatani and co-workers have reported Pd(II)-catalyzed alkynylation of non-acidic β C-H bonds with (triisopropylsilyl)ethynyl bromide with the assistance of 8-aminoquinoline as a directing group (see Chapter1, Scheme 1.24).[9a] Ruthenium- and palladium-catalyzed alkynylation of inert C-H bonds with the assistance of different directing groups were also independently reported by Chatani[4e,4o,9b] and Yu co-workers[10] Alkynylation of *N*-aryl-2-aminopyridine with (triisopropylsilyl)acetylene was achieved by Chang and co-workers under Pd-catalyzed condition.[11] Recently, Glorius,[12] Loh[13] and others[14] have independently reported Rh-catalyzed alkynylation of C(sp^2)-H bonds with hypervalent alkynyl iodine reagents (see Chapter1, Scheme 1.17). Copper-mediated alkynylation of arenes with terminal alkynes have been developed by research groups of Yu,[15] and Shi.[16] Several catalytic alkynylation of heteroarenes have also been developed using various metals based on Gevorgyan's pioneering work on the palladium-catalyzed alkynylation of *N*-fused heteroarenes.[3a,4c-d,4f] Among the various metals employed in this emerging area, nickel has gained significant attention owing to its abundance, economical and versatile reactivity.[17] Recently, nickel-catalyzed chelation-assisted C-H bond activation to construct carbon-carbon bond and carbon-heteroatom bond with the aid of bidentate directing groups has been developed by fewer groups (see Chapter 1, Scheme 1.23).[8a,8c,17-18] Inspired by these studies, we were motivated to test the possibility of alkynylation of **1** using (triisopropylsilyl)ethynyl bromide **2** as a coupling partner (Scheme 2A.1). In the present chapter, we disclose nickel(II)-catalyzed C(sp^2)-H alkynylation of benzamides using 8-aminoquinoline as a removable bidentate directing group to synthesis various *ortho*-alkynylbenzoic acids.[19-20] The present nickel-catalyzed C(sp^2)-alkynylation has a broad substrate scope and functional group tolerance. Notably, many



Scheme 2A.1. The bidentate directing group assisted in catalyzed C-H alkynylation of unactivated arenes.

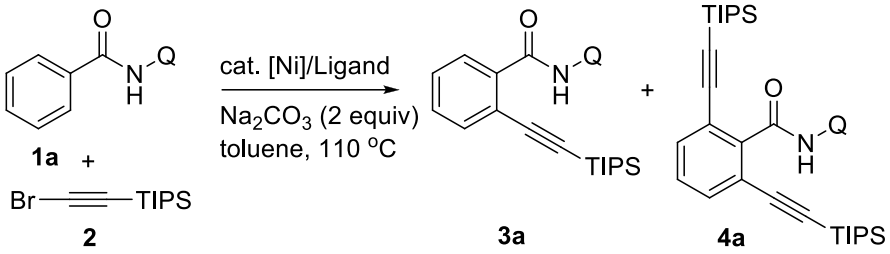
synthetically valuable groups such as halide (Cl, Br) could be reserved under our reaction reactions, which give chances for further modification of the products, wherein synthesis

of such products using the traditional approach, "Sonogashira coupling" is very difficult and rather scare.

2A.2 Results and Discussion

2A.2.1 Optimization of reaction condition

Table 2A.1. Optimization of the nickel-catalyzed "inverse Sonogashira coupling" of benzamides.[a]



Entry	Catalyst	Ligand	Yield[b]		Conversion of **1** (%)[b]
			3a	**4a** (%)	
1	$Ni(OTf)_2$	$PhCO_2H$	45%	25%	81%
2	$Ni(OTf)_2$	---	30%	24%	62%
3[c]	$Ni(OTf)_2$	$PhCO_2H$	19%	54%	77%
4[d]	$Ni(OTf)_2$	$PhCO_2H$	trace	---	6%
5	$Ni(OTf)_2$	$MesCO_2H$	16%	41%	63%
6	$Ni(OAc)_2$	$PhCO_2H$	15%	21%	47%
7	$NiCl_2$	$PhCO_2H$	17%	27%	55%
8	$NiBr_2$	$PhCO_2H$	15%	22%	46%
9	$Ni(acac)_2$	$PhCO_2H$	26%	29%	63%
10	$Ni(COD)_2$	$PhCO_2H$	22%	10%	41%

[a]Reaction conditions: **1a** (0.1 mmol), Ni catalyst (5 mol%), ligand (10 mol%), **2** (0.2 mmol), Na_2CO_3 (2 equiv), and toluene (1 mL) 110 °C for 24 hrs. [b]Conversion based on recovered yield of **1a**. [c]3 equiv of **2**. [d]In the absence of Na_2CO_3.

Preliminary studies revealed that *N*-(quinolin-8-yl)benzamide (**1a**) and (triisopropylsilyl)ethynyl bromide **2** (2 equiv), Na_2CO_3 (2 equiv) as a base and in the presence of $Ni(OTf)_2$ (5 mol %) as a catalyst and 10 mol% of benzoic acid as an additive at 110 °C (reflux temperature of toluene) after 24 hrs, afforded both mono-

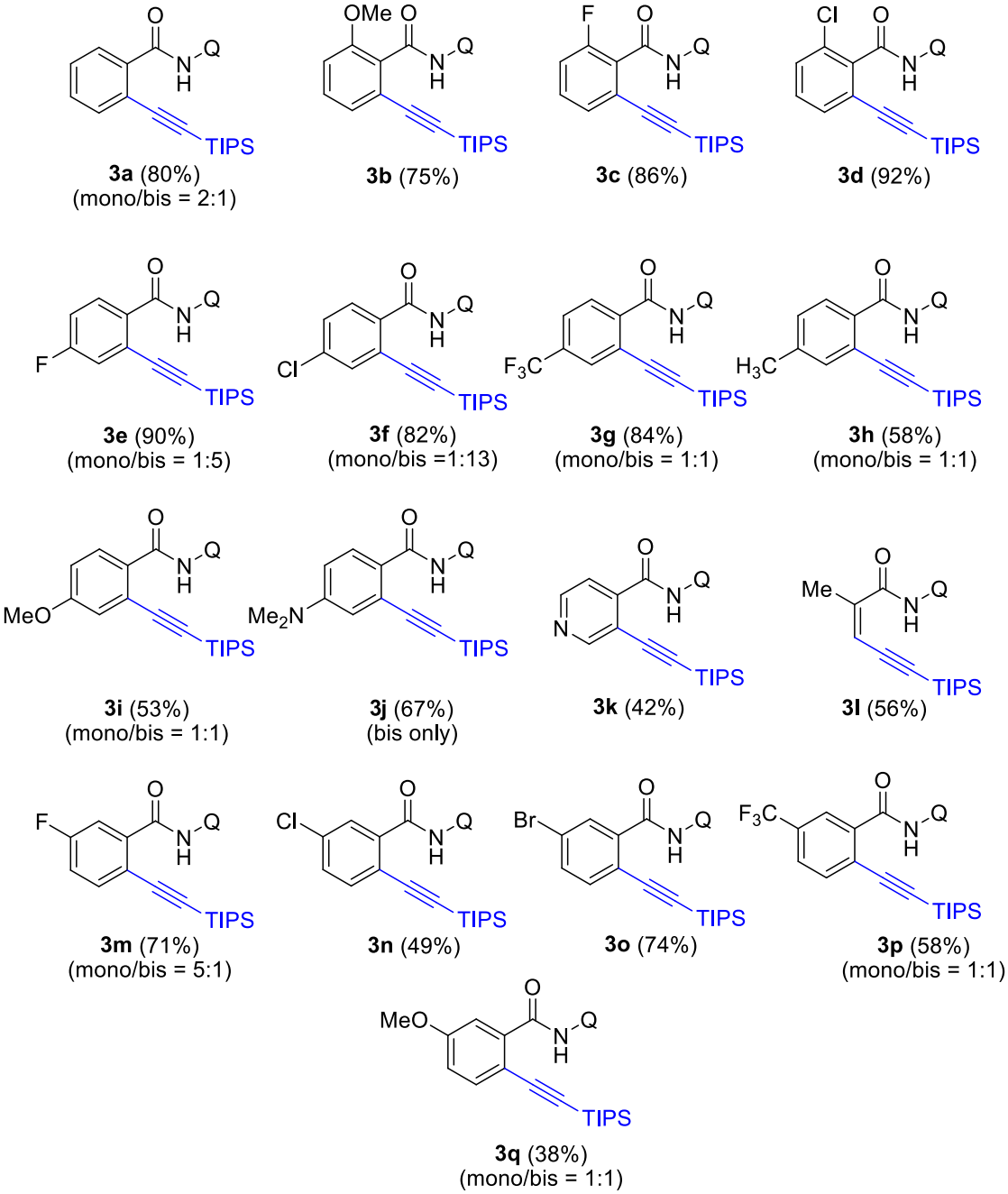
(**3a**) and bis-alkynylated products (**4a**) with the conversion of **1a** in 81%. Both mono- (**3a**) and bis-alkynylated products (**4a**) were isolated separately and the yields of **3a** and **4a** are 45% and 25% respectively (Table 2A.1, entry 1). In the absence of benzoic acid the yield of alkynylated products was decreased from 70% to 54% (Table 2A.1, entry 2). However, the efficiency of the reaction was significantly affected in the absence of Na_2CO_3 (Table 2A.1, entry 4) and clearly revealed the coordination of the amide **1a** to the Ni(II) followed by a ligand exchange with HX (X = -OTf, -Br, $PhCO_2$-) generation has been accelerated by the base.[21] This is because 8-aminoquinoline has a more acidic NH bond, which facilitates ligand exchange (promoted by a base). A series of nickel salts ($NiCl_2$, $NiBr_2$, and $Ni(acac)_2$) was evaluated under the optimal reaction condition (Table 2A.1, entries 6-9) and it was observed that $Ni(OTf)_2$ showed improved reactivity (entry 1). Importantly, a Ni(0) complex also showed a catalytic activity, resulting in moderate yields of the *ortho*-alkynylated product (Table 2A.1, entry 10). In all cases, unreacted starting material **1a** was recovered.

2A.2.2 Scope of amides

The scope of amides and selectivity of products under our reaction conditions is shown in Tables 2A.2. The reaction is general, and a variety of amides (aromatic, heteroaromatic and α,β-unsaturated) were compatible with this transformation. With the optimized reaction conditions in hand (Table 2A.2), various *ortho*-substituted benzamides were effectively alkynylated with excellent yields (up to 92%) under standard conditions (Table 2A.2). As shown in Table 2b, both electron-withdrawing (**1g**) and electron-donating groups (**1i-1j**) in the phenyl ring were well tolerated and to give alkynylated product in good yields. It is noteworthy that halide substituents were tolerated, as this is advantageous for further synthetic elaborations with transition-metal catalysis thereby broadening the diversity of the products. Thus, benzamides bearing halides such as chloro, bromo groups (**1c**, **1f**, and **1n-1o** in Table 2A.2) proceeded efficiently and leading to the corresponding alkynylated products in good yields under our catalytic conditions, wherein synthesis of such compounds using the traditional approach, "Sonogashira coupling" is very difficult and rather scare. In addition, alkynylation of heteroaromatic amide (**1k**) smoothly occurred under standard conditions and affording **3k** in 42% yield. To our delight,

challenging α,β-unsaturated amide (**1l**) also gave the corresponding alkynylated product in moderate yield (**3l** in 56% yield).

Table 2A.2 The scope of 8-aminoquinolinyl (para-substituted) amides.[a,b]

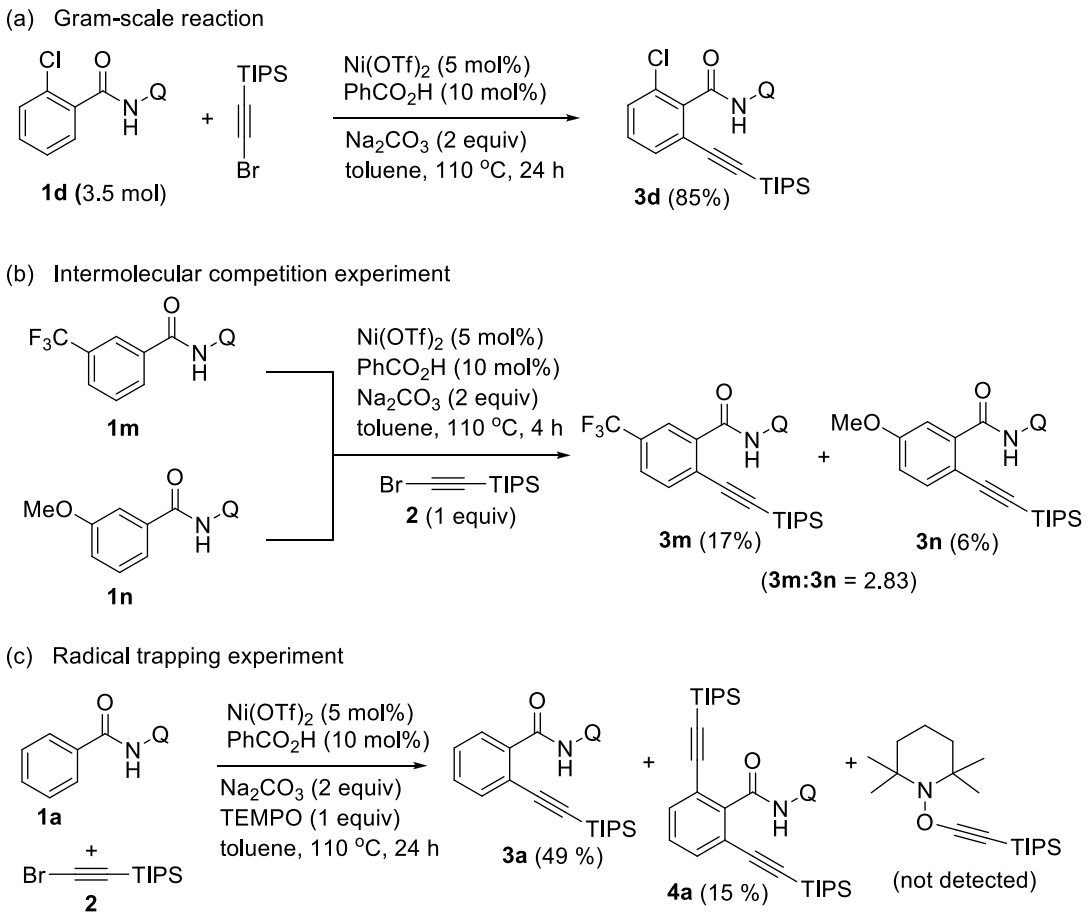


[a]Reaction conditions: **1** (0.1 mmol), catalyst (5 mol%), $PhCO_2H$ (10 mol%), **2** (0.3 mmol), Na_2CO_3 (2 equiv), and toluene (1 mL) at 110 °C for 24 hrs under argon. [b]Isolated yield.

When *meta*-substituted benzamides were used, the C-H alkynylation proceeded selectively at the less hindered position, providing the 1,2,5-trisubstituted amides with high regiocontrol (Table 2A.2).

2A.2.3 Mechanistic study

We have also successfully shown the scalability of this catalytic protocol under standard conditions to prepare 1.38 g of **3d** (Scheme 2A.2). A competition experiment with a different electronic substituent (*m*-CF_3 (**1p**) *vs* *m*-OCH_3 (**1q**); Scheme 2A.2b) revealed that the reaction favours the electron-withdrawing group. This finding showed that the acidity of the *ortho* C-H bond is important and the cleavage of the *ortho* C-H bond may experience a concerted metalation-deprotonation (CMD) mechanism. A similar trend also was observed in the previously reported palladium-catalyzed alkynylation reaction.[4o] To further gain some insights into the active catalytic species (Ni(II) *vs* Ni(0); Table 2A.1) involved in this C(sp^2)-alkynylation reaction, a series of product distribution studies were performed under standard conditions.[21] These studies clearly indicate that nickel(II) is the actual key catalytic species and not the nickel(0). In case of, Ni(0) salt (Table 2A.1, entry 10), the nickel(0) is oxidized to Ni(II) by the (triisopropylsilyl)ethynyl bromide under the reaction conditions and leading to the formation of (triisopropylsilyl)acetylene (**11**) *via* protonation and a self-coupled product 1,4-bis(triisopropylsilyl)buta-1,3-diyne (**12**) demonstrating that the actual catalytically active species is Ni(II) (Scheme 2A.4). Furthermore, performing the reaction in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under standard conditions, the reaction was not inhibited, and no *O*-alkynylated-TEMPO product also was detected, indicating that the single-electron transfer (SET) in this reaction could be ruled out (Scheme 2A.2c). Notably, alkynylation reaction progressed smoothly without the use of an oxidant.

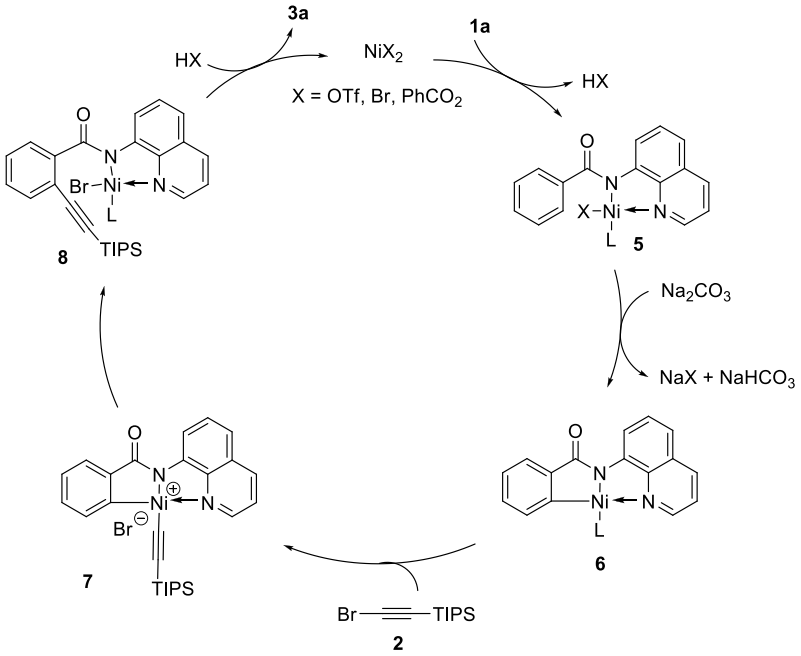


Scheme 2A.2. Mechanistic experiments.

2A.2.4 Plausible mechanism

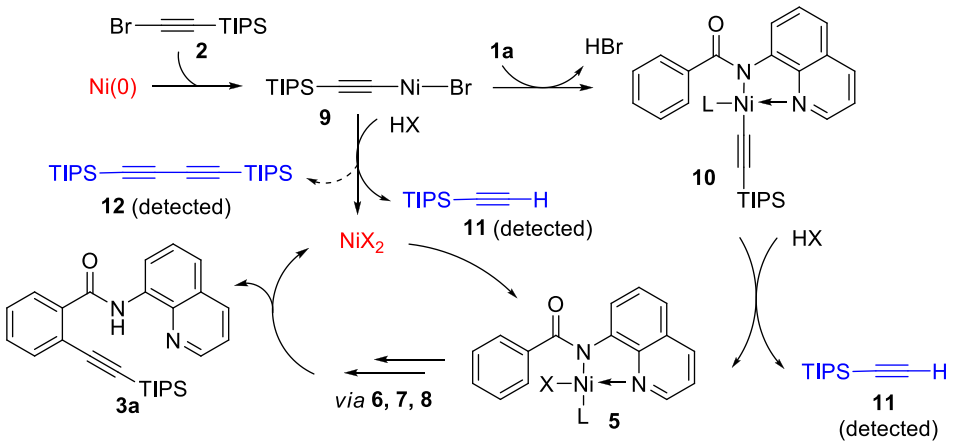
As shown in Scheme 2A.3, the coordination of the amide **1a** to the Ni(II) followed by ligand exchange with HX generation gives the complex **5**. This is because 8-aminoquinoline has a more acidic NH bond, which facilitates ligand exchange (promoted by a base). The complex **5** then undergoes cyclometalation to generate **6**, probably *via* a concerted metalation-deprotonation mechanism. The oxidative addition of TIPS-alkynyl bromide **2** leads to the formation of intermediate **7**. This is followed by a reductive elimination to give intermediate **8**, which is then protonated to afford the final alkynylated product with the regeneration of the active Ni(II) species. Surprisingly, other less hindered alkynyl halides (1-iodo-2-(trimethylsilyl)acetylene and (bromoethynyl)benzene) were not reactive, presumably a strong coordination of the alkyne moiety with the nickel center and thus may prevent the oxidative addition step, the amide-linked 8-aminoquinoline

directing group can be easily removed using previously reported strategy (Scheme 2A.5).[4o]



Scheme 2A.3 A plausible mechanism for the Ni(II)-catalyzed *ortho*-alkynylation of benzamides (**1a**) with **2**.

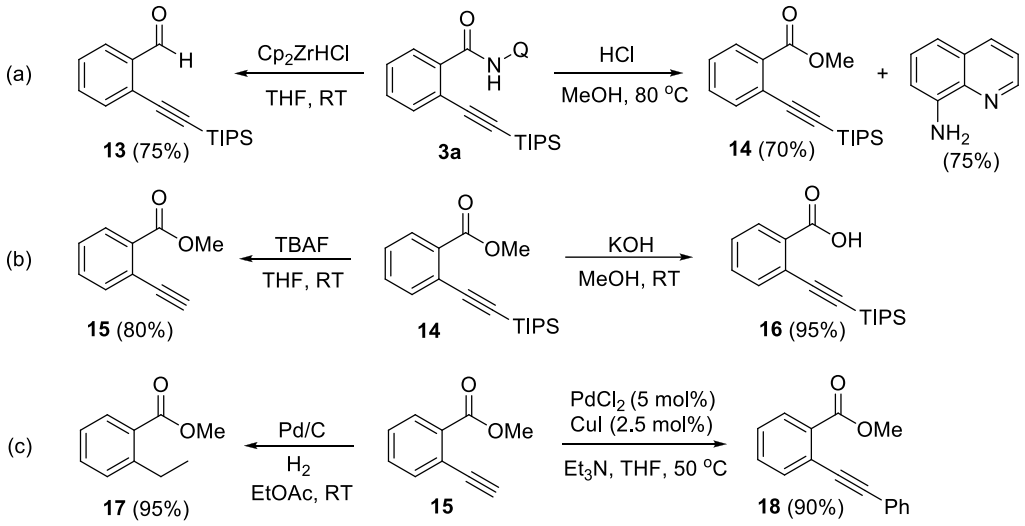
In the case of the Ni(0) catalyst, the reaction of the Ni(0) complex with **2** to form the oxidative addition product TIPS−Ni−Br (**9**) which can react with the benzamide **1a** and generates the Ni(II) complex **10**. This is followed by ligand exchange with HX gives the complex **5** with the formation of (triisopropylsilyl)acetylene (**11**) or the intermediate **9** can react with HX to generate catalytically active Ni(II) species with the generation of **11**. Alternatively, **9** can also give a self-coupled product 1,4-bis(triisopropylsilyl)buta-1,3-diyne (**12**) with the generation of a Ni(II) complex. Both the products (**11** and **12**) were experimentally observed under standard conditions (Scheme 2A.4).



Scheme 2A.4 Formation of Ni(II) from Ni(0) and identification of intermediates.

To further broaden the synthetic utility of this alkynylated product, several interesting organic transformations of **1a** were carried out (Scheme 2A.5).

2A.2.5 Diversification of alkynylated product



Scheme 2A.5 Removal of directing group and synthetic utility of alkynylated amide.

2A.3 Conclusion

In the present chapter 2A, we have reported a mild and regioselective nickel-catalyzed direct alkynylation of C(sp^2)-H bonds of amides using commercially available, inexpensive 8-aminoquinoline as a removable bidentate directing group.

Diverse halide substituted benzamides were selectively alkynylated under our conditions where as a synthesis of such compounds using the traditional approach, "Sonogashira coupling" is very difficult and rather scare. The present *ortho*-alkynylation has a broad substrate scope as well as functional group tolerance and can be scaled up.

2A.4 Experimental Section

2A.4.1 Synthesis of starting materials

All amides bearing 8-aminoquinoline moiety were prepared by the reaction of the corresponding acid chlorides with 8-aminoquinoline.[22, 23] (Bromoethynyl)triisopropylsilane (**2**, CAS 111409-79-1) was prepared by previously reported $AgNO_3$-catalyzed bromination of (triisopropylsilyl)acetylene with *N*-bromosuccinimide.[24]

2A.4.2 General procedure for the Ni(II)-catalyzed *ortho*-C-H alkynylation

To an oven-dried 10 mL screw-capped vial, *N*-(quinolin-8-yl)benzamide **1a** (0.1 mmol), (bromoethynyl)triisopropylsilane **2** (0.2 mmol), $Ni(OTf)_2$ (5 mol%), benzoic acid (10 mol%), Na_2CO_3 (0.2 mmol) and toluene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 24 hrs at 110 °C (reflux temperature of toluene) followed by cooling to room temperature. The mixture was filtered through a celite pad and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired alkynylated products.

2A.4.3 Gram-scale *ortho*-C-H alkynylation

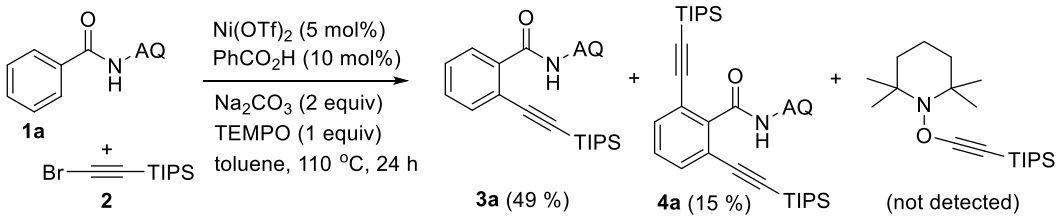
To an oven-dried 20 mL screw-capped vial, 2-chloro-*N*-(quinolin-8-yl)benzamide **1d** (987 mg, 3.5 mol), (bromoethynyl)triisopropylsilane **2** (1820 mg, 7 mol), $Ni(OTf)_2$ (62 mg, 5

mol%), benzoic acid (42 mg, 10 mol%), Na_2CO_3 (735 mg, 7 mol) and toluene (10 mL) were added under a gentle stream of argon. The mixture was stirred for 24 hrs at 110 °C (reflux temperature of toluene) followed by cooling to room temperature. The mixture was filtered through a celite pad and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc = 10/1) the yield of desired mono alkynylated product **3d** (1.377 g; 85%).

2A.4.4 Mechanistic investigation

2A.4.4a Radical Trapping Experiment

To an oven-dried 5 mL screw-capped vial, *N*-(quinolin-8-yl)benzamide **1a** (0.3 mmol), (triisopropylsilyl)ethynyl bromide (0.9 mmol), TEMPO (0.3 mmol), $Ni(OTf)_2$ (5 mol %), $PhCO_2H$ (10 mol%), Na_2CO_3 (0.6 mmol) and toluene (1 mL) were added under Ar. The mixture was stirred for 24 hrs at 110 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the alkynylated products **3a** and **4a** with isolated yield of 49% and 15% respectively along with 18% recovery of amide **1a**.



2A.4.4b Product Distribution Studies: Product Distribution by Ni(0)

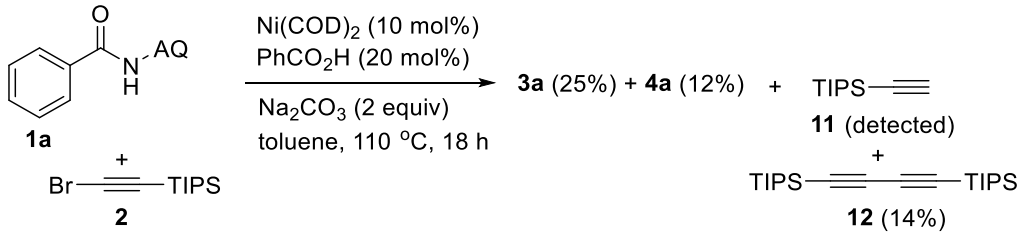
(a) To an oven-dried 5 mL screw-capped vial, *N*-(quinolin-8-yl)benzamide **1a** (0.3 mmol), (triisopropylsilyl)ethynyl bromide (0.9 mmol), $Ni(cod)_2$ (10 mol%), $PhCO_2H$ (20 mol%), Na_2CO_3 (0.6 mmol) and toluene (1 mL) were added under argon atm. The mixture was stirred for 18 hrs at 110 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated. The yields of (triisopropylsilyl)acetylene (**11**) and 1,4-bis(triisopropylsilyl)buta-1,3-diyne (**12**) were determined by GC. And the self-coupled product (**12**) was isolated (~10%; and the GC yield is 14%).

GC programming:

GC Column – HP-5 (30m x 0.25mm x 0.25mm); Injector temperature – 280 ^oC; Detector temperature – 280 ^oC; Column flow – 1.0 mL/min; Carrier gas – Nitrogen gas; Split Ratio – 10:1

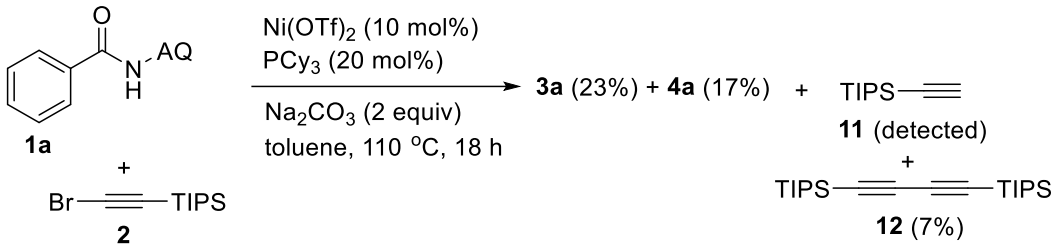
(80 ^oC hold for 5 min, heated up to 280 ^oC with ramping rate 10 ^oC/min)

(Triisopropylsilyl)acetylene (**11**) R_t: 5.201 min, and 1,4 bis(triisopropylsilyl)buta-1,3-diyne (**12**) R_t: 11.099 min).



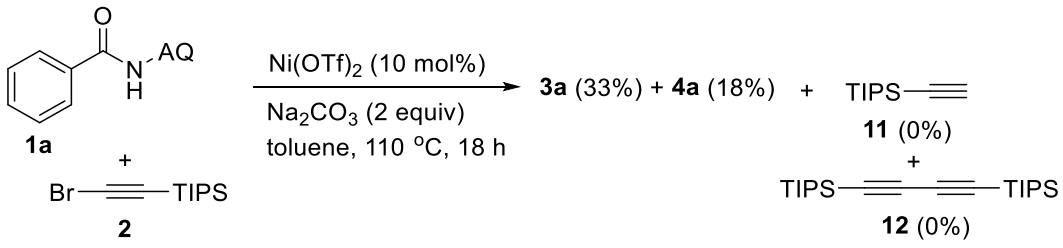
(b) To an oven-dried 5 mL screw-capped vial, *N*-(quinolin-8-yl)benzamide **1a** (0.3 mmol), (triisopropylsilyl)ethynyl bromide (0.9 mmol), $Ni(OTf)_2$ (10 mol%), PCy_3 (20 mol%), Na_2CO_3 (0.6 mmol) and toluene (1 mL) were added under Ar. The mixture was stirred for 18 hrs at 110 °C followed by cooling to room temperature. The solution was filtered

through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated. The yields of (triisopropylsilyl)acetylene (**11**) and 1,4-bis(triisopropylsilyl)buta-1,3-diyne (**12**) were determined by GC.



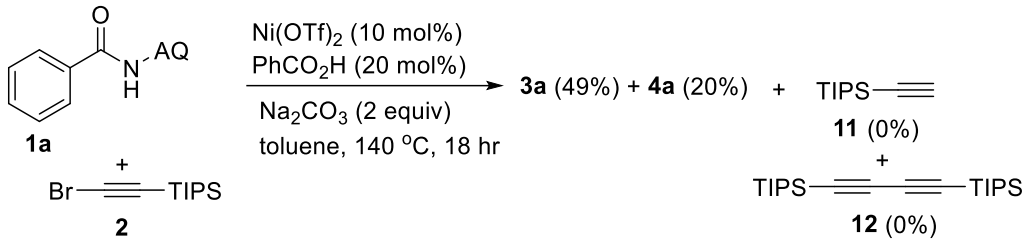
2a.4.4c Product Distribution by Ni(II)

(a) To an oven-dried 5 mL screw-capped vial, *N*-(quinolin-8-yl)benzamide (0.3 mmol), (triisopropylsilyl)ethynyl bromide (0.9 mmol), $Ni(OTf)_2$ (10 mol%), Na_2CO_3 (0.6 mmol) and toluene (1 mL) were added under argon atm. The mixture was stirred for 18 hrs at 110 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated. The products were analyzed by GC and GC-MS and no formation of either **11** or **12** were observed.



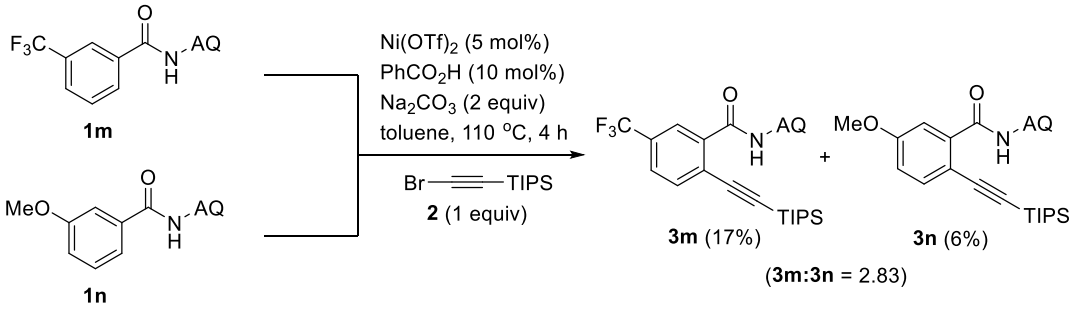
(b) To an oven-dried 5 mL screw-capped vial, *N*-(quinolin-8-yl)benzamide (0.3 mmol), (triisopropylsilyl)ethynyl bromide (0.9 mmol), $Ni(OTf)_2$ (10 mol%), $PhCO_2H$ (20 mol%), Na_2CO_3 (0.6 mmol) and toluene (1mL) were added under Ar. The mixture was stirred for 18 hr at 140 °C followed by cooling to room temperature. The solution was filtered through

a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated. The products were analyzed by GC, GC-MS and no formation of either **11** or **12** were observed.



2A.4.4d Competitive Experiment

To an oven-dried 5 mL screw-capped vial, benzamides **1m** (0.1 mmol) and **1n** (0.1 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.11 mmol), $Ni(OTf)_2$ (5 mol%), $PhCO_2H$ (10 mol%), Na_2CO_3 (0.2 mmol) and toluene (1 mL) were added under argon. The mixture was stirred for 4 hrs at 110 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated *in vacuo*. The products (**3m** and **3n**) and unreacted amides were isolated. Isolated yield of **3m** = 17%; **3n** = 6% Recovered yield of **1m** and **1n** are 76% and 91% respectively.



2A.5. Diversification of product

2A.5.5a Synthesis of 13

Under argon atm **3a** (100 mg, 0.23 mmol), Cp_2ZrHCl (0.46 mmol), and THF (2 mL) were charged to a 25 mL Schlenk tube. The reaction mixture was stirred at room temperature for 6 hrs before carefully being quenched by saturated ammonium chloride at 0°C. After being extracted with CH_2Cl_2 (3 × 25 mL), the combined organic extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford **13**.

2A.5.5b Synthesis of 14

To an oven-dried 5 mL screw-capped vial, alkynylated amide **3a** (100 mg, 0.23 mmol) and 1.25 M HCl in MeOH (3 mL) were added under a gentle stream of argon. The mixture was stirred for 24 hrs at 80 °C followed by cooling to room temperature. The mixture was concentrated *in vacuo* and EtOAc (15 mL) and saturated aq. $NaHCO_3$ (10 mL) were then added. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in *in vacuo*. The residue was purified by column chromatography on silica gel to afford **14**.

2A.5.5c Synthesis of 15

14 (50 mg, 0.15 mmol) was dissolved in THF (2.8 mL) and TBAF (1.0 M in THF, 0.45 mL) were then added at room temperature. The reaction progress was monitored by TLC. The mixture was concentrated *in vacuo*. The residue was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The obtained crude product was purified by column chromatography to afford the desired terminal alkyne **15**.

2A.5.5d Synthesis of 16

In a 25 mL of schlenk tube, **14** (50 mg, 0.15 mmol), KOH (0.3 mmol), and MeOH (1 mL) were added. The reaction mixture was stirred at room temperature for 1 h. Then the reaction was quenched by addition of ice-cold water. The aqueous portion was acidified to *p*H = 2 with 6 N hydrochloric acid and extracted with diethyl ether. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The desired carboxylic acid (**16**) was obtained after drying under vacuum and characterized by ^{1}H NMR.

2A.5.5e Synthesis of 17

To an oven-dried 100 mL Fischer-porter tube, **15** (50 mg, 0.31 mmol), Pd/C (5 mol%) and EtOAc (1 mL) were added and pressurized with H_2 gas (2 atm). The mixture was stirred for 6 hrs at room temperature. The mixture was filter through celite and concentrated *in vacuo* to afford the desired **17**.

2A.5.5f Synthesis of 18

Under argon atm **15** (100 mg, 0.3 mmol), iodobenzene (0.4 mmol), $PdCl_2$ (5 mol%), CuI (2.5mol%), Et_3N (0.9 mmol), and THF (2 mL) were charged to a 25 mL Schlenk tube. The reaction mixture was stirred at 50 °C for 6 hrs. The mixture was filter through celite and concentrated *in vacuo*. The obtained crude product was purified by column chromatography to afford **18**.

(i) For update data of all newly synthesized compounds, see Appendix A.

(ii) For copy of ^{1}H and ^{13}C NMR (only selected compounds) see Appendix B

2A.5 References

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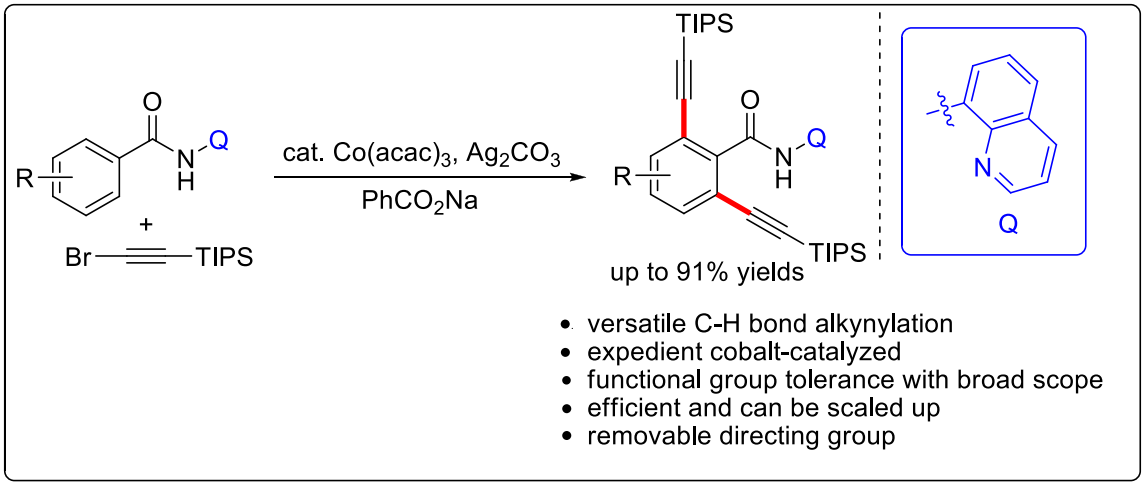
Chapter 2B

Cobalt Catalyzed Bis-Alkynylation of Amides *via* Double C-H Bond Activation

The first example of cobalt-catalyzed selective bis-alkynylation of amides *via* double C-H bond activation with the directing assistance of a removable bidentate auxiliary is describe in this chapter. The developed alkynylation strategy is simple, efficient and possesses various functional group tolerances including ether, amine, halides, and heterocyclic motifs. The reaction can be scaled up under mild conditions.



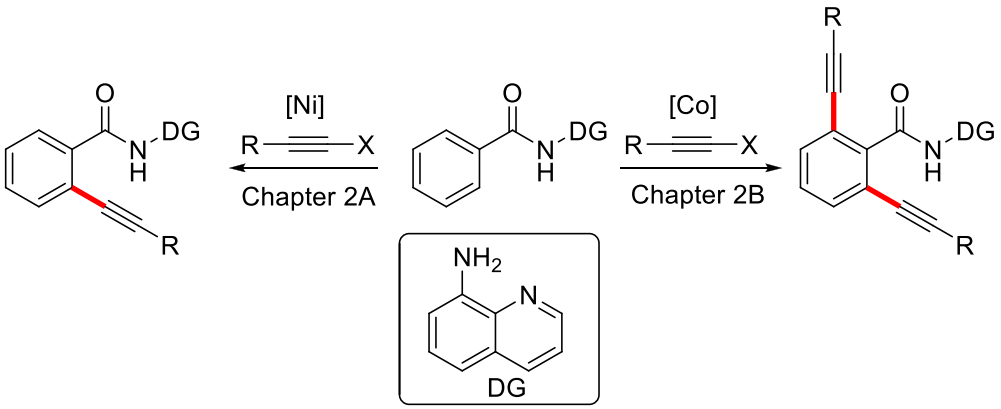
Vinod G. Landge *et al. Org. Lett.*, 2016, *18*, 812 – 815.

2B.1 Introduction

Transition-metal catalyzed direct functionalization of the inert C-H bond has emerged as a powerful strategy for the straightforward synthesis of value-added products with great step-economy and low waste production. Over the past decades, considerable efforts have been dedicated towards catalysts based upon precious metals such as Pd, Ru, Rh and Ir.[1] The replacement of expensive noble metal catalysts by utilizing economical, and environmentally-benign first-row transition-metal catalysts is an important paradigm in chemical synthesis. In this regard, earth-abundant first-row late transition metals have been intensely used in C-H bond activation strategy to emulate the selectivity and reactivity of precious-metal catalysts and thus, broaden the scope and practical viability.[2] However, their successful application in C-H bond functionalizations still remains at an early stage and can make it difficult to envisage and control catalytic reactivity, as they have a propensity to participate in one electron chemistry as opposed to classical two electron transformation ubiquitous in the second- and third-row transition-metals.

Alkynes are an exceptionally versatile functional group and are ubiquitous in pharmaceuticals, material science, and other functional compounds.[3] Thus, the development of an efficient strategy for the construction of alkynyl scaffolds is a key motivation in contemporary science and is usually achieved with the Sonogashira cross-coupling reaction between an aryl halide and a terminal alkyne.[4] However, the complementary approach, ‘‘inverse Sonogashira coupling’’ involving the direct alkynylation of inert aryl C-H bonds with easily accessible alkynyl halides, is very attractive and highly desirable in organic synthesis. In this context, alkynylation of unactivated arenes with the assistance of different directing groups has been developed as an efficient protocol to construct C(sp^2)-C(sp) bonds, which was mainly accomplished by Pd,[5a-d] Ru,[5e] and Rh-catalysts[5f-g] (see Chapter 1, Schemes 1.16, 1.17, and 1.24). A copper-mediated alkynylation of arenes assisted by bidentate amide-oxazoline and PIP (2-pyridinyl isopropyl) directing groups has been independently reported by Yu,[6a] and Shi,[6b] demonstrating the significant potential of inexpensive, first-row transition-metals in C(sp^2)-alkynylation; however, these transformations required a stoichiometric amount of copper salts. More recently, Shi,[7a-b] Li,[7c] and our group[7d] have independently developed nickel(II)-catalyzed alkynylation of arenes with the directing assistance of bidentate auxiliary[2f, 8] (see Chapter 1, Scheme 1.23). During the last decade, cobalt catalysts in various oxidation states have been recognized as simple, efficient and

increasingly viable catalysts for the C-H bond functionalization.[2d,2h-i,2k-l,9] Noteworthy works from the research groups of Kanai,[10] Nakamura,[11] Daugulis,[12] Glorius,[13] Yoshikai,[14] Song,[15] Ackermann,[16] Chang,[17] Ellman,[18] Sundararaju[19] and others[20] demonstrated the high potential of cobalt catalysts in C-H bond activation reactions. A recent report from Shi[20c] and Ackermann[16g] on Cp*Co(III)-catalyzed C(sp^2)-alkynylation of pyrimidin-2-yl)-1*H*-indoles with hypervalent iodine(III) reagents and 1-bromoalkyne (see Chapter 1, Scheme 1.18), respectively prompted us to disclose our first report on a simple, efficient, air-stable, cobalt(III)-catalyzed C(sp^2)-alkynylation of amides with the directing assistance of a removable 8-aminoquinoline in this chapter. The present alkynylation strategy has a broad substrate scope, functional group tolerance, and can be scaled up under mild conditions. Remarkably, halide groups could be reserved under our reaction conditions and thus, extend the spectrum to further modification of the products, wherein synthesis of halide-substituted alkyne derivatives using the classical approach, "Sonogashira coupling" is extremely difficult. In our previous chapter 2A, we described nickel-catalyzed selective mono-alkynylation of amides. However, in the present chapter 2B, we disclose an efficient, highly selective cobalt-catalyzed bis-alkynylation of amides.



Scheme 2B.1 Alkynylation of amides using nickel and cobalt catalysts.

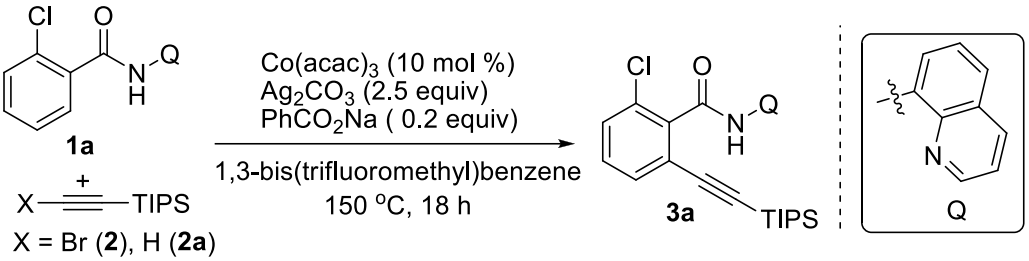
2B.2 Results and Discussion

2B.2.1 Optimization of reaction condition

Optimization studies on the *ortho* C-H bond alkynylation are summarized in Table 2B.1. We began our investigation using 2-chloro-*N*-(quinolin-8-yl)benzamide (**1a**) as a model

substrate and (triisopropylsilyl)ethynyl bromide **2** as a coupling reagent in presence of $Co(acac)_3$ (10 mol%), $PhCO_2Na$ (0.2 equiv), and Ag_2CO_3 as oxidant in toluene heated at 150 °C (bath temperature) for 18 h to yield the expected product **3a** in 31% isolated yield

Table 2B.1. Optimization of the reaction conditions.[a]



entry	reaction conditions	Yield (%)[b]
1	toluene used a solvent	31
2	PhF used a solvent	43
3	1,4-dioxane used a solvent	n.r.
4	standard conditions (using **2**)	80
5	without $PhCO_2Na$	52
6	NaOAc instead of $PhCO_2Na$	47
7	without Ag_2CO_3	6
8	AgOAc instead of Ag_2CO_3	55
9	$AgSbPF_6$ instead of Ag_2CO_3	n.r.
10	at 80 °C	28
11	without [Co] cat	n.r.
12	$Co(OAc)_2$ used as [Co] source	63
13	$CoCl_2$ used as [Co] source	Trace
14	$CoBr_2$ used as [Co] source	Trace
15	$[Cp^*Co(C_6H_6)][PF_6]_2$	n.r.
16	standard conditions (using **2a**)	28

[a]Reaction conditions: Condition A: **1a** (0.1 mmol), $Co(acac)_3$ (0.01 mmol), Ag_2CO_3 (0.25 mmol), **2** (0.12 mmol), sodium benzoate (0.02 mmol), and 1,3-bis(trifluoromethyl)benzene (1 mL) heated at 150 °C for 18 h under argon atm. [b]Isolated yields.

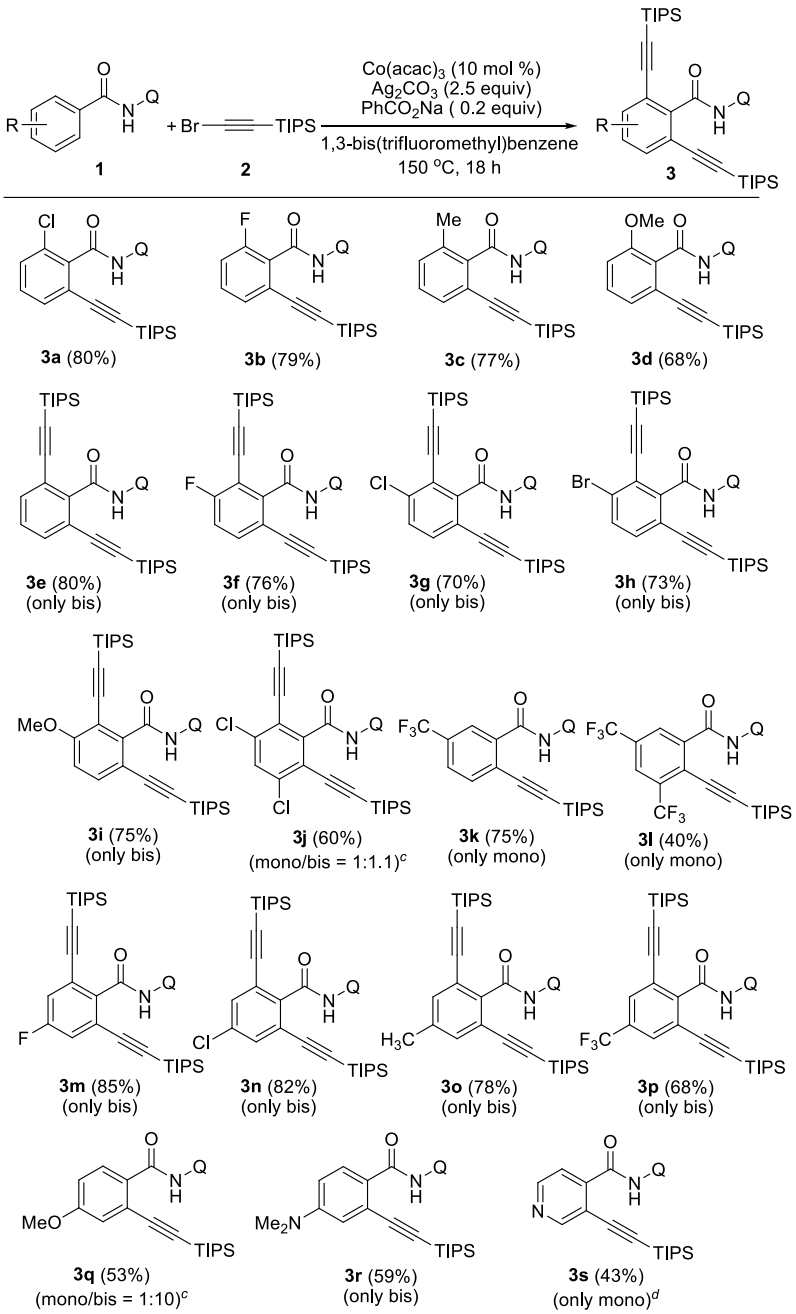
(Table 2B.1, entry 1). The solvent dependency of the same reaction was carried out (Table 2B.1, entries 1-4) and we found that the reaction proceeds efficiently in 1,3-bis(trifluoromethyl)benzene compared to other solvents with the isolated yield of **3a** in 80% (Table 2B.1, entry 4).[21] Notably, the efficiency of the reaction was significantly affected in the absence of $PhCO_2Na$ (Table 2B.1, entry 5) and clearly revealed the coordination of the 8-aminoquinolylamide to the cobalt-complex followed by a ligand exchange has been accelerated by the base.[22] By lowering the temperature, we obtained the product in lower yield (Table 2B.1, entry 10) and no reaction was observed in the absence of the cobalt catalyst (Table 2B.1, entry 11). Among a variety of different cobalt complexes, $Co(acac)_3$ proved to give optimal results (Table 2B.1, entries 4, 12−15). Gratifyingly, ethynyltriisopropylsilane (**2a**) was also effective for this alkynylation reaction and gave **3a** in lower yield (28%) under optimal conditions (Table 2B.1, entry 16). Notably, no (or trace) alkynylation was observed in the absence of an oxidant.[23]

2B.2.2 Scope of amides

With an optimized catalytic system in hand (Table 2B.1), we set out to probe its versatility in the C(sp^2)-alkynylation of various substituted amides. The developed synthetic methodology is general and has a broad substrate scope. As shown in Tabel 2B.2, the present cobalt-catalyzed alkynylation is compatible with various benzamides containing an electron-rich or electron-deficient substituent, according the expected alkynylated products in good to excellent yields. Alkynylation of *ortho*-substituted benzamides (**1a-d**) contains a range of functional groups, such as alkyl, methoxy, fluoro, and chloro, survived and gave the mono-alkynylation products (**3a-3d**) in good yields (up to 80%). Bis-alkynylated amides are the precursors of conjugated polymers by oxidative coupling on catalysts such as with Cp*Ru catalyst, as the alkyne groups cannot interact intramolecularly. However, selective bis-alkynylation of unactivated C-H bonds of benzamide (1) through double C-H activation strategy is difficult and rather rare, as it often tends to afford a mixture of both mono- and bis-alkynylated amides. Gratifyingly, our opted condition gave bis-alkynylated product as a single product with complete selectivity (**3e-3i**, **3m-3p**, and **3r**). Notably, with 3-bromo-*N*-(quinolin-8-yl)benzamide (**1h**), the alkynylation occurred on a sterically hindered position and yielded bis-alkynylation as a major product in 60% isolated yield. However, the electron-deficient 3-(CF_3)-substituted amides (**1k-1l**) underwent the reaction smoothly and gave mono-

alkynation as a single product with moderate yields (**3k**-**3l**), and perhaps because of the combination of both steric hindrance (in case of **1l**) and strong electron deficiency.

Tabel 2B.2. Cobalt-catalyzed alkynylation of amides: Scope of amides.[a,b]

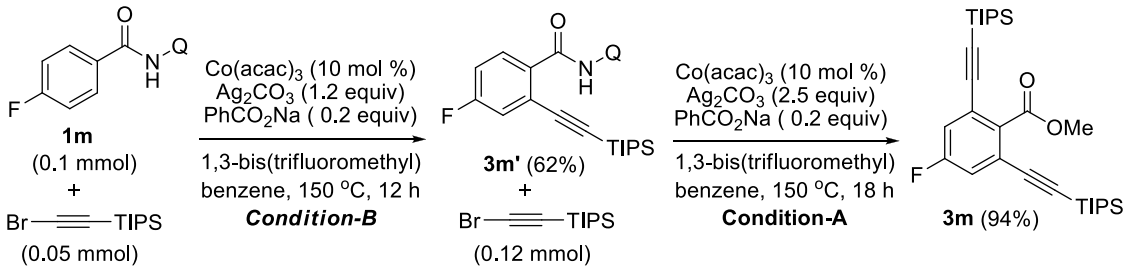


[a]Reaction conditions: **1** (0.1 mmol), $Co(acac)_3$ (0.01 mmol), Ag_2CO_3 (0.25 mmol), **2** (0.12 mmol (**1a**-**1d**) or 0.25 mmol (**1e**-**1s**)), $PhCO_2Na$ (0.02 mmol), and 1,3-bis(trifluoromethyl)benzene (1 mL) heated at 150 °C for 18 h under argon atm. [b]Isolated yields. [c]The ratio of mono- (a)/bis-alkynylation (b) products are based upon the individual isolated yields. [d]In the absence of $PhCO_2Na$.

[b]Isolatedyields. [c]The ratio of mono- (a)/bis-alkynylation (b) products are based upon the individual isolated yields. [d]In the absence of $PhCO_2Na$.

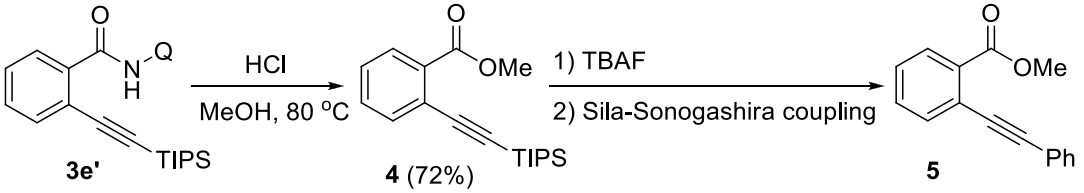
It is noteworthy that the synthetically valuable halide substituents could be reserved under our reaction conditions and can extend the spectrum to further modification of the products, wherein synthesis of halide-substituted alkyne derivatives using the classical approach, the Pd-catalyzed "Sonogashira coupling" is extremely difficult. In this regard, benzamides bearing halides such as chloro, bromo groups (**1a**, **1g-h**, **1j**, and **1n**) proceeded efficiently and yielded the corresponding alkynylated products in good yields under our catalytic conditions. To our delight, challenging heteroaromatic amide (**1s**) selectively gave the corresponding mono-alkynylated product in good yield (**3s** in 43% isolated yield) in the absence of $PhCO_2Na$.Selective mono-alkynylation and sequential bis-alkynylation were achieved successfully under conditions B and A respectively (Scheme 2B.2).

Scheme 2B.2 Sequential bis-alkynylation of **1m**.



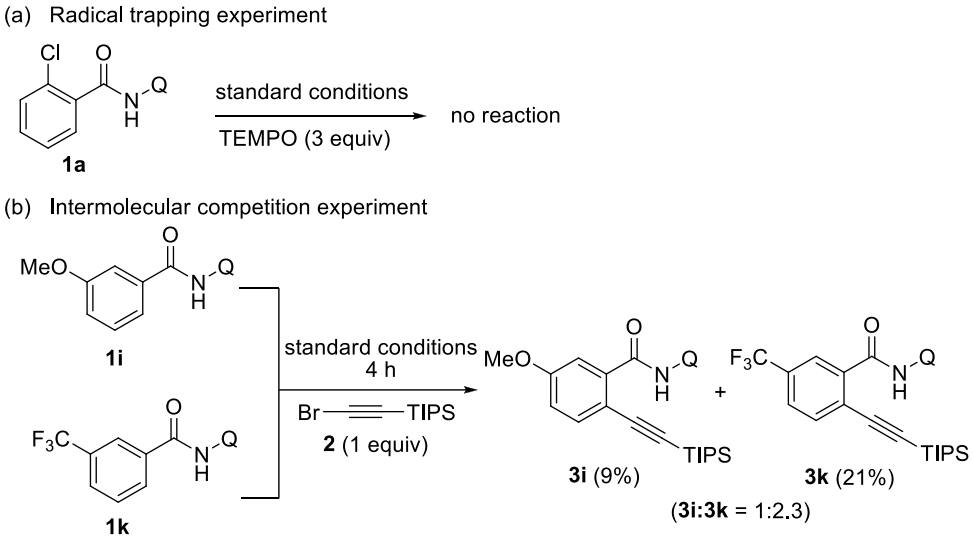
Condition-B: **1m** (0.1 mmol), $Co(acac)_3$ (0.01 mmol), Ag_2CO_3 (0.25 mmol), **2** (0.05 mmol), $PhCO_2Na$ (0.02 mmol), and 1,3-bis(trifluoromethyl)benzene (1 mL) heated at 150 °C for 18 h under argon atm.

The removal of the directing bidentate auxiliary (8-aminoquinonyl-group) was easily accomplished under mild reaction conditions.[7d] Subsequently, the chemoselective removal of the TIPS-group was achieved under standard reaction conditions, and further converted to a phenyl group to yield **5** in 72% overall yield through the Pd-catalyzedSila-Sonogashira coupling reaction (Scheme 2B.3).[24]



Scheme 2B.3 Diversification of alkynylated amides.

alkynylated product (**3a**) in 72% yield.[24] The reaction performed in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO; 3 equiv) and the reaction was completely inhibited, indicating that the radical reaction pathway could be involved in the catalytic cycle (Scheme 2B.4a). In addition, competitive experiments performed with electron-rich and electron-poor amide using (triisopropylsilyl)ethynyl bromide **2** showed that alkynylation is favoured with the electron-deficient substrate (Scheme 2B.4b).[25] This finding showed that the acidity of the *ortho* C-H bond is important. Similar trend also was observed in previously reported C(sp^2)-alkynylation.[7c-d] Importantly, the presence of the oxidant is essential for the success of the alkynylation, and no alkynylated products were observed when $AgSbF_6$ (Table 2B.1, entry 9) was used and indicating that the classical electrophilic-type C-H bond activation mechanism by the cationic cobalt(III) complex can be rolled out.[9,20b]

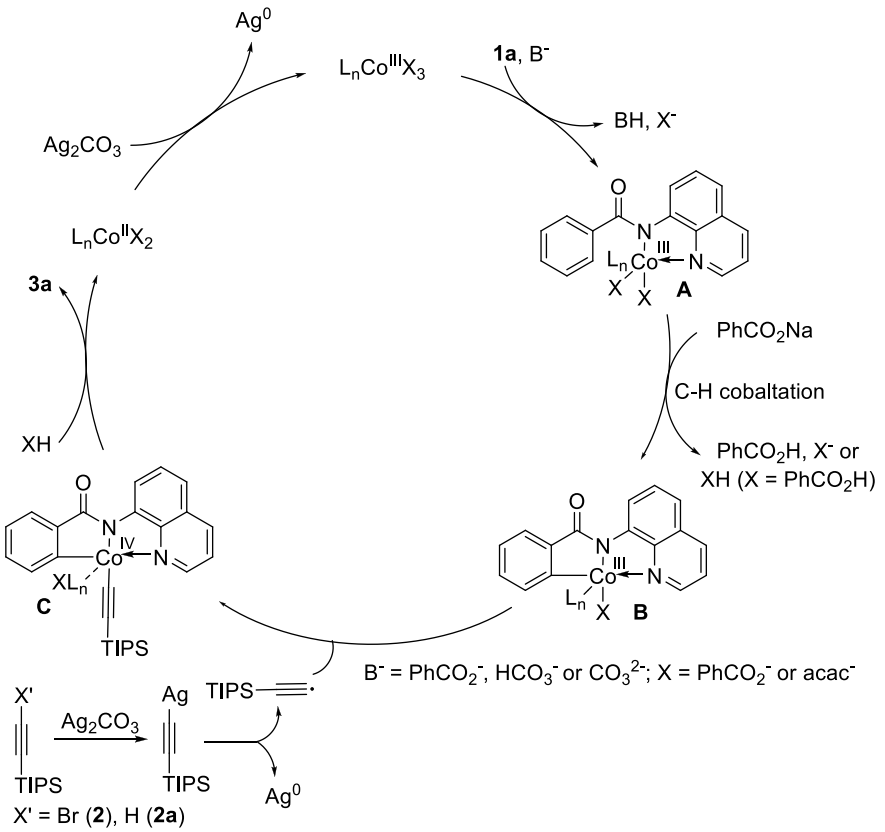


Scheme 2B.4 Mechanistic studies.

2B.2.4 Plausible mechanism

On the basis of these experiments and previous reports,[20b,25] a plausible catalytic cycle is outlined in Scheme 2B.5. The first step of the catalytic reaction is the coordination of the amide **1a** to the Co(III) followed by the base assisted or carboxylate assisted C-H bond cobaltation led to complex **B**. The attack of *in situ* generated alkyne radical into complex **B** gives the intermediate **C**, which undergoes the reductive elimination to give **3a** and generate the Co(II) species. The oxidation of Co(II) to Co(III) by silver salts further continues the catalytic cycles. Notably, ethynyltriisopropylsilane (**2a**) was also effective

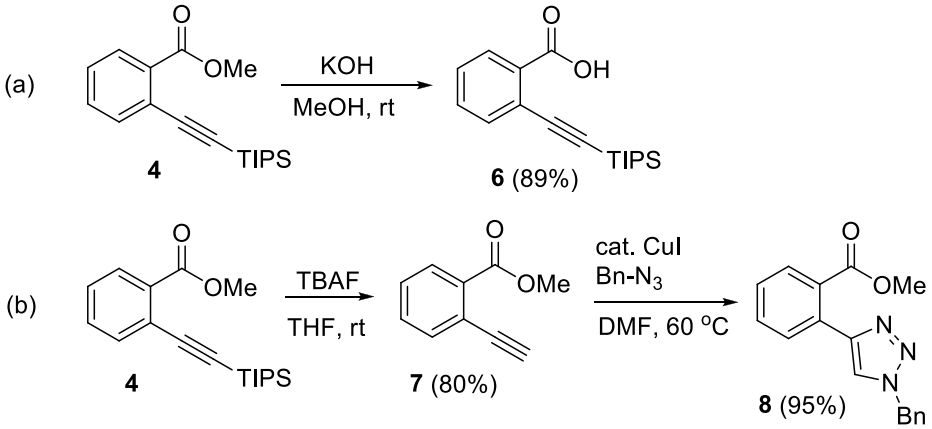
for this alkynylation reaction and yielded **3a** in lower yield (28%) under optimal conditions (Table 2B.1, entry 16).



Scheme 2B.5 Plausible mechanism.

2B.2.5 Diversification of alkynylated product

The synthetic utility of the versatile cobalt-catalyzed alkynylation was also demonstrated by further diversification of the products (Schemes 2B.3 and Scheme 2B.6).



Scheme 2B.6. Removal of directing group and click reaction of alkynylated amide.

2B.3 Conclusion

In conclusion, we have reported the first example of expedient cobalt-catalyzed selective bis-alkynylation of C(sp^2)-H bonds of amides through double C-H bond activation strategy using commercially available, inexpensive 8-aminoquinoline as a removable bidentate directing group. The present *ortho*-alkynylation has a broad substrate scope as well as functional group tolerance, and can thereby be scaled up in gram-scale synthesis.

2B.4. Experimental Section

2B.4.1 Synthesis of the starting materials

All amides bearing 8-aminoquinoline moiety were prepared by the reaction of the corresponding acid chlorides with 8-aminoquinoline.[26, 27]

2B.4.2 General procedure for the cobalt-catalyzed C(sp^2)-alkynylation

2B.4.2a (For compounds **1a-1c, 1p and 1q**)

To an oven-dried 10 mL screw-capped vial, amide **1** (0.1 mmol), (bromoethynyl)triisopropylsilane **2** (0.12 mmol), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (0.2 equiv) and bis(trifluoromethyl)benzene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 18 hrs at 150 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford **3**.

2B.4.2b (For compounds **3e-3s**)

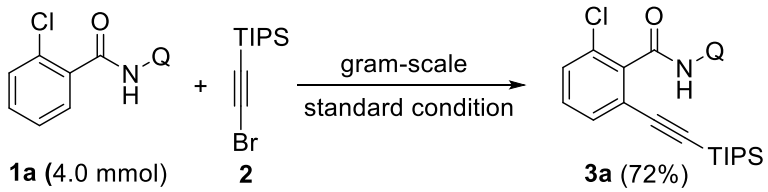
To an oven-dried 10 mL screw-capped vial, amide **1** (0.1 mmol), (bromoethynyl)triisopropylsilane **2** (0.25 mmol), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (0.25 equiv) and trifluoromethylbenzene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 18 hrs at 150 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The

residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford **3**.

2B.4.2c (For compounds **3m'**)

To an oven-dried 10 mL screw-capped vial, 4-fluoro-*N*-(quinolin-8-yl)benzamide **1m** (0.1 mmol), (bromoethynyl)triisopropylsilane **2** (0.05 mmol), $Co(acac)_3$ (10 mol%), Ag_2CO_3 (2.5 equiv), $PhCO_2Na$ (0.2 equiv) and bis(trifluoromethyl)benzene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 12 hrs at 150 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired alkynylated product **3m'**.

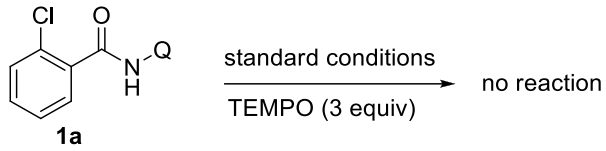
2B.4.3 Gram-scale synthesis



To an oven-dried 20 mL screw-capped vial, 2-chloro-*N*-(quinolin-8-yl)benzamide **1a** (1.13 g, 4.0 mmol), (bromoethynyl)triisopropylsilane **2** (1.25 g, 4.8 mmol), $Co(acac)_3$ (142 mg, 10 mol%), Ag_2CO_3 (2.76 g, 2.5 equiv), $PhCO_2Na$ (115 mg, 20 mol%) and 1,3-bis(trifluoromethyl)benzene (10 mL) were added under a gentle stream of argon. The mixture was stirred for 40 hrs at 150 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 10 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired alkynylated product **3a** (1.33 g, 72% yield).

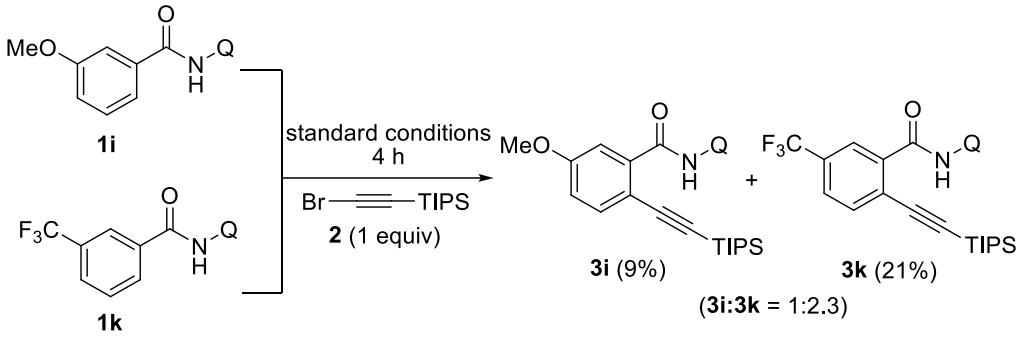
2B.4.4 Mechanistic investigation

2B.4.4a Radical Trapping Experiment



To an oven-dried 5 mL screw-capped vial, 2-chloro-N-(quinolin-8-yl)benzamide **1a** (0.3 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.36 mmol), TEMPO (0.9 mmol), $Co(acac)_3$ (10 mol %), Ag_2CO_3 (2.5 equiv), $PhCO_2Na$ (20 mol%) and 1,3-bis(trifluoromethyl)benzene (1 mL) were added under Ar. The mixture was stirred for 18 hrs at 150 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10 mL of dichloromethane. The filtrate was concentrated *in vacuo*. The complete starting material (**1a**) was recovered (~97%) from the crude reaction mixture.

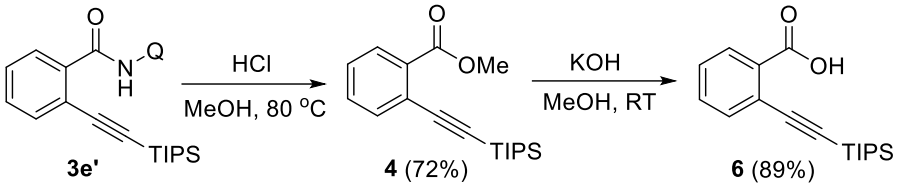
2B.4.4b Competitive Experiment



To an oven-dried 5 mL screw-capped vial, benzamides **1i** (0.1 mmol) and **1k** (0.1 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.1 mmol), $Co(acac)_3$ (10 mol%), Ag_2CO_3 (2.5 equiv), $PhCO_2Na$ (20 mol%) and 1,3-bis(trifluoromethyl)benzene (1 mL) were added under argon. The mixture was stirred for 4 hrs at 150 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with dichloromethane (3 x 5 mL). The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the alkynylated products **3i** (mono+bis) and **3k** with the isolated yields of 9% and 21% respectively.

2B.4.5 Synthetic application

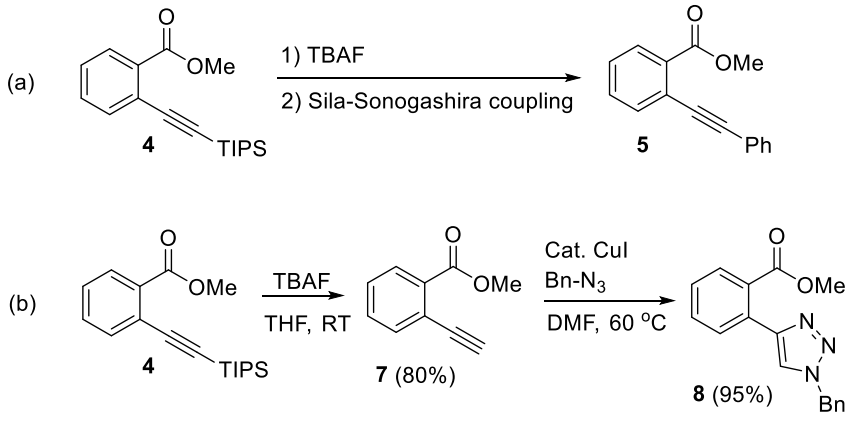
2B.4.5a Removal of directing group (Synthesis of *ortho*-alkynylated benzoic acid)



To an oven-dried 5 mL screw-capped vial, alkynylated amide **3e'** (99 mg, 0.23 mmol) and 1.25 M HCl in MeOH (3 mL) were added. The mixture was stirred for 24 hrs at 80 °C (bath temperature) followed by cooling to room temperature. The mixture was concentrated *in vacuo* followed by the addition of EtOAc (15 mL) and saturated aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford **4** (53 mg, 72% yield).

In a 25 mL of schlenk tube, **4** (50 mg, 0.16 mmol), KOH (0.3 mmol), and MeOH (1 mL) were added. The reaction mixture was stirred at room temperature for 1 hr. Then the reaction was quenched by addition of ice-cold water. The aqueous portion was acidified to *p*H = 2 with 6 N hydrochloric acid and extracted with diethyl ether. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The desired carboxylic acid (**6**) was obtained after drying under vacuum with the yield of 89% (43 mg).

2B.4.5b Diversification of alkynylated amides



Synthesis of 7

Compound **4** (50 mg, 0.16 mmol) was dissolved in THF (3 mL), and TBAF (1.0 M in THF, 0.45 mL) was then added at room temperature with constant stirring. The reaction progress was monitored by TLC. The mixture was concentrated *in vacuo*. The residue was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The obtained crude product was purified by column chromatography to afford the desired terminal alkyne **7** (21 mg, 80% yield).

Synthesis of 5

Under argon atm **7** (synthesized from compound **4** *via* desilylation) (48 mg, 0.3 mmol), iodobenzene (82 mg, 0.4 mmol), $PdCl_2$ (5 mol%), CuI (2.5 mol%), Et_3N (0.9 mmol), and THF (2 mL) were charged to a 25 mL Schlenk tube. The reaction mixture was stirred at 50 °C for 6 hrs. The mixture was filtered through celite and concentrated *in vacuo*. The obtained crude product was purified by column chromatography to afford **5** (64 mg, 90% yield).

Synthesis of 8

Under argon atm **7** (48 mg. 0.3 mmol, 1.0 equiv), CuI (5.9 mg, 10 mol %) and benzyl azide (41 mg, 0.3 mmol, 1.0 equiv) were dissolved in DMF (1 mL) and stirred at 60 °C for 16 hrs. After completion of the reaction saturated aq. NH_4Cl solution (5 mL) was added, and the mixture was extracted with dichloromethane (3 x 5 mL) and dried over anhydrous Na_2SO_4. After complete evaporation of the solvent, the obtained crude product was purified by column chromatography to afford **8** (83 mg, 95% yield).

(i) For update data of all newly synthesized compounds, see Appendix A.

(ii) For copy of ^{1}H and ^{13}C NMR (only selected compounds) see Appendix B

2B.5 References

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(21) Further screening using a common solvent, including apolar arenes (*o*-xylene and PhCl), or polar DMF, DMSO, DMA, DCE and CF_3CH_2OH proved ineffective in the C-H bond alkynylation.

(22) Other bases such as NaOAc, CsOAc, Li_2CO_3, Na_2CO_3, K_2CO_3 and Cs_2CO_3 proved ineffective and less formation (up to ~30%) of **3a** was observed under optimal conditions.

(23) Despite the use of economical cobalt catalysts often an expensive silver salt is required for reoxidation of Co(II) to Co(III) and *in situ* generation of alkynyl radical. Other oxidants such as Ag_2O, $AgSO_2CF_3$, AgOAc, Ag_3PO_4, $AgOC(O)CF_3$ did not improve the yield of the alkynylated products **3a** under optimal conditions.

(24) Compound **3e'** (Yield = 45%) was prepared under condition B.

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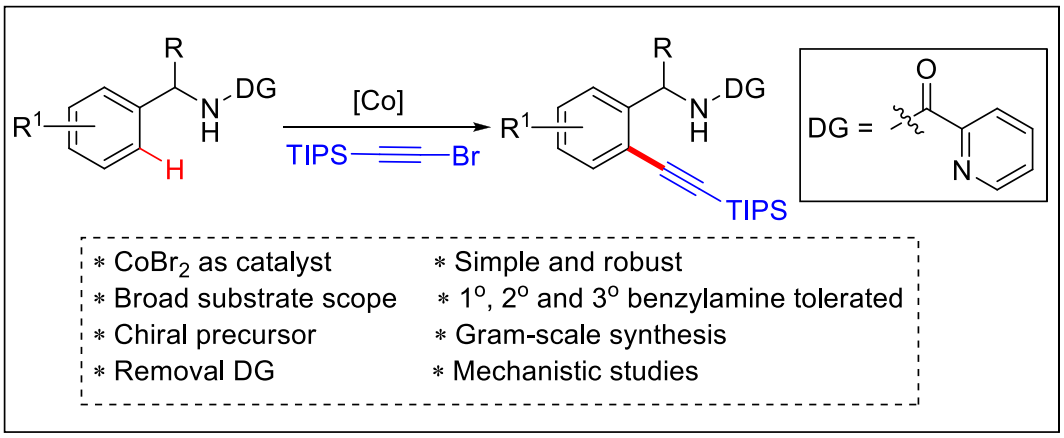
Chapter 3

Cobalt-Catalyzed C-H Alkynylation of Benzylamines

In this chapter, the first example of cobalt-catalyzed *ortho*-C-H bond alkynylation of benzylamines is reported. A simple, commercially available $CoBr_2$ was used as a cobalt source. The developed alkynylation strategy is robust, efficient and has a broad substrate scope including 1°, 2°, and 3° benzylamines. A mechanistic study revealed that rate of reaction is zero order with respect to the substrate, additive, and oxidant; nevertheless, depend on the catalyst.

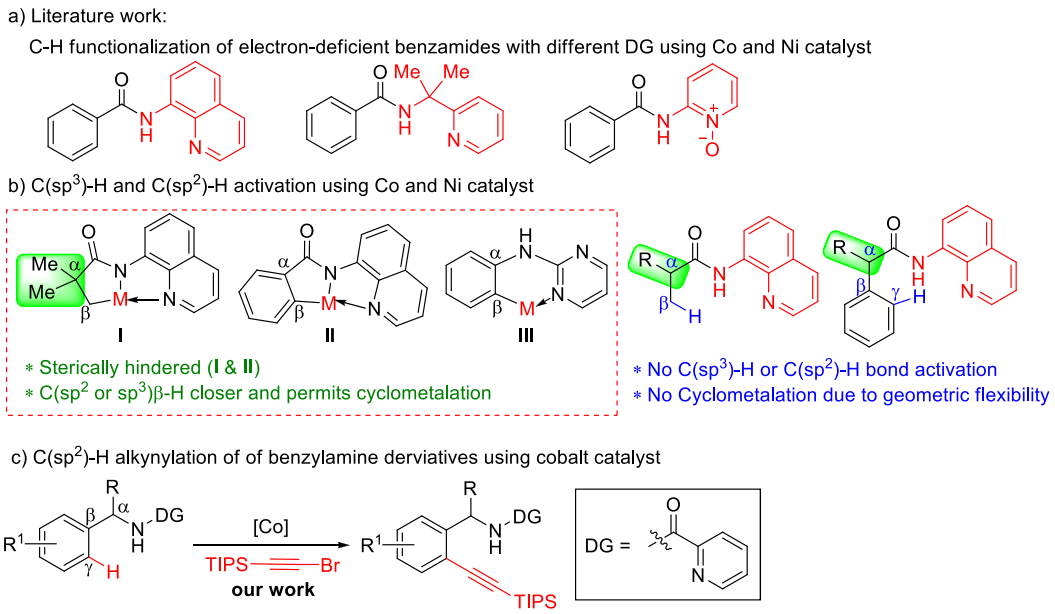


Vinod G. Landge *et al. Org. Lett.*, 2016, *18*, 5252 – 5255

3.1 Introducion

Transition-metal-catalyzed ubiquitous C-H bond activation circumvents the necessity of prefunctionalization of an organic molecule and has a great demand in chemical synthesis, pharmaceuticals and functional materials.[1] Particularly, C-H bond alkynylations have been identified as increasingly powerful alternatives to the the classical palladium-catalyzed cross-coupling reaction.[2] Until recently, a majority of C-H bond alkynylation strategy has relied on precious and less abundant 4d and 5d transition metals.[3] However, the development of catalysts based on the naturally more abundant, and economical first-row transition metals[4-6] for similar or better reactivity are still rare. On the other hand, after Daugulis's promising work[7] on bidentate directing-group assisted transition-metal- catalyzed activation of inert C-H bonds, several groups have been extensively exploited this strategy[8] (see Chapter 1,Scheme 1.11). It is well recognized that the bidentate directing-group stabilizes transition-metals in high oxidation states and able to deliver the active catalytic site to a proximal C-H bond, typically *via* the formation of a five- or a six-membered metallacycle intermediate and entail the C-H bond activation. In this context, the directing group assisted C-H bond activation of arenes catalyzed by inexpensive, benign first-row transition metals have gained considerable momentum with great potential applications to emulate the selectivity and reactivity of precious-metal catalysts.[9] In recent times, a notable progress in C-H bond functionalization being accomplished using air-stable, inexpensive cobalt-catalysts.[9m,10]

Despite notable efforts in a bidentate group directed C-H bond alkynylation catalyzed by cobalt(II)- and nickel(II)-based systems, previous reports have been limited to electron-deficient benzamide derivatives[4d-h,6c-d](see Chapter 1, Scheme 1.23).Moreover, Cp*Co(III)-catalyzed C_2-selective C-H bond alkynylation of indole derivatives was also reported using hypervalent iodine-alkyne reagents[6a] and bromoalkynes.[6b]However, the activation of *ortho*-C(sp^2)-H bond located further away from the coordinating functional group (or directing group; DG) remains a noteworthy challenge. To the best of our knowledge, there is no report on C-H bond activation of *ortho*-C(sp^2)-H bond ofbenzylamines catalyzed by first-row transition metals. This is due to the geometric flexibility of the substrate,and thus, the *ortho*-C(γ)-H bond fails to permit cyclometalation (Scheme 3.1b). Benzylamines constitute important synthetic precursors and are ubiquitous in agrochemical, peptide, pharmaceutical, and functional materials.[11]



Scheme 3.1 Directed-group assisted cobalt-catalyzed C-H bond activation.

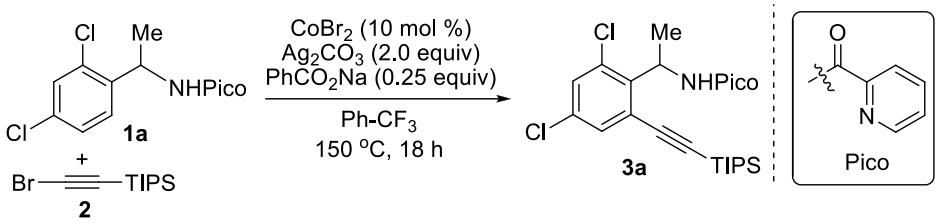
Various effective, practical methods have been developed to access benzylamines. Indeed, the stereochemistry at the benzylic position of α-substituted benzylamines can also be readily introduced using well-explored asymmetric synthesis technology. In this chapter, we disclose a versatile and efficient cobalt-catalyzed *ortho*-C(sp^2)-H alkynylation of benzylamine precursor with the directing assistance. The present cobalt-catalyzed alkynylation has a broad substrate scope and can be scaled up under mild conditions. Significantly, 1°, 2°, 3°, and enantiopure benzylamines were well tolerated.

3.2 Results and Discussion

3.2.1 Optimization of reaction condition

We began our cobalt-catalyzed *ortho*-C(sp^2)-H alkynylation of benzylamine precursor with an evaluation of a range of cobalt salt, oxidant, base, solvent, and temperature in the presence of *N*-(1-(2,4-dichlorophenyl)ethyl)picolinamide (**1a**) and (triisopropylsilyl)ethynyl bromide (**2**) as representative coupling partner (Table 3.1). Initially, the reaction of 1a and 2 in the presence of $Co(acac)_3$ (10 mol%), $PhCO_2Na$ (0.25 equiv), and Ag_2CO_3 as oxidant in trifluorotoluene heated at 150 °C (bath temperature) for 18 h to yield the expected product 3a in 41% isolated yield (Table 3.1, entry 1).

Table 3.1 Optimization of the reaction conditions.[a]



entry	reaction conditions	yield (%)[b]
1	$Co(acac)_3$ used as [Co] source	41
2	$Cp^*Co(CO)I_2$	n.r.
3	$[Cp^*Co(C_6H_6)][PF_6]_2$	n.r.
4	standard conditions	75 (69)[c]
5	Cobalt(II)oxalate	40
6	$Co(OAc)_2$ used as [Co] source	55
7	$CoCl_2$ used as [Co] source	65
8	$Co(acac)_2$ used as [Co] source	60
9	at 100 °C	32
10	without [Co] cat	n.r.
11	without Ag_2CO_3	6%
12	without $PhCO_2Na$	56%
13	$AgSbPF_6$ instead of Ag_2CO_3	n.r
14	NaOPiv instead of $PhCO_2Na$	51%
15	CF_3CH_2OH used as solvent	Trace

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.12 mmol), $CoBr_2$ (0.01 mmol), Ag_2CO_3 (0.20 mmol), sodium benzoate (0.025 mmol), and trifluorotoluene (1 mL) heated at 150 °C (bath temperature) for 18 h under argon atm. [b]Isolated yields. [c]Gram-scale synthesis. n.r. = no reaction

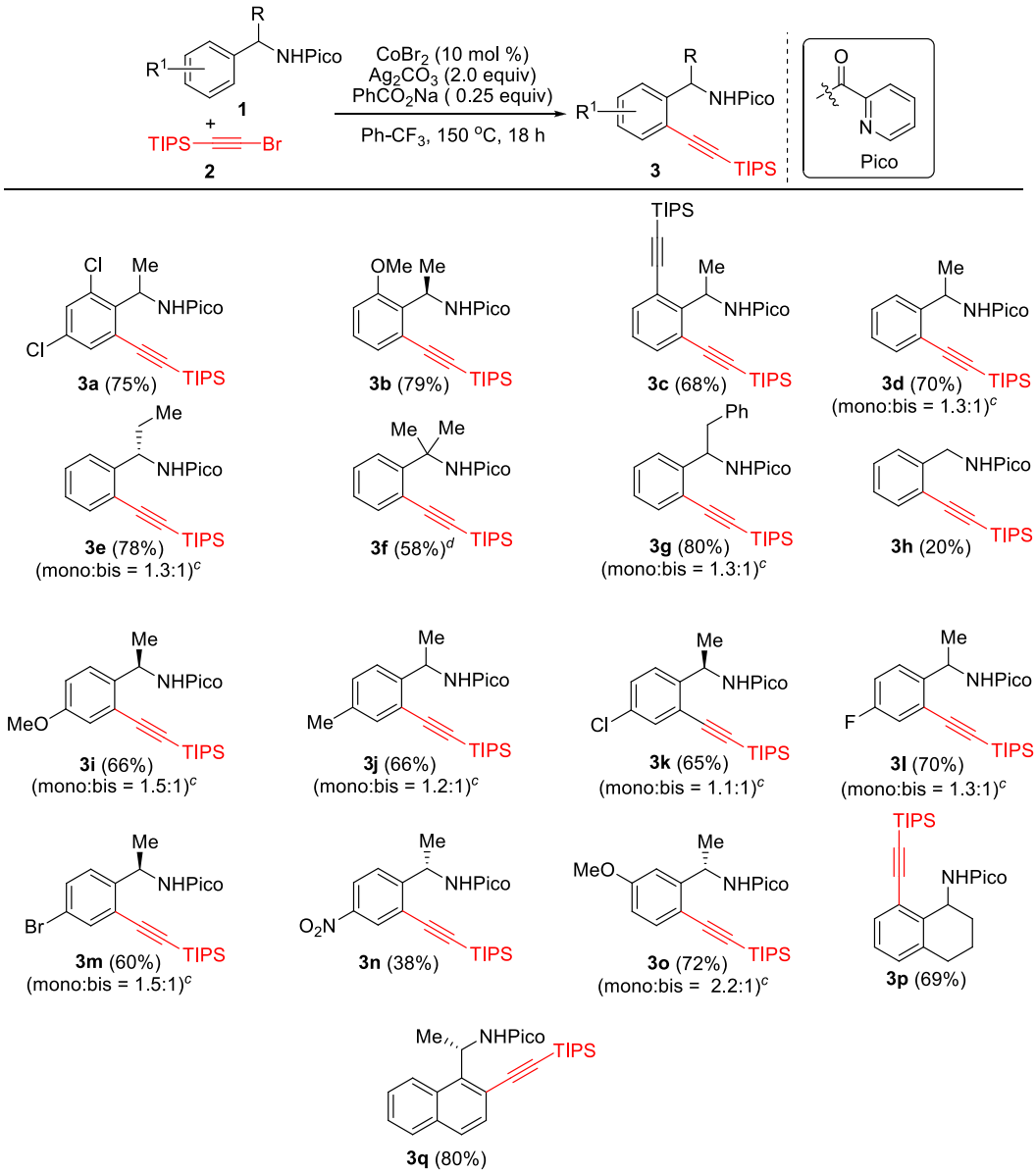
Among a variety of cobalt salt, $CoBr_2$ proved to give optimal results (Table 3.1, entries 3.1-8). The necessity of each of the key reaction components was demonstrated through a series of control experiments (Table 3.1, entries 9-12). By lowering the temperature from 150 °C to 100 °C, we obtained the product **3a** in lower yield (32%; Table 3.1, entry

9) and no reaction was observed in the absence of the cobalt catalyst (Table 3.1, entry 10). Notably, trace (~6%) amounts of C-H alkynylated product **3a** was observed in the absence of an oxidant (Table 3.1, entries 11 and 13).[12] The efficiency of the cobalt-catalyzed C-H bond alkynylation reaction was significantly affected in the absence of $PhCO_2Na$ (Table 3.1, entries 12 and 14) and evident that the coordination of the bidentate piconamide (DG) to the cobalt-complex followed by a ligand exchange has been accelerated by the (carboxylate) base.[13] The effect of solvent was also carried out (Table 3.1, entry 15) and we found that the reaction proceeds efficiently in trifluorotoluene. Other solvents such as DMA, DCE, and CF_3CH_2OH were found to be ineffective, and no (or trace) alkynylated product **3a** was observed under optimal conditions. The synthetic application of this new cobalt catalyzed C(sp^2)-H alkynylation strategy was further demonstrated through a gram-scale preparation of *ortho*-alkynylated benzylamine. As illustrated in Table 3.1 (entry 4), under the standard conditions, **1a** and **2** were smoothly converted to **3a** (1.1 g) in 69% isolated yield. This representative transformation helps manifest practical value that this method may offer for rapid and reliable access of *ortho*-alkynylated benzylamines under very mild reaction conditions.

With an optimized catalytic system in hand (Table 1), we set out to probe its versatility in the *ortho*-C(sp^2)-alkynylation of various substituted benzylamines. The developed synthetic methodology is general and has a broad substrate scope as well as functional group tolerance. As shown in Table 3.2, the present cobalt-catalyzed C-H activation strategy is compatible with various benzylamines containing an electron-rich and electron-deficient substituent, affording the expected alkynylated products in moderate to good yields. Various *ortho*-substituted benzylamines such as 2,4-dichloro, -OMe, and 1c are processed smoothly under our optimized conditions and gave the desired product in good yields (products 3a in 75%, 3b in 79% and 3c in 68% isolated yields).

3.2.2 Scope of benzylamines

Table 3.2. Cobalt-catalyzed *ortho*-C-H alkynylation of benzylamines.[a,b]



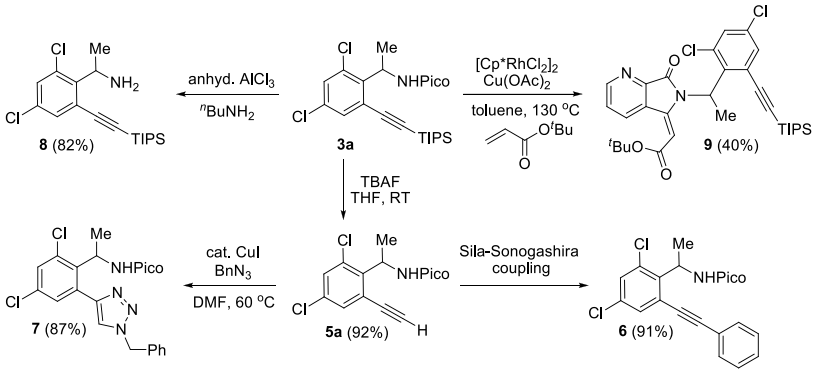
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol (**1a-1c** and **1p-1q**) or 0.25 mmol (**1d-1o**)), $CoBr_2$ (0.01 mmol), Ag_2CO_3 (0.20 mmol), $PhCO_2Na$ (0.025 mmol), and trifluoro toluene (1 mL) heated at 150 °C (bath temperature) for 18 h under argon atm. [b]Isolated yields. [c]The ratio of mono- (**3**)/bis-alkynylation (**4**) products are based upon the individual isolated yields. [d]0.05 mmol of **2** was used and yield based on **2**.

To our delight, diverse α-substituted benzylamines were also successfully alkynylated at *ortho* position. Thus, alkynylation of secondary and tertiary amines gave higher yield (**3d-3g**) compared to the corresponding primary benzylamine (e.g. in case of **1h**

relatively lower yield of **3h** was observed). This is due to the geometric flexibility of the primary benzylamine, which leads to the difficulty of a picolinamide-directed cyclometalation. It was found that a range of benzylamine bearing various electron-donating, -withdrawing, and halogen substituents at the *para* position of the arene ring were effectively coupled with **2** and yielded the *ortho*-alkynylated benzylamines (**3i-3m**) in 60-70% isolated yields. However, synthesis of halo-substituted *ortho*-alkynyl benzylamines using the traditional approach, Pd-catalyzed "Sonogashira coupling" is very difficult and rather scare. The strong electron-withdrawing nitro group gave only mono-alkynylated product **3n** in lower yield (38%). It is noteworthy that the cyclic amine (**1p**) and α-methyl naphthylamine (**1q**) also proceeded efficiently and yielded the corresponding alkynylated products in good yields (products **3p** in 69% and **3q** in 80% isolated yields) under our catalytic conditions. Both mono- and bis-alkynylated products were isolated easily because of different R_f values. Notably, the developed cobalt-catalyzed C-H alkynylation strategy is applicable for the practical synthesis of enantiomerically pure *ortho*-alkynylated benzylamines and observed no racemization was observed under our optimal conditions (products **3b**, **3e**, **3i**, **3k**, **3m-o**, and **3q** in Scheme 3.2, Scheme 3.3f).

3.2.3 Diversification of alkynylated product

The diversification of alkynylated benzylamine derivatives is shown in Scheme 3.2. The chemoselective removal of the TIPS-group of **3a** was easily achieved by treatment with TBAF under standard reaction conditions to afford **5a**.[14,15] The desilylated compound **5a** (derived from **3a**) provided the Sila-Sonogashira coupling product **6** in 91% isolated yield and the 'click' reaction of **5a** with benzyl azide yielded **7** in 87% yield.

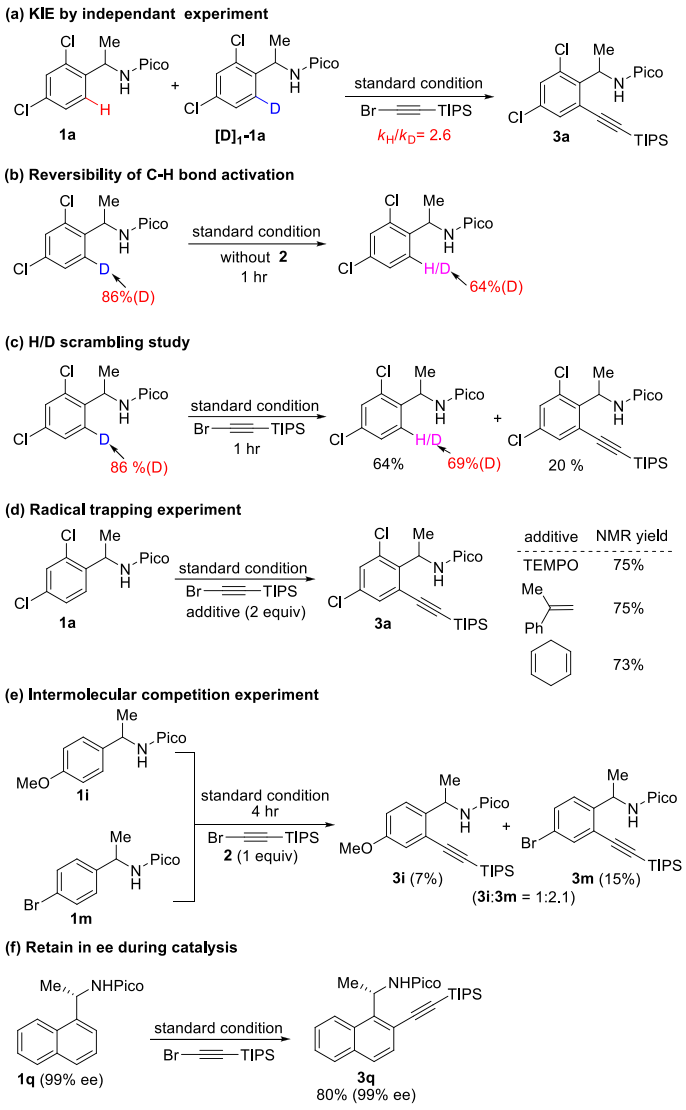


Scheme 3.2. Diversification of *ortho*-alkynylated benzylamines.

The deprotection of bidentate DG (picolinamide) can be easily achieved by using Lewis catalyst to get terminal *ortho*-alkynylated benzylamine **8** in 82% yield. A Rh(III)-catalyzed cascade oxidative olefination and cyclization of **3a** with *t*-butyl acrylate to enable **9** in 40% yield was also achieved.[14] Given the observed reactivity of the present $CoBr_2$ catalyzed alkynylation of benzylamine precursor, we embarked on the mechanistic studies to delineate a plausible catalytic pathway. In this regard, several control experiments were performed under standard conditions (Scheme 3.3). The intermolecular isotopic study of two parallel competition reactions between **1a** and [**D**$_1$]-**1a**, a kinetic isotope effect (KIE) of k_H/k_D = 2.6 was observed, thus demonstrating that the cleavage of the *ortho*-C(sp^2)-H bond is involved in the rate-determining step in the catalytic cycle. To understand the C-H bond reversibility, the reaction of [**D**$_1$]-**1a** was carried out in the absence of **2**. Indeed, the H/D exchange was observed in the *ortho* position on the recovered benzylamine and thus, clearly indicated that the present cobalt-catalyzed C-H bond activation is reversible. H/D scrambling was observed when the reaction was performed with an isotopically labeled substrate ([**D**$_1$]-**1a**), signifying that insertion of cobalt-metal into the C-H bond is also reversible. This study may indicate that the proto-decobaltation is faster than the alkyne insertion step. Furthermore, radical trapping experiment carried out using (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), cyclohexa-1,4-diene, and prop-1-en-2-ylbenzene under standard reaction condition and it was observed that the reaction was not inhibited, which confirms that the single-electron transfer (SET) mechanism could be ruled out. A competition experiment with a different electronic substituent on benzylamine revealed that the reaction favors the electron-withdrawing group. This finding can be rationalized in terms of cleavage of the *ortho* C-H bond may experience a concerted metalation-deprotonation (CMD) mechanism.

To find out the order of reaction in each component of the current cobalt-catalyzed alkynylation of benzylamine **1a** with (bromoethynyl)triisopropylsilane **2** was determined by individually by using the initial rate approximation (Figure 3.1). The rate of alkynylation reaction is nearly the same for various concentration of **1a.** It shows that the reaction is zeroth order with respect to the various concentration of **1a** (Figure 3.1 B). Similarly, the dependence of reaction with **2**, oxidant, and additive was carried out, and the results indicate that the time independent of reaction in various concentration of 2, oxidant (Ag_2CO_3) and additive ($PhCO_2Na$) (Sec 3.6.) However, by changing different

3.2.4 Mechanistic study



Scheme 3.3. Mechanistic studies.

loading of cobalt catalyst the rate of reaction increases and a slope of 0.25 was obtained from the plot of log(rate) *vs* log(conc. of catalyst), indicating a fractional order alkynylation reaction (Figure 1B).[14] Thus, the rate of reaction depends on the catalyst, which also supports KIE experiment suggesting C-H bond cleavage is the rate determine step.

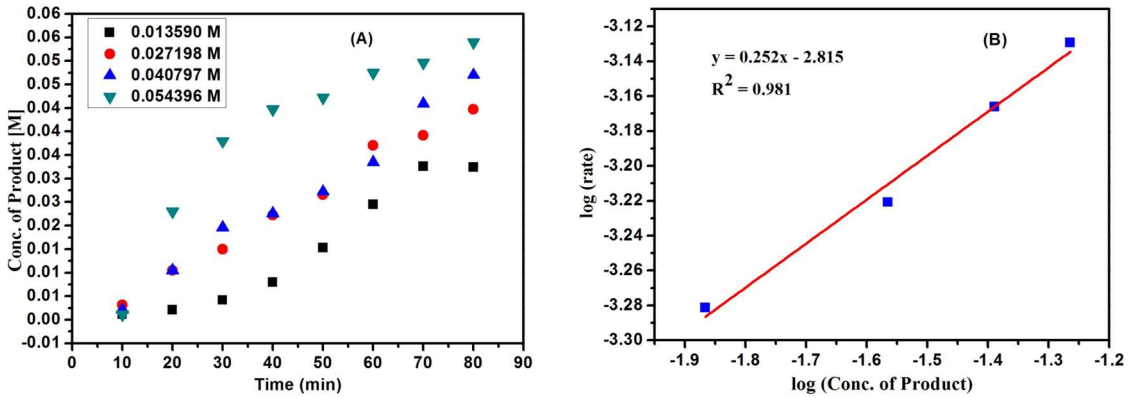


Figure 3.1. **(A)** Time-dependent formation of **3a** at different initial concentration **1a**. **(B)** Plot of log(rate) *vs* log(conc. of **1a**).

3.3 Conclusion

We have developed expedient, robust cobalt-catalyzed *ortho*-C(sp^2)-H alkynylation of benzylamines using easily removable piconamide as a bidentate auxiliary. This unified strategy has broad substrate scope including 1°, 2°, 3°, and enantiopure benzylamines and various functional group tolerance. The mechanistic study shows that C-H bond cleavage is the rate determining step and the kinetic study illustrates that the rate of reaction depends solely on the catalyst.

3.4 Experimental Section

3.4.1 Synthesis of the starting materials

Compounds **1d**, **1f**, **1h,** and **1n** were synthesized in accordance with the literature method.[15] Picolinamides were prepared by the reaction of picolinic acid with the corresponding benzylamines.[15,16]

3.4.1a Synthesis of [D_1]-1a

Compound **1a** (300 mg, 1.0 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) and CD_3COOD (99 atom %D, 10 mmol) were suspended CD_3OD (99 atom %D, 3 mL). The reaction mixture was heated at 125 °C in a sealed vial for 36 h. The reaction mixture was then cooled to

room temperature and concentrated *in vacuo*. The resulting residue was purified by silica gel flash chromatography to give [**D**$_1$]-**1a** (255 mg, 85%, white solid).

3.4.2 General procedure for the C(sp^2)-alkynylation of benzylamine

3.4.2a (For compounds **1a-1c, and 1p-1q**)

To an oven-dried 10 mL screw-capped vial, picolinamide **1** (0.1 mmol), (bromoethynyl)triisopropylsilane **2** (0.12 mmol), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (0.25 equiv) and trifluoromethylbenzene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 18 hrs at 150 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford **3**.

3.4.2b (For compounds **1d-1o**)

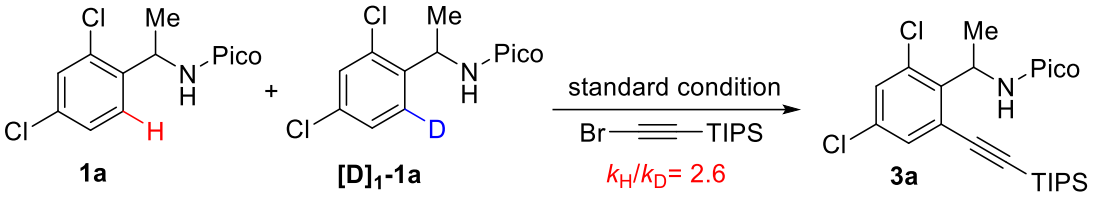
To an oven-dried 10 mL screw-capped vial, amide picolinamide **1** (0.1 mmol), (bromoethynyl)triisopropylsilane **2** (0.25 mmol), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (0.25 equiv) and trifluoromethylbenzene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 18 hrs at 150 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford product.

3.4.3 Procedure for the desilylation reaction (Removal of directing group)

The corresponding compound (mono- or bis-alknylated products) was dissolved in THF and 1.0 M TBAF in THF (1.5 equiv for mono-alkynylated benylamine and 3 equiv for bis-alkynylated benylamine) was then added at 0 ^oC with constant stirring. The reaction progress was monitored by TLC. The mixture was diluted with water extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The obtained crude product was purified by column chromatography to afford the desired terminal alkyne

3.4.4 Mechanistic investigation

3.4.4a Intermolecular kinetic isotopic effect (KEI)



Two independent reactions with **1a** or deuterated substrate **[D₁]-1a** under the standard conditions were performed. Suspensions of *N*-(1-(2,4-dichlorophenyl)ethyl)picolinamide (**1a**) (80 mg, 0.27 mmol) or **[D₁]-1a** (80 mg, 0.27 mmol), **2a** (84 mg, 0.32 mmol), $CoBr_2$(6mg, 10 mol%), Ag_2CO_3 (149 mg, 2 equiv), $PhCO_2Na$ (10 mg, 0.25 equiv), n-decane (38 mg, 0.27 mmol) as internal standard and trifluoromethylbenzene (2 mL) were added under a gentle stream of argon. The mixture was stirred for at 150 °C, a periodic aliquot was removed by syringe and analyzed by GC to determine the following conversions. It revealed that the cleavage of *ortho* C-H bond is rate determined step.

Time (min)/yield	30	50	70	90	110
3a yield (%)	1	11	18	30	39
3a' yield (%)	1	3	5	10	16

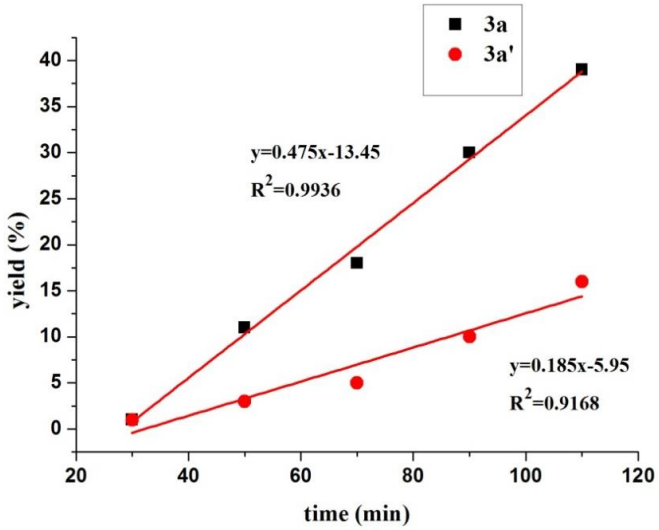
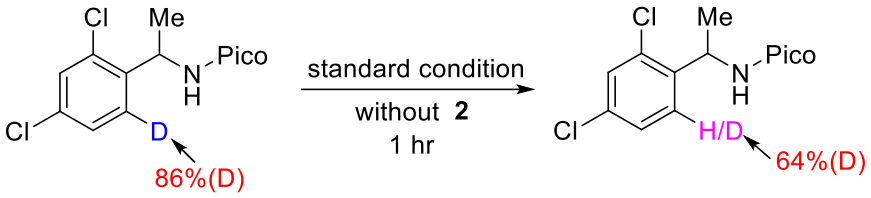


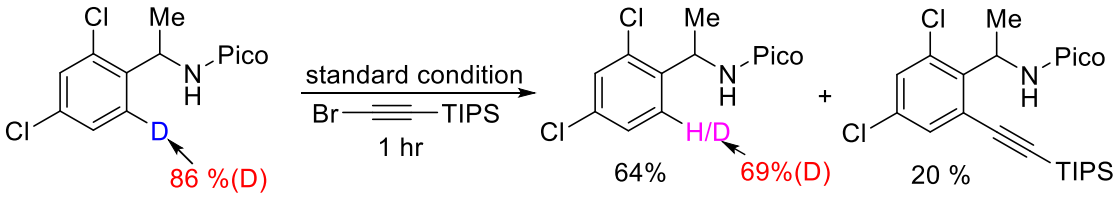
Figure 3.2. Intermolecular KIE (**3a** = product obtained from **1a**, and **3a'** = product obtained from **[D₁]-1a**).

3.4.4b Reversibility of C-H bond activation



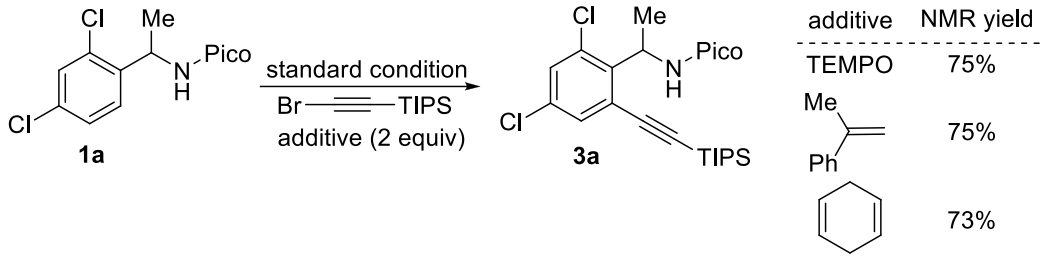
To an oven-dried 5 mL screw-capped vial, **[D_1]-1a** (40 mg, 0.13 mmol), $CoBr_2$ (10 mol %), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (25 mol%) and 1,3-bis(trifluoromethyl)benzene (1 mL) were added under argon atm. The mixture was stirred for 1 hr at 150 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10 mL of dichloromethane. The filtrate was concentrated *in vacuo* crude product was purified by column chromatography. The obtained product (34 mg, 84% yield) showed 64% *ortho*-deuteration.

3.4.4c H/D scrambling



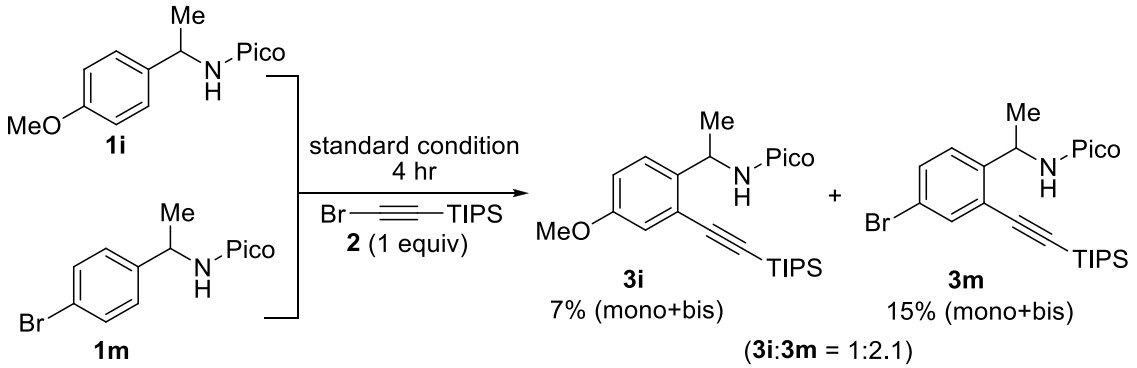
To an oven-dried 5 mL screw-capped vial, **[D_1]-1a** (40 mg, 0.13 mmol), **2** (35 mg, 0.156), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv.), $PhCO_2Na$ (25 mol%) and 1,3-bis(trifluoromethyl)benzene (1 mL) were added under argon atm. The mixture was stirred for 1 hr at 150 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10 mL of dichloromethane. The filtrate was concentrated *in vacuo* crude product was purified by column chromatography to afford **[D_1]-1a** (28 mg, 64% yield) and **3a (**13 mg, 20% yield).

3.4.4d Radical trapping experiment



To an oven-dried 5 mL screw-capped vial, **1a** (0.3 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.36 mmol), TEMPO or prop-1-en-2-ylbenzene or cyclohexa-1,4-diene (0.9 mmol), $CoBr_2$ (10 mol %), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (25 mol%) and 1,3-bis(trifluoromethyl)benzene (1 mL) were added under argon atm. The mixture was stirred for 18 hrs at 150 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10 mL of dichloromethane. The filtrate was concentrated *in vacuo*. The yield was determined by ^1H NMR.

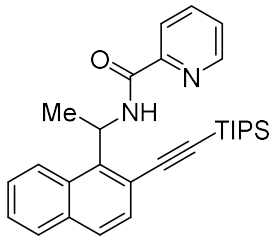
3.4.4e Intermolecular competition experiment



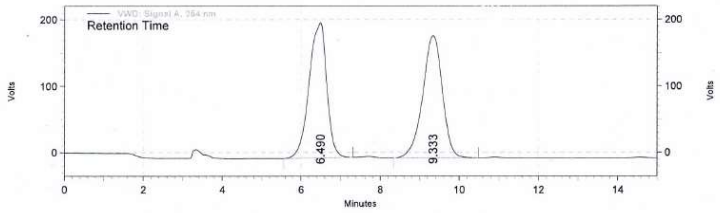
To an oven-dried 5 mL screw-capped vial, benzamides **1i** (0.3 mmol) and **1m** (0.3 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.3 mmol), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (25 mol%) and 1,3-bis(trifluoromethyl)benzene (1 mL) were added under argon atm. The mixture was stirred for 4 hrs at 150 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with dichloromethane (3 x 5 mL). The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the alkynylated products **3i** (mono+bis) and **3m** with the isolated yields of 7% and 15% respectively.

3.4.4f Retain in ee during catalysis

To an oven-dried 10 mL screw-capped vial, amide chiral (S)-*N*-(1-(naphthalen-1-yl)ethyl)picolinamide (**1q**) (0.1 mmol) or racemic *N*-(1-(naphthalen-1-yl)ethyl)picolinamide (0.1 mmol), (bromoethynyl)triisopropylsilane **2** (0.12 mmol), $CoBr_2$ (10 mol%), Ag_2CO_3 (2 equiv), $PhCO_2Na$ (0.25 equiv) and trifluoromethylbenzene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 12 hrs at 150 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired alkynylated product and submitted for HPLC.

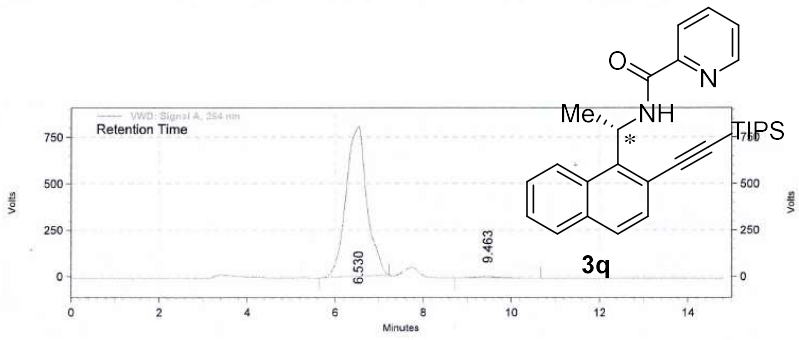


3q (racemic)



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %
6.490	105961429	49.95
9.333	106164937	50.05
Totals	212126366	100.00



VWD: Signal A, 254 nm Results

Retention Time	Area	Area %
6.530	448697327	98.93
9.463	4839447	1.07
Totals	453536774	100.00

3.4.5 Rate order determination

The rate order of the alkynylation reaction with various reaction components was determined by the initial rate method. The data of the concentration of the product *vs* time (min) plot was fitted linear with Origin Pro 8. The slope of the linear fitting represents the reaction rate. The order of the reaction was then determined by plotting the log(rate) *vs* log(conc) for a particular component.

3.4.5a Rate order determination for *N*-(1-(2,4-dichlorophenyl)ethyl)picolinamide (1a).

To determine the order of the alkynylation reaction on **1a**, the initial rates at different initial concentrations of **1a** were recorded. The final data was obtained by averaging the results of three independent runs for each experiment.

To an oven-dried 10 mL screw-capped vial, (bromoethynyl)triisopropylsilane **2** (71mg, 0.27 mmol), $CoBr_2$ (6mg, 10 mol%), Ag_2CO_3 (149 mg, 2 equiv), $PhCO_2Na$ (9.8mg, 0.25 equiv), specific amount of **1a** (as shown in table S1), n-decane (38.4 mg, 0.27 mmol) as internal standard and trifluorotoluene (2 mL) were added under a gentle stream of argon. The mixture was stirred at 150 °C (bath temperature). At regular intervals, the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with EtOAc and subjected to GC analysis. The concentration of the product **3a** obtained in each sample was determined with respect to the internal standard n-decane.

Table 3.3 Rate of cobalt-catalyzed alkynylation reaction at a different initial concentration of **1a.**

Experiment	Amount of **1a** (gm)	Initial concentration of **1a** [M]	Initial Rate $[Mmin^{-1}] \times 10^{-3}$
1	0.080	0.136	0.523
2	0.119	0.204	0.509
3	0.159	0.272	0.569
4	0.199	0.338	0.541

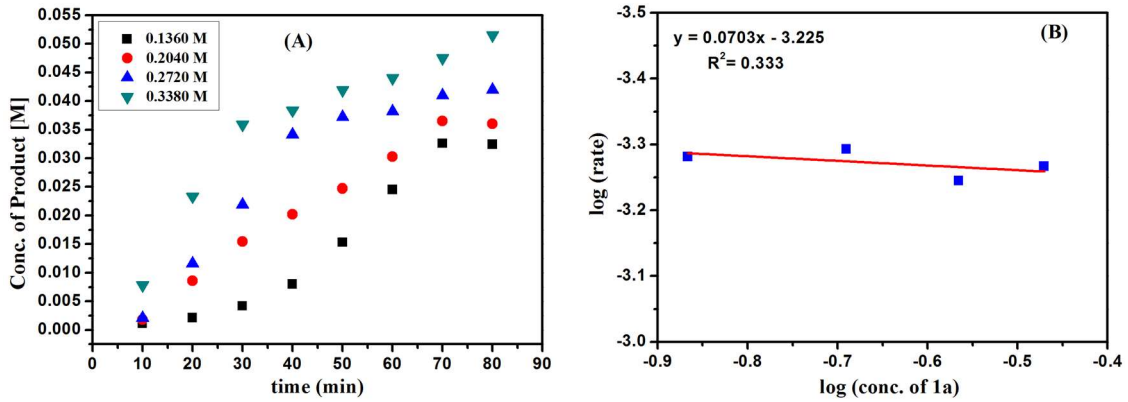


Figure 3.3 (A) Time-dependent formation of **3a** at different initial concentration of **1a**. (B) Plot of log(rate) *vs* log(conc. of **1a**).

3.4.5b Rate order determination for (bromoethynyl)triisopropylsilane.

To determine the order of the alkynylation reaction on (bromoethynyl)triisopropylsilane (**2**), the initial rates at different initial concentrations of (bromoethynyl)triisopropylsilane were recorded. The final data was obtained by averaging the result of three independent runs for each experiment.

Representative procedure was followed, employing **1a** (80 mg, 0.27mmol), $CoBr_2$ (6 mg, 10 mol%), Ag_2CO_3 (149 mg, 2 equiv), $PhCO_2Na$ (9.8 mg, 0.25 equiv) , specific amount of (bromoethynyl)triisopropylsilane **2** (as shown in table S2), n-decane (38.4 mg, 0.27 mmol) as internal standard and trifluorotoluene (2 mL).

Table 3.4 Rate of alkynylation reaction at different initial concentration of **2.**

Experiment	Amount of **2a** (gm)	Initial concentration of **2a** [M]	Initial Rate $[Mmin^{-1}] \times 10^{-3}$
1	0.070	0.137	1.28
2	0.140	0.270	1.76
3	0.210	0.407	1.49
4	0.240	0.542	1.27

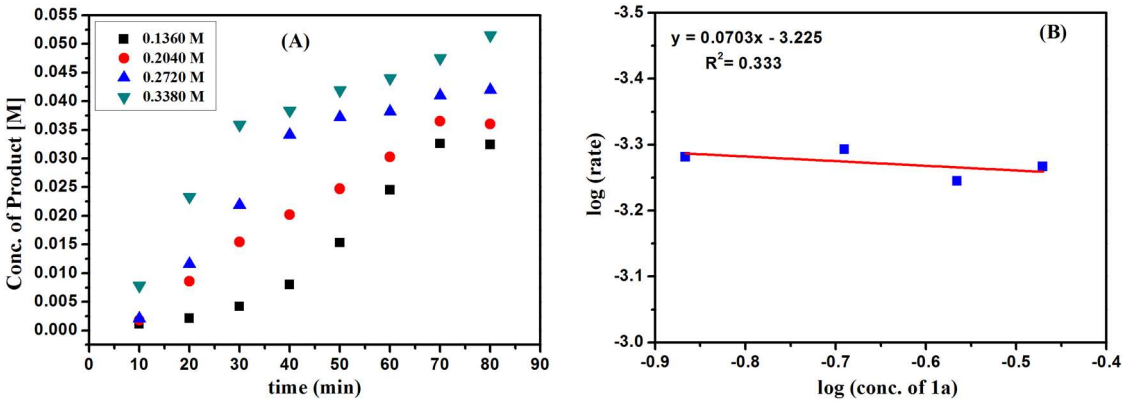


Figure 3.4 (A) Time-dependent formation of **3a** at different initial concentration of **2**. (B) Plot of log(rate) *vs* log(conc. **2**).

3.4.5c Rate order determination for $CoBr_2$.

To determine the order of the alkynylation reaction on catalyst, the initial rates at different mol% for catalyst were recorded. The final data was obtained by averaging the result of three independent runs for each experiment.

Representative procedure was followed, employing **1a** (80 mg, 0.27 mmol), **2** (70 mg, 0.27 mmol), Ag_2CO_3 (149 mg, 2 equiv), $PhCO_2Na$ (9.8 mg, 0.25 equiv), specific amount of $CoBr_2$ (as shown in table S3), n-decane (38.4 mg, 0.27 mmol) as internal standard and trifluorotoluene (2 mL).

Table 3.5 Rate of Alkynylation reaction at different mol % catalyst

Experiment	Amount of catalyst (gm)	Initial Rate [$Mmin^{-1}$] x 10^{-3}
1	0.006	0.523
2	0.012	0.601
3	0.018	0.682
4	0.024	0.724

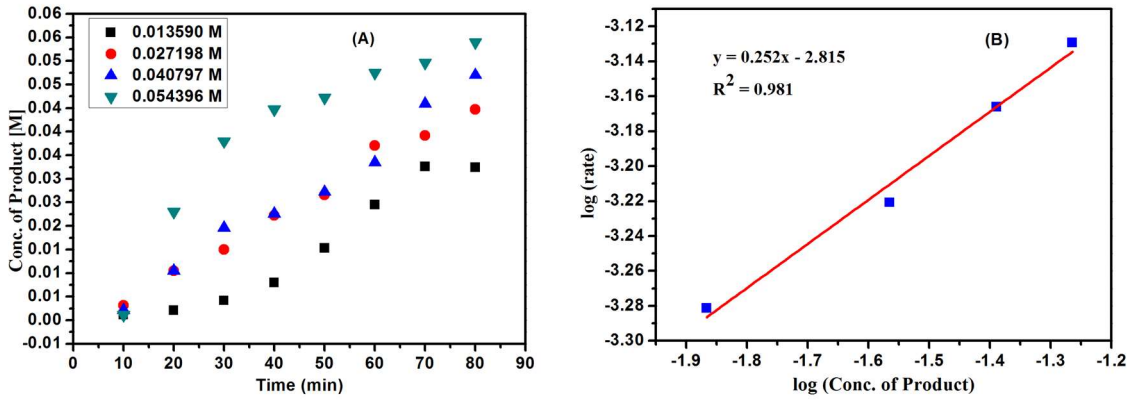


Figure 3.5 (A) Time-dependent formation of **3a** at a different initial concentration of catalyst. (B) Plot of log(rate) *vs* log(conc. of catalyst).

3.4.5d Rate order determination for sodium benzoate.

To determine the order of the alkynylation reaction on sodium benzoate, the initial rates at different initial concentrations of sodium benzoate were recorded. The final data was obtained by averaging the result of three independent runs for each experiment.

Representative procedure was followed, employing **1a** (80 mg, 0.27 mmol), **2** (70 mg, 0.27 mmol), $CoBr_2$ (6 mg, 10 mol%), Ag_2CO_3 (149 mg, 2 equiv), specific amount of sodium benzoate (as shown in table S4), n-decane (38.4 mg, 0.27 mmol) as internal standard and trifluorotoluene (2 mL).

Table 3.6 Rate of alkynylation reaction at a different initial concentration of sodium benzoate.

Experiment	Amount of sodium benzoate (g)	Initial concentration of sodium benzoate [M]	Initial Rate [$Mmin^{-1}$] x 10^{-3}
1	0.019	0.068	1.06
2	0.039	0.136	1.03
3	0.058	0.204	0.563
4	0.078	0.272	0.798

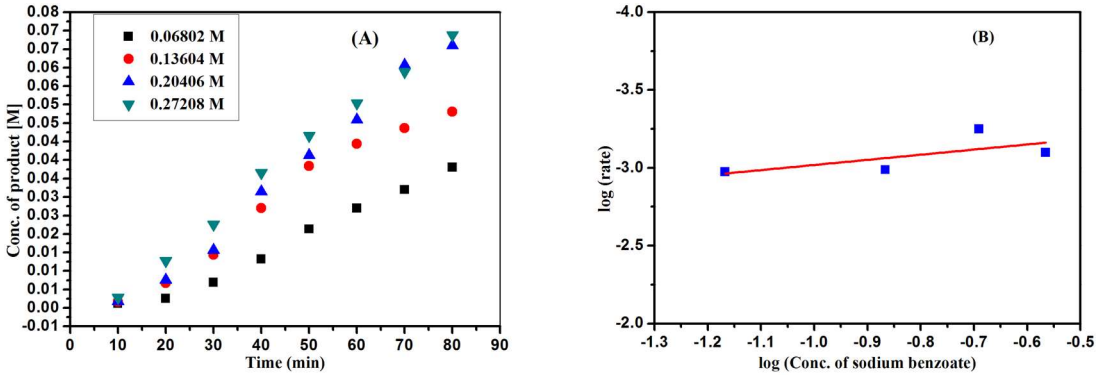


Figure 3.6 (A) Time-dependent formation of **3a** at a different initial concentration of sodium benzoate. (B) Plot of log(rate) *vs* log(conc. of sodium benzoate).

3.4.5e Rate order determination for silver carbonate (oxidant).

To determine the order of the alkynylation reaction on silver carbonate, the initial rates at different initial concentrations of silver carbonate were recorded. The final data was obtained by averaging the result of three independent runs for each experiment.

Representative procedure was followed, employing **1a** (80 mg, 0.27 mmol), **2** (70 mg, 0.27 mmol), $CoBr_2$ (6 mg, 10 mol%), $PhCO_2Na$ (9.8 mg, 0.25 equiv) specific amount of silver carbonate (as shown in table 4), n-decane (38.4 mg, 0.27 mmol) as internal standard and trifluorotoluene (2 mL).

Table 3.7 Rate of alkynylation reaction at a different initial concentration of silver carbonate.

Experiment	Amount of silver carbonate (gm)	Initial concentration of silver carbonate [M]	Initial Rate $[Mmin^{-1}] \times 10^{-3}$
1	0.149	0.2709	1.44
2	0.224	0.4072	1.96
3	0.299	0.5436	1.39
4	0.374	0.6800	2.11

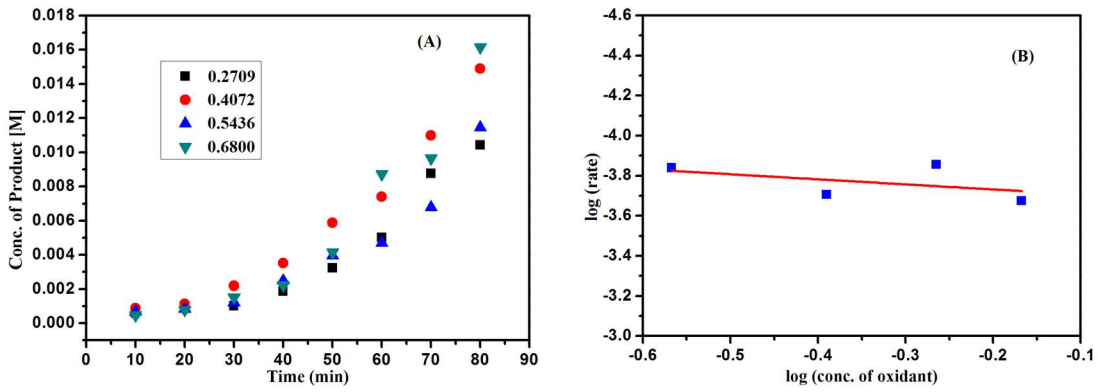


Figure 3.7 (A) Time-dependent formation of **3a** at different initial concentration of silver carbonate (oxidant). (B) Plot of log(rate) *vs* log(conc. of oxidant).

3.4.6 Synthetic application

3.4.6a Synthesis of 6

Under argon atm **5a** (prepared by the above mentioned procedure) (50 mg, 0.15 mmol), iodobenzene (37 mg, 0.18 mmol), $PdCl_2$ (5 mol%), CuI (2.5 mol%), Et_3N (1 mL) were charged to a 25 mL Schlenk tube. The reaction mixture was stirred at 50 °C for 6 hrs. The mixture was filter through celite and concentrated *in vacuo*. The obtained crude product was purified by column chromatography to afford **6** (54 mg, 91%, yellow liquid).

3.4.6b Synthesis of 7

Under argon atm **5a** (50 mg. 0.15 mmol, 1.0 equiv), CuI (10 mol %) and benzyl azide (21 mg, 0.15 mmol, 1.0 equiv) were dissolved in DMF (1 mL) and stirred at 60 °C for 16 hrs. After completion of the reaction saturated aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with dichloromethane (3 x 5 mL) and dried over anhydrous Na_2SO_4. After complete evaporation of the solvent, the obtained crude product was purified by column chromatography to afford **7** (62 mg, 87%, yellow liquid).

3.4.6c Synthesis of 8

To an oven-dried 10 mL screw-capped vial, *N*-(1-(2,4-dichloro-6-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide (**3a**) (50 mg, 0.10 mmol), n-butylamine (10 mmol,), and toluene (0.6 mL) were mixed under a gentle stream of argon. The mixture was shaken until the contents dissolved completely and followed by

the addition of anhydrous $AlCl_3$ (0.1 mmol, 14 mg). The reaction mixture was heated with constant stirring (at 90 °C). After 24 h, the reaction mixture was cooled to room temperature and the crude mixture was extracted with dichloromethane (3 x 5 mL) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired product **8** (31 mg, 82%, yellow liquid).

3.4.6d Synthesis of 9[17]

To an oven-dried 10 mL screw-capped vial, amide **3a** (50 mg, 0.1 mmol), *tert*-butyl acrylate (20 mg, 0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv), and toluene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 24 hrs at 130 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired product **9** (24 mg, 40%, yellow liquid).

(i) For update data of all newly synthesized compounds, see Appendix A.

(ii) For copy of ^1H and ^{13}C NMR (only selected compounds) see Appendix B

3.5 References

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(13) Other bases such as NaOAc, CsOAc, Li_2CO_3, Na_2CO_3, K_2CO_3 and Cs_2CO_3 proved ineffective and less formation (up to ~20%) of **3a** was observed under optimal conditions.

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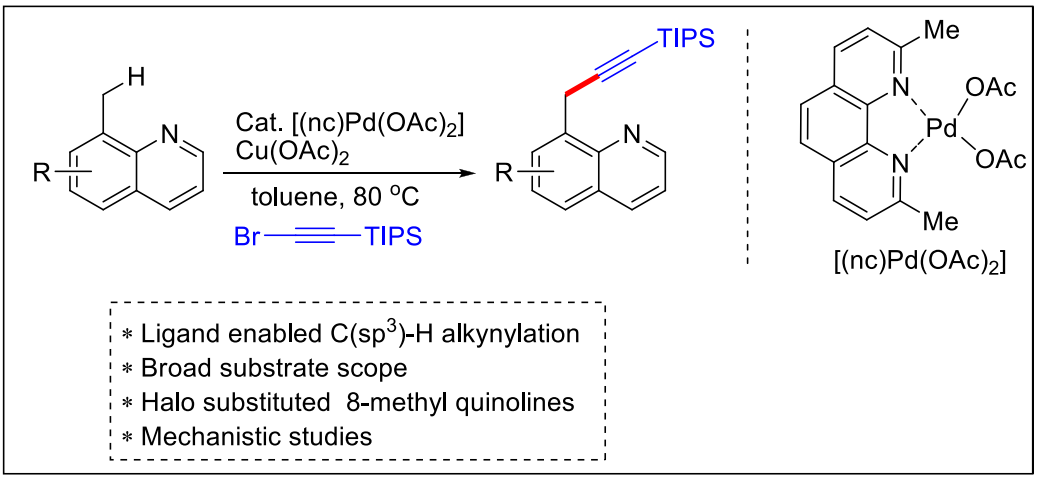
Chapter 4

Palladium Catalyzed C(sp^3)-H Bond Alkynylation of Heterocycles

A ligand-enabled C(sp^3)-H alkynylation of 8-methylquinoline is reported in this chapter. The reaction is catalyzed by the well-defined Pd(II)-complexes. The present C(sp^3)-alkynylation has a broad substrate scope as well as functional group tolerance and proceed efficiently under mild conditions.



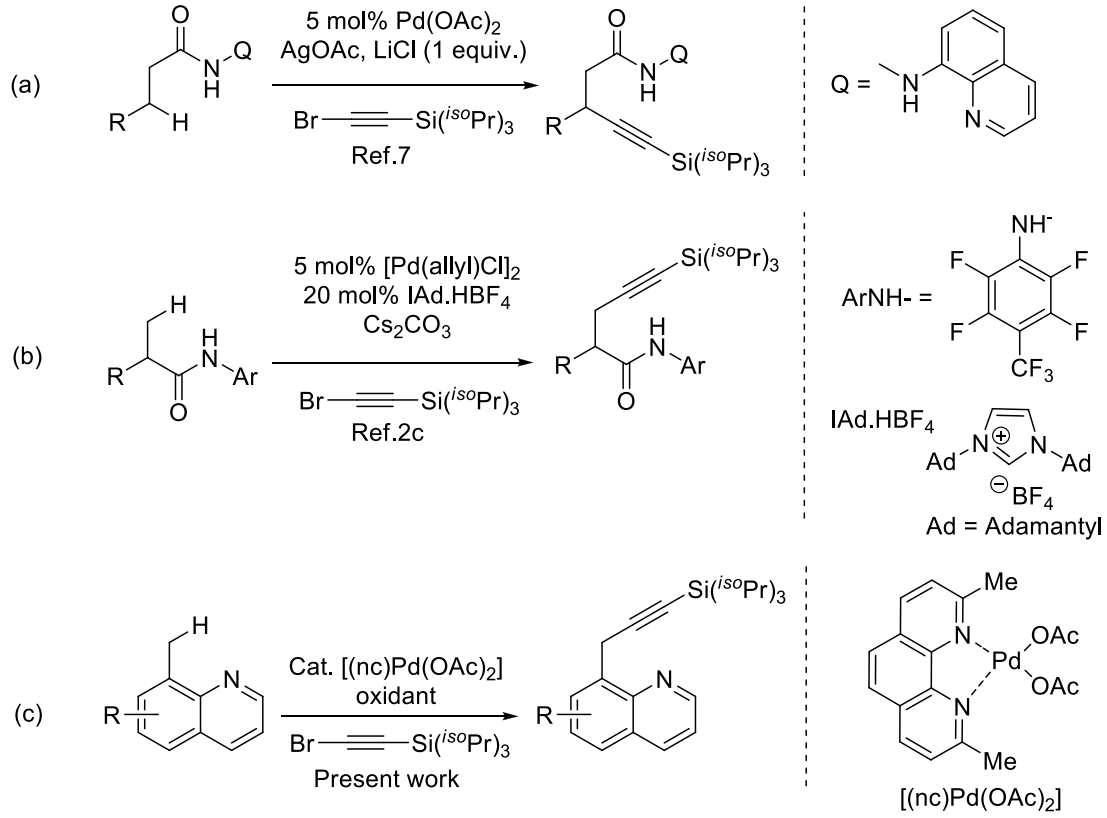
Vinod G. Landge *et al Dalton Trans.*, 2015, *44*, 15382-15386.

4.1 Introducion

Catalysts based direct activation of C-H bonds provides a sustainable and an atom-economical synthetic strategy to diverse organic molecules from simple, pre-functionalized substrates. The selection of ligands is very crucial in the design of such active catalytic systems. Ligands would alter the electronic and steric properties of the active catalyst, and thus they could significantly accelerate C-H activation and successive bond forming reactions. Although ligand-enabled C(sp^3)-H activation has emerged as a powerful tool for rapid, straightforward construction of the carbon-carbon and the carbon-heteroatom bonds, there still remains a significant challenge in the field of C(sp^3)-H activation.[1-2]

Development of the catalytic systems for direct conversion of inert C-H bonds into the C-alkynyl bonds is very attractive, simplest, and sustainable method as the alkyne moiety is of significant importance for various organic transformations including cycloaddition, metathesis, click reaction *etc.*[3] In addition, alkynes are excellent building blocks in synthetic chemistry and in material science and they are also a common motif in drugs.[4] Despite a number of reports concerning transition-metal catalyzed C(sp^2)-H alkynylation reactions,[5-6] methods to convert C(sp^3)-H bonds to C(sp^3)-alkynyl bonds remain extremely rare.[2c,7] To date, there are only two reports describing the C-H alkynylation of inert C(sp^3)-H bonds. The first example was reported by Chatani and his co-workers by chelate assisted strategy using the pre-installed bi-dentate ligand under Pd(II)/Pd(IV) catalysis (Scheme 4.1a).[7] Another example of Pd(0)/*N*-heterocyclic carbene (NHC) and Pd(0)/PR_3-catalyzed alkynylation of β-C(sp^3)-H bonds using an *N*-arylamide auxiliary was reported by research group of Yu (Scheme 4.1b).[2c] In recent times, due to cyclometalation ability of 8-methylquinoline several transition-metal catalyzed C(sp^3)-H bond activation of 8-methylquinoline has been reported by various groups.[8-9] Very recently, a rhodium(III)-catalyzed C(sp^3)-alkenylation of 8-methylquinolines with internal alkynes has been reported.[8u] However, to the best of our knowledge, there is no report describing the C(sp^3)-alkynylation of 8-methylquinolines prior to our report. Inspired by these studies, we were motivated to examine the possibility of C(sp^3)-H alkynylation of 8-methylquinoline **1a** using (triisopropylsilyl)ethynyl bromide **2** as an alkyne coupling partner. In this chapter, we described the first example of C(sp^3)-H alkynylation of 8-methylquinolines

catalysed by well-defined palladium complexes (Scheme 4.1c). Notably, this reaction is enabled by the neocuproine ligand to enhance the catalytic activity of active Pd(II) species. The present transformation has a broad substrate scope, functional group tolerance, and process efficiently under mild conditions.



Scheme 4.1 Direct conversion of inert C(sp^3)-H bonds into C(sp^3)-alkynyl bonds.

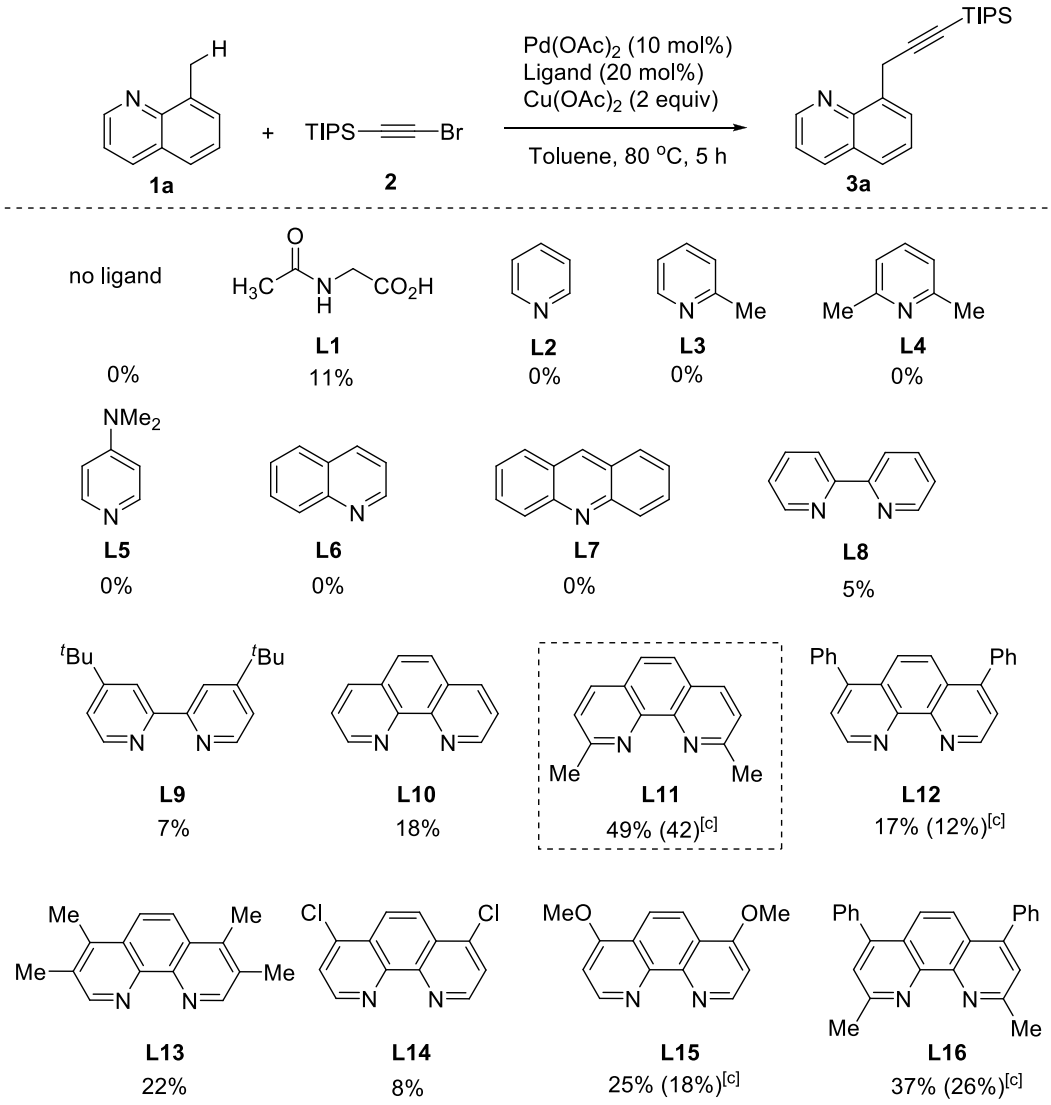
4.2 Results and Discussion

4.2.1 Optimization of reaction condition

Initial experiments were performed with 8-methylquinoline (**1a**) and TIPS-alkynyl bromide (**2**) in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% Ac-Gy-OH (**L1**) as the catalytic system and 2 equiv. of $Cu(OAc)_2$ as an oxidant at 80 °C in toluene afforded the C(sp^3)-alkynylated product **3a** only in 11% yield. With the preliminary results in hand, we were interested to investigate a more appropriate ligand that can potentially improve the yield of the reaction. Yu and his co-workers observed that the pyridine- and quinoline-based ligands are good commodities for C(sp^3)-H activation.[2b,2d] Thus a tool-box of ligands were tested

for the C(sp^3)-H alkynylation reaction of **1a**. Importantly, pyridine and quinoline-based ligands have no effects on alkynylation reaction, and 1,10-phenanthroline-based ligands have improved this transformation (Table 4.1).

Table 4.1 Screening of ligands for C(sp^3)-alkynylation.[a,b]

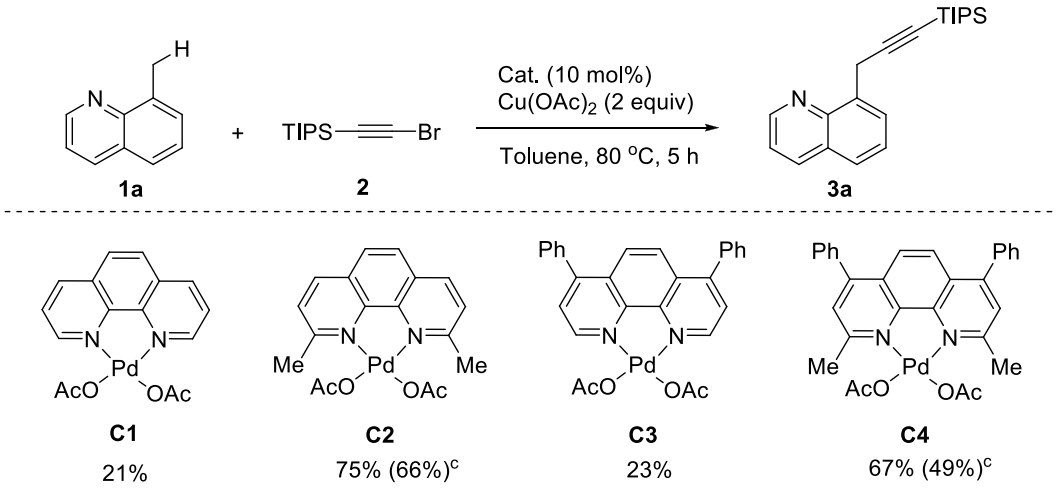


[a]Reaction conditions: **1a** (0.1 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), ligand (20 mol%), $Cu(OAc)_2$ (2 equiv), toluene (1 mL), 80 °C, 5 h. [b]The yield was determined by ^1H NMR analysis of the crude product using dibromomethane as the internal standard. [c]Yield of isolated product.

We have optimized the reaction conditions by performing extensive screening of Pd sources, mol% of catalyst, ligands, oxidants, solvent, temperature, and time to obtain the optimum yield of **3a**. After extensive screening, toluene was found to be

the optimal solvent as it suppressed the homocoupling of **2** and a combination of $Pd(OAc)_2$ and neocuproine (nc) **L11** were found to be more appropriate for this transformation and increased the yield (up to 49%) under standard conditions. It is important to note that, by using the pre-formed neocuproine palladium complex $[(nc)Pd(OAc)_2]$ **C2**, the yield of **3a** was increased to 75% (Table 4.2). A well-defined bathocuproine derived Pd(II)-complex **C4** also showed comparable reactivity and yielded **3a** in 67%. However, the reaction did not proceed in the absence of $Cu(OAc)_2$.

Table 4.2 Screening of well-defined Pd(II)-complexes for C(sp3)-alkynylation of **1a**.[a,b]

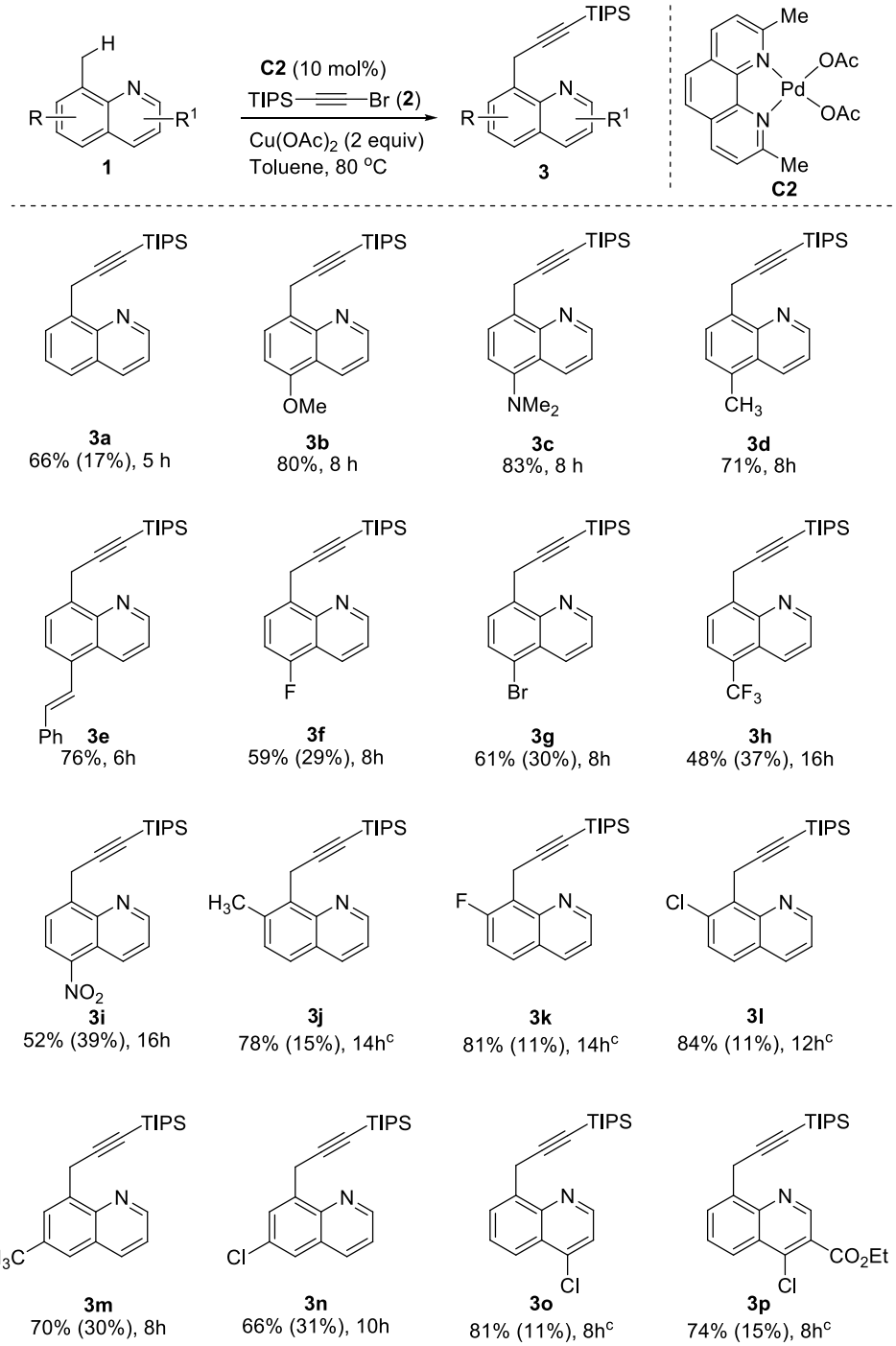


[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), catalyst (10 mol%), $Cu(OAc)_2$ (2 equiv), toluene (1 mL), 80 °C, 5 h. [b]The yield was determined by ^1H NMR analysis of the crude product using dibromomethane as the internal standard. [c]Yield of isolated product.

With the optimized reaction conditions in hand, we next explored the scope of the reaction. As shown in Table 4.3, C(sp^3)-H alkynylation proceeded at 80 °C in good to excellent yields with a variety of electronically diverse substrates. In all cases, a well-defined palladium complex $[(nc)Pd(OAc)_2]$ (10 mol%), and oxidant $Cu(OAc)_2$ (2 equiv) were used to achieve excellent yields. From the data in Table 4.3, we have observed the following trends in the C(sp^3)-H alkynylation reaction: i) Different substituents on the quinoline moiety were compatible with the alkynylation.

4.2.2 Scope of 8- methyl quinolines

Table 4.3. Scope studies of C(sp^3)-alkynylation of **1**.[a,b]



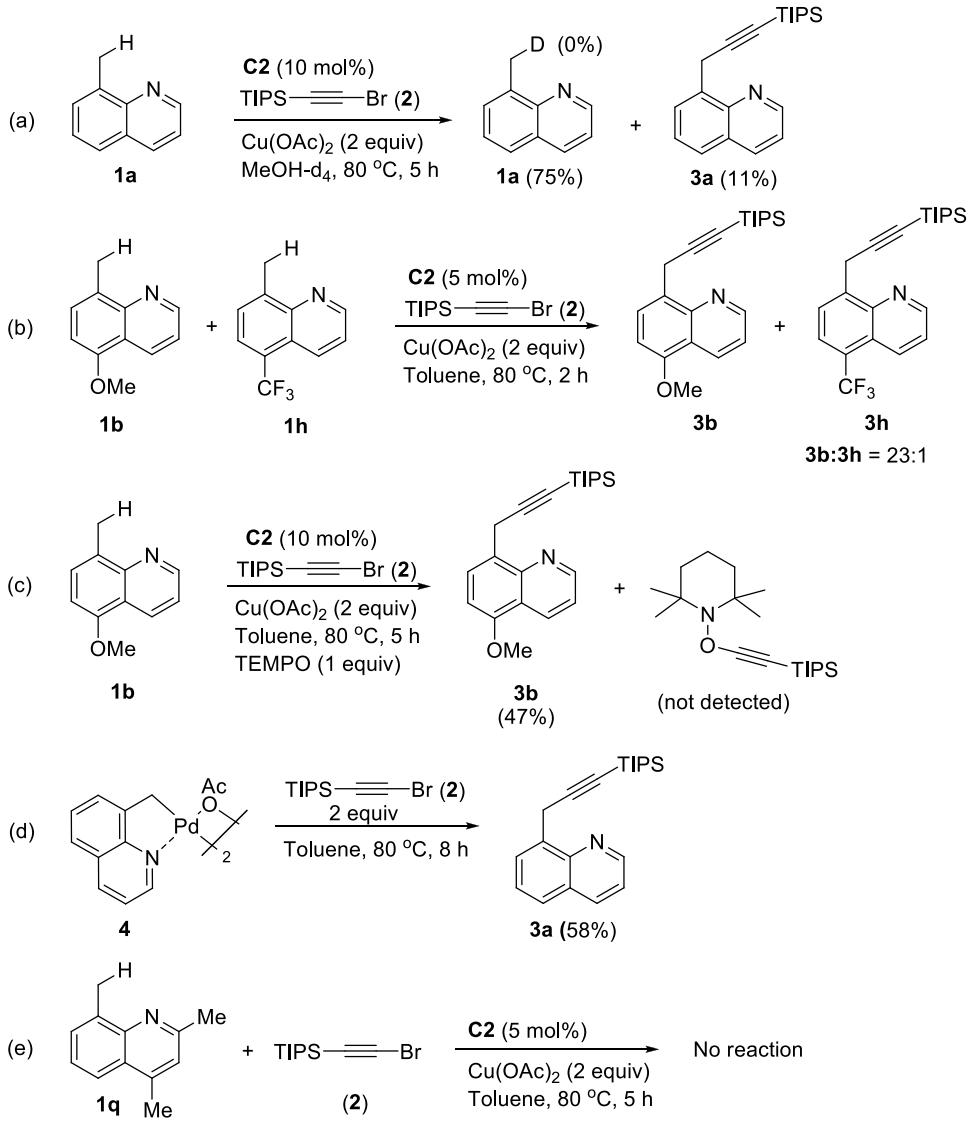
[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.15 mmol), complex **C2** (10 mol%), $Cu(OAc)_2$ (2 equiv) and toluene (1 mL) in a 10 mL screw-capped viol were heated at 80 °C for specified time. [b]Yields of isolated products and yields in parentheses are based upon recovered starting material. [c]25 mol% of complex **C2** was used.

Electron-donating groups proceeded smoothly to provide corresponding C(sp^3)-alkynylated products **3b**, **3c**, and **3e** in 80%, 83% and 76% isolated yields respectively, wherein electron-withdrawing groups were found to decrease the yields (48% of **3h** and 52% of **3i** respectively). ii) It is noteworthy that halide substituents were tolerated (**3f-3g**, **3k-3l**, and **3n-3p**), as this is advantageous for further synthetic elaborations with transition-metal catalysis thereby broadening the diversity of the products. iii) The position of the substituents on the quinoline moiety played a vital role, and thus 5-substituted substrates worked slightly better than 6-substituted substrates. In case of 7-substituted 8-methylquinolines (**3j-3l**) higher yield of alkynylated product (78% of **3j**, 81% of **3k**, and 84% of **3l**) was obtained by using 25 mol% of catalyst. A multisubstituted ethyl 4-chloro-8-methylquinoline-3-carboxylate (**3p**) also gave desired alkynylated product. Notably, 2,4-dimethyl-8-methylquinoline (**1q**, Scheme 4.2e) showed no reaction probably due to steric reasons. In most cases, the unreacted starting materials were recovered.[10]

To shed some light on the mechanism of this ligand enabled C(sp^3)-alkynylation reaction, a series of control experiments, deuterium-labeling, radical trapping studies were performed (Scheme 4.2).[11] When the reaction was carried out under standard condition in MeOH-d_4 at 80 ^oC for 5 hrs (Scheme 4.2a), no deuteration of the methyl C-H bonds was observed in the recovered **1a**, indicating that the C(sp^3)-H bond activation is irreversible, whereas it was found to be reversible in rhodium(III)-catalyzed alkenylation of 8-methylquinolines with alkynes.[8u] Competition experiment was used to determine the preference of the reaction for electronically different 8-methylquinoline compounds (Scheme 4.2b). When 5-methoxy-8-methylquinoline (**1b**) was used in competition with 8-methyl-5-(trifluoromethyl)quinoline (**1h**), the electron-donating group was preferentially alkynylated (**3b**/**3h**: ~23:1). These findings clearly confirmed that the acidity of the C(sp^3)-H bond being cleaved is trivial in the C-H activation and similar trend was observed in previously reported palladium-catalyzed *ortho*-alkynylation of aromatic C(sp^2)-H bonds.[6o] Additionally, we performed a radical trapping experiment to know whether a single electron transfer (SET) was involved in this reaction. Hence, performing the reaction in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) under standard conditions, the

reaction was not completely inhibited and no *O*-alkynylated-TEMPO product was detected, suggesting that the reaction does not involve SET mechanism. However, an alternative mechanism for Pd-catalyzed oxidative transformations involving binuclear Pd(III) species that does not involve free radicals is also possible.[13] The stoichiometric reaction of preformed palladacycle(II) of 8-methylquinoline (**4**) with 0.5 equiv of **2** in the absence of oxidant selectively yielded **3a** (58%), indicating that the $Pd^{II/IV}$ pathway may be operative for this alkynylation reaction.[14]

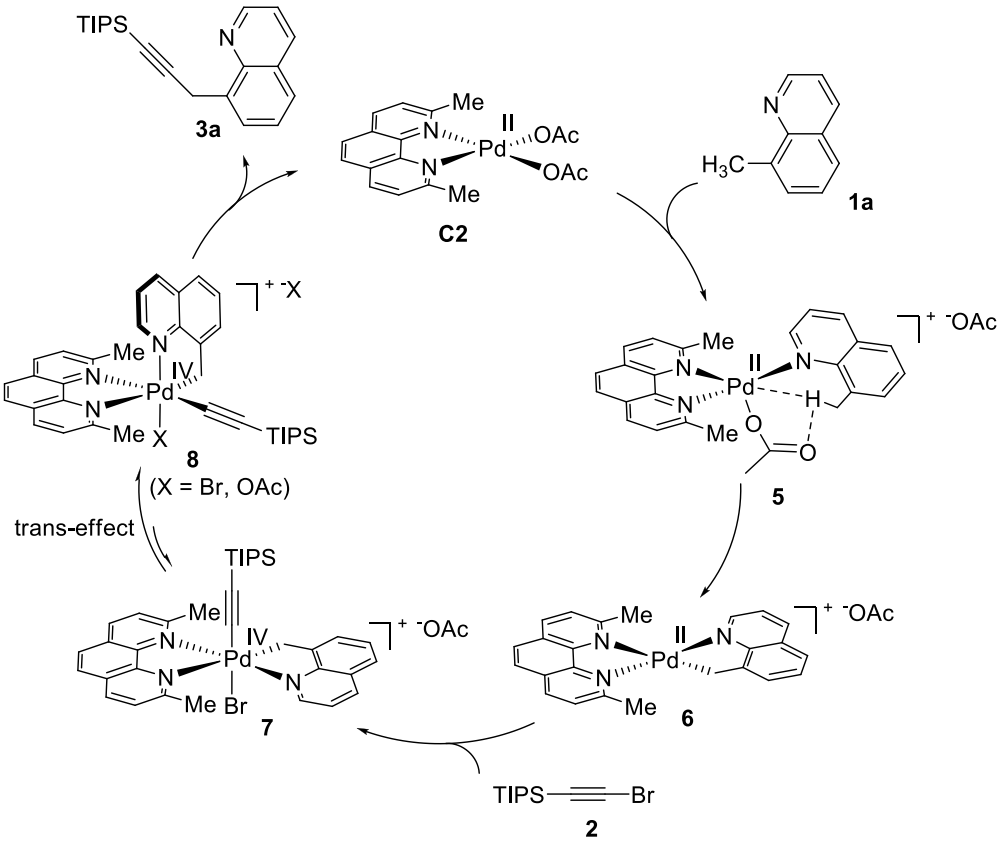
4.2.3 Mechanistic studies



Scheme 4.2 Mechanistic studies on C(sp^3)-alkynylation reaction.

Based on above experimental results and literature reports,[1c,12] we postulate that this Pd-catalyzed C(sp^3)-alkynylation reaction proceeds through a C-H palladation/coupling sequence and that a $Pd^{II/IV}$ manifold is operative and a plausible mechanism is shown in Scheme 4.3. As shown in Scheme 4.3, the coordination of the 8-methylquinoline **1a** to the Pd(II)-complex C2 followed by a cyclopalladation lead to the intermediate **6**. The oxidative addition of (triisopropylsilyl)ethynyl bromide **2**[14,15] lead to the formation of the hypervalent $Pd^{(IV)}$ intermediate **7**. The intermediate **7** may reassembled due to strong *trans-effect* of bidentate pyridyl ligand[16] (neocuproine) leading to **8** followed by a reductive elimination gives **3a** with the regeneration of the active $Pd^{(II)}$ species.

4.2.4 Plausible mechanism



Scheme 4.3 A plausible mechanism for the C(sp^3)-alkynylation of **1a** with **2** catalyzed by **C2**.

4.3 Conclusion

In conclusion, we have described the first example of ligand-enabled C(sp^3)-alkynylation of 8-methylquinolines with TIPS-alkynyl bromide with mechanistic studies. The reaction is catalyzed by the well-defined Pd(II)-complexes and proceed efficiently under mild conditions. The present C(sp^3)-C(sp) bond forming reaction has a broad substrate scope as well as functional group tolerance.

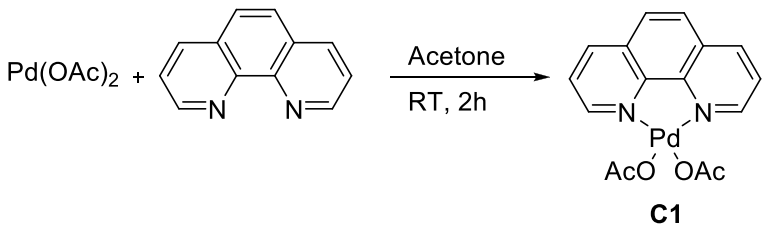
4.4 Experimental Section

4.4.1 Synthesis of the starting materials

All substituted 8-methylquinolines (**1**) were prepared by the known procedure[17-18] (Bromoethynyl)triisopropylsilane (**2**, CAS 111409-79-1) was prepared by previously reported $AgNO_3$-catalyzed bromination of (triisopropylsilyl)acetylene with *N*-bromosuccinimide.[19]

4.4.2 Synthesis of the palladium complexes

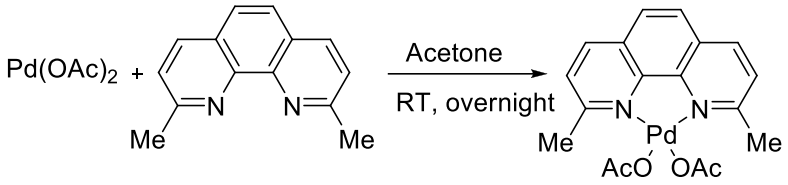
a) (Phen)Pd$(OAc)_2$ **C1** was prepared based on literature method as described below.[20] Palladium acetate (56 mg, 0.25 mmol) and 1,10-phenanthroline (Phen) (45 mg, 0.25 mmol) were dissolved in 3.0 mL and 1.0 mL of acetone with stirring, respectively. Then the palladium acetate solution was added dropwise to the 1,10-phenanthroline solution with stirring, forming a yellow precipitate, and the mixture was kept stirring for 2 h at room temperature. The precipitate was separated by centrifugation, dried at 60 ºC under vacuum for 8 h to yield (Phen)Pd$(OAc)_2$ **C1** as a yellow solid, 98 mg, 97% yield.



C1

b) (neocuproine)Pd$(OAc)_2$ **C2** was prepared according to a literature procedure as described below.[21]

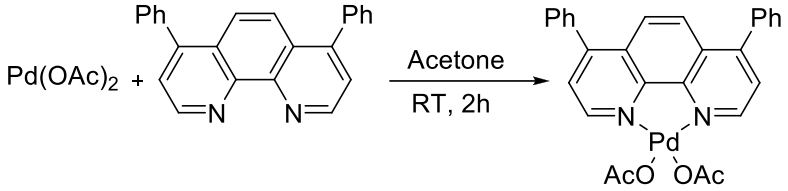
To a 100-ml round-bottom flask with stir bar was added neocuproine (0.600 g, 2.88 mmol), palladium(II) acetate (0.588 g, 2.62 mmol), and acetone (55 mL), and the reaction mixture was stirred overnight. The yellow precipitate was isolated by vacuum filtration, rinsed with acetone, and dried under vacuum to afford 0.87 g of (neocuproine)$Pd(OAc)_2$ **C2** (77% yield).



C2

c) (BPhen)$Pd(OAc)_2$ **C3** was prepared according to a literature procedure. [20]

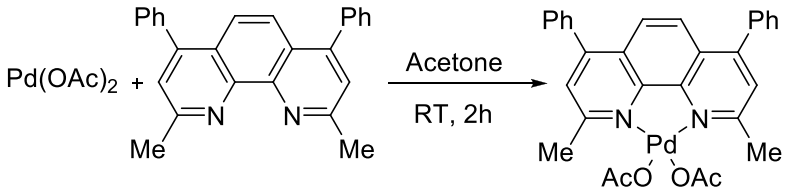
Yield: 88 % (yellow solid)



C3

d) (bc)$Pd(OAc)_2$ **C4** was prepared based on literature method as described below.[22]

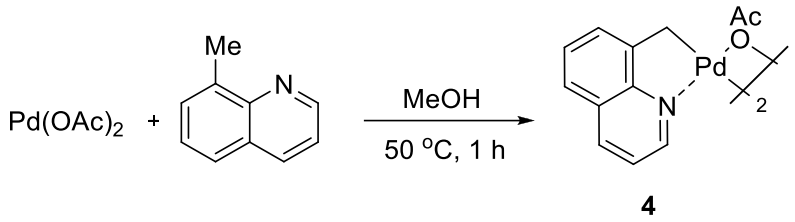
A solution of palladium(II)acetate (449 mg, 2 mmol) in 10 mL of freshly distilled dichloromethane is stirred under argon and bathocuproine (722 mg, 2 mmol) is added in one portion. The resulting solution is stirred under argon at room temperature for 3 hours before the solvent is reduced to a volume of approximately 2 mL. Absolute diethyl ether is added until precipitation occurs and the solution is allowed to stand for 2 hours. The precipitated material is filtered and dried under vacuum to give (bc)$Pd(OAc)_2$ **C4** as a light yellow solid (1.123 g, 1.92 mmol, 96 %yield).



C4

e) di(μ-aceto)bis[8-methylenylquinoline]dipalladium(II) **4** was synthesized according to a literature procedure.[23]

A solution of palladium acetate (0.5 g) and 8-methyl quinoline (0.33 g) in methanol (25 ml) was warmed at 50°C for 1h by which time the dark solution had become orange. Removal of solvent under vacuum and addition of diethyl ether to the residue gave a yellow solid which gave deep yellow crystals of complex **4**, (0.62 g, 88%) from chloroform/ether mixtures.

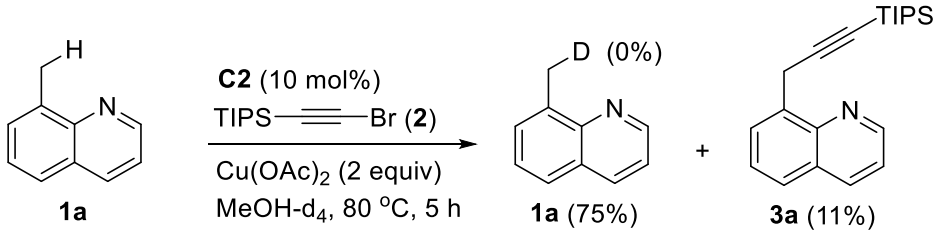


4

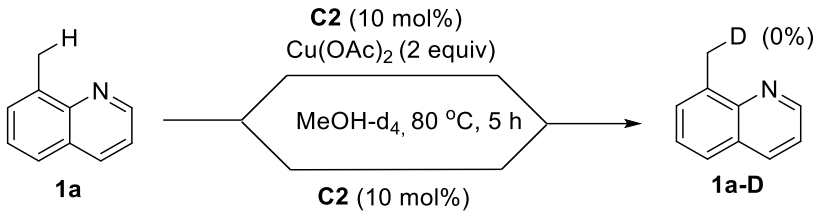
4.4.3 Mechanistic investigation

4.4.3a Irreversibility of C-H activation

i) To a flame dried 10 mL screw-capped vial, 8-methylquinoline **1a** (1 equiv), (bromoethynyl)triisopropylsilane **2** (0.15 mmol), (nc)$Pd(OAc)_2$ **C2** (10 mol%), $Cu(OAc)_2$ (2 equiv) and MeOH-d_4 (1 mL) were added. The mixture was stirred for 5 hr at 80 °C followed by cooling to room temperature. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the alkynylated product **3a** (11%) with a recovery of **1a** (75%) and the ^{1}H NMR reveled formation of deuterated **1a** was unobserved.

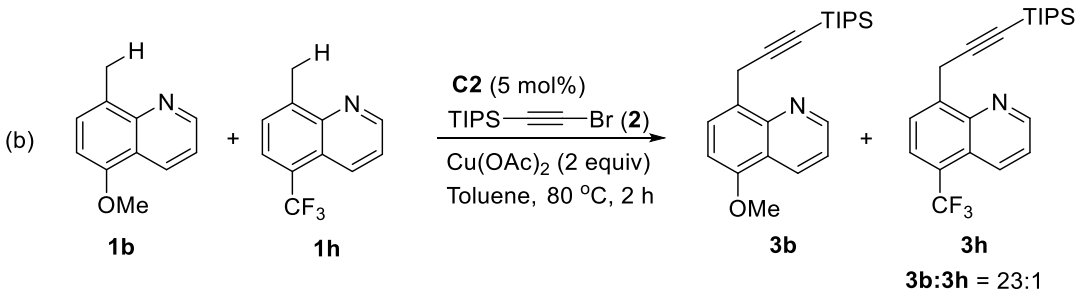


ii) To a flame dried 10 mL screw-capped vial, 8-methylquinoline **1a** (1 equiv), (nc)$Pd(OAc)_2$ **C2** (10 mol%), $Cu(OAc)_2$ (2 equiv) and MeOH-d_4 (1 mL) were added. The mixture was stirred for 5 hr at 80 °C followed by cooling to room temperature. ^{1}H NMR reveled formation of deuterated **1a** was unobserved.



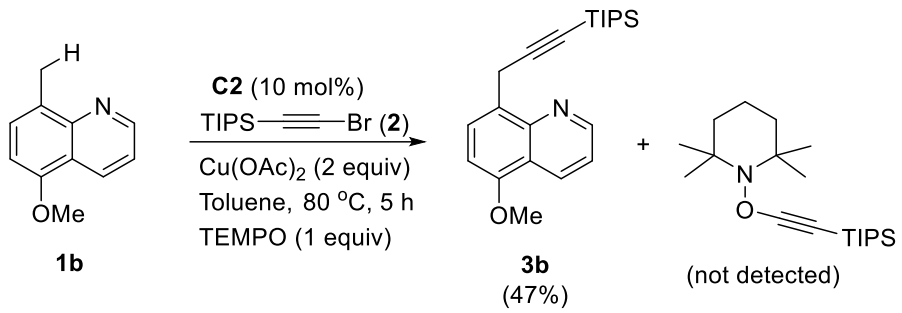
4.4.3b Competitive experiment

To a flame dried 10 mL screw-capped vial, 5-methoxy-8-methylquinoline **1b** (1 equiv) and 8-methyl-5-(trifluoromethyl)quinoline **1f** (1 equiv), (triisopropylsilyl)ethynyl bromide **2** (1 equiv), (nc)Pd(OAc)$_2$ (10 mol%), Cu(OAc)$_2$ (2 equiv) and toluene (1 mL) were added. The mixture was stirred for 2 hr at 80 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated and the residue was analyzed by ^{1}H NMR.



4.4.3c Radical trapping experiment

To a flame dried 10 mL screw-capped vial, 5-methoxy-8-methylquinoline **1b** (0.2 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.3 mmol), TEMPO (0.2 mmol), (nc)Pd(OAc)$_2$ **C2** (10 mol%), Cu(OAc)$_2$ (2 equiv) and toluene (1 mL) were added under Ar. The mixture was stirred for 5 hr at 80 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated *in vacuo*. The crude mixture analyzed by GC and GC-MS and formation of *O*-alkynylated-TEMPO was unobserved. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the alkynylated products **3b** with isolated yield of 47% along with 29% recovery of **1b**.



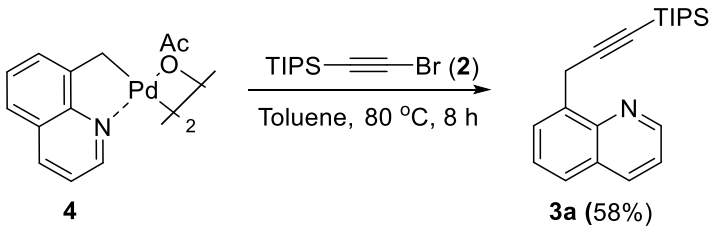
GC programming

GC Column – HP-5 (30m x 0.25mm x 0.25mm); Injector temperature – 280 °C; Detector temperature – 280 °C; Column flow – 1.0 mL/min; Carrier gas – Nitrogen gas; Split Ratio – 10:1

(80 °C hold for 5 min, heated up to 280 °C with ramping rate 10 °C/min)

4.4.3d Reaction of palladacycle(II) 4 with 2

To a flame dried 10 mL screw-capped vial, palladacycle(II) **4** (0.1 mmol), (triisopropylsilyl)ethynyl bromide **2** (0.25 mmol) and toluene (1 mL) were added under Ar. The mixture was stirred for 8 hr at 80 °C followed by cooling to room temperature. The solution was filtered through a celite pad and washed with 10-20 mL of dichloromethane. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the alkynylated products **3a** with an isolated yield of 58%.



(i) For update data of all newly synthesized compounds, see Appendix A.

(ii) For copy of ^{1}H and ^{13}C NMR (only selected compounds) see Appendix B

4.5 References

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(10) In the reaction of 1a with 2 catalyzed by C2, at prolonged heating (10 h at 120 ^{o}C) formation of 8-(bromomethyl)quinoline (15%) and quinolin-8-ylmethyl acetate (7%)

along with 3a (37%) were also observed. These results indicating that direct nucleophilic substitution at the electrophilic carbon is also operative (under higher temperature) and thus leads to C-X bond formation (X = Br, OAc). Also see ref. 8q.

(11) See Supporting Information for details.

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(14) The use of $Cu(OAc)_2$ as an oxidant is important and responsible for the Pd(II)-Pd(IV) oxidation since the TIPS-alkynyl bromide probably is not enough oxidising to do that (Scheme 4.3). Moreover, as suggested it also acts as an additive (e.g., a base responsible for binding HBr and as an acetate source) in the catalyst regeneration step. Thus, we can hardly believe that $Cu(OAc)_2$ acts as both an additive and an oxidant.

(15) Other less hindered alkynyl halides (1-iodo-2-(trimethylsilyl)acetylene and (bromoethynyl)benzene) were not reactive, presumably a strong coordination of the alkyne moiety with the palladium center and thus may prevent the oxidative addition step (also see ref. 2c).

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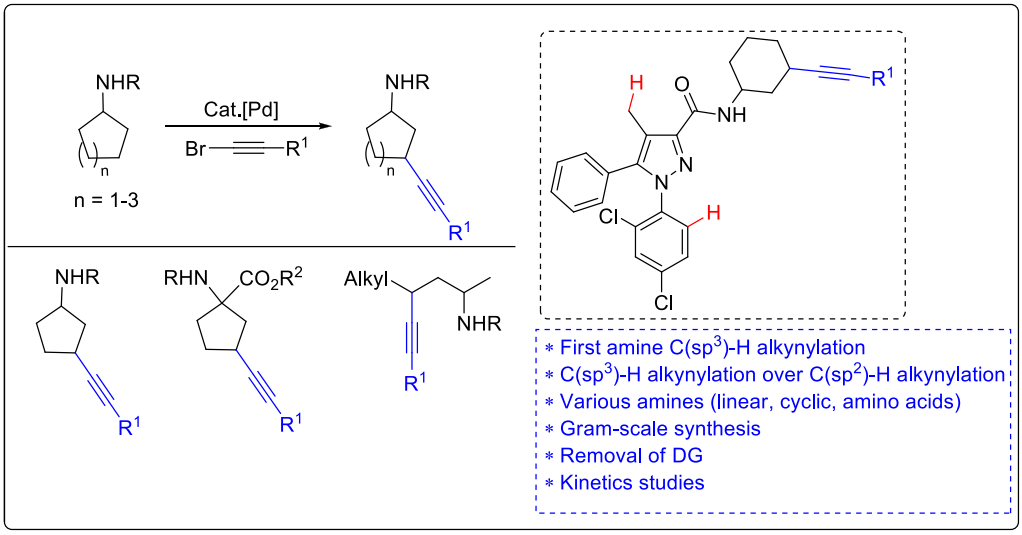
Chapter 5

Pd(II)-Catalyzed γ-C(sp^3)-H Alkynylation of Amines

In this chapter, a palladium(II)-catalyzed alkynylation of unactivated gamma C(sp^3)–H bond of alkyl amines (cyclic and linear) is described. The site-selective γ-alkynylation is highly compatible with the amine substrates and various picoli-namide-based auxiliaries. The kinetic experiment shows that the rate of the reaction depends on the coupling partner and the amines. Late-stage diversification of alkynylated amines was developed by utilizing amine and alkyne functionalities.



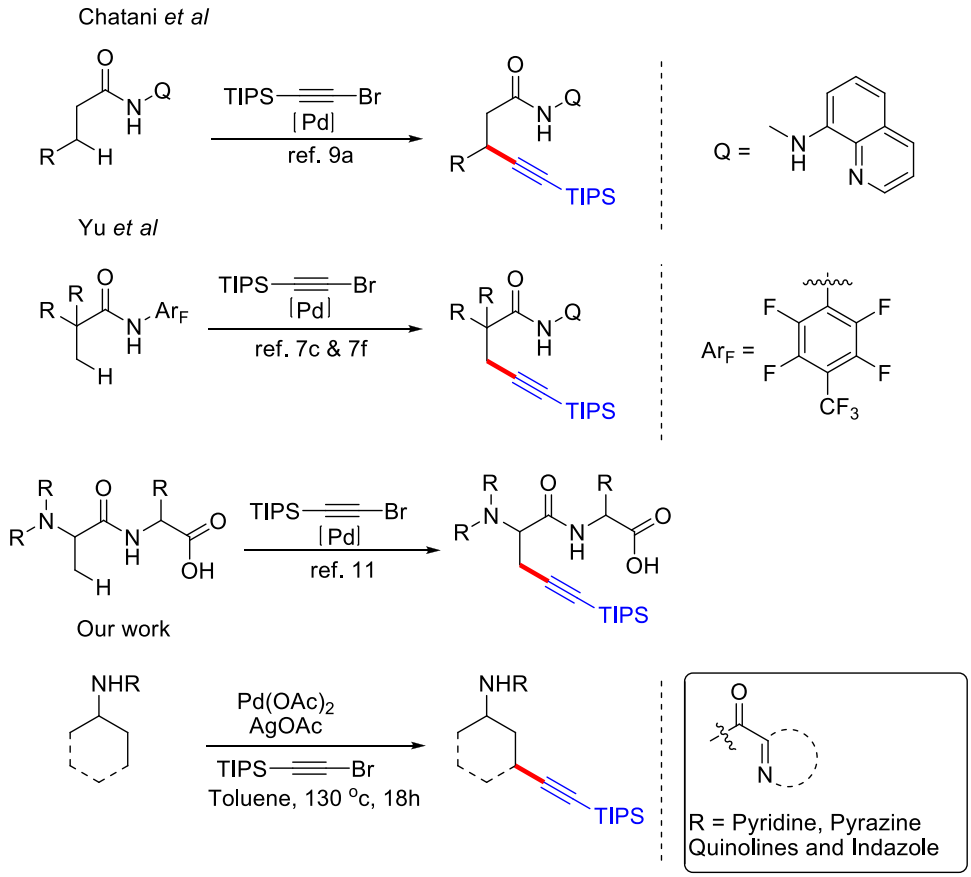
Vinod G. Landge *et al. Chem. Commun.*, 2018, *54*, 7483-7486

5.1 Introduction

New approaches that selectively incorporate versatile functional group into remote C(sp^3)–H bond is an emerging field of research in contemporary organic synthesis. Alkynes are an essential functional group in organic synthesis and can be used as versatile building blocks in drug discovery, material science, and the chemical industry, employing cross-coupling, metathesis and cycloaddition reactions.[1,2] Pd-catalyzed Sonogashira coupling which couple alkynes with aryl halides is a promising strategy for the incorporation of alkyne into aryl through the sp-sp^2 coupling.[3] The scope of alkynylation is further elaborated by coupling of alkynyl halides (sp) with inert aryl C(sp^2)-H bond, namely "inverse Sonogashira coupling".[4] In addition to Pd-catalyzed alkynylation, other transition metal-catalyzed C-H alkynylation strategy provides a plethora method to selectively functionalize sp^2 and sp^3 C-H bond with high efficiency.[5-8] However, transition metal-catalyzed activation of remote and inert C(sp^3)-H bonds remain extremely rare and underdeveloped.

A few examples are explored for the alkynylation of inert C(sp^3)-H with the aid of directing groups (DG). Noteworthy work by Chatani and co-workers reported a palladium (II)-catalyzed *β*-alkynylation of secondary C(sp^3)-H bonds of acids derivatives using a bidentate auxiliary[9] (see Chapter 1, Scheme 1.24). Yu and co-workers reported a Pd(0)/NHC catalyzed alkynylation of *β*-methyl C(sp^3)-H bonds of acids applying an *N*-arylamide auxiliary[7c] (see Chapter 1, Scheme 1.25).The recyclable heterogeneous catalytic system is developed using gold supported Pd-nanoparticle for direct ethynylation of secondary C(sp^3)-H aliphatic carboxylic derivatives.[9b] Chen and co-workers developed a diastereoselective *β*-alkynylation of α-amino acids using Pd(II) *via* aminoquinoline directed primary[10a] and secondary[10b] C(sp^3)-H bond activation. A research group of Chen and Shi have identified the unique directing group, 1,2,3-triazole amine for selective Pd(II)-catalyzed C(sp^3)-H bond activation under silver-free condition followed by alkynylation strategy[7e] (see Chapter 1, Scheme 1.26). Subsequently, Yu and co-workers introduced Pd(II)/pyridine-based catalytic system for methyl C(sp^3)-H alkynylation of α-quaternary carbon centers of acid derivatives[7f] (see Chapter 1, Scheme 1.27). Similarly, Pd(II)-catalyzed site-selective C(sp^3)–H alkynylation of oligopeptides was developed using tetrabutylammoniun acetate as a key additive[11] (see Chapter 1, Scheme 1.28). Nevertheless, this type of C-H bond activations has been mostly achieved for the *β*-C(sp^3)–H alkynylation of acid derivatives. The accomplishment of C−H

alkynylation of alkyl amines, a fundamental class of synthetic substrates, has not been developed to date.



Scheme 5.1 Palladium-catalyzed C(sp^3)-H bond activation strategies.

Amines constitute essential synthetic precursors and are ubiquitous in agrochemical, peptide, pharmaceutical, and functional materials.[12] The representative examples of amine-containing biologically active molecules are shown in Figure 5.1. In light of our interest and continuation of transition metal-catalyzed alkynylation reactions,[5r-5t,7d] In this chapter we disclose unprecedented palladium(II)-catalyzed alkynylation of *gamma*-C(sp^3)-H bond of amines with the assistance of a removable picolinamide as DG (Scheme 5.1). The present alkynylation strategy is general and has a broad substrate scope. Remarkably, various ring size, α-quaternary, *N*-cyclic, and linear amines were alkynylated under our reaction conditions.

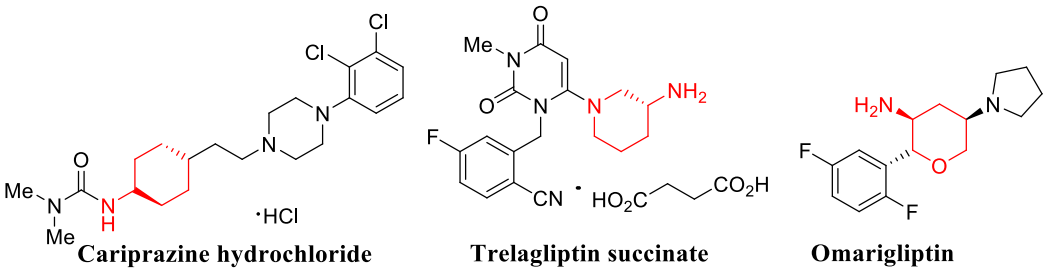


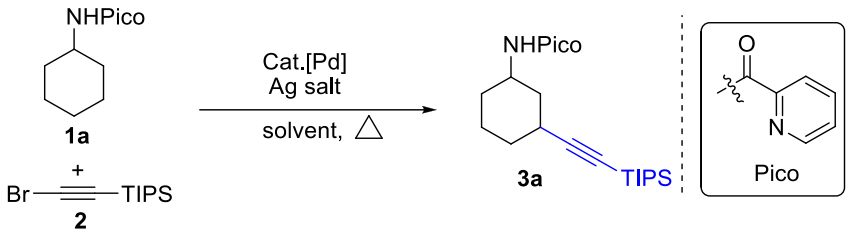
Figure 5 1 Representative examples of amine-containing biologically active molecules.

5.2 Results and Discussion

5.2.1 Optimization of reaction condition

The preliminary investigation on palladium-catalyzed *gamma* sp^3 C-H alkynylation of amines is carried out with an evaluation of a range of palladium catalysts, oxidants, bases, solvents, and temperature using *N*-cyclohexylpicolinamide (**1a**), and (triisopropylsilyl)ethynyl bromide **2** as representative coupling partner (Table 5.1). Initially, the reaction of **1a** and **2** in the presence of $Pd(PPh_3)Cl_2$ (10 mol%), AgOAc (2 equiv) as oxidant in toluene at 130 ^oC (bath temperature) for 18 h to yield the expected product **3a** in 15% isolated yield (Table 5.1, entry 1). Among a variety of palladium salt, $Pd(OAc)_2$ found to be the optimal catalyst to provide the C-H alkynylation product **3a** in 85 % isolated yield with a recovery of **1a** in 8% (Table 5.1, entries 1-7). The necessity of each of the key reaction components was demonstrated through a series of control experiments (Table 5.1, entries 9-13). By lowering the temperature from 130 ^oC to 100 ^oC, we obtained the product **3a** in 75% yield (Table 1, entry 8) and no reaction was observed in the absence of the palladium catalyst (Table 5.1, entry 9). Notably, trace (~6%) amounts of C-H alkynylated product **3a** was observed in the absence of an oxidant (Table 5.1, entries 10). When the reaction was carried out with (bromoethynyl)benzene instead of **2**, there is no formation of the corresponding desired product (Table 5.1, entry 11). The effect of solvent was also carried out (Table 5.1, entries 14-15), and found that the reaction proceeded efficiently in toluene. Other solvents such as DMA, DCE, HFIP, and CF_3CH_2OH were found to be ineffective, and no (or trace) alkynylated product **3a** was observed under optimal conditions.

Table 5.1. Optimization of the reaction conditions.[a]



Entry	Reaction conditions	Yield of **3a** (%)[b]	Recovered **1a** (%)[b]
1	$Pd(PPh_3)_2Cl_2$ used as [Pd] source	15%	78%
2	$Pd(TFA)_2$ used as [Pd] source	n.r.	98%
3	standard conditions	85%	8%
4	$Pd(dba)_3$ used as [Pd] source	20%	71%
5	$Pd(CH_3CN)_4BF_4$ used as [Pd] source	trace	97%
6	$PdCl_2$ used as [Pd] source	trace	98%
7	$Pd(acac)_2$ used as [Pd] source	trace	97%
8	at 100 °C	75%	21%
9	without [Pd] cat	n.r.	95%
10	without AgOAc	trace	92%
11	(bromoethynyl)benzene instead of **2**	n.r.	99%
12	Ag_2CO_3instead of AgOAc	75%	10%
13	$PhCO_2Ag$ instead of AgOAc	35%	58%
14	HFIP used as solvent	trace	98%
15	CF_3CH_2OH used as solvent	trace	97%

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.12 mmol), $Pd(OAc)_2$ (0.01 mmol), AgOAc (0.20 mmol) and toluene (1 mL) heated at 130 °C (bath temperature) for 18 h under argon atm. [b]Isolated yields. n.r.= no reaction.

5.2.2 Scope of amides

With an optimized catalytic system in hand, we set out to probe its versatility in the *gamma*-C(sp^3)-alkynylation of various amine substrates using (triisopropylsilyl)ethynyl bromide **2** as coupling partner (Table 5.2). The developed synthetic methodology is

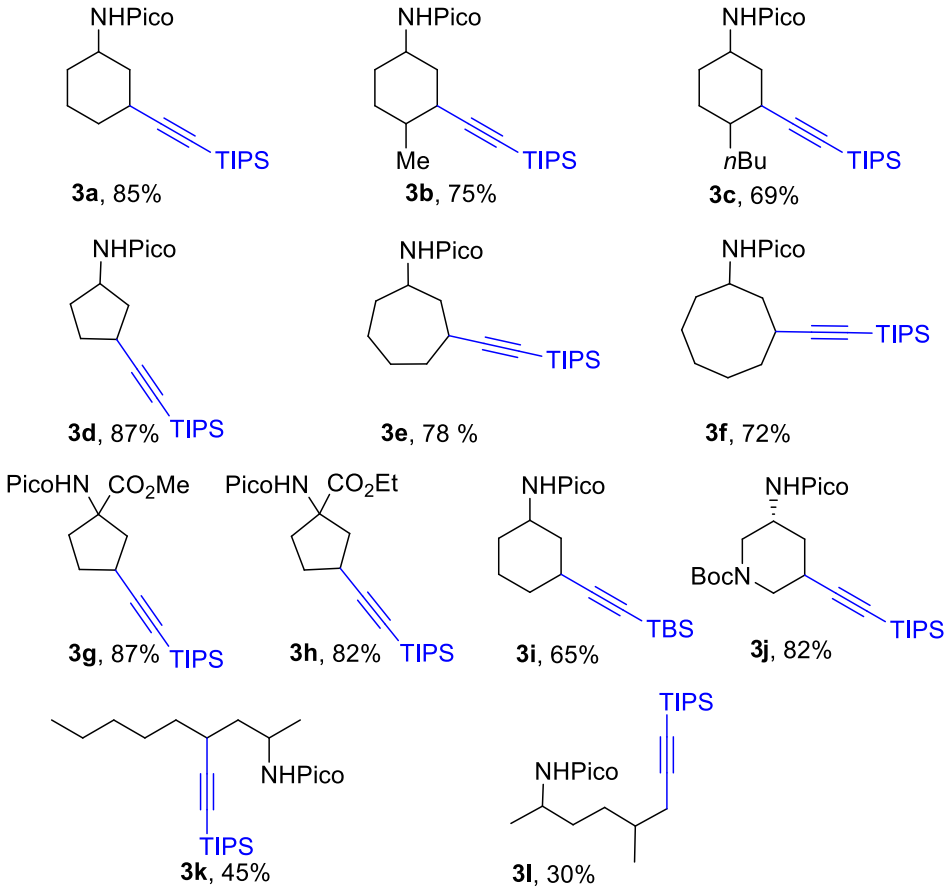
general and has a broad substrate scope. As shown in table 5.2, the 4-substituted cyclohexyl amines such as **1b** and **1c** were well tolerated under our optimized conditions and gave the desired products in good yields (**3b** in 75%, **3c** in 69 %). To our delight, carbocyclic amines which containing 5, 7 and 8-membered rings were also successfully alkynylated at the *gamma* position of amines in good to very excellent yields {**3d** (87%), **3e** (78%) and **3f** (72%)}. The present method was also found to be effective for the alkynylation of amino acid substrates containing α-quaternary carbon centers. Thus, compounds **1g** and **1h** gave the corresponding *gamma*-alkynylated amines {**3g** (87%) & **3h** (82%)} in very good yields, which can be used as a linker for the bivalent interaction and the bio-conjugation process. The alternative alkyne coupling partner (*tert*-butyldimethylsilyl)ethynyl bromide was applied with **1a** under standard conditions to give the alkynylated product **3i** in 65% yield. To our delight, the chiral *N*-Boc protected heterocylic amine which is privileged structures in medicinal chemistry was applied for alkynylation reaction under standard conditions to provide **3j** in excellent yield (82%). In addition to that, aliphatic linear amines also proceed smoothly under an optimal condition such as the 2-heptyl amine to give **3k** in 45% yield. The lower in yield in case of aliphatic amines are due to the geometric flexibility of the amines, leading to the complication of a picolinamide-directed cyclometalation. Surprisingly, the alkynylation of alkyl amine **1l** showed the ε-alkynylated amines **3l** in 30% yields yield. In all the reactions the unreacted starting material (**1a**) was recovered. Gratifyingly, except *gamma*-alkynylation product no different alkynylated product was observed. We have also successfully shown the scalability of this catalytic protocol. In this regard, the present palladium-catalyzed alkynylation was tested for the gram-scale synthesis of **3a** (5.0 mmol scale), and it worked excellently with an expected alkynylated product (**3a**) in 82% yield.

Furthermore, we also evaluated the influence of different protecting groups under the standard conditions, including various picolinic acid-based directing groups and other amide-type directing groups (Table 5.2). The 2- or 3-substituted picolinic acid derived

amines underwent the alkynylation reaction with (triisopropylsilyl)ethynyl bromide to afford **3m** (63%) and **3n** (75%) in good yields. Various heterocycles such as pyrazine, quinoline, and isoquinoline based were also used as DG, the corresponding γ-alkynylated products {**3o** (63%), **3p** (75%), **3q** (62%) and **3r** (75%)} were obtained in good yields.

We observed that five-membered heterocyclic indazoline as DG afforded the desired γ-alkynylated product **3s** in 45% isolated yield with a recovery of **1s** in 47%.

Table 5.2 Pd-catalyzed γ-sp^3-C-H alkynylation of amines.[a,b]



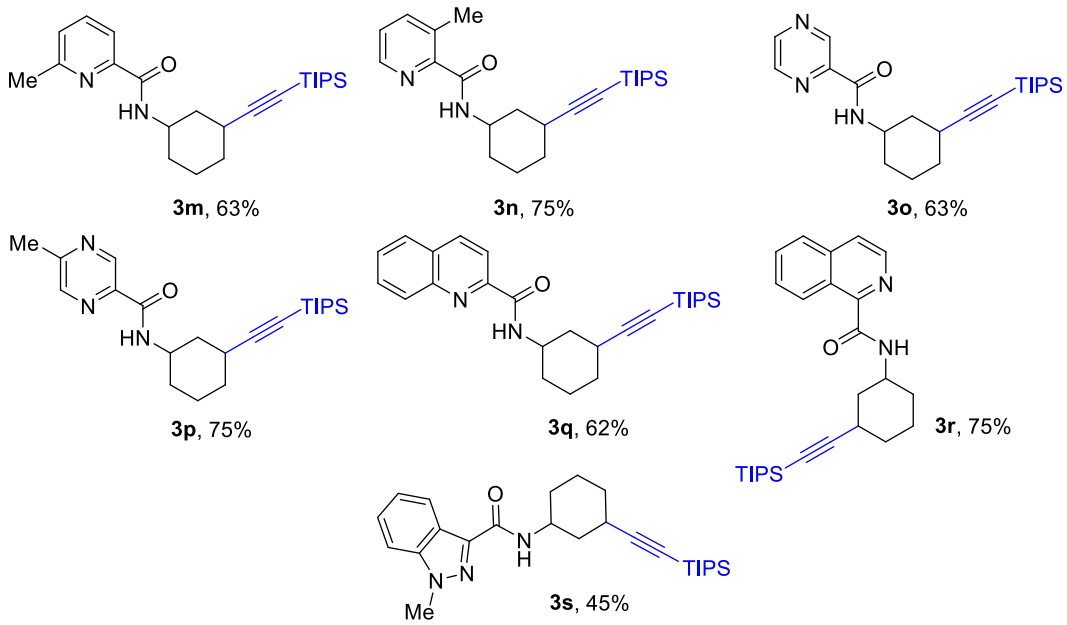
[a]Reaction conditions: amine (0.25 mmol), **2** (0.27 mmol), $Pd(OAc)_2$ (0.025 mmol), AgOAc (0.50 mmol) and toluene (1 mL) heated at 130 ^oC for 18 h under argon atm. [b]Isolated yields

To highlight the synthetic utility of the DG, the competitive site-selective alkynylation study was carried out in the presence of alkyl amine **1t**, conjugated with pyrazole moiety containing both Ar-C(sp^3)–H and Ar-C(sp^2)-H bond for chelation (Scheme 5.2). Significantly, *gamma*- C(sp^3)-H bond of amine alkynylation (**3t**) was observed over C(sp^2)-H alkynylation under standard reaction conditions in 55% yield with a recovery of **1t** in 37%.

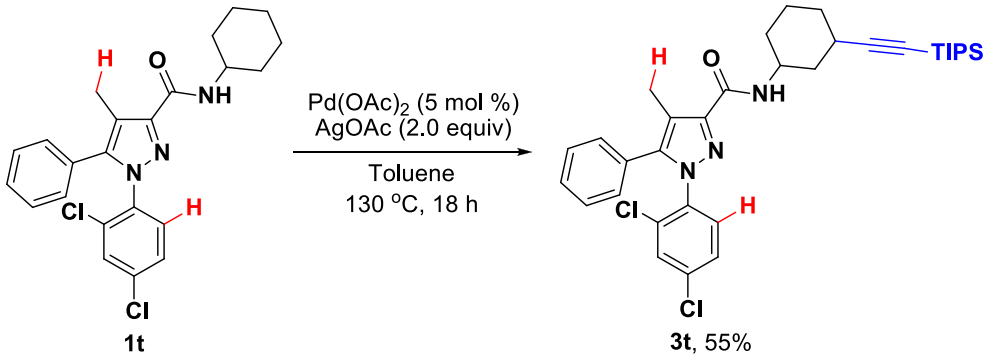
5.2.3 Diversification of alkynylated product

The diversification of alkynylated amine derivatives is shown in Scheme 5.3. The deprotection of picolinamide was achieved by using Lewis catalyst (Zn/HCl) to obtain terminal *o*-alkynylbenzylamine **4a** in 80% yield. A rhodium(III)-catalyzed cascade oxidative olefination and cyclization of **3a** with ethyl acrylate to enable **4b** in 72% isolated yield. The deprotection of the TIPS group of **3a** was easily achieved by

Table 5.2 Influence of different auxiliary groups under the standard conditions.[a,b]

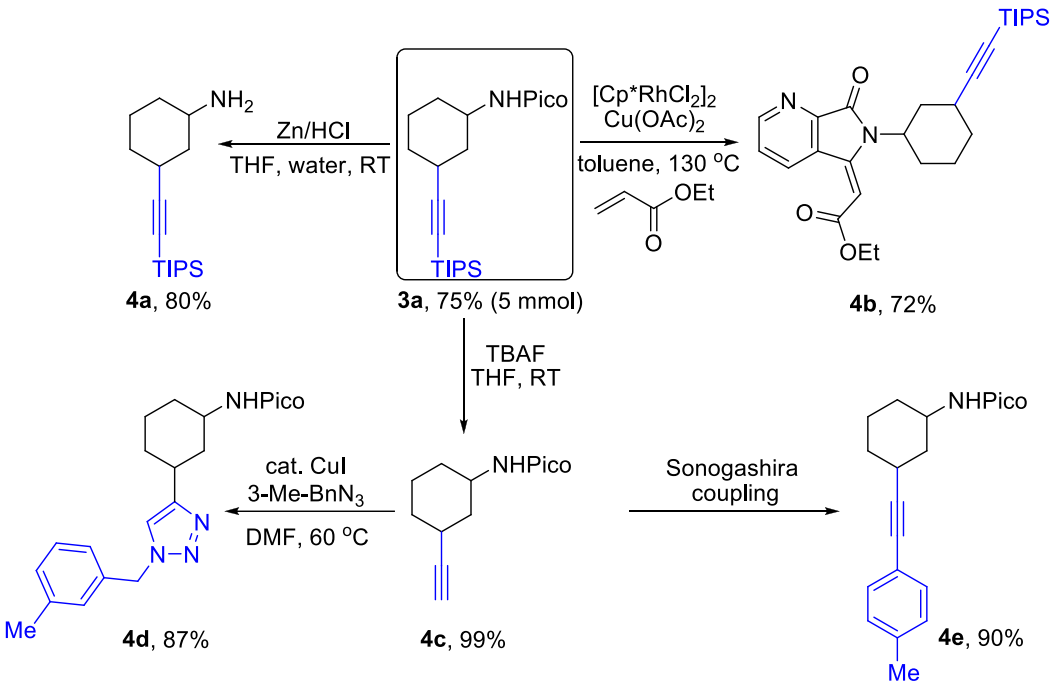


[a]Reaction conditions: amine (0.25 mmol), **2** (0.27 mmol), $Pd(OAc)_2$ (0.025 mmol), AgOAc (0.50 mmol) and toluene (1 mL) heated at 130 °C for 18 h under argon atm. [b]Isolated yields.



Scheme 5.2 Site-selective alkynylation strategy.

treatment with TBAF under standard reaction conditions to afford **4c** in quantitative yield. The desilylated compound **4c** was applied for the Sonogashira coupling to provide **4e** in 90% isolated yield. The compound **4c** was also successfully employed for the "click" reaction with *m*-methyl benzyl azide to yield **4d** in 87% under standard reaction conditions.



Scheme 5.3 Diversification of γ-alkynylated amine **3a.**

The kinetic studies were carried out to determine the order of reaction on palladium-catalyzed γ-alkynylation of amine **1a** with **2** by using the initial rate approximation (Figure 5.2). The data shows that the increasing the concentration of **1a** enhance the rate of reaction with a slope of 0.86 obtained from the plot of log(rate) vs log(conc of **1a**), indicating a fractional order alkynylation reaction. Similarly, with increasing the concentration of **2**, the rate of reaction increased, and a slope of 1.01 was obtained from the plot of log(rate) *vs* log(conc of **2**). Thus, the rate of reaction depends on both the substrates.

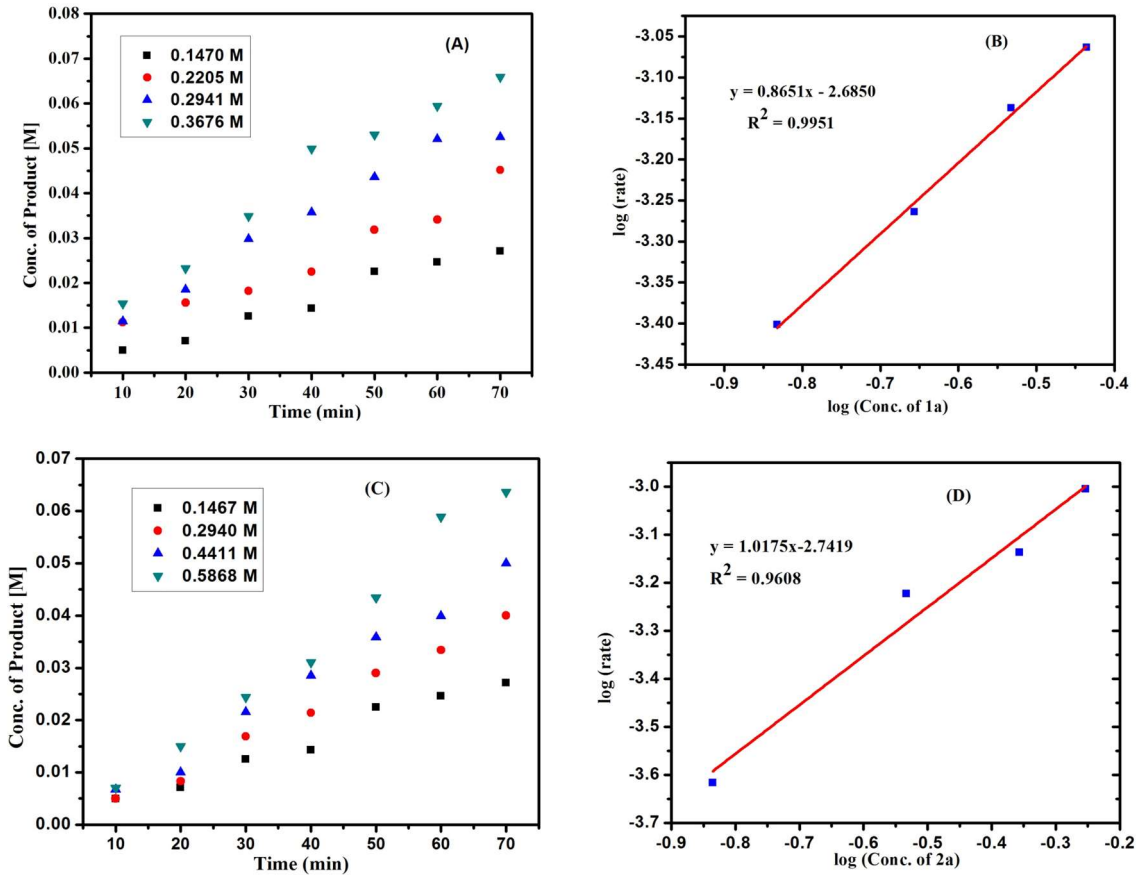


Figure 5.2 (**A**) The graph of product concentration *vs* time with increasing concentration of **1a**. (**B**) graph of log(rate) *vs* log(conc. of **1a**). (**C**) Graph of product concentration *vs* time with increasing concentration of **2**. (**D**) Graph of log(rate) *vs* log(conc. of **2**).

5.3 Conclusion

In summary, we have described the first example of *γ*-alkynylation of various alkyl amines in this chapter. Easily removable picolinamide and its derivatives were identified as suitable auxiliaries for enabling Pd-catalyzed *γ*-alkynylation process. The substrate scope was successfully expanded applying carbocyclic and acyclic alkyl amines. Interestingly, the present protocol showed site-selective *γ*-alkynylation C(sp^3)-H bond in the presence of accessible Ar-C(sp^3)–H and Ar-C(sp^2)-H bonds.

5.4 Experimental Section

5.4.1 Synthesis of the starting materials

Picolinamides were prepared by the reaction of picolinic acid with the corresponding amines.[13, 14, 15]

5.4.2 General procedure for the Pd-catalyzed C(sp^3)-alkynylation of amine

To an oven-dried 10 mL screw-capped vial, picolinamide (0.25 mmol), (bromoethynyl)triisopropylsilane **2** (0.27 mmol), $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2 equiv), and toluene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 18 hrs at 130 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired alkynylated product **3**.

5.4.3 Synthetic application

5.4.3a Synthesis of 4a (Removal of directing group)

To a suspension of the starting **3a** (0.15 mmol, 1.0 equiv) in THF (1.5 mL) was added water (1.5 mL) followed by 12M HCl (0.37 mL) and the mixture was stirred for 5 minutes at rt. Zinc dust (145 mg, 2.24 mmol, 15 equiv) was then added in three portions and the mixture was stirred at rt. After 1.5 h, the reaction was filtered through a celite plug. The filtrate was transferred to a separating funnel with 2M NaOH (50 mL) and extracted twice with DCM (2 x 50 mL). The combined organic phase was dried over Na_2SO_4 and and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: MeOH/DCM) to afford the desired product **4a** (33 mg, 80%, yellow liquid).

5.4.3b Synthesis of 4b

To an oven-dried 10 mL screw-capped vial, amide **3a** (38 mg, 0.1 mmol), ethyl acrylate (20 mg, 0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2 equiv), and toluene (1 mL) were added under a gentle stream of argon. The mixture was stirred for 24 hrs at 130 °C (bath temperature) followed by cooling to room temperature. The mixture was filtered

through a celite pad with several washings (3 x 3 mL dichloromethane) and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: pet ether/EtOAc) to afford the desired product **4b** (34 mg, 72%, yellow liquid).

5.4.3c Synthesis of 4c

The corresponding compound **3a** (500 mg, 1.3 mmol), was dissolved in THF and 1.0 M TBAF in THF (1.5 equiv) was then added at 0 ^{o}C with constant stirring. The reaction progress was monitored by TLC. The mixture was diluted with water extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered and evaporated *in vacuo*. The obtained crude product was purified by column chromatography to afford the desired terminal alkyne. product **4c** (294 mg, 99%, yellow liquid).

5.4.3d Synthesis of 4e

Under argon atm **3a** (prepared by the above mentioned procedure) (34 mg, 0.15 mmol), iodobenzene (39 mg, 0.18 mmol), $PdCl_2$ (5 mol%), CuI (2.5 mol%), Et_3N (1 mL) were charged to a 25 mL Schlenk tube. The reaction mixture was stirred at 50 °C for 12 hrs. The mixture was filtered through celite and concentrated *in vacuo*. The obtained crude product was purified by column chromatography to afford **4e** (43 mg, 90%, white solid).

5.4.3e Synthesis of 4d

Under argon atm **3a** (34 mg. 0.15 mmol, 1.0 equiv), CuI (10 mol %) and 3-methyl benzyl azide (20 mg, 0.15 mmol, 1.0 equiv) were dissolved in DMF (1 mL) and stirred at 60 °C for 16 hrs. After completion of the reaction saturated aq. NH_4Cl solution (5 mL) was added and the mixture was extracted with dichloromethane (3 x 5 mL) and dried over anhydrous Na_2SO_4. After complete evaporation of the solvent, the obtained crude product was purified by column chromatography to afford **4d** (49 mg, 87%, yellow solid).

5.4.4 Rate order determination

The rate order of the alkynylation reaction with various reaction components was determined by the initial rate method. The data of the concentration of the product *vs* time (min) plot was fitted linear with Origin Pro 8. The slope of the linear fitting

represents the reaction rate. The order of the reaction was then determined by plotting the log(rate) *vs* log(conc) for a particular component.

5.4.4a Rate order determination for *N*-(3-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide (3a).

To determine the order of the alkynylation reaction on **1a**, the initial rates at different initial concentrations of **1a** were recorded. The final data was obtained by averaging the results of three independent runs for each experiment.

To an oven-dried 10 mL screw-capped vial, (bromoethynyl)triisopropylsilane **2** (71mg, 0.27 mmol), $Pd(OAc)_2$ (6mg, 10 mol%), AgOAc (149 mg, 2 equiv), specific amount of **1a** (as shown in table S1), n-decane (38.4 mg, 0.27 mmol) as internal standard and toluene (2 mL) were added under a gentle stream of argon. The mixture was stirred at 130 °C (bath temperature). At regular intervals, the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with EtOAc and subjected to GC analysis. The concentration of the product **3a** obtained in each sample was determined with respect to the internal standard n-decane.

Table 5.3 Rate of Palladium-catalyzed alkynylation reaction at different initial concentration of **1a**.

Experiment	Amount of **1a** (gm)	Initial concentration of **1a** [M]	Initial Rate [$Mmin^{-1}$] x 10^{-3}
1	0.060	0.147	0.397
2	0.090	0.220	0.544
3	0.119	0.294	0.729
4	0.150	0.367	0.864

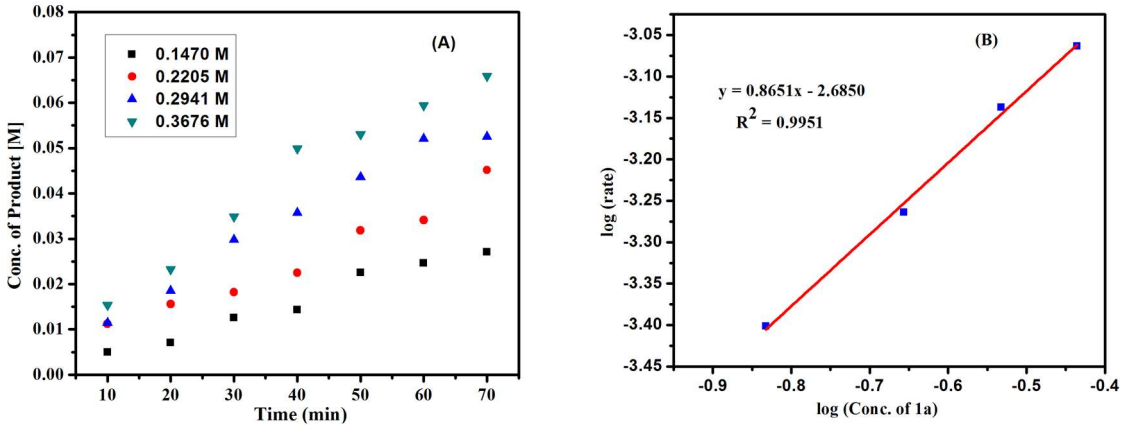


Figure 5.3. (A) Time-dependent formation of **3a** at different initial concentration of **1a**. (B) Plot of log(rate) *vs* log(conc. of **1a**).

5.4.4b Rate order determination for (bromoethynyl)triisopropylsilane.

To determine the order of the alkynylation reaction on (bromoethynyl)triisopropylsilane (**2**), the initial rates at different initial concentrations of (bromoethynyl)triisopropylsilane were recorded. The final data was obtained by averaging the result of three independent runs for each experiment.

Representative procedure was followed, employing **1a** (80 mg, 0.27mmol), $Pd(OAc)_2$ (6 mg, 10 mol%), AgOAc (149 mg, 2 equiv), specific amount of (bromoethynyl)triisopropylsilane **2** (as shown in table S2), n-decane (38.4 mg, 0.27 mmol) as internal standard and toluene (2 mL).

Table 5.4 Rate of alkynylation reaction at different initial concentration of **2**.

Experiment	Amount of **2a** (gm)	Initial concentration of **2a** [M]	Initial Rate $[Mmin^{-1}] \times 10^{-3}$
1	0.076	0.146	0.242
2	0.152	0.293	0.597
3	0.228	0.440	0.728
4	0.304	0.558	0.987

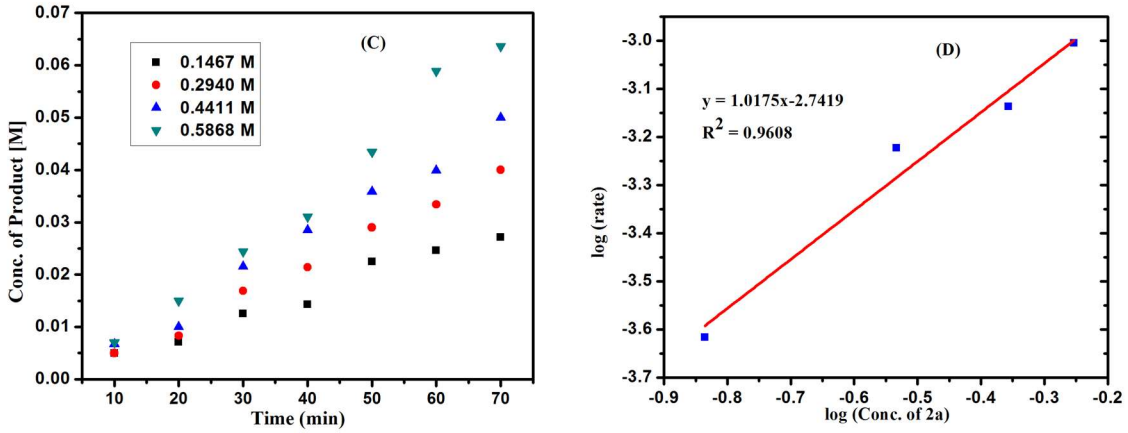


Figure 5.4 (A) Time-dependent formation of **3a** at different initial concentration of **2**. (B) Plot of log(rate) *vs* log(conc. of **2**).

(i) For update data of all newly synthesized compounds, see Appendix A.

(ii) For copy of ^{1}H and ^{13}C NMR (only selected compounds) see Appendix B

5.5 References

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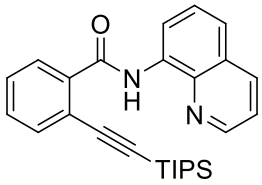
Appendix

Appendix A

NMR and HRMS Data of Compounds

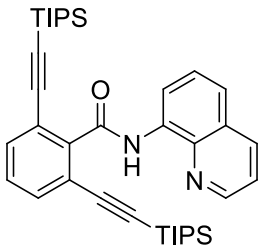
Chapter 2A and Chapter 2B

_N_-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



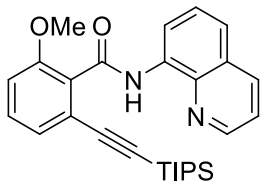
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80-0.85 (m, 21H), 7.42-7.47 (m, 3H), 7.54-7.64 (m, 3H), 7.80 (m, 1H), 8.16-8.18 (dd, *J* = 8.2 Hz, 1H), 8.76 (dd, *J* = 4.2, 1H), 8.93-8.95 (dd, *J* = 6.1 Hz, 1H), 10.51 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 18.3, 97.1, 103.9, 117.1, 120.7, 121.4, 121.8, 127.3, 127.9, 128.7, 130.1, 133.9, 134.7, 136.2, 138.9, 139.2, 148.2, 166.4; HRMS (EI): *m/z* Calcd for $C_{27}H_{33}N_2OSi$ $[M+H]^+$: 429.2362; Found: 429.2357.

_N_-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



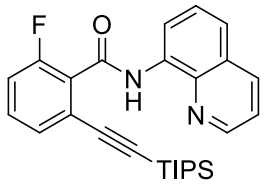
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84-0.87 (m, 42H),7.31-7.35 (t, *J* = 7.6 Hz, 1H), 7.40-7.43 (dd, *J* = 8.2 Hz, 1H), 7.51-7.58 (m, 4H), 8.14-8.16 (dd, *J* = 8.2 Hz, 1H), 8.72 (dd, *J* = 4.2, 1H), 8.98-9.00 (dd, *J* = 7.3 Hz, 1H), 10.06 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 18.3, 95.8, 103.0, 117.0, 121.3, 121.4, 121.4, 127.2, 127.7, 128.7, 132.3, 134.9, 136.0, 138.5, 143.5, 147.9, 165.5; HRMS (EI): *m/z* Calcd for $C_{38}H_{53}N_2OSi_2$ $[M+H]^+$: 609.3696; Found: 609.3691.

2-methoxy-*N*-(quinolin-8-yl)-6-((triisopropylsilyl)ethynyl)benzamide



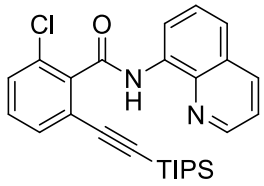
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (m, 21H), 4.17 (s, 3H), 7.04-7.06 (d, *J* = 7.9 Hz, 1H), 7.14-7.15 (d, *J* = 7.3 Hz, 1H), 7.42-7.59 (m, 3H), 8.12-8.14 (d, *J* = 7.9 Hz, 1H), 8.39-8.40 (d, *J* = 7.6 Hz, 1H), 8.84 (s, 1H), 9.07-9.08 (d, *J* = 6.1 Hz, 1H), 12.36 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 18.9, 55.9, 61.7, 83.4, 111.4, 117.1, 121.1, 121.3, 121.3, 122.2, 127.4, 127.9, 132.2, 133.0, 135.6, 136.0, 139.1, 148.1, 157.6, 163.4; HRMS (EI): *m/z* Calcd for $C_{28}H_{35}N_2O_2Si$: 459.2468; Found: 459.2462.

2-fluoro-*N*-(quinolin-8-yl)-6-((triisopropylsilyl)ethynyl)benzamide



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 21H), 7.14-7.17 (m, 1H),7.37-7.39 (m, 2H), 7.43-7.45 (q, *J* = 4.2 Hz, 1H), 7.55-7.61 (m, 2H), 8.16-8.18 (d, *J* = 8.2 Hz, 1H), 8.75-8.76 (d, *J* = 4.2 Hz, 1H), 8.97-8.99 (d, *J* = 7.3 Hz, 1H), 10.20 (brs, 1H);^{13}C NMR (125MHz, $CDCl_3$) δ 10.9, 18.2, 97.1, 102.3, 116.3, 116.4, 117.0, 121.5, 121.9, 122.0, 123.1, 123.2, 127.3, 127.8, 128.2, 128.4, 128.9, 128.9, 130.7, 130.8, 134.4, 136.2, 138.4, 148.2, 148.9, 158.2, 160.2, 162.1; HRMS (EI): *m/z* Calcd for $C_{27}H_{32}N_2OFSi$ $[M+H]^+$: 447.2268; Found: 447.2262.

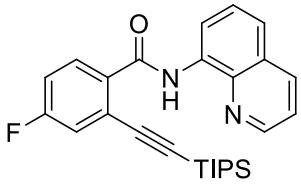
2-chloro-*N*-(quinolin-8-yl)-6-((triisopropylsilyl)ethynyl)benzamide



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 21H), 7.28-7.33 (m, 1H),7.40-7.48 (m, 3H), 7.53-7.60 (m, 2H), 8.14-8.16 (d, *J* = 8.3 Hz, 1H), 8.73-8.74 (q, *J* = 4.1 Hz, 1H), 8.99-9.01 (dd,

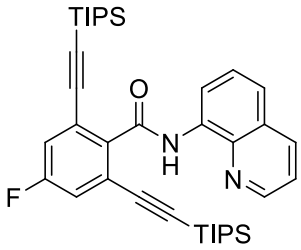
J = 7.0 Hz, 1H), 10.11 (brs, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 10.9, 18.2, 96.8, 102.4, 116.9, 121.5, 121.9, 122.9, 127.1, 127.7, 129.6, 129.9, 131.1, 131.3, 134.3, 136.1, 138.3, 139.3, 148.1, 164.0; HRMS (EI): *m/z* Calcd for $C_{27}H_{32}ClN_2OSi$: 463.1972; Found: 463.1967.

4-fluoro-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



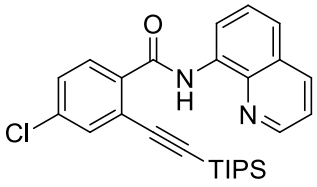
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80-0.86 (m, 21H), 7.13-7.17 (dt, *J* = 8.3 Hz, 1H), 7.29-7.32 (dd, *J* = 9.0 Hz, 1H), 7.42-7.45 (dd, *J* = 8.3 Hz, 1H), 7.54-7.61 (m, 2H), 7.80-7.84 (dd, *J* = 8.8 Hz, 1H), 8.16-8.18 (dd, *J* = 8.3 Hz, 1H), 8.77-8.78 (dd, *J* = 4.1, 1H), 8.99-8.91 (dd, *J* = 7.5 Hz, 1H), 10.50 (brs, 1H);^{13}C NMR (126 MHz,$CDCl_3$) δ 10.9, 18.3, 98.8, 102.6, 116.1, 116.3, 117.1, 120.2, 120.4, 121.5, 121.9, 122.8, 122.9, 127.3, 127.9, 131.0, 131.1, 134.5, 135.5, 135.5, 136.2, 138.8, 148.3, 161.9, 164.4, 165.4; HRMS (EI): *m/z* Calcd for $C_{27}H_{32}N_2OFSi$ $[M+H]^+$: 447.2268; Found: 447.2262.

4-fluoro-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



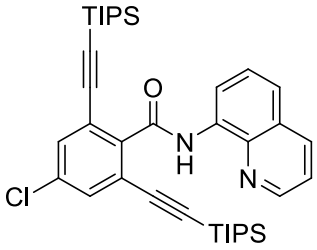
^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 42H), 7.20-7.22 (d, *J* = 8.5 Hz, 2H), 7.40-7.43 (dd, *J* = 8.3 Hz, 1H), 7.51-7.58 (m, 2H), 8.14-8.16 (dd, *J* = 8.2 Hz, 1H), 8.73-8.74 (dd, *J* = 4.4 Hz, 1H), 8.95-8.98 (dd, *J* = 7.3 Hz, 1H), 10.06 (brs, 1H); ^{13}C NMR (126 MHz $CDCl_3$) 10.9, 18.3, 97.4, 101.9, 117.0, 119.2, 119.4, 121.3, 121.6, 123.9, 123.5, 127.1, 127.7, 134.7, 136.1, 138.4, 140.1, 147.9, 160.4, 162.9, 164.8; HRMS (EI): *m/z* Calcd for $C_{38}H_{52}FN_2OSi_2$: 627.3602; Found: 627.3597.

4-chloro-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



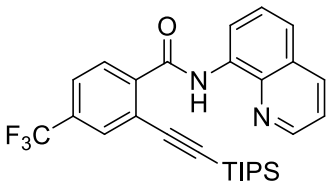
^{1}H NMR (500 MHz,$CDCl_3$) δ 0.83 (s, 21H), 7.41-7.46 (m, 2H),7.55-7.61 (m, 3H), 7.75-7.76 (d, *J* = 8.5 Hz, 1H), 8.17-8.19 (dd, *J* = 8.2 Hz, 1H), 8.76-8.78 (dd, *J* = 4.2 Hz, 1H), 8.88-8.90 (dd, *J* = 7.6 Hz, 1H), 10.51 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.3, 98.9, 102.4, 117.1, 121.5, 122.0, 122.3, 127.3, 127.9, 128.9, 130.2, 133.4, 134.4, 136.1, 136.2, 137.5, 138.8, 148.3, 165.3; HRMS (EI): *m/z* Calcd for $C_{27}H_{32}ClN_2OSi$: 463.1972; Found: 463.1967.

4-chloro-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 42H), 7.40-7.42 (d, *J* = 4.2 Hz, 1H),7.48 (s, 2H), 7.51-7.57 (m, 2H), 8.14-8.15 (d, *J* = 8.2 Hz, 1H), 8.72-8.73 (dd, *J* = 4.2 Hz, 1H), 8.95-8.97 (dd, *J* = 7.6 Hz, 1H), 10.07 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 10.9, 18.2, 97.5, 101.7, 116.9, 121.3, 121.6, 122.9, 127.1, 127.6, 131.9, 134.4, 134.6, 136.0, 138.3, 141.8, 147.9, 164.6; HRMS (EI): *m/z* Calcd for $C_{38}H_{51}ClN_2OSi_2$: 642.3228; Found: 642.3806 (we did not good HRMS data for this compound).

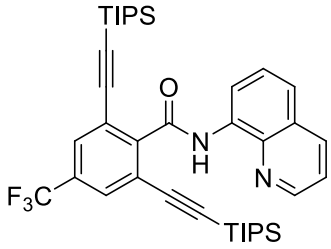
***N*-(quinolin-8-yl)-4-(trifluoromethyl)-2-((triisopropylsilyl)ethynyl)benzamide**



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 21H), 7.44-7.48 (dd, *J* = 8.2 Hz, 1H), 7.56-7.62 (m, 2H), 7.68-7.70 (dd, *J* = 8.2 Hz, 1H), 7.86 (s, 1H), 7.90-7.91 (d, *J* = 7.9 Hz, 1H), 8.17-8.19 (dd, *J* = 8.2 Hz, 1H), 8.76-8.77 (dd, *J* = 4.2 Hz, 1H), 8.92-8.94 (d, *J* = 7.3 Hz, 1H), 10.51 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.2, 99.3, 117.2, 121.6, 122.2,

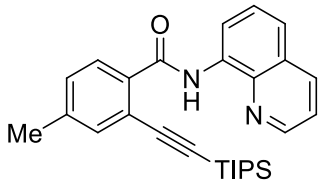
125.2, 125.2, 127.3, 127.9, 129.2, 130.5, 134.3, 136.2, 138.2, 138.7, 142.3, 148.3, 165.1; HRMS (EI): *m/z* Calcd for $C_{28}H_{32}F_3N_2OSi$: 497.2236; Found: 497.2231.

_N_-(quinolin-8-yl)-4-(trifluoromethyl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



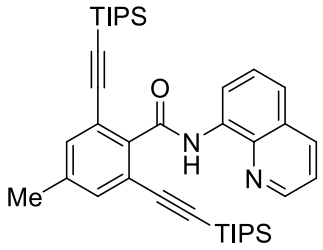
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 42H), 7.41-7.44 (m, 1H), 7.53-7.57 (m, 2H), 7.75 (s, 2H) 8.15-8.17 (d, *J* = 8.2 Hz, 1H), 8.72-8.74 (m, 1H) 8.97 (d, *J* = 7.2 Hz, 1H), 10.11 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.3, 98.3, 101.5, 117.1, 121.4, 121.8, 121.5, 127.1, 127.7, 128.7, 128.7, 134.5, 136.1, 138.4, 146.1, 148.6, 164.3; HRMS (EI): *m/z* Calcd for $C_{39}H_{52}F_3N_2OSi_2$: 677.3570; Found: 677.3565.

4-methyl-_N_-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



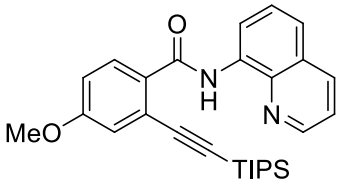
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85-0.87 (s, 21H), 2.43 (s, 3H), 7.27-7.29 (d, *J* = 7.3 Hz, 1H), 7.43-7.46 (m, 2H), 7.54-7.62 (m, 2H), 7.73-7.75 (d, *J* = 7.9 Hz, 1H), 8.17-8.19 (dd, *J* = 8.2 Hz, 1H), 8.77-8.79 (dd, *J* = 4.2 Hz, 1H), 8.92-8.94 (d, *J* = 7.3 Hz, 1H), 10.51 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 18.3, 21.1, 96.7, 104.1, 117.1, 120.6, 121.4, 121.7, 127.3, 127.9, 128.9, 129.6, 134.3, 134.8, 136.1, 138.9, 140.4, 148.2, 166.4; HRMS (EI): *m/z* Calcd for $C_{28}H_{35}N_2OSi$: 443.2519; Found: 443.2513.

4-methyl-_N_-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



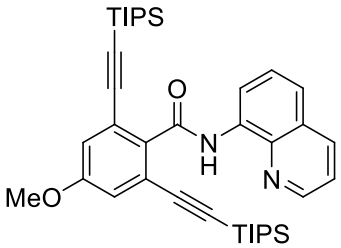
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 42H), 2.36 (s, 3H), 7.34 (s, 1H), 7.40-7.42 (dd, *J* = 8.2 Hz, 1H), 7.50-7.57 (m, 2H), 8.14-8.16 (dd, *J* = 8.2 Hz, 1H), 8.72-8.73 (dd, *J* = 4.2 Hz, 1H), 8.96-8.98 (dd, *J* = 7 Hz, 1H), 10.03 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 11.1, 18.4, 20.7, 95.3, 103.3, 116.9, 121.3, 121.3, 127.3, 127.7, 133.0, 134.9, 136.0, 138.5, 138.8, 141.0, 147.9, 165.8; HRMS (EI): *m/z* Calcd for $C_{39}H_{55}N_2OSi_2$: 623.3853; Found: 623.3847.

4-methoxy-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



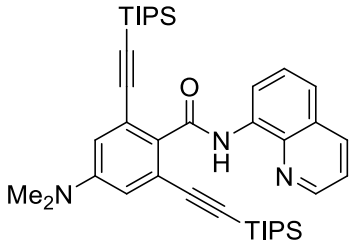
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84-0.85 (m, 21H), 3.88 (s, 1H), 6.97-7.00 (dd, *J* = 8.5 Hz, 1H), 7.10-7.11 (d, *J* = 2.7 Hz, 1H), 7.42-7.44 (dd, *J* = 8.2 Hz, 1H), 7.52-7.54 (dd, *J* = 6.7 Hz, 1H), 7.57-7.60 (td, *J* = 7.6 Hz, 1H), 7.79-7.81(d, *J* = 8.5 Hz, 1H), 8.15-8.17 (dd, *J* = 8.2 Hz, 1H), 8.76-8.78 (dd, *J* = 4.2 Hz, 1H), 8.88-8.90 (dd, *J* = 7.6 Hz, 1H), 10.53 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 18.3, 55.5, 97.3 103.9, 114.9, 117.1, 118.5, 121.4, 121.6, 122.1, 127.3, 127.9, 130.8, 131.7, 134.8, 136.1, 138.9, 148.2, 160.7, 166.0; HRMS (EI): *m/z* Calcd for $C_{28}H_{35}N_2O_2Si$: 459.2468; Found: 459.2462.

4-methoxy-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



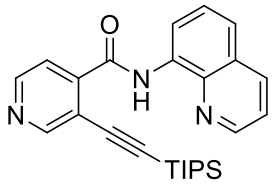
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (m, 42H), 3.86 (s, 1H), 7.03 (s, 1H), 7.40-7.42 (q, *J* = 4.2 Hz, 1H), 7.50-7.57 (m, 2H), 8.14-8.16 (dd, *J* = 7.9 Hz, 1H), 8.72-8.73 (dd, *J* = 4.2 Hz, 1H), 8.96-8.98 (dd, *J* = 7.6 Hz, 1H), 10.03 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 18.3, 55.6, 95.5, 103.0, 116.9, 117.9, 121.2, 127.2, 127.7, 134.9, 136.0, 136.8, 138.4, 147.8, 159.1, 165.5. HRMS (EI): *m/z* Calcd for $C_{39}H_{55}N_2O_2Si_2$: 639.3802; Found: 639.3802.

4-(dimethylamino)-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



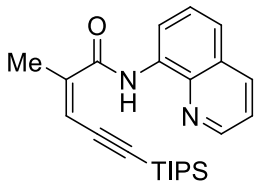
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (m, 42H), 3.01 (s, 6H), 6.81 (s, 2H), 7.39-7.41 (dd, *J* = 4.2 Hz, 1H), 7.48-7.54 (m, 2H), 8.13-8.15 (dd, *J* = 8.2 Hz, 1H), 8.71-8.72 (dd, *J* = 3.9, 1H), 8.97-8.99 (d, *J* = 7.6 Hz, 1H), 10.02 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 18.4, 40.3, 94.0, 104.2, 110.7, 115.8, 116.8, 120.9, 121.1, 122.0, 127.3, 127.7, 131.9, 132.3, 135.3, 138.6, 147.8, 150.0, 166.1.

***N*-(quinolin-8-yl)-3-((triisopropylsilyl)ethynyl)isonicotinamide**



^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (m, 21H),7.45-7.48 (q, *J* = 4.1 Hz, 1H), 7.59-7.61 (m, 2H), 7.68-7.69 (d, *J* = 5.1 Hz, 1H), 8.18-8.20 (d, *J* = 7.5 Hz, 1H), 8.68-8.69 (d, *J* = 4.8, 1H), 8.78-8.79 (d, *J* = 3.4 Hz, 1H), 8.88-8.90 (m, 2H), 10.58 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$,) δ 10.9, 18.2, 100.5, 116.8, 117.4, 121.6, 121.9, 122.5, 127.2, 127.9, 134.0, 136.3, 138.7, 145.2, 148.4, 149.1, 154.4, 164.0; HRMS Calcd for $C_{26}H_{32}N_3OSi$ $[M+H]^+$: 430.2314; Found: 430.2315.

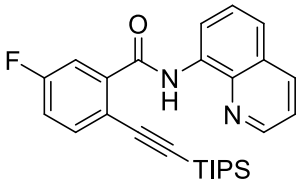
(*Z*)-2-methyl-*N*-(quinolin-8-yl)-5-(triisopropylsilyl)pent-2-en-4-ynamide



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72-0.78 (m, 21H), 5.94 (s, 1H), 7.41-7.43 (q, *J* = 4.2 Hz, 1H), 7.51-7.54 (m, 2H), 8.13-8.15 (d, *J* = 8.2 Hz, 1H), 8.78-8.82 (dd, *J* = 7.0 Hz, 2H), 10.42 (brs, 1H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 10.9, 18.1, 20.2, 98.7, 101.9, 111.1,

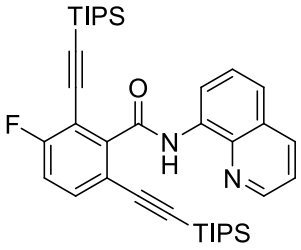
117.1, 121.3, 121.8, 127.2, 127.8, 134.2, 136.1, 138.8, 145.7, 148.2, 166.3; HRMS Calcd for $C_{24}H_{33}N_2OSi$ $[M+H]^+$: 393.2362; Found: 393.2362.

5-fluoro-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



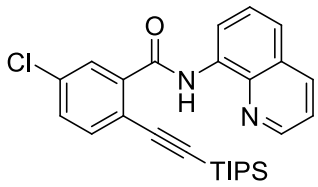
^{1}H NMR (500 MHz, CDCl,) δ 0.82 (s, 21H), 7.14-7.16 (dt, *J* = 8.2 Hz, 1H), 7.44-7.46 (dd, *J* = 8.2 Hz, 1H), 7.51-7.53 (m, 2H), 7.56-7.64 (m, 1H), 8.17-8.19 (dd, *J* = 8.5 Hz, 1H), 8.77-8.79 (dd, *J* = 5.8 Hz, 1H), 8.89-8.91 (dd, *J* = 8.5 Hz, 1H), 10.54 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 18.2, 96.9, 102.8, 115.9, 116.1, 116.9, 117.3, 117.5, 117.7, 121.5, 122.1, 127.3, 127.9, 134.4, 135.9, 136.0, 136.2, 138.9, 141.2, 141.3, 148.3, 161.3, 163.3, 164.9; HRMS (EI): *m/z* Calcd for $C_{27}H_{32}FN_2OSi$: 447.2268; Found: 447.2262.

3-fluoro-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



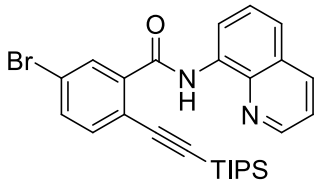
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85-0.86 (s, 42H), 7.08-7.12 (t, *J* = 8.5 Hz, 1H), 7.41-7.44 (dd, *J* = 4.2 Hz, 1H), 7.47-7.50 (dd, *J* = 8.5 Hz, 1H), 7.53-7.56 (m, 2H), 8.15-8.17 (d, *J* = 8.5 Hz, 1H), 8.73-8.74 (dd *J* = 4.2 Hz, 1H), 8.96-8.98 (d, *J* = 7 Hz, 1H), 10.09 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.3, 95.4, 95.8, 102.1, 102.2, 110.8, 116.1, 116.3, 117.1, 117.4, 117.4, 121.4, 121.7, 127.1, 127.7, 133.8, 133.9, 134.6, 136.1, 138.4, 145.3, 148.0, 161.4, 163.5, 164.2; HRMS (EI): *m/z* Calcd for $C_{38}H_{52}FN_2OSi_2$: 627.3602; Found: 627.3597.

5-chloro-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



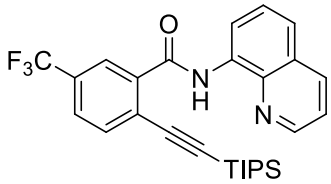
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 21H), 7.40-7.45 (m, 2H), 7.55-7.61 (m, 3H), 7.78-7.79 (d, *J* = 2.1 Hz, 1H), 8.16-8.18 (dd, *J* = 8.2 Hz, 1H), 8.77-8.78 (d, *J* = 3.9 Hz, 1H), 8.89-8.91 (dd, *J* = 7.3 Hz, 1H), 10.50 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 10.9, 18.2, 984, 102.7, 117.2, 119.1, 121.5, 122.1, 127.3, 127.8, 128.8, 130.3, 134.3, 134.8, 135.0, 136.2, 134.3, 134.7, 135.0, 136.2, 138.8, 140.5, 148.3, 164.9; HRMS (EI): *m/z* Calcd for $C_{27}H_{32}ClN_2OSi$: 463.1972; Found: 463.1967.

5-bromo-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 21H), 7.44-7.46 (dd, *J* = 3.9 Hz,1H), 7.48-7.49 (d, *J* = 8.5 Hz, 1H), 7.56-7.61 (m, 3H), 7.94-7.95 (d, *J* = 2.1 Hz, 1H), 8.17-8.19 (dd, *J* = 8.5 Hz, 1H), 8.77-8.78 (dd, *J* = 4.2 Hz, 1H), 8.89-8.90 (dd, *J* = 7.2 Hz, 1H), 10.94 (brs, 1H); ^{13}C NMR (125 MHz,$CDCl_3$) δ 10.9, 18.3, 102.6, 117.2, 119.6, 121.5, 122.1, 122.8, 127.3, 127.9, 131.7, 122.2, 134.4, 135.1, 127.9, 131.7, 133.2, 134.4, 135.1, 136.2, 138.8, 140.7, 148.3, 164.8; HRMS (EI): *m/z* Calcd for $C_{27}H_{32}BrN_2OSi$: 507.1467; Found: 507.1462.

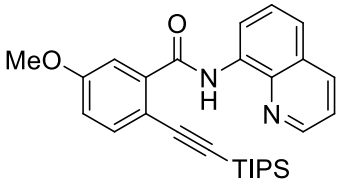
***N*-(quinolin-8-yl)-5-(trifluoromethyl)-2-((triisopropylsilyl)ethynyl)benzamide**



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (s, 21H), 7.43-7.46 (dd, *J* = 4.2 Hz, 1H), 7.56-7.62 (m, 2H), 7.68-7.70 (d, *J* = 8.2 Hz, 1H), 7.73-7.75 (d, *J* = 8.2 Hz, 1H), 8.09 (s, 1H), 8.17-

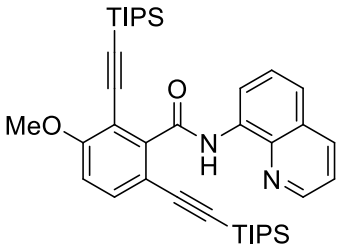
8.19 (dd, *J* = 8.2 Hz, 1H), 8.76-8.78 (dd, *J* = 3.9 Hz, 1H), 8.91-8.93 (dd, *J* = 7.3 Hz, 1H), 10.55 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.2, 100.6, 102.4, 117.2, 121.5, 122.2, 124.2, 125.9, 126.6, 126.6, 127.3, 127.9, 134.3, 136.2, 138.7, 139.7, 148.3, 164.9; HRMS (EI): *m/z* Calcd for $C_{28}H_{32}F_3N_2OSi$: 497.2236; Found: 497.2231.

5-methoxy-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



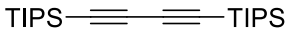
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76-0.83 (m, 21H), 3.88 (s,1H), 6.97-7.00 (dd, *J* = 8.5 Hz, 1H),7.33-7.34 (s, 1H), 7.42-7.45 (m, 1H), 7.54-7.59 (m, 3H), 8.15-8.18 (dd, *J* = 8.2 Hz, 1H), 8.77-8.78 (s, 1H), 8.90-8.92 (dd, *J* = 7.9 Hz, 1H), 10.56 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.0, 18.2, 55.6, 95.2, 103.9, 112.9, 113.1, 117.1, 117.2, 121.4, 121.9, 127.9, 127.9, 134.6, 135.4, 136.1, 138.9, 140.6, 148.3, 159.7, 166.1; HRMS (EI): *m/z* Calcd for $C_{28}H_{35}N_2O_2Si$: 459.2468; Found: 459.2462.

3-methoxy-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



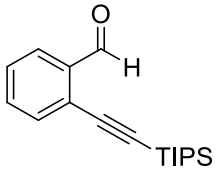
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (m, 42H), 3.92 (s,1H), 6.86-7.6.88 (d, *J* = 8.8 Hz, 1H),7.39-7.42 (dd, *J* = 4.2 Hz, 1H),7.47-7.57 (m, 3H), 8.13-8.15 (d, *J* = 8.2 Hz, 1H), 8.71-8.72 (d, *J* = 4.2 Hz, 1H), 8.96-8.98 (d, *J* = 7.3 Hz, 1H), 10.56 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 18.4, 18.3, 56.3, 93.4, 98.8, 10.4, 103.1, 112.2, 113.3, 116.9, 121.3, 121.3, 127.2, 127.6, 133.8, 134.9, 135.9, 138.5, 145.3, 147.9, 160.5, 165.2; HRMS (EI): *m/z* Calcd for $C_{39}H_{55}N_2O_2Si_2$: 639.3802; Found: 639.3802.

1,4-bis(triisopropylsilyl)buta-1,3-diyne



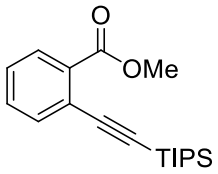
^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 42H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 18.5, 81.5, 90.2.

2-((triisopropylsilyl)ethynyl)benzaldehyde



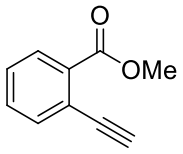
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14-1.18 (s, 21H), 7.42-7.45 (t, *J* = 7.6 Hz, 1H), 7.53-7.56 (t, *J* = 7.3 Hz, 1H), 7.60-7.61 (d, *J* = 7.6 Hz, 1H), 7.92-7.93 (d, *J* = 7.9 Hz, 1H), 10 62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 18.6, 99.1, 101.9, 126.8, 127.1, 128.6, 133.6, 133.8, 136.1, 191.7; HRMS Calcd for $C_{18}H_{27}O$ Si$[M+H]^+$: 287.1831; Found: 287.1831.

methyl 2-((triisopropylsilyl)ethynyl)benzoate



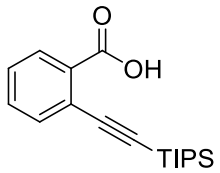
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.35-7.38 (t, *J* = 7.6 Hz, 1H), 7.42-7.45 (t, *J* = 7.6 Hz, 1H), 7.59-7.61 (d, *J* = 7.9 Hz, 1H), 7.88-7.90 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 18.6, 52.1, 96.2, 105.0, 123.3, 127.9, 130.1, 132.5, 134.8, 167.1; HRMS Calcd for $C_{16}H_{29}O_2$ Si$[M+H]^+$: 317.1936; Found: 317.1937.

methyl 2-ethynylbenzoate



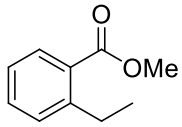
^{1}H NMR (500 MHz, CDCl,) δ 3.41 (s, 1H), 3.93 (s,1H), 7.39-7.43 (t, *J* = 7.5 Hz, 1H), 7.46-7.50 (t, *J* = 7.5 Hz, 1H), 7.62-7.64 (d, *J* = 7.5 Hz, 1H), 7.93-7.96 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.1, 81.9, 82.2, 122.5, 128.4, 130.2, 131.6, 132.4, 134.9, 166.4; HRMS Calcd for $C_{10}H_9O_2[M+H]^+$: 161.060; Found: 161.0603.

2-((triisopropylsilyl)ethynyl)benzoic acid



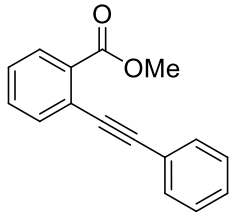
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (s, 21H), 7.40-7.43 (t, *J* = 6.7 Hz, 1H), 7.50-7.53 (t, *J* = 7.3 Hz, 1H), 7.64-7.66 (d, *J* = 7.3 Hz, 1H), 8.06-8.08 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 18.6, 98.3, 104.6, 124.1, 128.0, 130.9, 131.2, 132.2, 134.9, 170.7.

methyl 2-ethylbenzoate



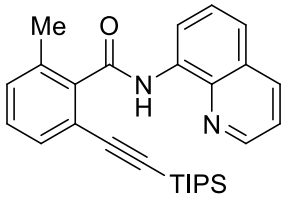
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25-1.28 (t, *J* = 7.6 Hz, 3H), 2.98-3.02 (q, *J* = 7.6 Hz, 2H), 3.91 (s, 3H), 7.24-7.30 (m, 2H), 7.43-7.44 (t, *J* = 6.4 Hz, 1H), 7.86-7.88 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.8, 27.5, 51.8, 125.6, 129.3, 130.1, 130.4, 131.9, 145.9, 168.1.

methyl 2-(phenylethynyl)benzoate (18)



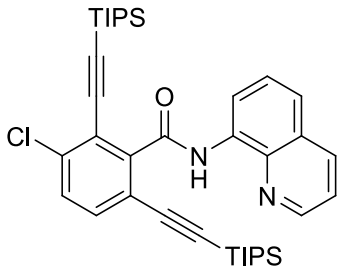
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.36-7.40 (m, 4H), 7.48-7.51 (t, *J* = 7.6 Hz, 1H), 7.60-7.61 (d, *J* = 6.4 Hz, 2H), 7.65-7.67 (d, *J* = 7.6 Hz, 1H), 7.98-8.00 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.0, 88.1, 94.2, 123.2, 123.5, 127.7, 128.2, 128.4, 130.3, 131.6, 131.7, 133.8, 166.6; HRMS Calcd for $C_{16}H_{13}O_2$ $[M+H]^+$: 237.0915; Found: 237.0916.

2-methyl-*N*-(quinolin-8-yl)-6-((triisopropylsilyl)ethynyl)benzamide



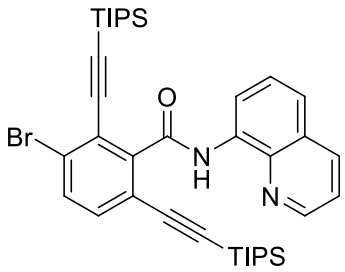
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77-0.78 (s, 21H), 2.47 (s, 3H), 7.24-7.31 (m, 2H),7.42-7.45 (m, 2H), 7.54-7.59 (m, , 2H), 8.16-8.18 (dd, *J* = 8.2 Hz, 1H), 8.74-8.75 (d, *J* = 3.9 Hz, 1H), 9.00-9.01 (dd, *J* = 8.8 Hz, 1H), 10.9 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.2, 19.5, 94.9, 103.9, 116.8, 120.8, 121.4, 127.3, 127.9, 128.8, 130.3, 130.5, 134.7, 135.7, 136.2, 138.5, 140.1, 148.0, 167.2; HRMS (EI): *m/z* Calcd for $C_{28}H_{35}N_2OSi$ $[M+H]^+$: 443.2519; Found: 443.2513.

3-chloro-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (s, 21H), 0.87 (s, 21H), 7.42-7.44 (m, 3H), 7.54-7.56 (m, 2H),8.16-8.18 (dd, *J* = 8.2 Hz, 1H), 8.73-8.75 (dd, *J* = 4.2 Hz, 1H), 8.94-8.96 (dd, *J* = 7.3 Hz, 1H), 10.5 (brs, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 10.1, 18.3, 96.8, 99.3, 102.1, 102.5, 117.1, 119.7, 121.4, 121.7, 127.2, 127.7, 129.6, 132.7, 134.6, 136.1, 136.6, 138.4, 144.9, 148.0, 164.4; HRMS (EI): *m/z* Calcd for $C_{38}H_{52}ClN_2OSi_2$: 643.3307; Found: 643.3276.

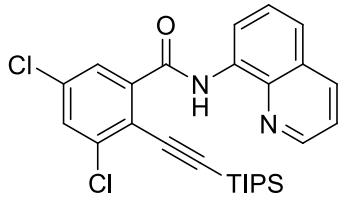
3-bromo-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 21H), 0.88 (s, 21H), 7.33-7.35 (d, *J* = 8.5 Hz, 1H), 7.42-7.45 (q, *J* = 4.2 Hz, 1H), 7.54-7.59 (m, , 2H), 7.60-7.62 (d, *J* = 8.2 Hz, 1H),

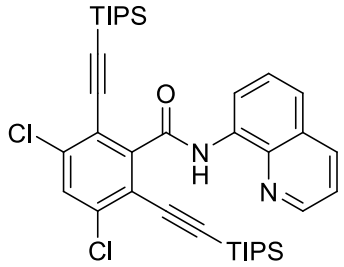
8.15-8.17 (d, *J* = 8.2 Hz, 1H), 8.73-8.75 (d, *J* = 4.2 Hz, 1H), 8.94-8.96 (d, *J* = 7.3 Hz, 1H), 10.0 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 18.3, 97.1, 101.1, 102.0, 102.1, 117.1, 120.3, 121.4, 121.7, 126.2, 127.2, 127.7, 132.7, 132.8, 134.7,, 136.1, 138.4, 148.0, 164.6; HRMS (EI): *m/z* Calcd for $C_{38}H_{52}BrN_2OSi_2$: 687.2802; Found: 687.2764.

3,5-dichloro-*N*-(quinolin-8-yl)-2-((triisopropylsilyl)ethynyl)benzamide



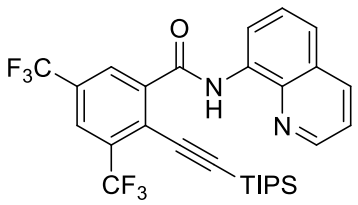
^{1}H NMR (500 MHz, CDCl,) δ 0.82 (s, 21H), 7.45-7.47 (q, *J* = 4.2 Hz, 1H), 7.57-7.60 (m, 3H), 7.65-7.65 (d, *J* = 2.1 Hz, 1H), 8.18-8.20 (dd, *J* = 8.2 Hz, 1H), 8.77-8.78 (dd, *J* = 4.2 Hz, 1H), 8.87-8.89 (dd, *J* = 6.7 Hz, 1H), 10.4 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.2, 98.9, 105.0, 117.2, 119.2, 121.6, 122.3, 127.0, 127.3, 128.8, 130.7, 134.1, 134.6, 136.3, 138.4, 138.7, 142.1, 148.3, 164.2; HRMS (EI): *m/z* Calcd for $C_{27}H_{31}N_2OCl_2Si$ $[M+H]^+$: 497.1583; Found: 497.1577.

3,5-dichloro-*N*-(quinolin-8-yl)-2,6-bis((triisopropylsilyl)ethynyl)benzamide



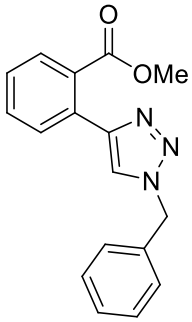
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (s, 42H), 7.44-7.45 (s, 1H), 7.55-7.57 (d, *J* = 8.2 Hz, 1H), 8.16-8.18 (d, *J* = 7.6 Hz, 1H), 8.75 (s, 1H), 8.93 (s, 1H), 10.0, (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9, 18.3, 98.6, 103.4, 117.2, 119.9, 121.4, 121.8, 127.1, 127.7, 130.1, 134.4, 136.1, 136.6, 138.4, 145.8, 148.1, 163.; HRMS (EI): *m/z* Calcd for $C_{38}H_{51}N_2OCl_2Si_2$ $[M+H]^+$: 677.2917; Found: 677.2911.

***N*-(quinolin-8-yl)-3,5-bis(trifluoromethyl)-2-((triisopropylsilyl)ethynyl)benzamide**



^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (s, 21H), 7.46-7.49 (q, *J* = 4.2 Hz, 1H), 7.61-7.62 (m, 2H), 8.03 (s, 1H), 8.16 (s,1H), 8.20-8.22 (dd, *J* = 8.2 Hz, 1H), 8.77-8.79 (dd, *J* = 3.9 Hz, 1H), 8.91-8.93 (dd, *J* = 5.4 Hz, 1H), 10.4 (brs, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 10.9, 18.1, 97.4, 108.7, 117.3, 121.7, 122.5, 123.6, 123.9, 124.3, 127.3, 127.8, 128.4, 130.1, 130.4, 134.0, 136.3, 138.5, 142.9, 148.4, 164.1; HRMS (EI): *m/z* Calcd for $C_{29}H_{31}N_2OF_6Si$ $[M+H]^+$: 565.2110; Found: 565.2104.

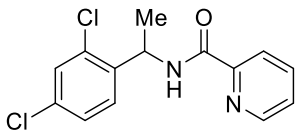
methyl 2-(1-benzyl-1H-1,2,3-triazol-4-yl)benzoate



^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (s, 3H), 5.54 (s, 2H), 7.27-7.38 (m, 6H), 7.48-7.51 (m, 1H),7.74-7.77 (m,3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 51.9, 53.8,122.4, 127.7, 127.8, 128.4, 128.8, 129.4, 129.7, 129.9, 130.0, 131.1, 134.6, 145.8, 168.6; HRMS (EI): *m/z* Calcd for $C_{17}H_{16}N_3O_2$ $[M+H]^+$: 294.1243; Found: 294.1237.

Chapter 3

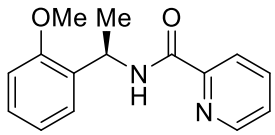
***N*-(1-(2,4-dichlorophenyl)ethyl)picolinamide**



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.51 - 1.65 (m, 4H), 5.54 (t, *J* = 7.06 Hz, 1H), 7.20 (dd, *J* = 8.39, 1.91 Hz, 1H), 7.28 - 7.41 (m, 2H), 7.41 - 7.48 (m, 1H), 7.77 - 7.88 (m, 1H) 8.16 (d, *J* = 7.63 Hz, 1H), 8.44 (d, *J* = 6.87 Hz, 1H), 8.52 - 8.60 (m, 1 H). ^{13}C NMR (126

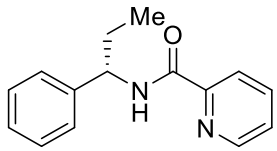
MHz, $CDCl_3$) δ ppm 20.9 (s), 46.5, 122.2, 126.3, 127.3, 127.7, 129.6, 133.3, 133.4, 137.3, 139.5, 148.0, 149.5, 163.4. HRMS (EI): *m/z* Calcd for $C_{14}H_{13}N_2OCl_2$: 295.0405; Found: 295.0399.

(*R*)-*N*-(1-(2-methoxyphenyl)ethyl)picolinamide



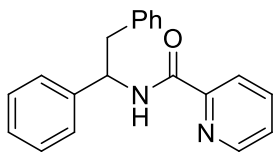
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.59 (d, *J* = 6.87 Hz, 3 H), 3.91 (s, 3 H), 5.51 (dd, *J* = 8.77, 6.87 Hz, 1 H), 6.85 - 6.96 (m, 2 H), 7.23 (td, *J* = 7.82, 1.53 Hz, 1 H), 7.31 (dd, *J* = 7.25, 1.53 Hz, 1 H), 7.38 (ddd, *J* = 7.53, 4.86, 0.95 Hz, 1 H), 7.80 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.19 (d, *J* = 8.01 Hz, 1 H), 8.55 (d, *J* = 4.96 Hz, 1 H), 8.81 (d, *J* = 8.01 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 21.5, 46.4, 55.4, 111.0, 120.7, 122.2, 125.8, 127.4, 128.3, 131.1, 137.1, 148.0, 150.2, 157.0, 163.0. HRMS (EI): *m/z* Calcd for [M+Na] $C_{15}H_{16}N_2ONa$: 279.1109; Found: 279.1104.

(*S*)-*N*-(1-phenylpropyl)picolinamide



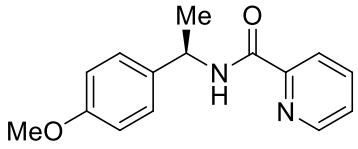
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.98 (t, *J* = 7.44 Hz, 3 H), 1.89 - 2.06 (m, 2 H), 5.09 (d, *J* = 8.01 Hz, 1 H), 7.21 - 7.29 (m, 1 H), 7.31 - 7.45 (m, 5 H), 7.82 (dt, *J* = 3.53, 1.86 Hz, 1 H), 8.19 (d, *J* = 7.63 Hz, 1 H), 8.37 (br s, 1 H, 8.50 - 8.60 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 10.8, 29.4, 54.9, 122.2, 126.0, 126.6, 127.2, 128.5, 137.3, 142.2, 147.9, 149.8, 163.5. HRMS (EI): *m/z* Calcd for [M+Na] $C_{15}H_{16}N_2NaO$: 263.1160; Found: 263.1155.

***N*-(1,2-diphenylethyl)picolinamide**



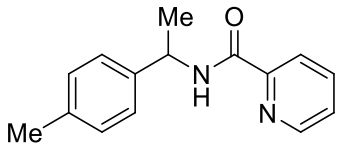
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.27 (dd, *J* = 18.12, 7.06 Hz, 2 H), 5.46 (d, *J* = 8.39 Hz, 1 H), 7.11 - 7.28 (m, 6 H), 7.34 (d, *J* = 4.20 Hz, 4 H), 7.43 (ddd, *J* = 7.63, 4.96, 1.14 Hz, 1 H), 7.84 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.17 (d, *J* = 7.63 Hz, 1 H). 8.55 - 8.59 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 43.0, 54.8, 122.2, 126.1, 126.5, 126.7, 127.3, 128.3, 128.5, 129.4, 137.3, 137.4, 141.5, 148.0, 149.8, 163.5. HRMS (EI): *m/z* Calcd for $C_{20}H_{19}N_2O$: 303.1497; Found: 303.1492.

(*R*)-*N*-(1-(4-methoxyphenyl)ethyl)picolinamide



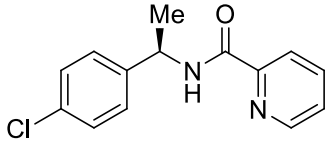
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.62 (d, *J*=6.87 Hz, 4 H), 3.79 (s, 3 H), 5.23 - 5.34 (m, 1 H), 6.86 - 6.91 (m, 2 H), 7.35 (m, *J* = 8.77 Hz, 2 H), 7.41 (ddd, *J* = 7.53, 4.67, 1.14 Hz, 1 H), 7.83 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.20 (d, *J* = 8.01 Hz, 1 H), 8.27 (d, *J*=7.25 Hz, 1 H), 8.53 (d, *J* = 4.58 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 21.9, 48.2, 55.2, 114.0, 122.2, 126.0, 127.4, 135.4, 137.3, 148.0, 150.0, 158.8, 163.3.

***N*-(1-p-tolylethyl)picolinamide**



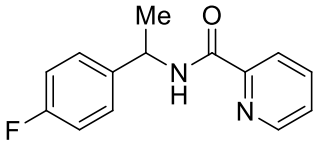
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.62 (d, *J* = 6.87 Hz, 3 H), 2.34 (s, 3 H), 5.24 - 5.36 (m, 1 H), 7.17 (m, *J* = 8.01 Hz, 2 H), 7.32 (m, *J* = 8.01 Hz, 2 H), 7.40 (ddd, *J* = 7.53, 4.86, 0.95 Hz, 1 H), 7.82 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.20 (d, *J* = 7.63 Hz, 1 H), 8.48 - 8.56 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 20.9, 21.9, 48.5, 122.2, 126.0, 126.1, 129.2, 136.8, 137.2, 140.3, 147.9, 149.9, 163.2. HRMS (EI): *m/z* Calcd for $C_{15}H_{17}N_2O$: 241.1341; Found: 241.1335.

(*R*)-*N*-(1-(4-chlorophenyl)ethyl)picolinamide



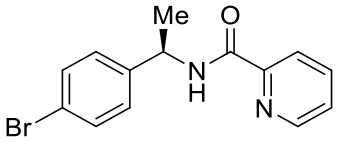
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.61 (d, *J* = 6.87 Hz, 3 H), 5.22 - 5.35 (m, 1 H), 7.28 - 7.37 (m, 4 H), 7.43 (ddd, *J* = 7.53, 4.86, 0.95 Hz, 1 H), 7.76 - 7.90 (m, 1 H), 8.19 (d, *J* = 8.01 Hz, 1 H), 8.31 (d, *J* = 6.87 Hz, 1 H), 8.55 (d, *J* = 4.58 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 22.0, 48.3, 122.3, 126.2, 127.6, 128.7, 133.0, 137.4, 141.9, 148.0, 149.7, 163.4. HRMS (EI): *m/z* Calcd for [M+H] $C_{14}H_{14}N_2OCl$: 261.0795; Found: 261.0789.

_N_-(1-(4-fluorophenyl)ethyl)picolinamide



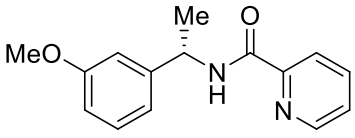
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.61 (d, *J*=7.25 Hz, 4 H), 5.21 - 5.37 (m, 1 H), 6.98 - 7.07 (m, 2 H), 7.33 - 7.45 (m, 3 H), 7.84 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.16 - 8.21 (m, 1 H), 8.25 - 8.38 (m, 1 H), 8.47 - 8.59 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 22.0, 48.16, 115.3, 115.5, 122.3, 126.2, 127.8, 127.8, 137.3, 139.1, 139.1, 148.0, 149.7, 160.9, 162.9, 163.4. HRMS (EI): *m/z* Calcd for [M+H] $C_{14}H_{14}N_2OF$: 245.1090; Found: 245.1085.

(*R*)-*N*-(1-(4-bromophenyl)ethyl)picolinamide



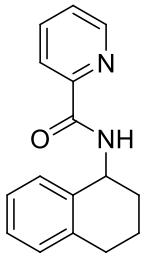
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.61 (d, *J* = 6.87 Hz, 3 H), 5.18 - 5.33 (m, 1 H), 7.29 (d, *J* = 8.39 Hz, 2 H), 7.34 - 7.53 (m, 3 H), 7.75 - 7.92 (m, 1 H), 8.19 (d, *J* = 7.63 Hz, 1 H), 8.31 (d, *J* = 6.87 Hz, 1 H), 8.55 (d, *J* = 4.96 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 22.0, 48.3, 121.1, 122.3, 126.3, 128.0, 131.7, 137.4, 142.5, 148.0, 149.7, 163.5. HRMS (EI): *m/z* Calcd for [M+Na] $C_{14}H_{13}BrN_2NaO$: 327.0109; Found: 327.0103.

(*S*)-*N*-(1-(3-methoxyphenyl)ethyl)picolinamide



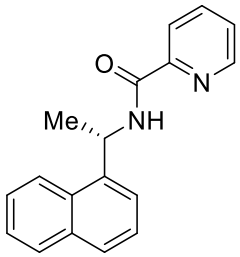
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.61 (d, *J* = 6.87 Hz, 3 H), 3.74 - 3.81 (m, 3 H), 5.23 - 5.34 (m, 1 H), 6.80 (dd, *J* = 8.01, 2.29 Hz, 1 H), 6.96 (t, *J* = 2.10 Hz, 1 H), 7.01 (d, *J* = 7.63 Hz, 1 H), 7.26 (t, *J* = 8.01 Hz, 1 H), 7.38 (ddd, *J* = 7.53, 4.86, 0.95 Hz, 1 H), 7.80 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.19 (d, *J* = 7.63 Hz, 1 H), 8.35 (br s, 1 H), 8.47 - 8.58 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 21.9, 48.6, 55.0, 112.1, 112.2, 118.3, 122.0, 125.9, 129.5, 137.1, 144.8, 147.8, 149.7, 159.6, 163.21.

_N_-(1,2,3,4-tetrahydronaphthalen-1-yl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.80 - 2.03 (m, 3 H), 2.11 - 2.21 (m, 1 H), 2.74 - 2.93 (m, 2 H), 5.34 - 5.45 (m, 1 H), 7.08 - 7.24 (m, 3 H), 7.35 (d, *J* = 7.25 Hz, 1 H), 7.41 (ddd, *J* = 7.63, 4.58, 1.14 Hz, 1 H), 7.86 (td, *J* = 7.82, 1.53 Hz, 1 H), 8.27 (d, *J* = 8.01 Hz, 1 H), 8.35 (d, *J* = 8.01 Hz, 1 H), 8.50 (d, *J* = 4.20 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 20.1, 29.2, 30.2, 47.4, 122.2, 126.0, 126.1, 127.2, 128.7, 129.1, 136.6, 137.2, 137.5, 147.9, 149.9, 163.5. HRMS (EI): *m/z* Calcd for [M+Na] $C_{16}H_{16}N_2NaO$: 275.1160; Found: 275.1155.

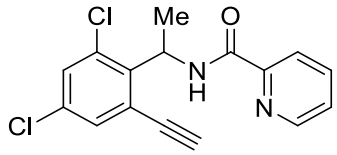
(*S*)-*N*-(1-(naphthalen-1-yl)ethyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.81 (d, *J* = 6.87 Hz, 3 H), 7.33 - 7.43 (m, 1 H), 7.45 - 7.53 (m, 2 H), 7.55 (td, *J* = 7.72, 1.34 Hz, 1 H), 7.64 (d, *J* = 6.87 Hz, 1 H), 7.77 - 7.85 (m, 2 H), 7.88 (d, *J* = 8.01 Hz, 1 H), 8.25 (dd, *J* = 8.01, 4.58 Hz, 2 H), 8.41 (d, *J* = 8.01 Hz, 1 H), 8.47 (d, *J* = 4.58 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 21.2, 44.6, 122.2, 122.5, 123.3, 125.2, 125.7, 126.1, 126.4, 128.2, 128.7, 131.0, 133.9, 137.2,

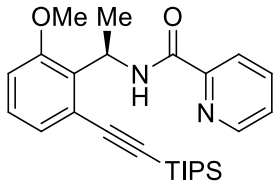
138.5,147.9, 149.7, 163.1. HRMS (EI): *m/z* Calcd for $C_{18}H_{17}N_2O$: 277.1341; Found: 277.1335.

_N_-(1-(2,4-dichloro-6-ethynylphenyl)ethyl)picolinamide



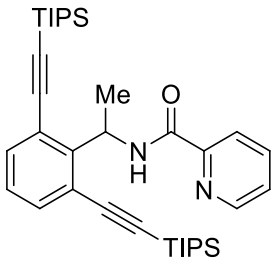
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.66 (d, *J* = 7.25 Hz, 4 H), 3.60 (s, 1 H), 5.93 - 6.13 (m, 1 H), 7.28 - 7.40 (m, 3 H), 7.69 - 7.86 (m, 1 H), 8.13 (d, *J* = 7.63 Hz, 1 H), 8.41 - 8.64 (m, 1 H), 9.14 (d, *J* = 8.01 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 19.1, 45.8, 76.7, 77.3, 80.1, 84.9, 122.1, 123.3, 126.0, 130.5, 132.5, 132.7, 133.9, 137.1, 141.1, 148.0, 149.6, 163.1. HRMS (EI): *m/z* Calcd for $C_{16}H_{13}Cl_2N_2O$: 319.0405; Found: 319.0399.

(*R*)-*N*-(1-(2-methoxy-6-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



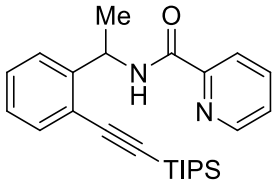
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.14 - 1.27 (m, 22 H), 1.63 (d, *J* = 7.25 Hz, 3 H), 3.96 (s, 3 H), 6.20 (dd, *J* = 9.54, 6.87 Hz, 1 H), 6.90 (dd, *J* = 7.25, 2.29 Hz, 1 H), 7.08 - 7.19 (m, 2 H), 7.37 (ddd, *J* = 7.44, 4.77, 1.14 Hz, 1 H), 7.80 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.21 (d, *J* = 8.01 Hz, 1 H), 8.54 (d, *J* = 4.20 Hz, 1 H), 9.43 (d, *J* = 9.16 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 18.7, 20.5, 55.9, 96.5, 104.8, 111.9, 122.4, 123.0, 125.6, 126.3, 127.6, 133.0, 137.0, 147.9, 150.7, 157.2, 163.1. HRMS (EI): *m/z* Calcd for $C_{26}H_{37}N_2O_2Si$: 437.2624; Found: 437.2619.

_N_-(1-(2,6-bis((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



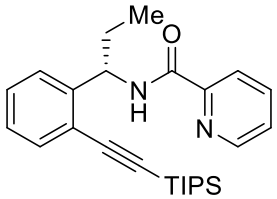
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.16 (br s, 42 H), 1.77 (d, *J* = 6.10 Hz, 3 H), 6.17 - 6.32 (m, 1 H), 7.09 - 7.19 (m, 1 H), 7.37 (br s, 1 H), 7.46 (d, *J* = 7.25 Hz, 2 H), 7.78 (br s, 1 H), 8.17 (d, *J* = 7.25 Hz, 1 H), 8.49 (br s, 1 H), 9.23 (d, *J* = 6.87 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 18.7, 19.9, 47.4, 76.8, 77.0, 77.3, 92.1, 95.0, 97.5, 104.6, 122.5, 125.7, 126.5, 134.2, 136.9, 146.6, 147.8, 150.6, 163.3. HRMS (EI): *m/z* Calcd for $C_{36}H_{55}N_2OSi_2$: 587.3853; Found: 587.3847.

_N_-(1-(2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.12 - 1.24 (m, 22 H), 1.73 (d, *J* = 6.87 Hz, 3 H), 5.57 - 5.67 (m, 1 H), 7.18 - 7.26 (m, 1 H), 7.28 - 7.33 (m, 1 H), 7.39 (d, *J* = 7.63 Hz, 1 H), 7.43 (ddd, *J* = 7.53, 4.67, 1.14 Hz, 1 H), 7.54 (dd, *J* = 7.63, 1.14 Hz, 1 H), 7.84 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.20 (d, *J* = 7.63 Hz, 1 H), 8.56 (d, *J* = 4.20 Hz, 1 H), 8.72 (d, *J* = 7.63 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 18.7, 21.6, 48.8, 76.7, 77.3, 96.5, 104.9, 121.5, 122.3, 125.9, 126.0, 126.9, 128.8, 134.1, 137.2, 145.3, 147.9, 150.1, 163.3. HRMS (EI): *m/z* Calcd for $C_{25}H_{35}N_2OSi$: 407.2519; Found: 407.2513.

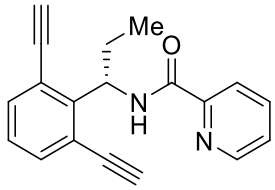
(*S*)-*N*-(1-(2-((triisopropylsilyl)ethynyl)phenyl)propyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.00 (s, 3 H), 1.12 - 1.27 (m, 22 H), 2.01 - 2.24 (m, 2 H), 5.36 - 5.44 (m, 1 H), 7.17 - 7.23 (m, 1 H), 7.26 - 7.30 (m, 1 H), 7.32 - 7.36 (m, 1

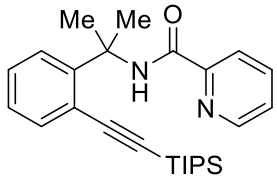
H), 7.41 (ddd, *J* = 7.53, 4.86, 0.95 Hz, 1 H), 7.50 - 7.54 (m, 1 H), 7.82 (td, *J*=7.63, 1.53 Hz, 1 H), 8.18 (d, *J* = 8.01 Hz, 1 H), 8.54 (d, *J* = 4.96 Hz, 1 H), 8.79 (d, *J* = 8.39 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.0, 11.4, 18.7, 28.6, 54.7, 96.3, 105.2, 121.5, 122.3, 126.0, 126.8, 126.9, 128.6, 134.2, 137.2, 144.2, 147.9, 150.1, 163.6. HRMS (EI): *m/z* Calcd for $C_{26}H_{37}N_2OSi$: 421.2675; Found: 421.2670.

(*S*)-*N*-(1-(2,6-diethynylphenyl)propyl)picolinamide



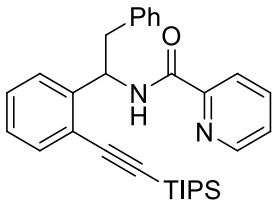
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.00 (t, *J* = 7.44 Hz, 4 H), 2.17 (quin, *J* =7.53 Hz, 3 H), 3.51 (s, 2 H), 5.93 - 6.04 (m, 1 H), 7.17 (t, *J* = 7.82 Hz, 1 H), 7.40 (ddd, *J* = 7.53, 4.86, 0.95 Hz, 1 H), 7.50 (d, *J* = 7.63 Hz, 2 H), 7.81 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.18 (d, *J* = 8.01 Hz, 1 H), 8.57 (d, *J* = 4.20 Hz, 1 H), 9.36 (d, *J* = 9.16 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.1, 27.8, 52.7, 81.7, 83.2, 122.4, 125.9, 126.7, 134.5, 137.2, 146.8 , 148.1, 150.2, 163.6. HRMS (EI): *m/z* Calcd for $C_{19}H_{17}N_2O$: 289.1341; Found: 289.1355.

***N*-(2-(2-((triisopropylsilyl)ethynyl)phenyl)propan-2-yl)picolinamide**



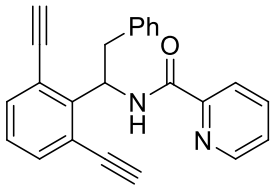
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.02 (s, 22 H), 2.02 (s, 6 H), 7.17 - 7.23 (m, 1 H), 7.33 (td, *J*=7.63, 1.53 Hz, 1 H), 7.38 (ddd, *J* = 7.44, 4.77, 1.14 Hz, 1 H), 7.50 - 7.58 (m, 2 H), 7.78 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.10 (d, *J* = 7.63 Hz, 1 H), 8.52 (d, *J* = 4.20 Hz, 1 H), 8.64 (s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.3, 18.5, 27.7, 55.4, 97.3, 107.2, 120.7, 121.9, 125.7, 125.7, 126.5, 128.3, 136.3, 137.1, 147.1, 147.7, 150.6, 162.7. HRMS (EI): *m/z* Calcd for $C_{26}H_{37}N_2OSi$: 421.2675; Found: 421.2670.

***N*-(2-phenyl-1-(2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide**



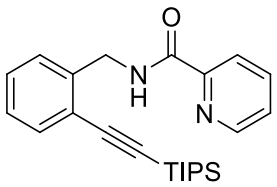
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.27 (br s, 22 H), 3.45 (dd, *J* = 12.78, 7.06 Hz, 1 H), 3.62 (dd, *J* = 13.16, 6.68 Hz, 1 H), 5.83 (d, *J* = 6.87 Hz, 1 H), 7.10 - 7.18 (m, 1 H), 7.18 - 7.31 (m, 7 H), 7.45 (br s, 1 H), 7.56 - 7.66 (m, 1 H), 7.86 (t, *J* = 7.06 Hz, 1 H), 8.21 (d, *J* = 7.63 Hz, 1 H), 8.58 (br s, 1 H), 9.01 (d, *J* = 7.63 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 18.7, 41.0, 54.3, 96.9, 105.3, 121.4, 122.2, 126.0, 126.3, 127.0, 127.7, 128.1, 128.4, 129.4, 134.3, 137.1, 137.6, 142.8, 147.9, 149.9, 163.4. HRMS (EI): *m/z* Calcd for $C_{31}H_{39}N_2OSi$: 483.2832; Found: 483.2826.

_N_-(1-(2,6-diethynylphenyl)-2-phenylethyl)picolinamide



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.44 (d, *J* = 7.83 Hz, 2 H), 3.52 (br s, 2 H), 6.29 - 6.43 (m, 1 H), 7.11 - 7.25 (m, 6 H), 7.34 - 7.43 (m, 1 H), 7.48 (d, *J* = 7.34 Hz, 2 H), 7.78 (t, *J* = 7.34 Hz, 1 H), 8.11 (d, *J* = 7.82 Hz, 1 H), 8.56 (d, *J* = 4.40 Hz, 1 H), 9.45 (d, *J* = 9.29 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 40.5, 52.5, 78.8, 81.4, 83.3, 122.3, 125.9, 126.4, 126.9, 128.2, 129.4, 134.4, 137.1, 137.5, 148.1, 150.0, 163.4. HRMS (EI): *m/z* Calcd for $C_{24}H_{19}N_2O$: 351.1497; Found: 351.1492.

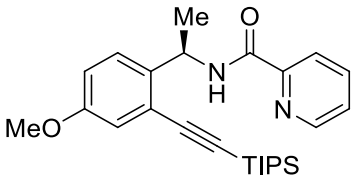
_N_-(2-((triisopropylsilyl)ethynyl)benzyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.12 - 1.21 (m, 21 H), 4.86 (d, *J* = 6.49 Hz, 2 H), 7.23 - 7.28 (m, 1 H), 7.32 (td, *J* = 7.53, 1.34 Hz, 1 H), 7.40 - 7.50 (m, 2 H), 7.51 - 7.57 (m, 1 H), 7.86 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.23 (d, *J* = 8.01 Hz, 1 H), 8.53 (d, *J* = 4.58

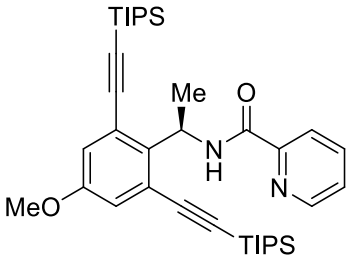
Hz, 1 H), 8.66 (br s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.3, 18.7, 42.3, 96.0, 104.6, 122.2, 122.8, 126.1, 127.3, 128.4, 128.8, 132.9, 137.2, 140.2, 148.0, 149.9, 164.2. HRMS (EI): *m/z* Calcd for $C_{24}H_{33}N_2OSi$: 393.2362; Found: 393.2357.

(*R*)-*N*-(1-(4-methoxy-2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



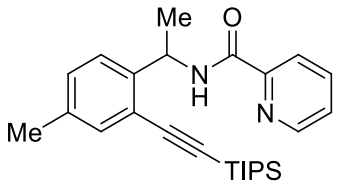
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.15 (br s, 22 H), 1.69 (d, *J* = 6.10 Hz, 3 H), 3.78 (br s, 3 H), 5.53 (t, *J* = 6.68 Hz, 1 H), 6.84 (d, *J* = 8.39 Hz, 1 H), 7.03 (br s, 1 H), 7.29 (br s, 1 H), 7.40 (br s, 1 H), 7.81 (t, *J* = 7.44 Hz, 1 H), 8.17 (d, *J* = 7.25 Hz, 1 H), 8.52 (br s, 1 H), 8.58 - 8.71 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.3, 18.7, 21.7, 48.3, 55.4, 76.7, 77.3, 96.3, 104.8, 114.9, 118.8, 122.2, 122.3, 125.9, 127.2, 137.1, 137.7, 147.9, 150.1, 158.1, 163.2. HRMS (EI): *m/z* Calcd for $C_{26}H_{37}N_2O_2Si$: 437.2624; Found: 437.2619.

(*R*)-*N*-(1-(4-methoxy-2,6-bis((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



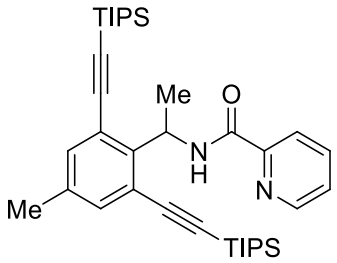
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.16 (s, 43 H), 1.75 (d, *J* = 7.25 Hz, 3 H), 3.79 (s, 3 H), 6.11 - 6.26 (m, 1 H), 6.95 - 7.03 (m, 2 H), 7.36 (td, *J* = 6.20, 0.95 Hz, 1 H), 7.78 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.17 (d, *J* = 8.01 Hz, 1 H), 8.48 (d, *J* = 4.20 Hz, 1 H), 9.17 (d, *J* = 8.39 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 20.1, 46.9, 55.5, 97.1, 104.5, 119.8, 122.4, 123.1, 125.6, 136.9, 139.3, 147.8, 150.7, 157.3, 163.2. HRMS (EI): *m/z* Calcd for $C_{37}H_{57}N_2O_2Si_2$: 617.3959; Found: 617.3953.

***N*-(1-(4-methyl-2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide**



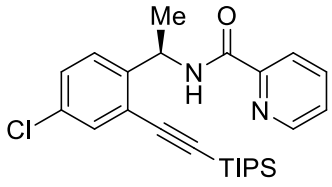
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.18 (s, 22 H), 1.72 (d, *J*= 6.87 Hz, 3 H), 2.32 (s, 3 H), 5.51 - 5.63 (m, 1 H), 7.08 - 7.14 (m, 1 H), 7.28 (d, *J* = 8.39 Hz, 1 H), 7.36 (s, 1 H), 7.42 (ddd, *J* = 7.44, 4.77, 1.14 Hz, 1 H), 7.83 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.19 (d, *J* = 8.01 Hz, 1 H), 8.52 - 8.58 (m, 1 H), 8.70 (d, *J* = 7.63 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 18.7, 20.7, 21.6, 48.6, 96.0, 105.1, 121.2, 122.3, 125.9, 129.6, 134.5, 136.5, 137.1, 142.4, 147.9, 150.1, 163.3. HRMS (EI): *m/z* Calcd for $C_{26}H_{37}N_2OSi$: 421.2675; Found: 421.2670.

_N_-(1-(4-methyl-2,6-bis((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.17 (s, 42 H), 1.76 (d, *J* = 7.25 Hz, 3 H), 2.29 (s, 3 H), 6.15 - 6.27 (m, 1 H), 7.29 (d, *J* = 3.05 Hz, 2 H), 7.38 (ddd, *J* = 7.44, 4.77, 1.14 Hz, 1 H), 7.80 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.15 - 8.23 (m, 1 H), 8.49 (dt, *J* = 4.10, 1.19 Hz, 1 H), 9.22 (d, *J* = 8.77 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.1, 18.4, 19.7, 20.2, 46.9, 96.6, 104.5, 122.2, 125.4, 134.6, 136.0, 136.6, 143.5, 147.5, 150.4, 163.0.

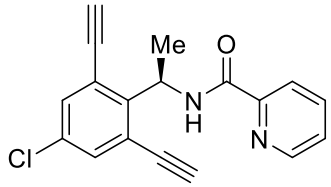
(*R*)-*N*-(1-(4-chloro-2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.06 - 1.26 (m, 21 H), 1.68 (d, *J* = 6.87 Hz, 3 H), 5.54 (quin, *J* = 7.15 Hz, 1 H), 7.24 (dd, *J* = 8.20, 2.10 Hz, 1 H), 7.30 (d, *J* = 8.01 Hz, 1 H), 7.43 (ddd, *J* = 6.87, 5.53, 0.95 Hz, 1 H), 7.48 (d, *J* = 1.91 Hz, 1 H), 7.83 (td, *J* = 7.63,

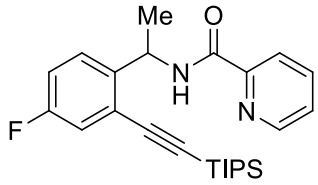
1.53 Hz, 1 H), 8.17 (d, *J* = 7.63 Hz, 1 H), 8.55 (d, *J* = 4.58 Hz, 1 H), 8.62 (d, *J* = 7.25 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.3, 18.6, 18.7, 21.5, 48.3, 98.1, 103.4, 122.3, 123.1, 126.1, 127.1, 128.9, 132.4, 133.4, 137.3, 144.0, 148.0, 149.9, 163.4. HRMS (EI): *m/z* Calcd for $C_{25}H_{34}N_2OSiCl$: 441.2129; Found: 441.2123.

(*R*)-*N*-(1-(4-chloro-2,6-diethynylphenyl)ethyl)picolinamide



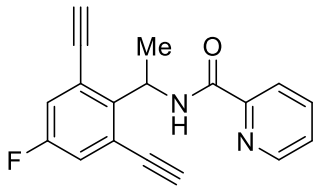
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.71 (d, *J* = 7.25 Hz, 4 H), 3.54 (s, 2 H), 6.03 - 6.15 (m, 1 H), 7.41 (ddd, *J* = 7.44, 4.77, 1.14 Hz, 1 H), 7.47 (s, 2 H), 7.82 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.17 (d, *J* = 8.01 Hz, 1 H), 8.55 - 8.59 (m, 1 H), 9.25 (d, *J* = 8.39 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 20.0, 46.7, 80.2, 84.3, 122.4, 122.4, 126.0, 132.2, 134.1, 137.2, 146.4, 148.1, 149.9, 163.3. HRMS (EI): *m/z* Calcd for $C_{18}H_{14}N_2OCl$: 309.0795.; Found: 309.0789.

***N*-(1-(4-fluoro-2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide**



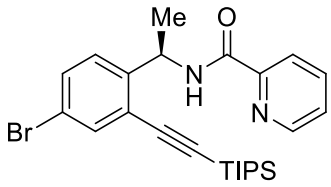
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.07 - 1.25 (m, 21 H), 1.69 (d, *J* = 7.32 Hz, 3 H), 5.56 (t, *J* = 7.32 Hz, 1 H), 6.98 (td, *J* = 8.39, 2.75 Hz, 1 H), 7.20 (dd, *J* = 8.54, 2.44 Hz, 1 H), 7.33 (dd, *J* = 8.54, 5.49 Hz, 1 H), 7.42 (dd, *J* = 7.02, 5.19 Hz, 1 H), 7.77 - 7.89 (m, 1 H), 8.17 (d, *J* = 7.93 Hz, 1 H), 8.54 (d, *J* = 4.27 Hz, 1 H), 8.64 (d, *J* = 6.71 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 11.3, 18.6, 21.6, 48.2, 97.8, 103.5, 115.8, 116.0, 120.2, 120.4, 122.3, 123.0, 123.1, 126.1, 127.4 (br d, *J* = 8.0 Hz), 127.5, 137.2, 141.4, 147.9, 149.9, 159.9 (br d, *J* = 245.0 Hz), 162.3, 163.3. HRMS (EI): *m/z* Calcd for $C_{25}H_{34}N_2OFSi$: 425.2424; Found: 425.2419.

***N*-(1-(2,6-diethynyl-4-fluorophenyl)ethyl)picolinamide**



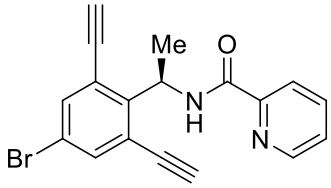
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.71 (d, *J* = 7.25 Hz, 4 H), 3.55 (s, 2 H), 6.04 - 6.16 (m, 1 H), 7.20 (d, *J* = 8.77 Hz, 2 H), 7.41 (ddd, *J* = 7.63, 4.96, 1.14 Hz, 1 H), 7.82 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.18 (d, *J* = 7.63 Hz, 1 H), 8.53 - 8.63 (m, 1 H), 9.28 (d, *J* = 8.39 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 20.2, 46.6, 80.4, 84.1, 121.3, 121.5 (br d, *J* = 22.0 Hz), 122.4, 122.6 (br d, *J* = 9.0 Hz), 122.6, 126.0, 128.4, 130.1, 133.5, 137.2, 144.1, 148.1, 150.0, 161.1 (br d, *J* = 247.0 Hz), 163.2. HRMS (EI): *m/z* Calcd for $C_{18}H_{14}N_2OF$: 293.1090; Found: 293.1085.

(*R*)-*N*-(1-(4-bromo-2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.13 - 1.22 (m, 22 H), 1.71 (d, *J* = 6.49 Hz, 3 H), 5.55 (t, *J* = 6.87 Hz, 1 H), 7.25 (br s, 1 H), 7.40 - 7.48 (m, 2 H), 7.66 (br s, 1 H), 7.86 (t, *J* = 7.44 Hz, 1 H), 8.19 (d, *J* = 7.25 Hz, 1 H), 8.57 (br s, 1 H), 8.65 (d, *J* = 6.48 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.3, 18.6, 21.4, 98.3, 103.2, 120.2, 122.3 , 123.4, 126.2, 127.3, 131.8, 136.2, 137.3, 144.5, 148.0, 149.8, 163.4. HRMS (EI): *m/z* Calcd for $C_{25}H_{34}N_2OBrSi$: 485.1624; Found: 485.1618.

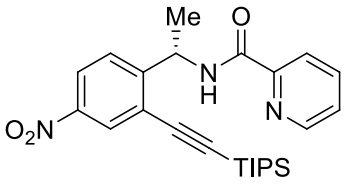
(*R*)-*N*-(1-(4-bromo-2,6-diethynylphenyl)ethyl)picolinamide



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.72 (d, *J* = 6.87 Hz, 3 H), 3.56 (s, 2 H), 6.09 (dd, *J* = 8.96, 7.06 Hz, 1 H), 7.40 - 7.48 (m, 1 H), 7.64 (s, 2 H), 7.84 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.18 (d, *J* = 8.01 Hz, 1 H), 8.58 (d, *J* = 4.58 Hz, 1 H), 9.26 (d, *J* = 8.77 Hz, 1 H). ^{13}C

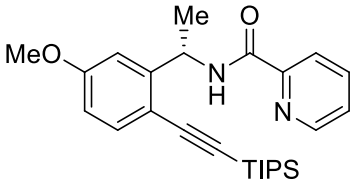
NMR (126 MHz, $CDCl_3$) δ ppm 19.8, 19.9, 46.8, 80.1, 84.4, 119.8, 122.4, 122.6, 126.0, 136.9, 137.2, 146.9, 148.1, 149.9, 163.3. HRMS (EI): *m/z* Calcd for $C_{18}H_{14}N_2OBr$: 353.0290; Found: 353.0284.

(*S*)-*N*-(1-(4-nitro-2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



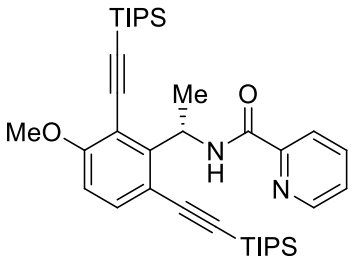
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.13 - 1.25 (m, 22 H), 1.71 (d, *J* = 7.25 Hz, 3 H), 5.63 (quin, *J* = 7.06 Hz, 1 H), 7.47 (dd, *J* = 6.87, 5.34 Hz, 1 H), 7.53 (d, *J* = 8.77 Hz, 1 H), 7.86 (td, *J* = 7.72, 1.34 Hz, 1 H), 8.10 (dd, *J* = 8.58, 2.48 Hz, 1 H), 8.15 (d, *J* = 7.63 Hz, 1 H), 8.33 (d, *J* = 2.67 Hz, 1 H), 8.58 (d, *J* = 4.58 Hz, 1 H), 8.62 (d, *J* = 6.87 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.3, 18.6, 18.7, 21.2, 48.5, 100.0, 102.2, 122.3, 122.9, 123.4, 126.3, 126.4, 128.5, 137.4, 146.6, 148.1, 149.5, 152.7, 163.6. HRMS (EI): *m/z* Calcd for $C_{25}H_{34}N_3O_3Si$: 425.2369; Found: 425.2364.

(*S*)-*N*-(1-(5-methoxy-2-((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



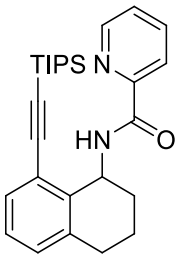
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.10 - 1.23 (m, 22 H), 1.71 (d, *J* = 6.87 Hz, 3 H), 3.79 (s, 3 H), 5.48 - 5.58 (m, 1 H), 6.73 (dd, *J* = 8.77, 2.67 Hz, 1 H), 6.90 (d, *J* = 2.67 Hz, 1 H), 7.36 - 7.49 (m, 2 H), 7.82 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.17 (d, *J* = 8.01 Hz, 1 H), 8.54 (d, *J* = 4.20 Hz, 1 H), 8.71 (d, *J* = 8.01 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 18.7, 21.5, 48.9, 55.3, 94.6, 105.0, 111.9, 112.1, 113.6, 122.3, 126.0, 135.5, 137.2, 147.2, 147.9, 150.0, 159.9, 163.3. HRMS (EI): *m/z* Calcd for $C_{26}H_{37}N_2O_2Si$: 437.2624; Found: 437.2619.

(*S*)-*N*-(1-(3-methoxy-2,6-bis((triisopropylsilyl)ethynyl)phenyl)ethyl)picolinamide



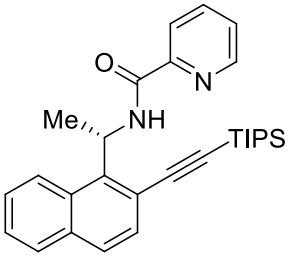
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.12 - 1.21 (m, 43 H), 1.76 (d, *J* = 6.87 Hz, 3 H), 3.85 (s, 3 H), 6.18 - 6.30 (m, 1 H), 6.70 (d, *J* = 8.39 Hz, 1 H), 7.36 (ddd, *J* = 7.53, 4.67, 1.14 Hz, 1 H), 7.43 (d, *J* = 8.77 Hz, 1 H), 7.77 (td, *J* = 7.72, 1.72 Hz, 1 H), 8.17 (d, *J* = 7.63 Hz, 1 H), 8.44 - 8.51 (m, 1 H), 9.27 (d, *J* = 8.77 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.4, 11.4, 18.6, 18.7, 19.7, 47.5, 55.9, 95.1, 100.1, 102.7, 104.7, 109.2, 111.7, 122.4, 125.6, 135.1, 136.8, 147.8, 148.4, 150.7, 161.7, 163.3. HRMS (EI): *m/z* Calcd for $C_{37}H_{57}N_2O_2Si_2$: 617.3959; Found: 617.3953.

_N_-(8-((triisopropylsilyl)ethynyl)-1,2,3,4-tetrahydronaphthalen-1-yl)picolinamide



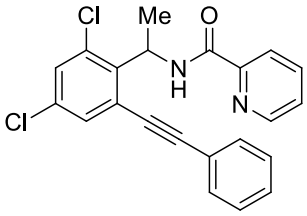
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 0.94 (br s, 11 H), 0.99 (s, 12 H), 1.78 - 1.92 (m, 3 H), 2.52 (d, *J* = 11.83 Hz, 1 H), 2.74 - 2.85 (m, 1 H), 2.85 - 2.95 (m, 1 H), 5.51 (br s, 1 H), 7.15 (d, *J* = 7.63 Hz, 1 H), 7.21 (t, *J* = 7.63 Hz, 1 H), 7.34 - 7.45 (m, 2 H), 7.80 - 7.87 (m, 1 H), 8.06 (d, *J* = 5.72 Hz, 1 H), 8.23 (d, *J* = 8.01 Hz, 1 H), 8.46 (d, *J* = 4.20 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.2, 17.9, 18.5, 18.5, 28.5, 29.5, 46.5, 95.8, 104.3, 122.1, 124.8, 125.7, 127.3, 129.6, 131.7, 136.9, 137.1, 138.6, 147.8, 150.4, 162.7. HRMS (EI): *m/z* Calcd for $C_{27}H_{37}N_2OSi$: 433.2675; Found: 433.2670.

(*S*)-*N*-(1-(2-((triisopropylsilyl)ethynyl)naphthalen-1-yl)ethyl)picolinamide



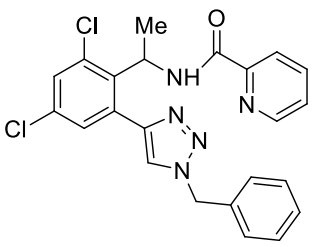
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.14 - 1.38 (m, 21 H), 1.95 (d, *J* = 7.25 Hz, 3 H), 6.53 - 6.62 (m, 1 H), 7.38 (ddd, *J* = 7.44, 4.77, 1.14 Hz, 1 H), 7.46 - 7.53 (m, 1 H), 7.54 - 7.64 (m, 2 H), 7.70 (d, *J* = 8.39 Hz, 1 H), 7.75 - 7.84 (m, 2 H), 8.17 (d, *J* = 7.63 Hz, 1 H), 8.39 - 8.57 (m, 2 H), 9.54 (br. s, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.2, 11.5, 18.7, 20.4, 43.8, 99.0, 106.8, 118.8, 122.3, 123.4, 125.9, 126.6, 127.1, 127.4, 128.7, 130.5, 131.0, 133.5, 137.0, 142.0, 147.9, 150.2, 163.6. HRMS (EI): *m/z* Calcd for [M-H] $C_{29}H_{36}N_2O_2Si$: 455.2516; Found: 455.2513. HPLC conditions: Chiralpack-IB, 97:3 *n*-Hexane/IPA, Flow rate 1.0 mL/min; λ = 254 nm; R_t = 6.53 min (major), R_t = 9.46 min (minor).

***N*-(1-(2,4-dichloro-6-(phenylethynyl)phenyl)ethyl)picolinamide**



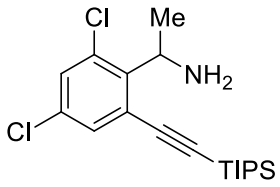
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.74 (d, *J* = 6.87 Hz, 3 H), 6.16 (dd, *J* = 8.58, 7.44 Hz, 1 H), 7.31 - 7.51 (m, 5 H), 7.63 - 7.75 (m, 2 H), 7.80 (td, *J* = 7.63, 1.53 Hz, 1 H), 8.17 (d, *J* = 7.63 Hz, 1 H), 8.32 (d, *J* = 4.20 Hz, 1 H), 9.44 (d, *J* = 8.01 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 19.7, 45.6, 86.0, 96.9, 122.2, 122.3, 126.0, 128.4, 129.1, 129.8, 131.8, 132.2, 132.8, 134.1, 137.2, 140.5, 147.9, 149.7, 163.2. HRMS (EI): *m/z* Calcd for $C_{22}H_{17}N_2O_2Cl_2$: 395.0718; Found: 395.0712.

***N*-(1-(2-(1-benzyl-1H-1,2,3-triazol-4-yl)-4,6-dichlorophenyl)ethyl)picolinamide**



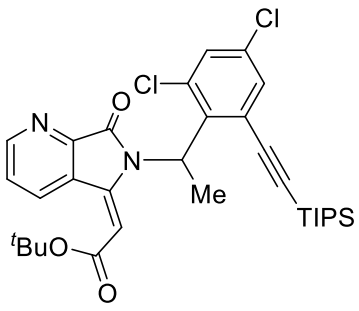
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.70 (d, *J* = 6.87 Hz, 3 H), 5.51 - 5.67 (m, 2 H), 5.74 - 5.89 (m, 1 H), 7.16 - 7.43 (m, 8 H), 7.79 (td, *J* = 7.79, 1.83 Hz, 1 H), 7.95 - 8.19 (m, 2 H), 8.44 - 8.62 (m, 1 H), 9.02 (d, *J* = 8.70 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 19.8, 45.9, 54.2, 122.0, 123.2, 126.0, 128.0, 128.7, 129.1, 129.7, 130.5, 132.8, 133.2, 134.4, 134.5, 137.0, 137.1, 145.9, 148.2, 149.6, 163.2. HRMS (EI): *m/z* Calcd for $C_{23}H_{20}N_5OCl_2$: 452.1045; Found: 452.1039.

1-(2,4-dichloro-6-((triisopropylsilyl)ethynyl)phenyl)ethanamine



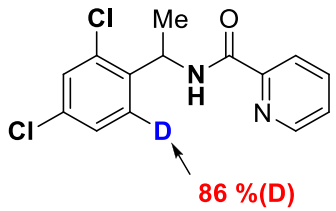
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.15 - 1.17 (m, 22 H), 1.57 (d, *J* = 7.25 Hz, 4 H), 2.09 (br s, 2 H), 4.81 (q, *J* = 6.87 Hz, 1 H), 7.33 (d, *J* = 2.29 Hz, 1 H), 7.39 (d, *J* = 2.29 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 11.3, 18.6, 21.6, 49.0, 76.7, 77.3, 100.2, 103.4, 124.0, 130.1, 132.0, 133.1, 133.5, 145.0.HRMS (EI): *m/z* Calcd for $C_{19}H_{30}N_2Cl_2Si$: 370.1525; Found: 370.1519.

(*E*)-tert-butyl 2-(6-(1-(2-chloro-6-((triisopropylsilyl)ethynyl)phenyl)ethyl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-ylidene)acetate



^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.15 (d, *J* = 3.91 Hz, 21 H), 1.48 (s, 10 H), 2.18 (d, *J* = 7.34 Hz, 3 H), 5.64 (s, 1 H), 5.92 (q, *J* = 7.34 Hz, 1 H), 7.32 (d, *J* = 2.45 Hz, 1 H), 7.41 - 7.56 (m, 2 H), 8.81 (d, *J* = 4.40 Hz, 1 H), 9.21 (d, *J* =7 .82 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 11.2, 18.3, 18.7, 28.1, 29.7, 54.3, 81.1, 100.9, 101.5, 104.0, 125.3, 126.4, 128.0, 131.7, 132.0, 133.5, 133.9, 135.6, 138.2, 145.2, 148.4 , 152.6, 165.2, 165.5 (s, 1 C). HRMS (EI): *m/z* Calcd for $C_{32}H_{41}N_2O_3Cl_2Si$: 599.2264; Found: 599.2258.

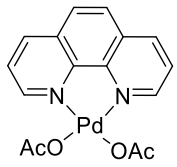
[D1]-1a



^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.61 (d, *J* = 6.87 Hz, 4 H), 5.54 (t, *J* = 7.25 Hz, 1 H), 7.18 - 7.25 (m, 1 H), 7.39 (d, *J* = 2.29 Hz, 1 H), 7.45 (ddd, *J* = 7.53, 4.86, 0.95 Hz, 1 H), 7.79 - 7.89 (m, 1 H), 8.17 (d, *J* = 8.01 Hz, 1 H), 8.44 (d, *J* = 6.49 Hz, 1 H), 8.54 - 8.64 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 21.0, 46.6, 122.3, 126.3, 127.3, 129.7, 133.4, 133.5, 137.4, 139.5, 148.1, 149.6, 163.4. HRMS (EI): *m/z* Calcd for $C_{14}H_{12}DN_2OCl_2$: 296.0468; Found: 296.0462.

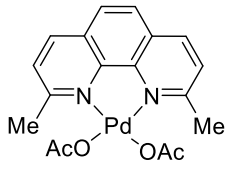
Chapter 4

(1,10-phenanthroline)-palladium(II) acetate



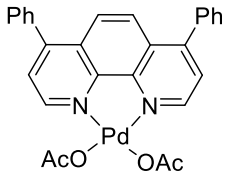
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21 (s, 6H), 7.78-7.81 (q, *J* = 5.4 Hz, 2H), 7.96 (s, 2H), 8.51-8.52 (d, *J* = 4.2 Hz, 2H), 8.61-8.62 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 125.2, 127.2, 129.6, 138.8, 146.3, 150.5, 178.6.

(2,9-Dimethyl-1,10-phenanthroline)-palladium(II) acetate



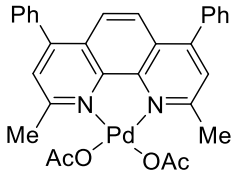
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 6H), 2.87 (s, 6H), 7.39-7.41 (q, *J* = 8.5 Hz, 2H), 7.85 (s, 2H), 8.37-8.38 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 24.4, 126.3, 127.8, 138.4, 147.1, 165.1, 178.5.

(2,9-Dimethyl-4,7-diphenyl-1,10-phenanthroline)-palladium(II) acetate



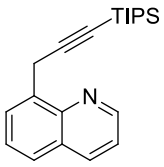
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.03 (s, 6H), 2.99 (s, 6H), 7.43 (s, 2H), 7.46-7.48 (m,4H), 7.55-7.57 (m, 6H), 7.80 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 24.7, 124.3, 126.5, 126.8, 129.0, 129.2, 129.7, 135.4, 148.2, 150.9, 1647, 178.4.

(4,7-diphenyl-1,10-phenanthroline)-palladium(II) acetate



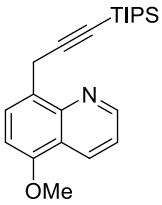
^{1}H NMR (500 MHz, CDCl) δ 2.21 (s, 6H), 7.51-7.52 (m, 4H), 7.59-7.60 (m, 6H), 7.74-7.76 (d, *J* = 5.4 Hz, 2H), 7.99 (s, 2H), 8.67-8.69 (d, *J* = 5.19 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$,) δ 23.4, 125.2, 125.3, 128.1, 129.2, 129.4, 130.1, 135.0, 147.3, 149.9, 151.7, 178.5.

8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



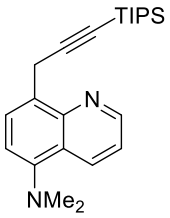
^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 21H), 4.40 (s, 2H), 7.39-7.45 (dd, *J* = 8.2 Hz, 1H), 7.52-7.60 (t, *J* = 7.0 Hz, 1H), 7.71-7.76 (d, *J* = 7.7 Hz, 1H), 8.06-8.11 (dd, *J* = 7.0 Hz, 1H), 8.14-8.19 (dd, *J* = 8.3 Hz, 1H), 8.90-8.94 (dd, *J* = 4.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.4, 18.7, 22.1, 83.5, 106.2, 121.0, 126.4, 126.5, 127.9, 128.2, 135.4, 136.2, 143.0, 149.. HRMS Calcd for $C_{21}H_{30}NSi$ $[M+H]^+$: 324.2148; Found: 324.2142.

5-methoxy-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



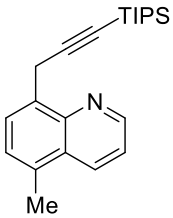
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21H), 4.01 (s, 3H), 4.29 (s, 2H), 6.87-6.89 (d, *J* = 7.9 Hz, 1H), 7.38-7.41 (dd, *J* = 8.5 Hz, 1H), 7.95-7.96 (d, *J* = 7.9 Hz, 1H), 8.57-8.59 (dd, *J* = 8.5 Hz, 1H), 8.90-8.91 (d, *J* = 4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 18.7, 21.7, 55.7, 83.2, 103.9, 106.7, 120.1, 120.6, 126.9, 127.8, 103.8, 146.5, 149.6, 154.0. HRMS Calcd for $C_{22}H_{32}NOSi$ $[M+H]^+$: 354.2253; Found: 354.2248

_N,N_-dimethyl-8-(3-(triisopropylsilyl)prop-2-ynyl)quinolin-5-amine



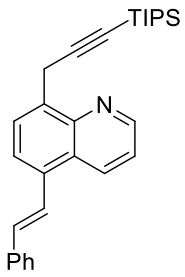
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21H), 2.89 (s,6H), 4.31 (s, 2H), 7.13-7.14 (d, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 7.40-7.41 (d, *J* = 4.5 Hz, 1H), 7.96-7.97 (d, *J* = 7.6 Hz, 1H), 8.56-8.57 (d, *J* = 8.2 Hz, 2H), 8.88 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 18.7, 21.9, 45.4, 83.2, 106.7, 114.2, 119.9, 123.7, 127.9, 129.4, 132.8, 146.9, 148.9, 149.8. HRMS Calcd for $C_{23}H_{35}N_2Si$ $[M+H]^+$: 367.2570; Found: 367.2564

5-methyl-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



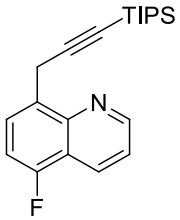
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21H), 2.68 (s, 3H), 4.36 (s, 2H), 7.39-7.40 (d, *J* = 7.3 Hz, 1H), 7.44-7.46 (dd, *J* = 4.2 Hz, 1H), 7.95-7.96 (d, *J* = 7.0 Hz, 1H), 8.32-8.34 (dd, *J* = 8.5 Hz, 1H), 8.92-8.92 (d, *J* =4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 18.7, 18.5, 18.6, 83.3, 106.5, 120.6, 126.8, 127.4, 127.8, 132.6, 133.1, 133.3, 146.2, 148.7. HRMS Calcd for $C_{22}H_{32}NSi$ $[M+H]^+$: 338.2304; Found: 338.2299.

(*E*)-5-styryl-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



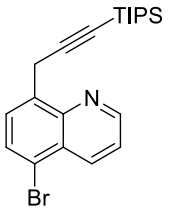
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 21H), 4.41 (s, 2H), 7.18-7.21 (d, *J* = 16.1 Hz, 1H), 7.31-7.34 (t, *J* = 7.3 Hz, 1H), 7.41-7.44 (t, *J* = 7.6 Hz, 2H), 7.46-7.48 (q, *J* = 3.9 Hz, 1H), 7.60-7.62 (d, *J* = 7.6 Hz, 2H), 7.78-7.81 (d, *J* = 16.1 Hz, 1H), 7.84-7.85 (d, *J* = 7.6 Hz, 1H), 8.10-8.11 (d, *J* = 7.6 Hz, 1H), 8.56-8.58 (dd, *J* = 8.5 Hz, 1H), 8.94-8.95 (dd, *J* = 3.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 18.7, 22.1, 83.6, 106.2, 120.8, 123.7, 124.2, 126.1, 126.6, 127.9, 128.0, 128.8, 132.3, 132.3, 133.9, 135.0, 127.3, 146.1, 129.1. HRMS Calcd for $C_{29}H_{36}NSi$ $[M+H]^+$: 426.2617; Found: 426.2612.

5-fluoro-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



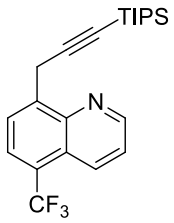
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21H), 4.32 (s, 2H), 7.21-7.24 (t, *J* = 8.2 Hz, 1H), 7.46-7.49 (q, *J* = 3.9 Hz, 1H), 7.97-8.00 (t, *J* = 6.7 Hz, 1H), 8.42-8.44 (dd, *J* = 8.2 Hz, 1H), 8.94-8.96 (dd, *J* = 4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 18.6, 21.9, 83.7, 105.9, 109.6, 109.8, 118.7, 118.8, 121.1, 127.5, 127.5, 129.4, 129.4, 131.2, 146.18, 150.1, 155.8, 157.8. HRMS Calcd for $C_{21}H_{29}NSi$ $[M+H]^+$: 342.2053; Found: 342.2048.

5-bromo-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



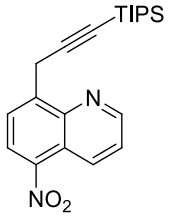
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21H), 4.34 (s, 2H), 7.51-7.53 (dd, *J* = 4.2 Hz, 1H), 7.84-7.86 (d, *J* = 7.3 Hz, 1H), 7.93-7.95 (d, *J* = 7.9 Hz, 1H), 8.53-8.58 (d, *J* = 8.5 Hz, 1H), 8.92-8.93 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 18.7, 22.1, 84.0, 105.5, 120.2, 122.1, 127.1, 128.5, 130.1, 135.6, 146.6, 149.3, 149.8; HRMS Calcd for $C_{21}H_{29}BrNSi$ $[M+H]^+$: 402.1253 ; Found: 402.1247.

5-(trifluoromethyl)-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



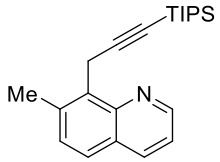
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 21H), 4.44 (s, 2H), 7.54-7.57 (dd, *J* = 8.8 Hz, 1H), 7.95-7.96 (dd, *J* = 7.6 Hz, 1H), 8.13-8.14 (d, *J* = 7.3 Hz, 1H), 8.50-8.52 (d, *J* = 8.5 Hz, 1H), 8.99-9.00 (d, *J* =4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 18.7, 22.7, 84.5, 105.1, 122.2, 122.7, 123.1, 124.0, 125.0, 125.0, 126.5, 128.7, 132.3, 140.7, 146.0, 149.8, 150.5. HRMS Calcd for $C_{22}H_{29}F_3NSi$ $[M+H]^+$: 392.2021; Found: 392.2016.

5-nitro-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



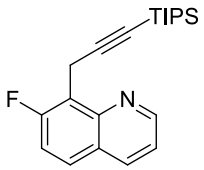
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.14 (s, 21H), 4.47 (s, 2H), 7.66-7.68 (dd, *J* = 8.8 Hz, 1H), 8.18-8.20 (d, *J* = 7.6 Hz, 1H), 8.43-8.44 (d, *J* = 7.9 Hz, 1H), 9.01-9.03 (dd, *J* = 3.9 Hz, 1H), 9.05-9.07 (dd, *J* =8.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 16.7, 23.2, 85.2, 104.4, 120.8, 123.8, 124.7, 126.3, 132.2, 143.9, 144.4, 150.4, 158.9. HRMS Calcd for $C_{21}H_{29}N_2O_2Si$ $[M+H]^+$: 369.1998; Found: 369.1996.

7-methyl-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



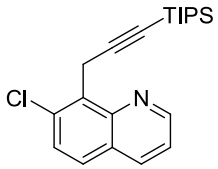
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 21H), 2.69 (s, 3H), 4.42 (s, 2H), 7.34-7.35 (d, *J* = 4.2 Hz, 1H), 7.40-7.41 (q, *J* = 8.2 Hz, 1H), 7.64-7.65 (d, *J* = 8.2 Hz, 1H), 8.09-8.11 (dd, *J* = 8.2 Hz, 1H), 8.93-8.94 (d, *J* = 4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 17.9, 18.6, 20.3, 79.9, 106.7, 120.0, 126.0, 126.7, 129.8, 133.4, 135.9, 137.9, 146.1, 149.5. HRMS Calcd for $C_{22}H_{32}NSi$ $[M+H]^+$: 338.2304; Found: 338.2299.

7-fluoro-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



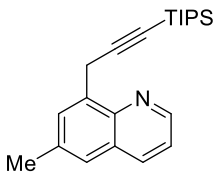
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 21H), 4.29 (s, 2H), 7.34-7.36 (d, *J* = 8.8 Hz, 1H), 7.38-7.40 (q, *J* = 4.2 Hz, 1H), 7.72-7.75 (q, *J* = 6.1 Hz, 1H), 8.13-8.15 (dd, *J* = 8.2 Hz, 1H), 8.97-8.98 (dd, *J* = 4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 18.5, 14.7, 80.0, 105.9, 116.9, 117.1, 120.2, 120.7, 120.8, 125.3, 127.9, 128.0, 136.0, 146.8, 146.9, 150.4, 159.6, 161.6. HRMS Calcd for $C_{21}H_{29}NFSi$ $[M+H]^+$: 342.2053; Found: 342.2048.

7-chloro-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



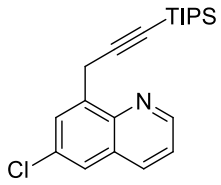
^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (s, 21H), 4.46 (s, 2H), 7.41-7.43 (q, *J* = 4.2 Hz, 1H), 7.55-7.56 (d, *J* = 8.8 Hz, 1H), 7.67-7.69 (d, *J* = 8.8 Hz, 1H), 8.12-8.14 (dd, *J* = 8.2 Hz, 1H), 8.97-8.99 (d, *J* = 4.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.2, 18.5, 19.3, 80.4, 105.4, 121.0, 126.8, 127.3, 128.2, 133.9, 135.1, 136.1, 146.6, 150.4. HRMS Calcd for $C_{21}H_{29}NClSi$ $[M+H]^+$: 358.1758 ; Found: 358.1752.

6-methyl-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



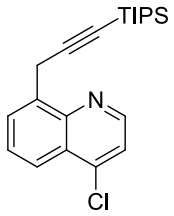
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 21H), 2.54 (s, 3H), 4.36 (s, 2H), 7.36-7.39 (q, *J* = 4.2 Hz, 1H), 7.49 (s, 1H), 7.97 (s, 1H), 8.05-8.07 (dd, *J* = 8.2 Hz, 1H), 8.84-8.85 (d, *J* = 4.2 Hz, 1H). ^{13}C NMR (125MHz, $CDCl_3$) δ 11.4, 18.7, 21.6, 22.1, 83.7, 106.4, 121.0, 125.2, 128.1, 130.7, 134.8, 135.5, 136.2, 144.7, 148.4. HRMS Calcd for $C_{22}H_{32}NSi$ $[M+H]^+$: 338.2304 ; Found: 338.2299.

6-chloro-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



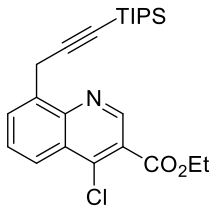
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 21H), 4.35 (s, 2H), 7.42-7.44 (q, *J* = 4.2 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 8.05-8.07 (m, 2H), 8.88-8.90 (dd, *J* = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 18.7, 22.2, 84.7, 105.2, 121.9, 124.9, 128.6, 129.3, 132.3, 135.3, 137.7, 144.4, 149.4 ; HRMS Calcd for $C_{21}H_{29}NClSi$ $[M+H]^+$: 358.1758; Found: 358.1752.

4-chloro-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21H), 4.39 (s, 2H), 7.50-7.51 (d, *J* = 4.8 Hz, 1H), 7.64-7.67 (t, *J* = 7.9 Hz, 1H), 8.13-8.17 (t, *J* = 9.1 Hz, 2H), 8.76-8.77 (t, *J* = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 18.7, 22.5, 83.9, 105.8, 121.2, 122.8, 126.2, 127.39, 129.1, 135.9, 142.7, 146.9, 148.6. HRMS Calcd for $C_{21}H_{29}NClSi$ $[M+H]^+$: 358.1758; Found: 358.1572.

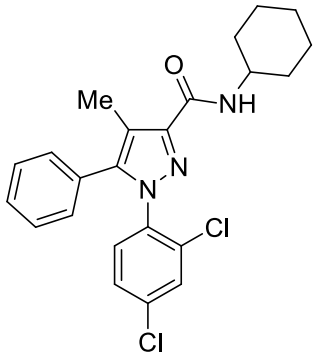
ethyl 4-chloro-8-(3-(triisopropylsilyl)prop-2-ynyl)quinoline-3-carboxylate



^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 21H), 1.46-1.49 (t, *J* = 7.0 Hz, 3H), 4.39 (s, 2H), 4.50-4.52 (q, *J* = 7.0 Hz, 2H), 7.70-7.73 (t, *J* = 7.9 Hz, 1H), 8.19-8.21 (d, *J* = 6.7 Hz, 1H), 8.33-8.35 (d, *J* = 8.5 Hz, 1H), 9.20 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.3, 14.2, 18.7, 22.4, 62.0, 84.2, 105.6, 122.9, 124.1, 125.9, 128.2, 130.7, 136.2, 143.5, 147.3, 148.9, 164.6; HRMS Calcd for $C_{24}H_{31}NClO_2Si$ $[M-H]^+$: 428.1813; Found: 428.1807

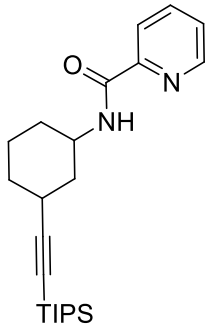
Chapter 5

_N_-cyclohexyl-1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-1H-pyrazole-3-carboxamide



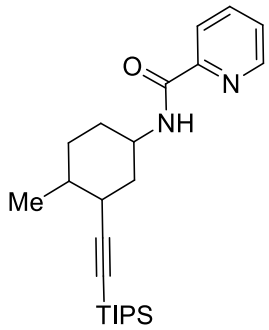
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 7.41 (d, *J* = 1.1 Hz, 1 H), 7.34 - 7.22 (m, 5 H), 7.13 (td, *J* = 2.8, 3.9 Hz, 2 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 4.02 - 3.87 (m, 1 H), 2.42 - 2.32 (m, 3 H), 2.10 - 1.96 (m, 2 H), 1.76 (td, *J* = 3.4, 13.4 Hz, 2 H), 1.70 - 1.57 (m, 1 H), 1.50 - 1.36 (m, 2 H), 1.32 - 1.19 (m, 4 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 162.0, 145.2, 144.2, 136.3, 135.7, 133.1, 130.7, 130.2, 129.6, 128.9, 128.6, 128.5, 127.7, 117.5, 47.9, 33.2, 25.6, 25.1, 9.5 HRMS (EI): *m/z* Calcd for [M+H] $C_{23}H_{24}ON_3Cl_2$: 428.1291; Found: 428.1289

_N_-(2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide



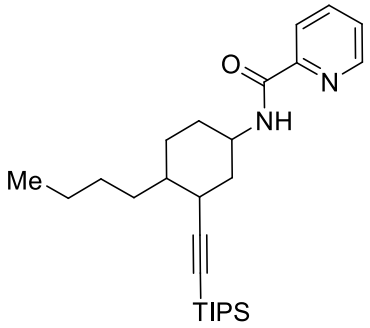
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.54 (d, *J* = 4.2 Hz, 1 H), 8.20 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.84 (dt, *J* = 1.7, 7.7 Hz, 1 H), 7.47 - 7.37 (m, 1 H), 4.06 - 3.86 (m, 1 H), 2.54 - 2.42 (m, 1 H), 2.37 (d, *J* = 12.6 Hz, 1 H), 2.10 - 1.93 (m, 2 H), 1.84 (td, *J* = 3.1, 13.5 Hz, 1 H), 1.46 - 1.22 (m, 4 H), 1.04 (s, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.3, 150.0, 147.9, 137.3, 126.1, 122.3, 112.1, 79.5, 77.3, 76.7, 47.6, 39.4, 32.5, 32.3, 29.8, 24.4, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{20}H_{31}N_2OSi$: 343.2200; Found: 343.2200.

_N_-(4-methyl-2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide



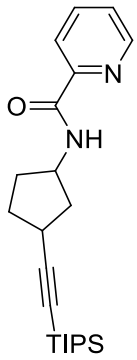
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.55 - 8.49 (m, 1 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 7.88 - 7.78 (m, 1 H), 7.45 - 7.33 (m, 1 H), 2.81 - 2.70 (m, 1 H), 2.20 - 2.02 (m, 2 H), 2.02 - 1.96 (m, 1 H), 1.86 - 1.64 (m, 3 H), 1.61 (d, *J* = 9.2 Hz, 2 H), 1.13 - 1.09 (m, 4 H), 1.08 - 0.98 (m, 22 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.5, 163.4, 150.1, 150.0, 147.9, 137.3, 137.2, 126.0, 126.0, 122.3, 122.2, 111.2, 110.8, 81.6, 80.6, 47.7, 47.1, 39.4, 37.2, 37.2, 33.5, 33.3, 33.2, 32.7, 31.4, 29.3, 27.3, 20.4, 18.6, 11.2. . HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{39}N_2OSi$: 399.2826; Found: 399.2827.

_N_-(4-butyl-2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide



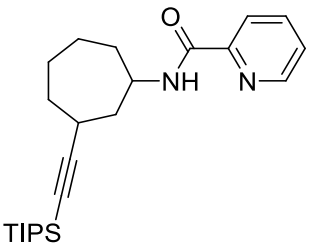
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.53 (dd, *J* = 4.6, 9.2 Hz, 1 H), 8.20 (dd, *J* = 3.4, 7.6 Hz, 1 H), 8.00 - 7.77 (m, 2 H), 7.50 - 7.32 (m, 1 H), 3.93 (dtd, *J* = 4.2, 7.9, 12.0 Hz, 1 H), 2.40 (dd, *J* = 2.3, 12.6 Hz, 1 H), 2.23 (d, *J* = 2.3 Hz, 1 H), 2.14 - 1.96 (m, 1 H), 1.96 - 1.85 (m, 1 H), 1.80 - 1.71 (m, 1 H), 1.71 - 1.56 (m, 2 H), 1.54 - 1.39 (m, 2 H), 1.39 - 1.17 (m, 8 H), 1.14 - 0.96 (m, 23 H), 0.96 - 0.84 (m, 3 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.4, 150.0, 147.9, 137.3, 137.2, 126.0, 125.9, 122.3, 122.2, 111.3, 80.8, 47.7, 41.9, 39.7, 35.8, 34.1, 34.0, 32.7, 32.1, 32.0, 29.9, 27.2, 26.1, 22.6, 22.5, 18.6, 14.1, 11.3, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{39}N_2OSi$: 441.3296; Found: 441.3293.

_N_-(2-((triisopropylsilyl)ethynyl)cyclopentyl)picolinamide



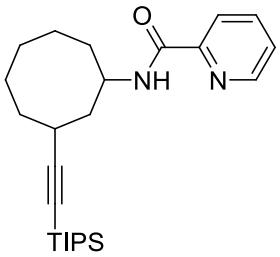
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.52 (d, *J* = 4.6 Hz, 1 H), 8.27 - 8.05 (m, 2 H), 7.84 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.41 (dd, *J* = 5.0, 6.5 Hz, 1 H), 4.50 (d, *J* = 7.2 Hz, 1 H), 2.87 (t, *J* = 7.2 Hz, 1 H), 2.55 - 2.37 (m, 1 H), 2.16 (dd, *J* = 5.5, 7.4 Hz, 1 H), 2.07 - 1.97 (m, 1 H), 1.97 - 1.86 (m, 1 H), 1.86 - 1.65 (m, 3 H), 1.09 - 1.00 (m, 22 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.8, 149.9, 147.9, 137.2, 126.0, 122.1, 112.7, 80.3, 50.1, 41.1, 32.5, 32.5, 29.7, 18.7, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{22}H_{35}N_2OSi$: 371.2513; Found: 371.2516.

_N_-(2-((triisopropylsilyl)ethynyl)cycloheptyl)picolinamide



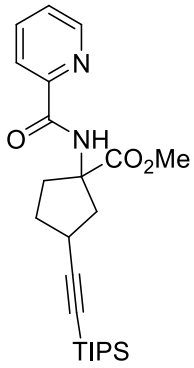
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.52 (d, *J* = 4.2 Hz, 1 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 8.14 (d, *J* = 8.0 Hz, 1 H), 7.83 (dt, *J* = 1.5, 7.8 Hz, 1 H), 7.41 (dd, *J* = 4.8, 6.7 Hz, 1 H), 4.22 (td, *J* = 4.6, 9.2 Hz, 1 H), 2.83 - 2.71 (m, 1 H), 2.28 (td, *J* = 3.4, 14.1 Hz, 1 H), 2.06 (ddd, *J* = 3.8, 6.9, 13.7 Hz, 1 H), 1.95 - 1.85 (m, 2 H), 1.84 - 1.64 (m, 5 H), 1.59 - 1.45 (m, 1 H), 1.14 - 0.96 (m, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 162.9, 150.1, 147.9, 137.2, 126.0, 122.2, 113.1, 80.6, 77.3, 76.7, 48.9, 41.4, 35.5, 34.9, 29.4, 25.8, 24.3, 18.6, 11.2 HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{39}N_2OSi$: 399.2826; Found: 399.2827.

_N_-(2-((triisopropylsilyl)ethynyl)cyclooctyl)picolinamide



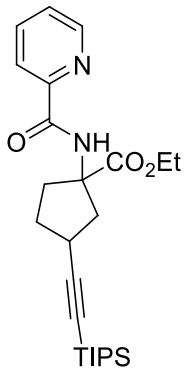
^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.54 (d, *J* = 4.3 Hz, 1 H), 8.20 (d, *J* = 7.9 Hz, 1 H), 8.08 (d, *J* = 7.9 Hz, 1 H), 7.84 (t, *J* = 7.0 Hz, 1 H), 7.42 (dd, *J* = 4.9, 7.3 Hz, 1 H), 4.19 (dd, *J* = 4.3, 7.9 Hz, 1 H), 2.84 (dd, *J* = 4.0, 7.0 Hz, 1 H), 2.22 - 2.09 (m, 1 H), 2.06 - 1.92 (m, 3 H), 1.92 - 1.65 (m, 5 H), 1.61 (br. s., 5 H), 1.10 - 0.97 (m, 22 H). ^{13}C NMR (101MHz, $CDCl_3$) δ ppm 162.9, 150.2, 148.0, 137.3, 126.0, 122.2, 113.4, 79.9, 48.3, 39.3, 33.8, 31.9, 30.2, 26.8, 23.4, 22.5, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{25}H_{41}N_2OSi$: 413.1983; Found: 413.2985.

methyl 1-(picolinamido)-3-((triisopropylsilyl)ethynyl)cyclopentanecarboxylate



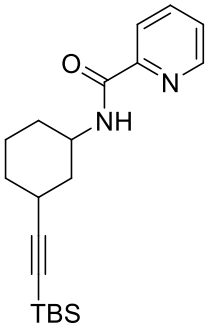
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.55 (brs., 1 H), 8.51 (brs., 1 H), 8.15 (d, *J* = 7.2 Hz, 1 H), 7.84 (brs., 1 H), 7.44 (brs., 1 H), 3.74 (brs., 3 H), 3.08 (brs., 1 H), 2.85 - 2.76 (m, 1 H), 2.51 - 2.39 (m, 1 H), 2.35 - 2.24 (m, 1 H), 2.24 - 2.14 (m, 2 H), 2.02 (d, *J* = 8.0 Hz, 1 H), 1.00 (br. s., 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 174.0, 164.1, 149.5, 148.0, 137.3, 126.3, 122.1, 111.4, 80.7, 65.1, 52.7, 44.9, 37.2, 33.1, 30.5, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{37}N_2O_3Si$: 429.2568; Found: 429.2568.

ethyl 1-(picolinamido)-3-((triisopropylsilyl)ethynyl)cyclopentanecarboxylate



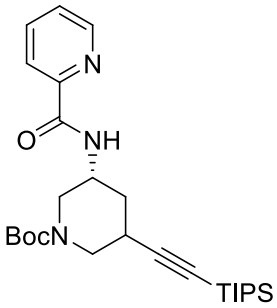
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.65 - 8.47 (m, 2 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 7.84 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.43 (dd, *J* = 5.0, 6.9 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.08 (t, *J* = 7.6 Hz, 1 H), 2.80 (dd, *J* = 8.4, 13.7 Hz, 1 H), 2.50 - 2.36 (m, 1 H), 2.34 - 2.26 (m, 1 H), 2.26 - 2.13 (m, 2 H), 2.02 (dd, *J* = 8.0, 12.6 Hz, 1 H), 1.24 (t, *J* = 7.1 Hz, 4 H), 1.08 - 0.89 (m, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 173.4, 164.0, 149.6, 148.0, 137.2, 126.2, 122.0, 111.5, 80.7, 65.1, 61.5, 44.8, 37.1, 33.2, 30.6, 18.6, 14.1, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{25}H_{39}N_2O_3Si$: 443.2724; Found: 443.2727.

***N*-(2-((tert-butyldimethylsilyl)ethynyl)cyclohexyl)picolinamide**



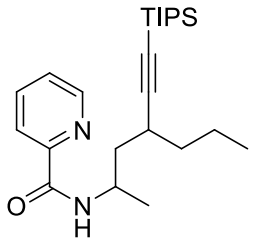
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.53 (d, *J* = 4.6 Hz, 1 H), 8.19 (d, *J* = 7.6 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.84 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.41 (dd, *J* = 5.0, 6.9 Hz, 1 H), 4.02 - 3.83 (m, 1 H), 2.52 - 2.40 (m, 1 H), 2.34 (d, *J* = 12.6 Hz, 1 H), 2.09 - 1.94 (m, 2 H), 1.88 - 1.78 (m, 1 H), 1.44 - 1.21 (m, 4 H), 0.90 (s, 10 H), 0.06 (s, 6 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.3, 150.0, 147.9, 137.3, 126.0, 122.2, 110.7, 81.9, 47.5, 39.1, 32.3, 32.2, 29.6, 26.0, 24.2, 16.4, -4.5. HRMS (EI): *m/z* Calcd for [M+H] $C_{20}H_{31}N_2OSi$: 343.2200; Found: 343.2200.

(3*R*)-tert-butyl 3-(picolinamido)-5-((triisopropylsilyl)ethynyl)piperidine-1-carboxylate



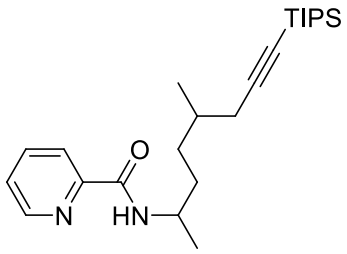
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.53 (d, *J* = 4.2 Hz, 1 H), 8.19 (d, *J* = 7.6 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.85 (t, *J* = 7.2 Hz, 1 H), 7.56 - 7.36 (m, 1 H), 4.30 (br. s., 2 H), 4.15 - 3.91 (m, 1 H), 2.75 - 2.59 (m, 2 H), 2.45 (d, *J* = 12.2 Hz, 1 H), 1.52 - 1.43 (m, 9 H), 1.13 (dd, *J* = 5.0, 7.2 Hz, 2 H), 1.09 - 0.93 (m, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.7, 154.3, 149.6, 147.9, 137.3, 126.3, 122.2, 107.7, 81.9, 80.3, 48.5, 48.0, 45.0, 37.7, 28.8, 28.3, 18.8, 18.8, 18.5, 12.5, 11.4, 11.0. HRMS (EI): *m/z* Calcd for [M+H] $C_{27}H_{44}N_3O_3Si$: 486.3146; Found: 486.3150.

***N*-(4-((triisopropylsilyl)ethynyl)heptan-2-yl)picolinamide**



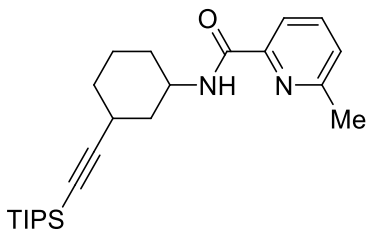
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.54 (d, *J* = 4.2 Hz, 1 H), 8.21 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 6.9 Hz, 1 H), 7.87 - 7.78 (m, 1 H), 7.42 (dd, *J* = 5.3, 6.9 Hz, 1 H), 4.48 - 4.25 (m, 1 H), 2.59 - 2.48 (m, 1 H), 1.92 - 1.84 (m, 1 H), 1.84 - 1.77 (m, 1 H), 1.77 - 1.65 (m, 1 H), 1.61 (br. s., 2 H), 1.50 - 1.41 (m, 3 H), 1.38 - 1.29 (m, 4 H), 1.13 - 1.02 (m, 23 H), 0.94 - 0.90 (m, 4 H).^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.5, 150.3, 147.9, 137.3, 126.0, 122.2, 111.9, 81.4, 76.8, 44.5, 42.7, 37.6, 30.0, 21.1, 20.3, 18.6, 13.9, 11.3. HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{41}N_2OSi$: 401.2983; Found: 401.2978.

_N_-(7-methyl-1-(triisopropylsilyl)oct-1-yn-4-yl)picolinamide



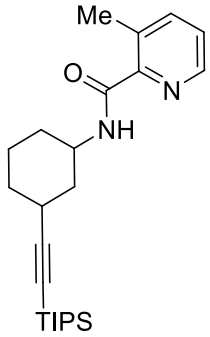
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.46 (d, *J* = 4.2 Hz, 2 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 7.82 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.39 (dt, *J* = 1.0, 6.2 Hz, 1 H), 4.19 (d, *J* = 8.4 Hz, 1 H), 2.52 (s, 1 H), 2.45 (d, *J* = 17.5 Hz, 2 H), 2.03 (d, *J* = 6.5 Hz, 2 H), 1.65 - 1.55 (m, 2 H), 1.41 (t, *J* = 9.0 Hz, 1 H), 1.32 - 1.21 (m, 1 H), 1.19 - 0.95 (m, 25 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.7, 150.3, 147.8, 137.0, 125.8, 122.3, 108.9, 84.2, 77.3, 76.7, 52.4, 48.3, 42.9, 40.3, 38.8, 28.1, 27.3, 18.6, 11.3 HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{41}N_2OSi$: 401.2983Found: 401.2978.

6-methyl-_N_-(2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide



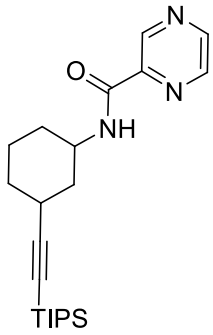
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.08 - 7.93 (m, 2 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.29 (s, 1 H), 3.95 (td, *J* = 3.7, 12.1 Hz, 1 H), 2.59 (s, 3 H), 2.54 - 2.44 (m, 1 H), 2.39 (d, *J* = 12.6 Hz, 1 H), 2.05 (t, *J* = 13.0 Hz, 2 H), 1.90 - 1.79 (m, 1 H), 1.47 - 1.26 (m, 4 H), 1.12 - 0.94 (m, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.5, 157.0, 149.3, 137.4, 125.7, 119.3, 112.1, 79.4, 47.6, 39.4, 32.6, 32.4, 29.8, 24.5, 24.2, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{39}N_2OSi$: 399.2826; Found: 399.2827.

3-methyl-*N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)picolinamide



^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.37 (d, *J* = 4.2 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.29 (dd, *J* = 4.6, 8.0 Hz, 1 H), 3.97 - 3.80 (m, 1 H), 2.74 (s, 3 H), 2.52 - 2.42 (m, 1 H), 2.36 (d, *J* = 12.2 Hz, 1 H), 2.02 (t, *J* = 12.8 Hz, 2 H), 1.83 (td, *J* = 3.2, 13.4 Hz, 1 H), 1.45 - 1.21 (m, 4 H), 1.10 - 0.95 (m, 22 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 165.1, 147.3, 145.3, 140.8, 135.4, 125.5, 112.2, 79.4, 47.4, 39.5, 32.6, 32.4, 29.8, 24.4, 20.5, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{24}H_{39}N_2OSi$: 399.2826; Found: 399.2827.

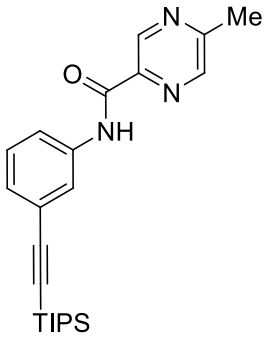
***N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)pyrazine-2-carboxamide**



^{1}H NMR (500MHz , $CDCl_3$) δ ppm 9.42 (s, 1 H), 8.76 (d, *J* = 2.3 Hz, 1 H), 8.53 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 1 H), 3.99 (d, *J* = 8.0 Hz, 1 H), 2.57 - 2.47 (m, 1 H), 2.38 (d, *J* = 11.8

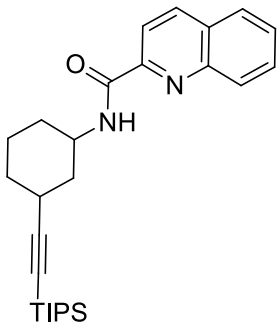
Hz, 1 H), 2.10 - 2.02 (m, 3 H), 1.87 (td, *J* = 3.0, 13.4 Hz, 1 H), 1.48 - 1.25 (m, 4 H), 1.17 - 1.09 (m, 2 H), 1.09 - 0.96 (m, 20 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 162.0, 147.2, 144.5, 144.5, 142.4, 111.8, 79.7, 47.7, 39.2, 32.4, 32.2, 29.6, 24.2, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{22}H_{36}N_3OSi$: 386.2622; Found: 386.2621.

5-methyl-*N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)pyrazine-2-carboxamide



^{1}H NMR (500MHz, $CDCl_3$) δ ppm 9.26 (s, 1 H), 8.36 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 4.05 - 3.86 (m, 1 H), 2.65 (s, 3 H), 2.53 - 2.41 (m, 1 H), 2.36 (d, *J* = 12.6 Hz, 1 H), 2.07 - 1.97 (m, 2 H), 1.89 - 1.79 (m, 1 H), 1.46 - 1.29 (m, 3 H), 1.29 - 1.22 (m, 1 H), 1.11 - 0.92 (m, 22 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 162.3, 156.9, 143.4, 142.1, 141.8, 111.9, 79.6, 47.6, 39.3, 32.4, 32.3, 29.7, 24.3, 21.8, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{23}H_{38}N_3OSi$: 400.2779; Found: 400.2777.

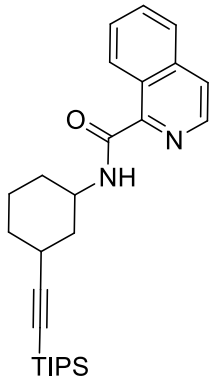
***N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)quinoline-2-carboxamide**



^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.35 - 8.21 (m, 2 H), 8.20 - 8.04 (m, 2 H), 7.87 (d, *J* = 8.4 Hz, 1 H), 7.76 (t, *J* = 7.6 Hz, 1 H), 7.67 - 7.53 (m, 1 H), 4.08 - 3.92 (m, 1 H), 2.57 - 2.48 (m, 1 H), 2.43 (d, *J* = 12.6 Hz, 1 H), 2.15 - 1.99 (m, 2 H), 1.93 - 1.82 (m, 1 H), 1.53 - 1.29 (m, 4 H), 1.14 - 0.94 (m, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.5, 149.9, 146.4, 137.4, 130.0, 129.6, 129.3, 127.8, 127.7, 118.9, 112.1, 79.5, 47.8, 39.5, 32.6, 32.4,

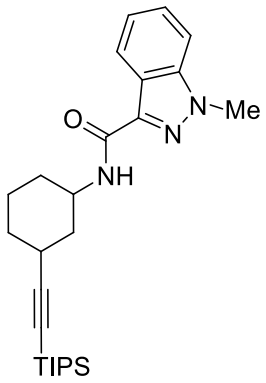
29.8, 24.5, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M-H] $C_{27}H_{37}N_2OSi$: 433.2670; Found: 433.2666.

_N_-(2-((triisopropylsilyl)ethynyl)cyclohexyl)isoquinoline-1-carboxamide



^{1}H NMR (500MHz, $CDCl_3$) δ ppm 9.60 (d, *J* = 8.4 Hz, 1 H), 8.45 (d, *J* = 5.3 Hz, 1 H), 8.12 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 5.3 Hz, 1 H), 7.75 - 7.64 (m, 2 H), 4.08 - 3.92 (m, 1 H), 2.60 - 2.48 (m, 1 H), 2.44 (d, *J* = 12.6 Hz, 1 H), 2.10 (d, *J* = 12.2 Hz, 1 H), 2.03 (d, *J* = 13.0 Hz, 1 H), 1.87 (td, *J* = 3.1, 13.5 Hz, 1 H), 1.50 - 1.26 (m, 4 H), 1.08 - 0.93 (m, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 165.2, 148.4, 140.1, 137.4, 130.4, 128.6, 127.9, 127.0, 126.7, 124.2, 112.1, 79.5, 47.7, 39.4, 32.6, 32.3, 29.8, 24.4, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M-H] $C_{27}H_{37}N_2OSi$: 433.2670; Found: 433.2666.

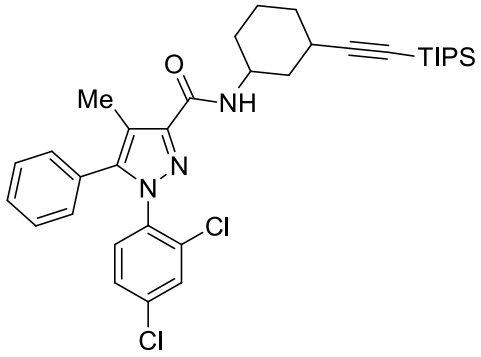
1-methyl-_N_-(2-((triisopropylsilyl)ethynyl)cyclohexyl)-1H-indazole-3-carboxamide



^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.38 (d, *J* = 8.4 Hz, 1 H), 7.48 - 7.37 (m, 2 H), 7.29 (d, *J* = 7.2 Hz, 1 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 4.09 (s, 3 H), 4.05 - 3.93 (m, 1 H), 2.58 - 2.46 (m, 1 H), 2.42 (d, *J* = 12.6 Hz, 1 H), 2.14 - 1.97 (m, 2 H), 1.90 - 1.77 (m, 1 H), 1.47 - 1.24 (m, 4 H), 1.10 - 0.94 (m, 22 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 161.7, 141.2,

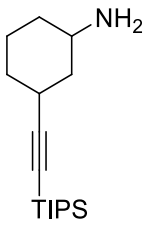
137.3, 126.8, 122.9, 122.8, 122.5, 112.2, 109.0, 79.4, 47.2, 39.6, 35.9, 32.5, 29.8, 24.4, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{26}H_{40}N_3OSi$: 438.2935; Found: 438.2935.

1-(2,4-dichlorophenyl)-4-methyl-5-phenyl-*N*-(2-((triisopropylsilyl)ethynyl)cyclohexyl)-1H-pyrazole-3-carboxamide



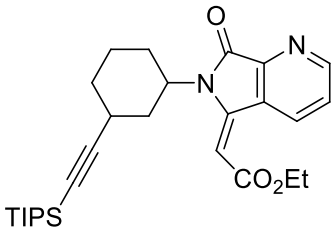
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 7.21 - 7.10 (m, 7 H), 7.04 - 6.93 (m, 2 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 3.87 - 3.71 (m, 1 H), 2.37 - 2.30 (m, 1 H), 2.26 - 2.18 (m, 4 H), 1.95 - 1.81 (m, 2 H), 1.71 - 1.63 (m, 1 H), 1.29 - 1.22 (m, 1 H), 1.21 - 1.03 (m, 5 H), 0.96 - 0.89 (m, 22 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 162.0, 144.9, 144.2, 136.2, 135.7, 133.1, 130.6, 130.2, 129.6, 128.8, 128.6, 128.5, 127.7, 117.6, 112.2, 79.4, 47.3, 39.6, 32.5, 32.4, 29.8, 24.5, 18.6, 18.5, 11.3, 11.2, 9.5. HRMS (EI): *m/z* Calcd for [M+H] $C_{34}H_{44}ON_3Cl_2Si$: 608.2625; Found: 608.2623.

2-((triisopropylsilyl)ethynyl)cyclohexanamine



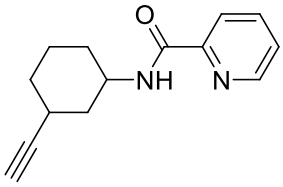
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 5.00 (brs., 3 H), 2.97 (br. s., 1 H), 2.33 (d, *J* = 12.2 Hz, 1 H), 2.05 (d, *J* = 6.1 Hz, 1 H), 1.96 (brs., 2 H), 1.82 (brs., 1 H), 1.38 - 1.26 (m, 4 H), 1.06 - 1.02 (m, 21 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 111.1, 80.2, 49.7, 38.1, 32.1, 31.2, 29.4, 23.8, 18.6, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{17}H_{34}Si$: 280.2455; Found: 280.2457.

(*E*)-ethyl 2-(7-oxo-6-(2-((triisopropylsilyl)ethynyl)cyclohexyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-ylidene)acetate



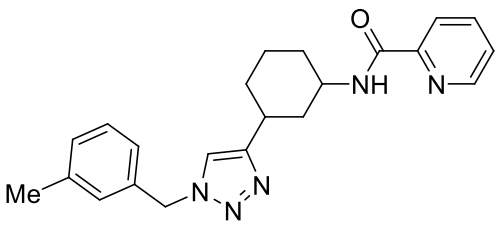
^{1}H NMR (500MHz, $CDCl_3$) δ ppm 9.34 (dd, *J* = 1.0, 8.2 Hz, 1 H), 8.82 (d, *J* = 3.8 Hz, 1 H), 7.53 (dd, *J* = 4.8, 8.2 Hz, 1 H), 5.96 (brs., 1 H), 4.31 (q, *J* = 7.0 Hz, 2 H), 2.48 (d, *J* = 9.5 Hz, 3 H), 2.14 - 1.98 (m, 2 H), 1.98 - 1.87 (m, 1 H), 1.78 (d, *J* = 12.6 Hz, 1 H), 1.56 - 1.33 (m, 6 H), 1.08 - 0.98 (m, 22 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 165.8, 165.0, 152.8, 148.3, 135.9, 128.7, 126.4, 111.2, 80.2, 60.9, 35.6, 32.1, 30.9, 28.4, 25.3, 18.6, 18.3, 14.3, 11.2. HRMS (EI): *m/z* Calcd for [M+H] $C_{28}H_{41}N_2O_3Si$: 481.2881; Found: 481.2875.

_N_-(2-ethynylcyclohexyl)picolinamide



^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.53 (d, *J* = 4.2 Hz, 1 H), 8.19 (d, *J* = 7.6 Hz, 1 H), 8.11 - 7.89 (m, 1 H), 7.83 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.45 - 7.30 (m, 1 H), 4.03 - 3.88 (m, 1 H), 2.52 - 2.37 (m, 1 H), 2.32 (d, *J* = 12.6 Hz, 1 H), 2.11 - 1.93 (m, 3 H), 1.93 - 1.75 (m, 1 H), 1.48 - 1.24 (m, 4 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.3, 150.0, 147.9, 137.3, 126.0, 122.2, 87.5, 68.1, 47.3, 38.7, 32.2, 32.0, 28.2, 23.9. HRMS (EI): *m/z* Calcd for [M+H] $C_{14}H_{17}N_2O$: 229.1335; Found: 229.1335.

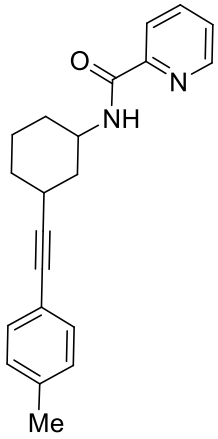
_N_-(2-(1-(3-methylbenzyl)-1H-1,2,3-triazol-4-yl)cyclohexyl)picolinamide



^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.51 (d, *J* = 4.6 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.82 (t, *J* = 7.6 Hz, 1 H), 7.40 (dd, *J* = 5.3, 6.9 Hz, 1 H), 7.27 -

7.21 (m, 1 H), 7.19 - 7.10 (m, 2 H), 7.10 - 7.00 (m, 2 H), 5.43 (s, 2 H), 4.07 (dt, *J* = 3.8, 7.8 Hz, 1 H), 2.98 - 2.77 (m, 1 H), 2.41 (d, *J* = 12.2 Hz, 1 H), 2.33 (s, 3 H), 2.18 - 2.05 (m, 2 H), 2.03 - 1.88 (m, 2 H), 1.61 - 1.51 (m, 1 H), 1.47 - 1.37 (m, 2 H), 1.36 - 1.27 (m, 1 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.3, 152.5, 150.0, 147.9, 138.8, 137.3, 134.7, 129.3, 128.9, 128.7, 126.0, 125.1, 122.1, 119.3, 54.0, 48.2, 38.9, 34.3, 32.5, 32.0, 24.6, 21.3. HRMS (EI): *m/z* Calcd for [M+H] $C_{22}H_{26}N_2O$: 376.2132; Found: 376.2130.

_N_-(2-(p-tolylethynyl)cyclohexyl)picolinamide

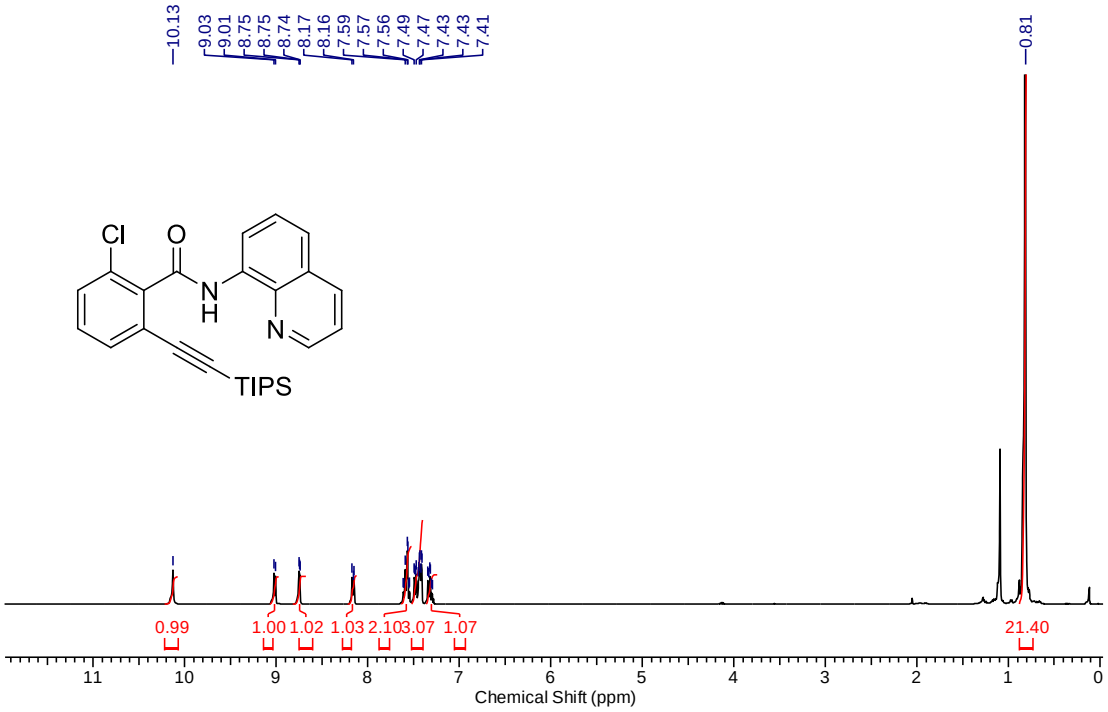


^{1}H NMR (500MHz, $CDCl_3$) δ ppm 8.45 (d, *J* = 4.2 Hz, 1 H), 8.20 (d, *J* = 7.6 Hz, 1 H), 8.15 - 8.03 (m, 1 H), 7.83 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.47 - 7.32 (m, 1 H), 7.32 - 7.21 (m, 2 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 4.13 - 3.95 (m, 1 H), 2.78 - 2.62 (m, 1 H), 2.42 - 2.28 (m, 4 H), 2.07 - 1.96 (m, 2 H), 1.90 (dd, *J* = 3.8, 9.9 Hz, 1 H), 1.59 - 1.42 (m, 3 H), 1.42 - 1.30 (m, 1 H). ^{13}C NMR (126MHz, $CDCl_3$) δ ppm 163.4, 150.0, 147.9, 137.5, 137.2, 131.4, 128.9, 126.0, 122.2, 120.7, 92.2, 77.3, 76.7, 47.3, 38.7, 32.2, 32.1, 28.9, 23.7, 21.4. HRMS (EI): *m/z* Calcd for [M+H] $C_{21}H_{23}N_2O$: 319.1805; Found: 319.1805.

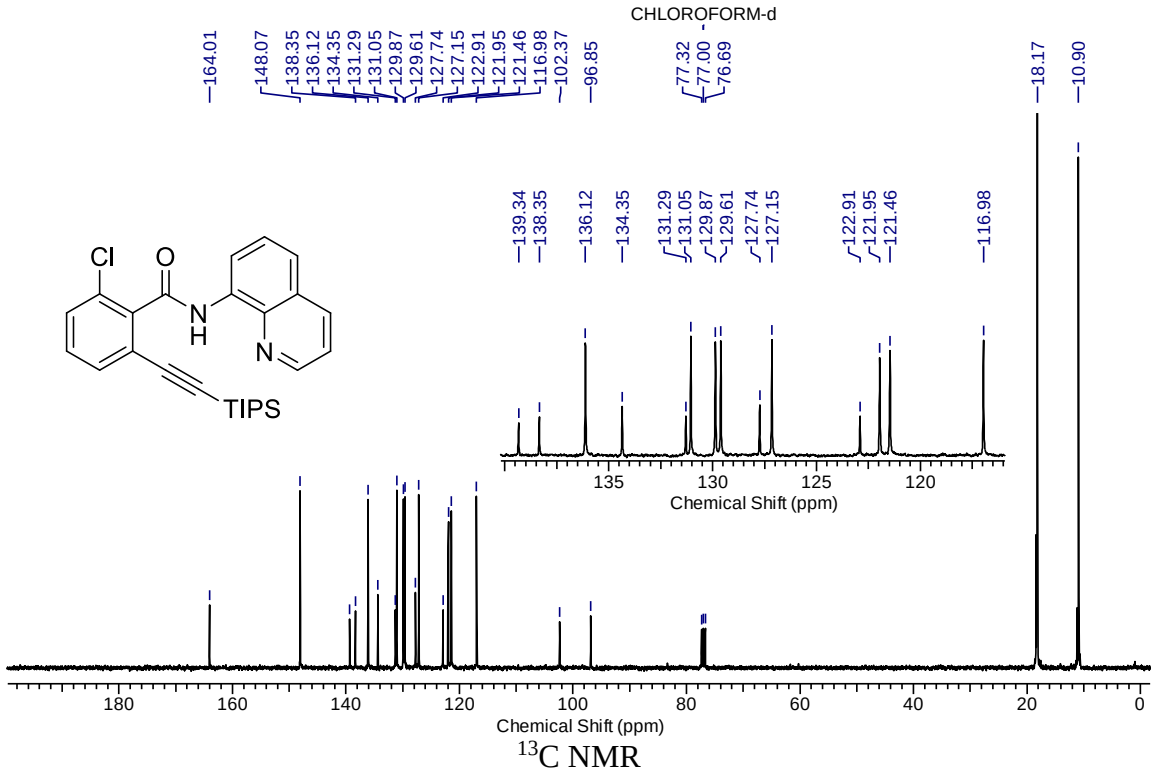
Appendix B

Copy of ^{1}H and ^{13}C Spectra

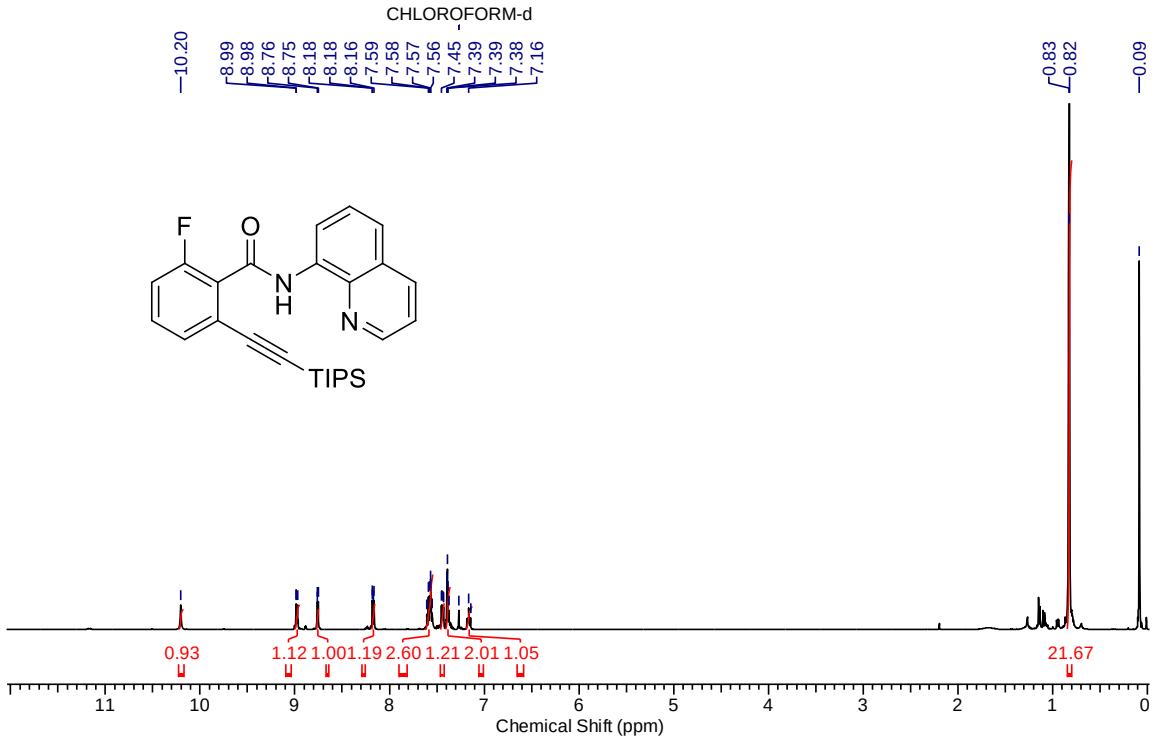
Chapter 2 and Chapter 3



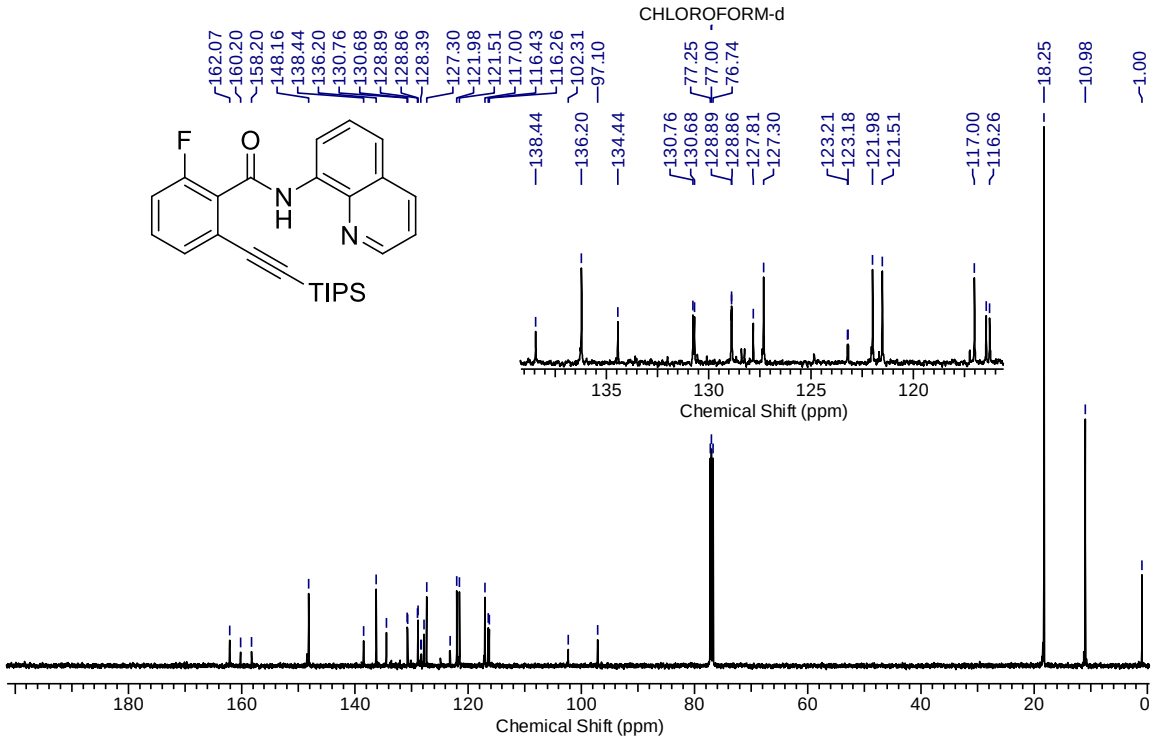
^{1}H NMR



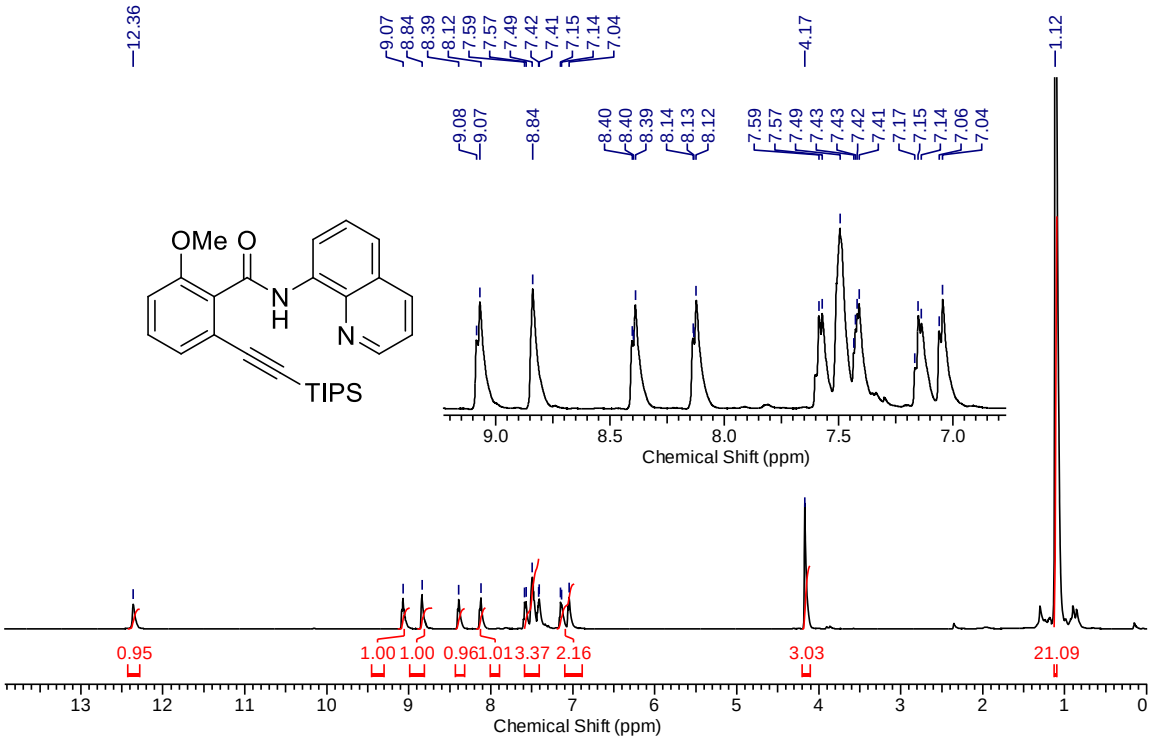
^{13}C NMR



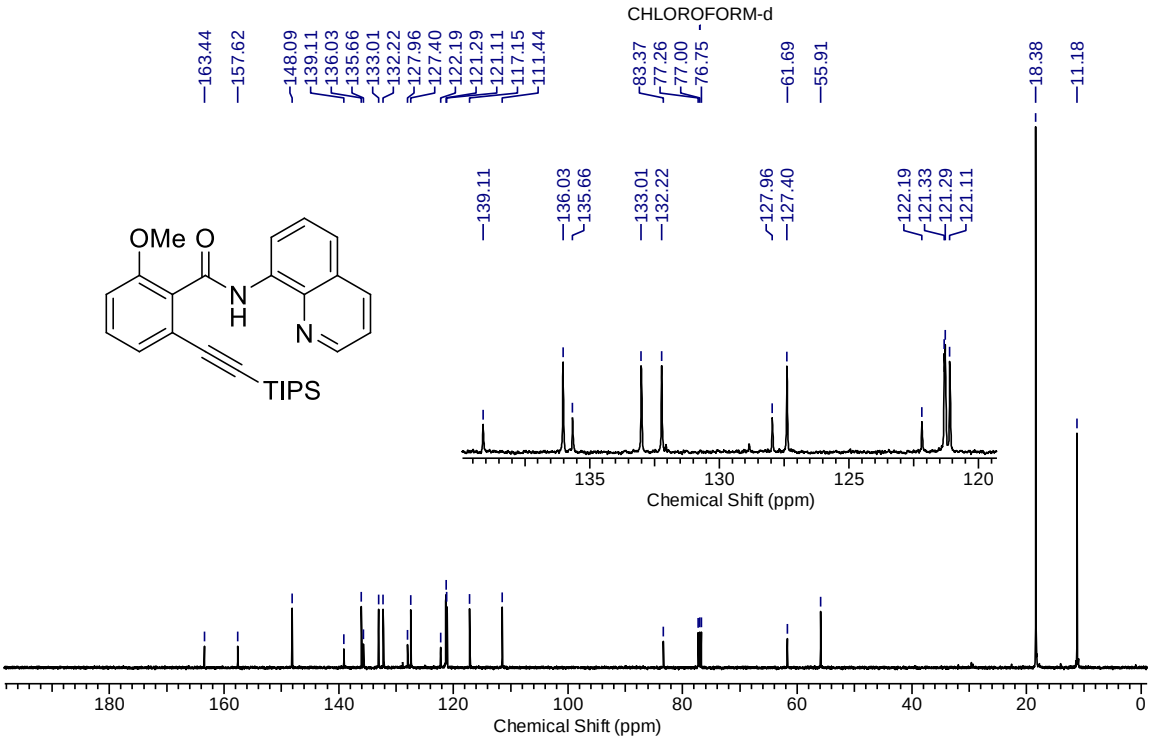
^{1}H NMR



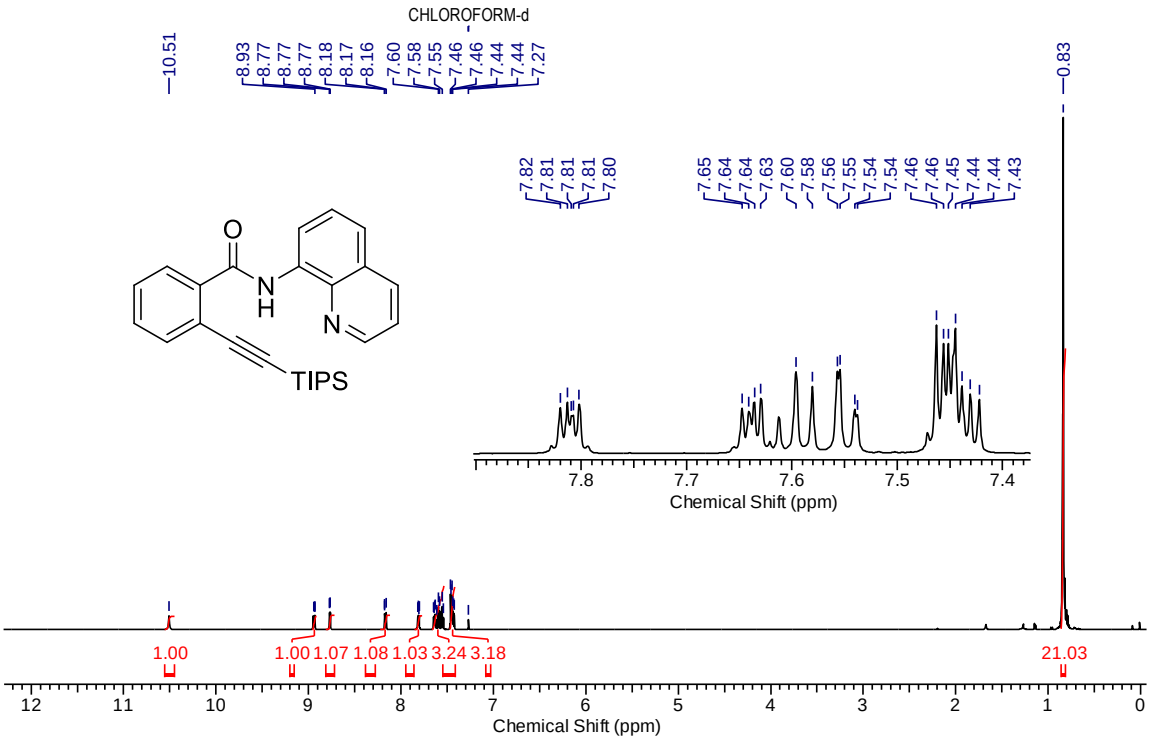
^{13}C NMR



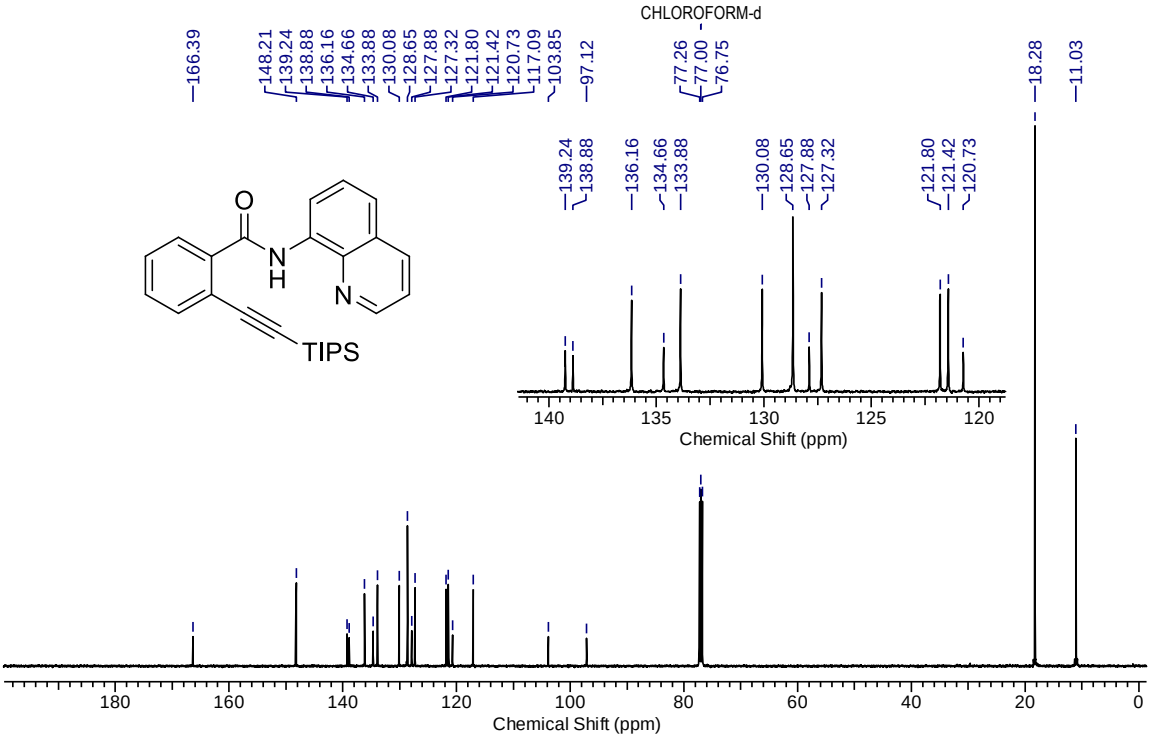
^{1}H NMR



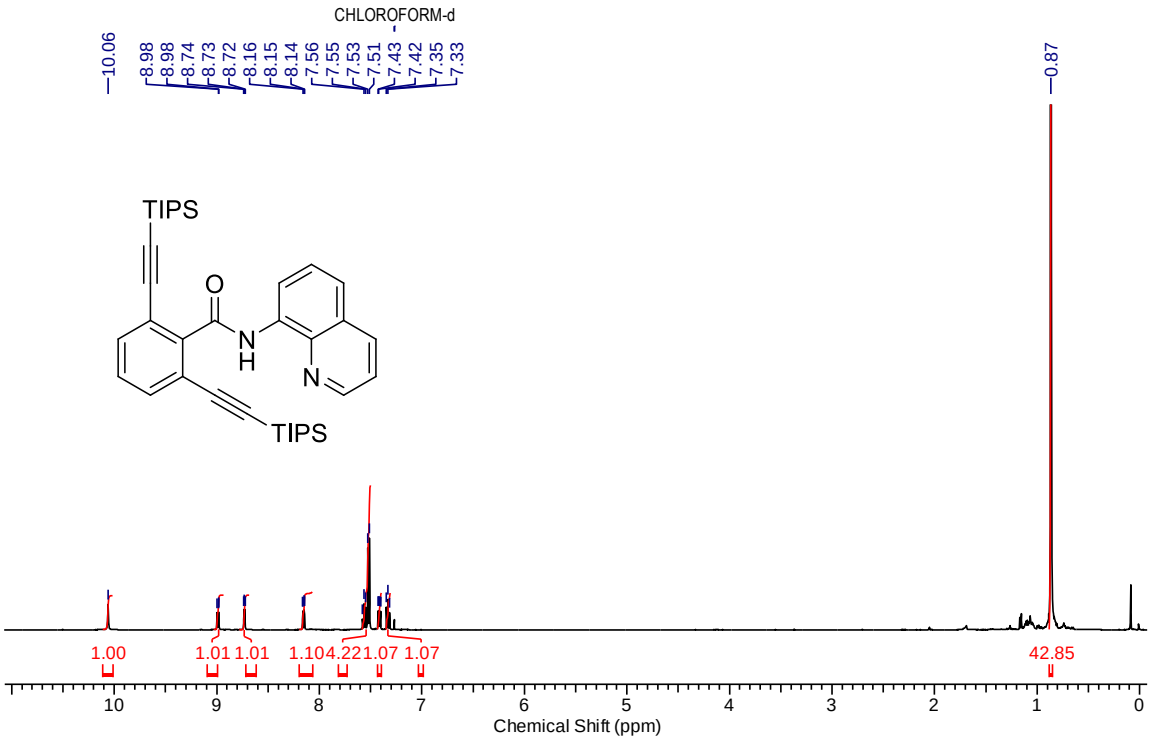
^{13}C NMR



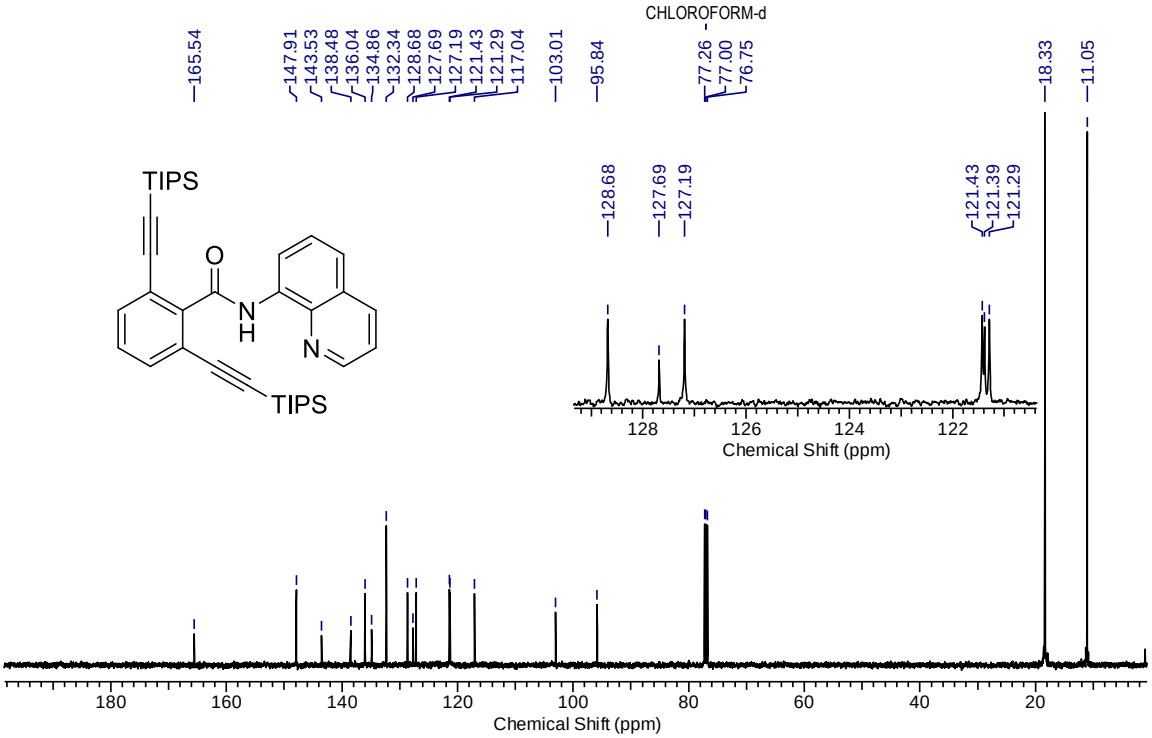
^{1}H NMR



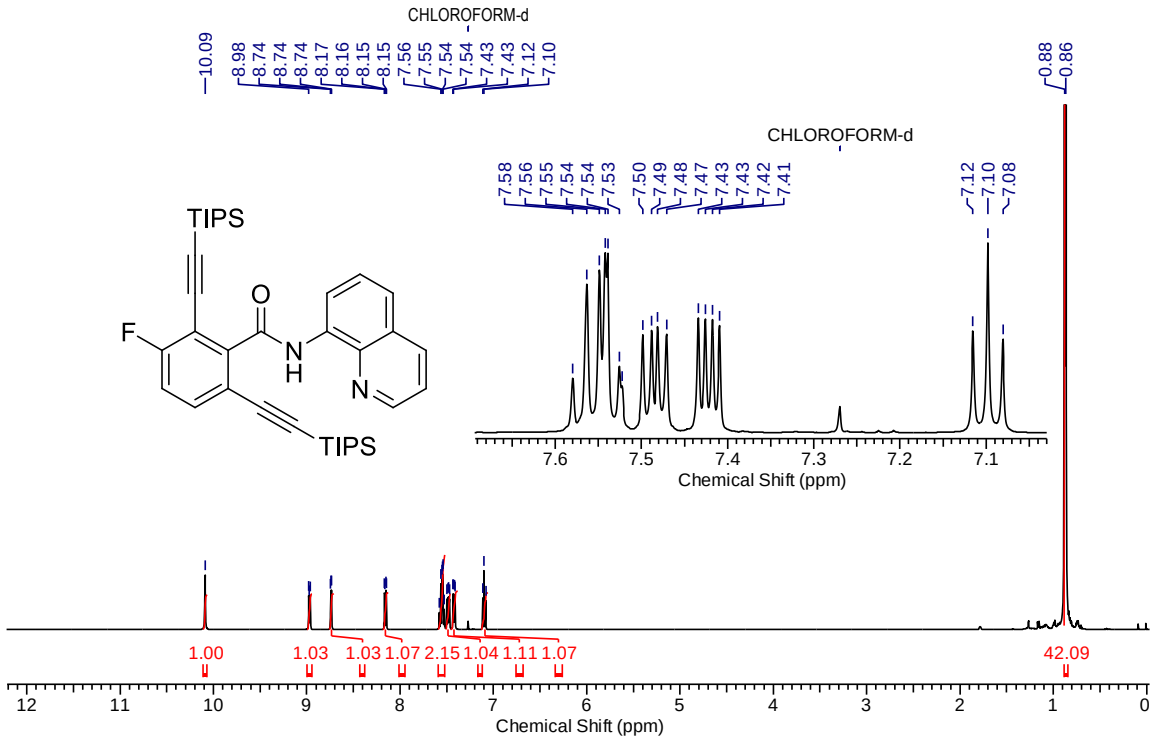
^{13}C NMR



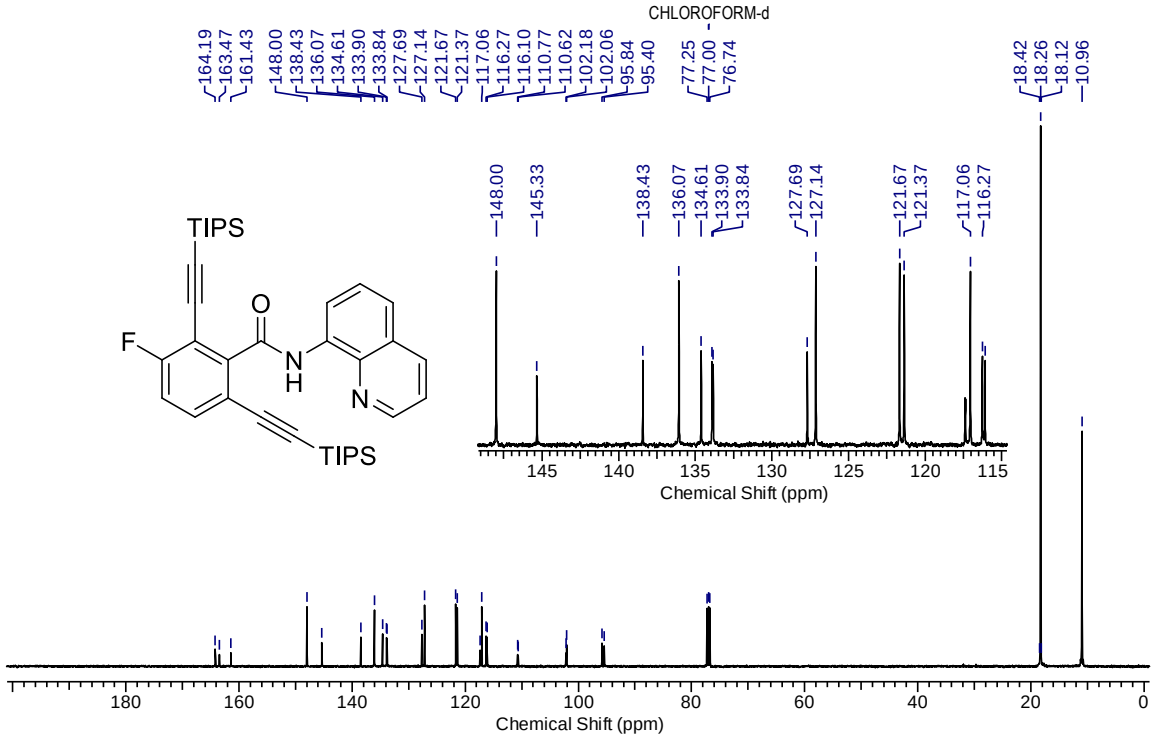
^{1}H NMR



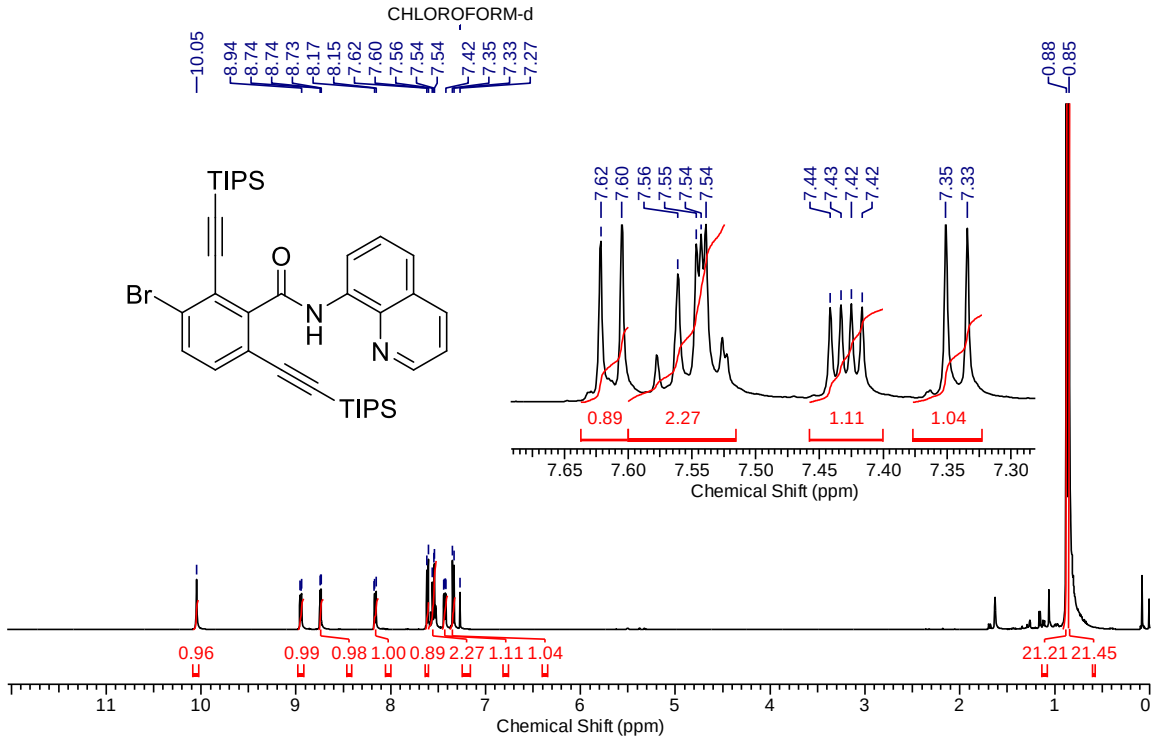
^{13}C NMR



^{1}H NMR



^{13}C NMR



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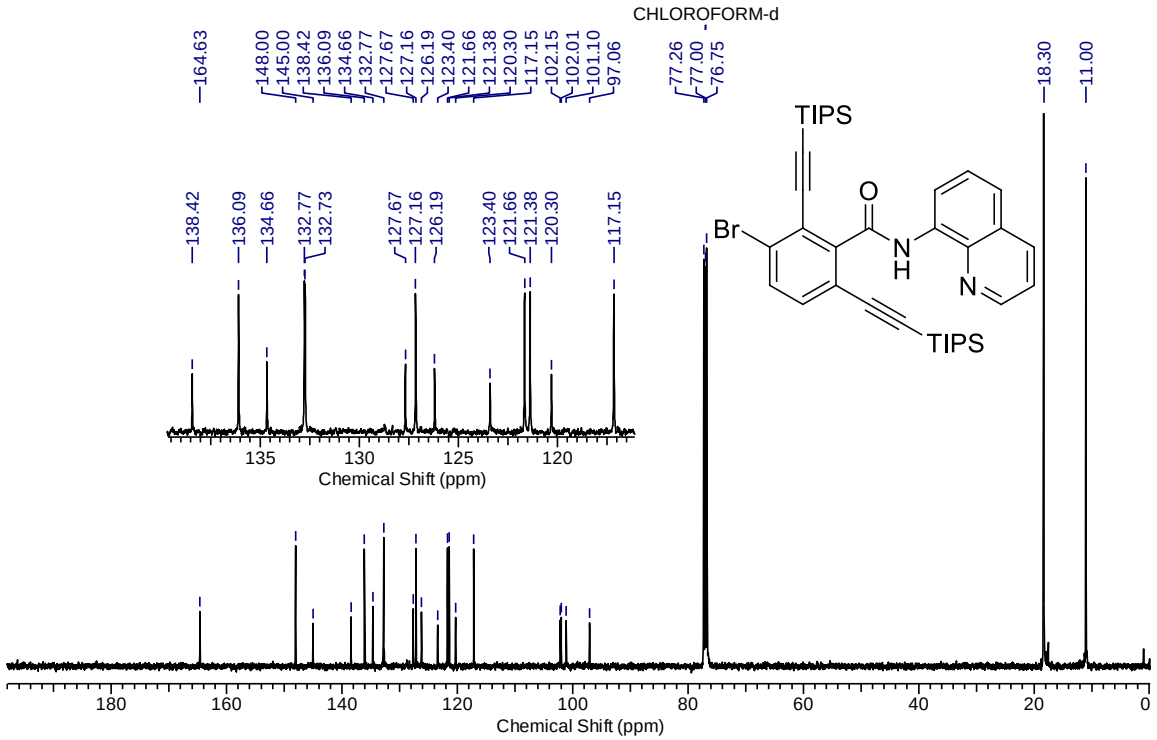

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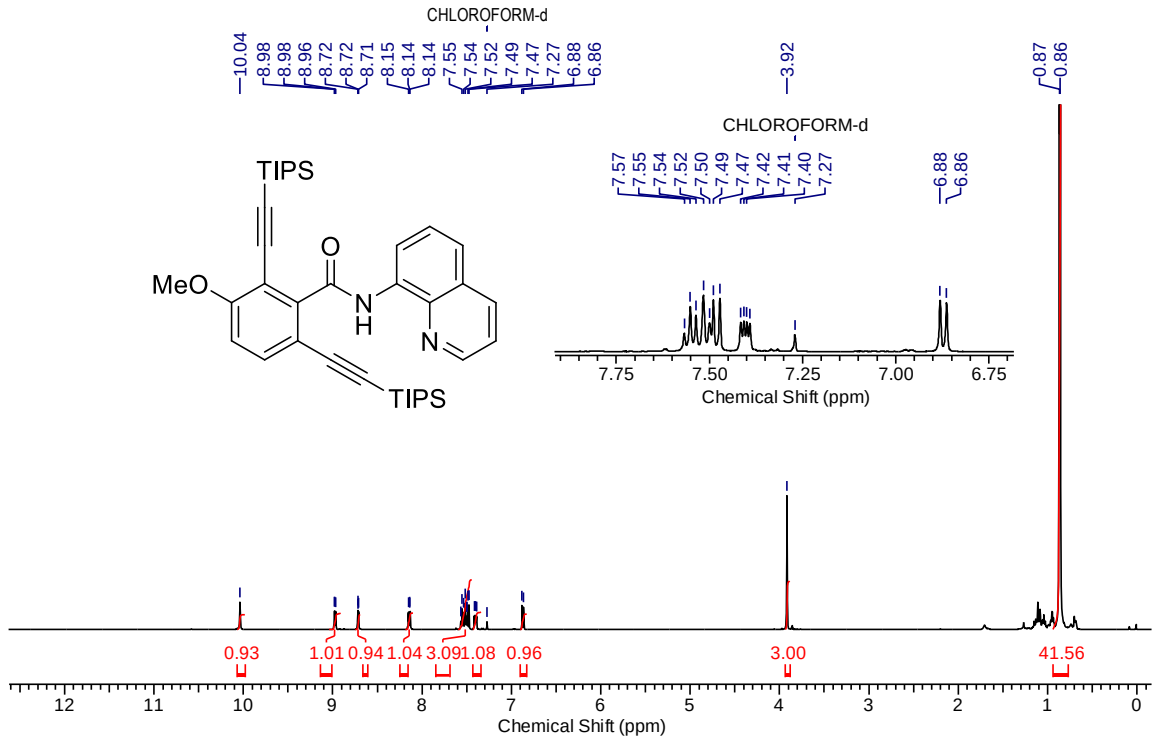
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7.54
7.52
7.49
7.47
7.27
6.88
6.86
3.92
0.87
0.86
TIPS
MeO
O
N
H
N
TIPS
CHLOROFORM-d
7.57
7.55
7.54
7.52
7.50
7.49
7.47
7.42
7.41
7.40
7.27
6.88
6.86
7.75
7.50
7.25
7.00
6.75
Chemical Shift (ppm)
0.93
1.01
0.94
1.04
3.09
1.08
0.96
3.00
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10
9
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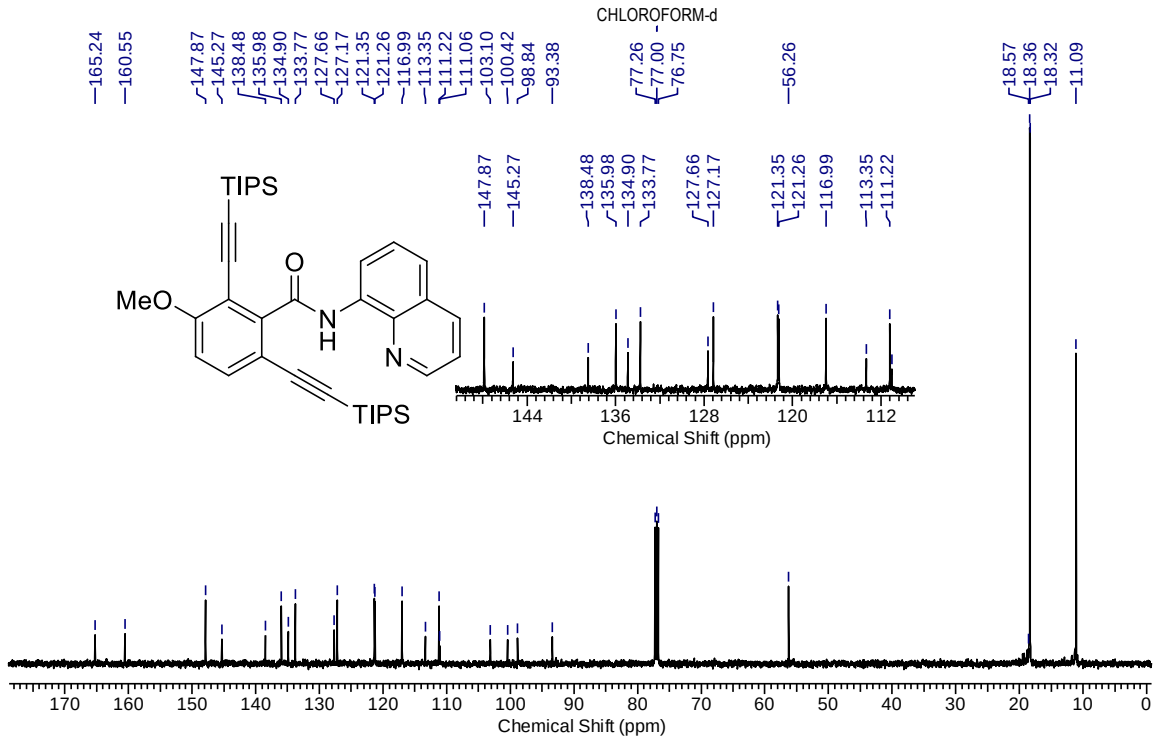
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

^{1}H NMR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76.75
56.26
18.57
18.36
18.32
11.09
TIPS
MeO
O
N
H
N
TIPS
147.87
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134.90
133.77
127.66
127.17
121.35
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116.99
113.35
111.22
144
136
128
120
112
Chemical Shift (ppm)
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20
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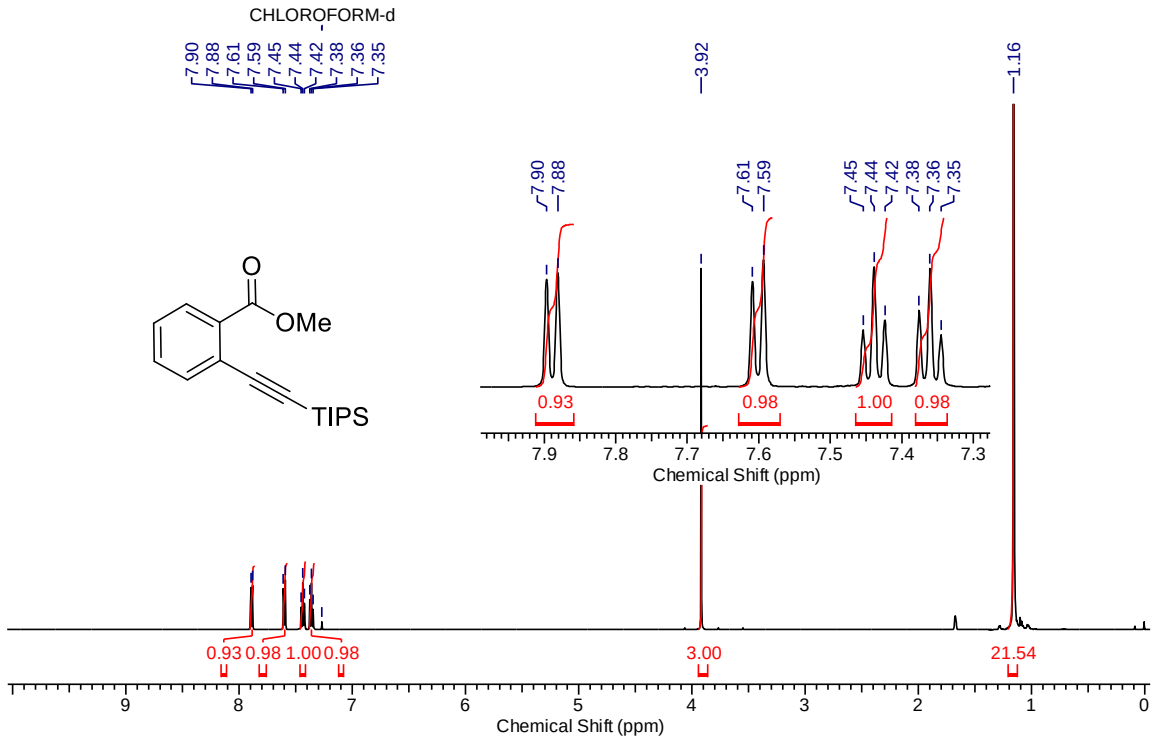
Chemical Shift (ppm)

^{1C} NMR



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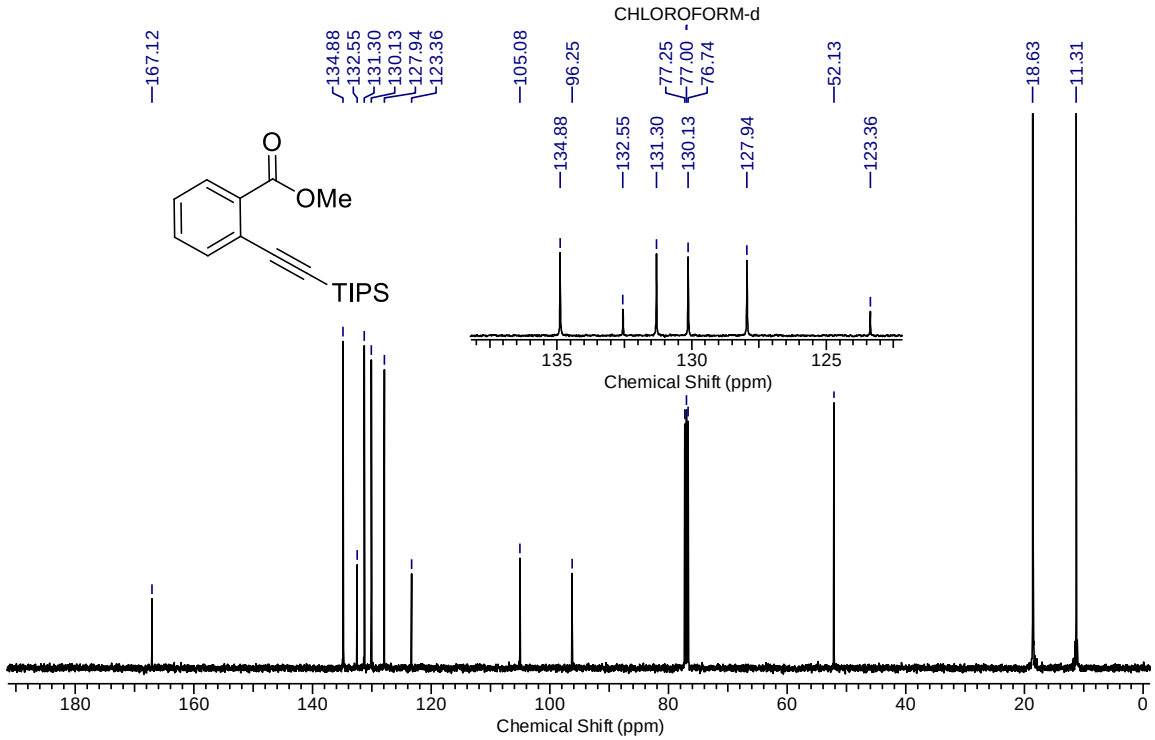
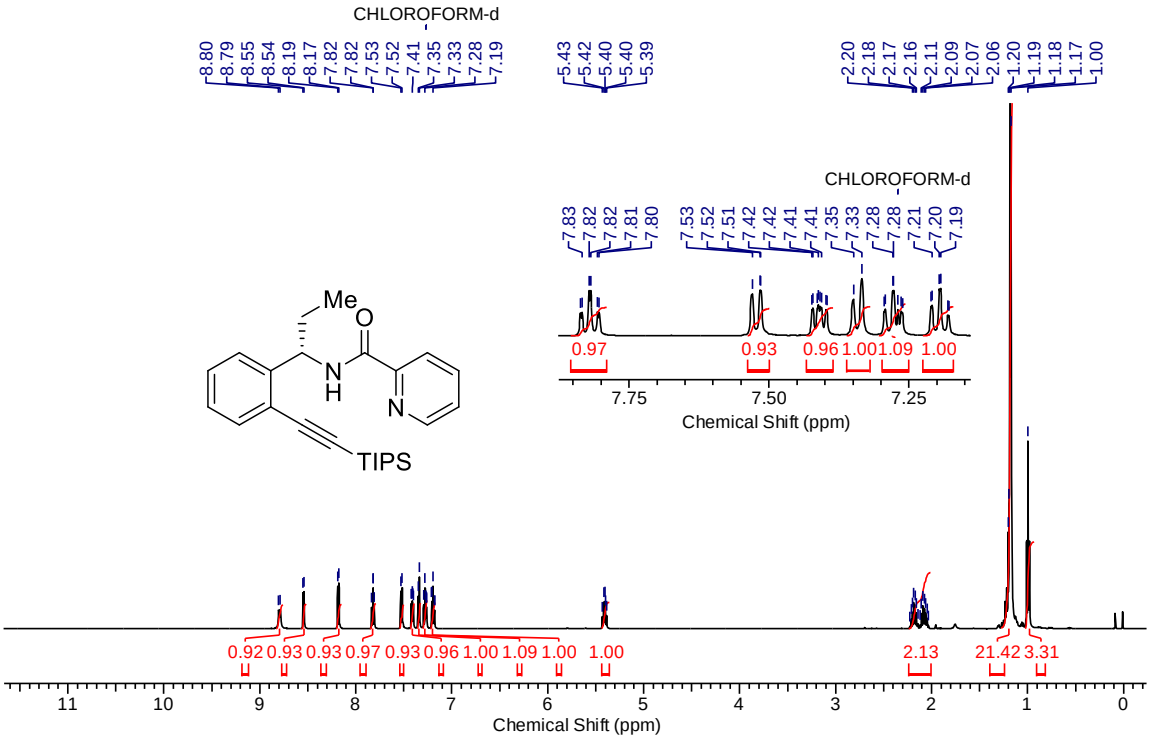


^{13}C NMR

Chapter-3



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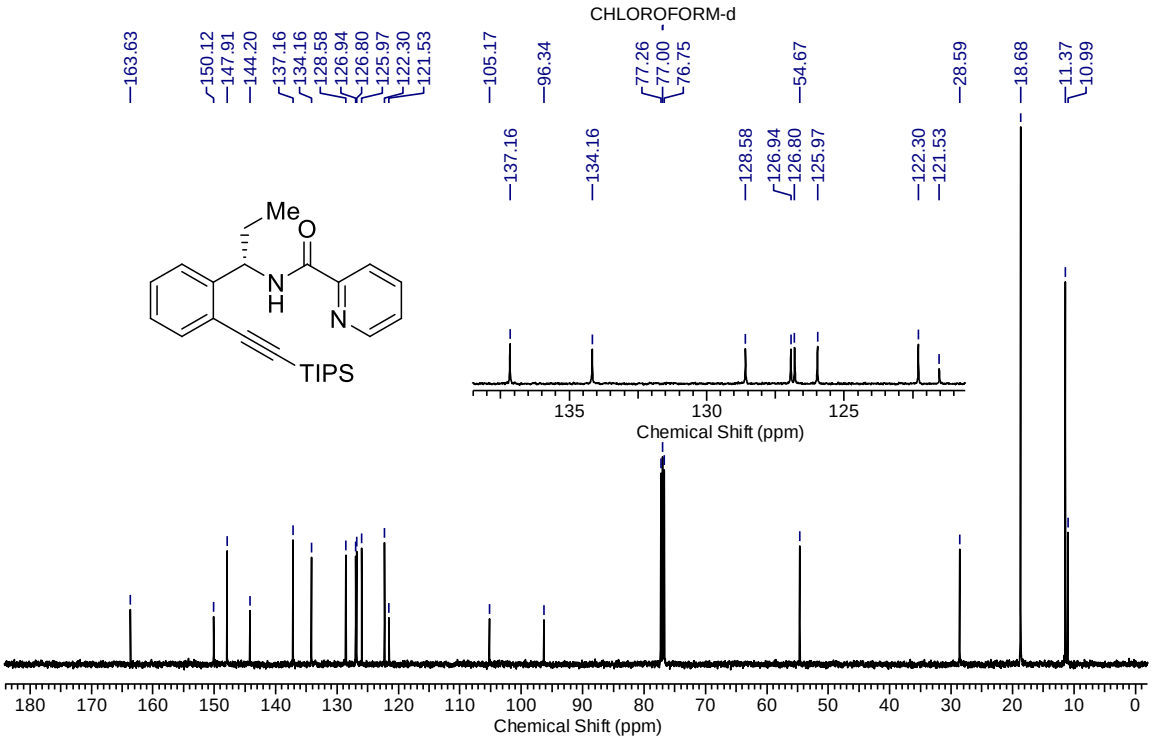

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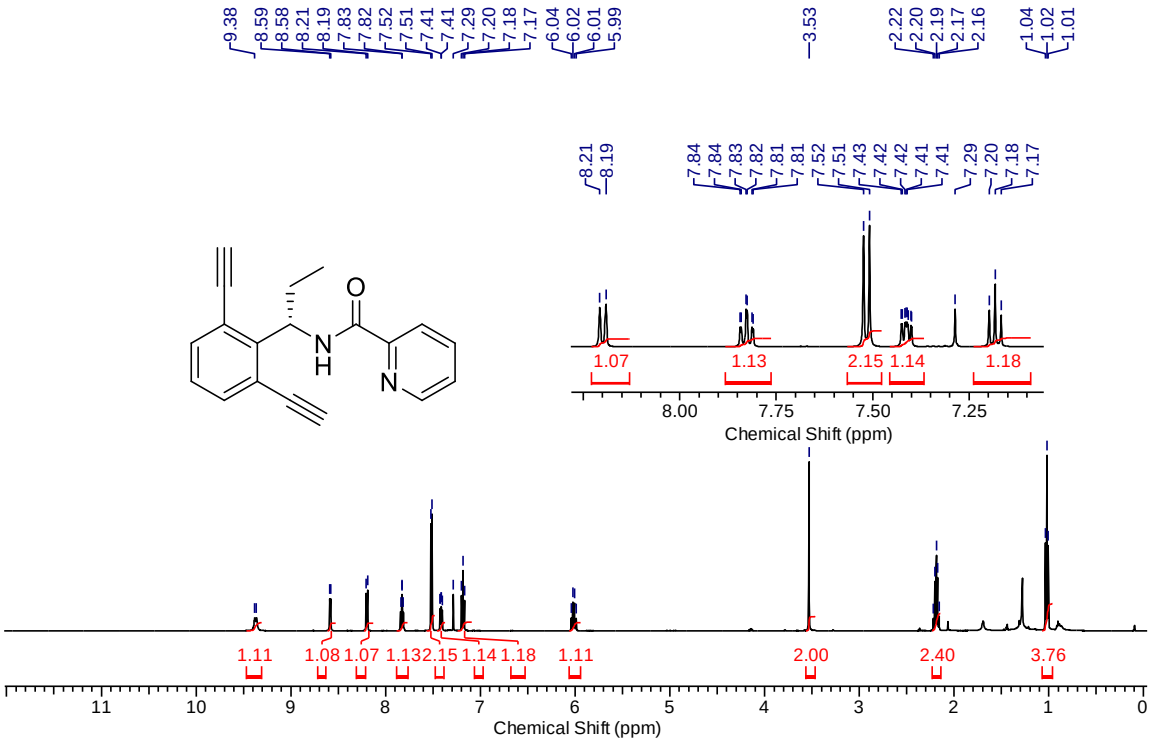

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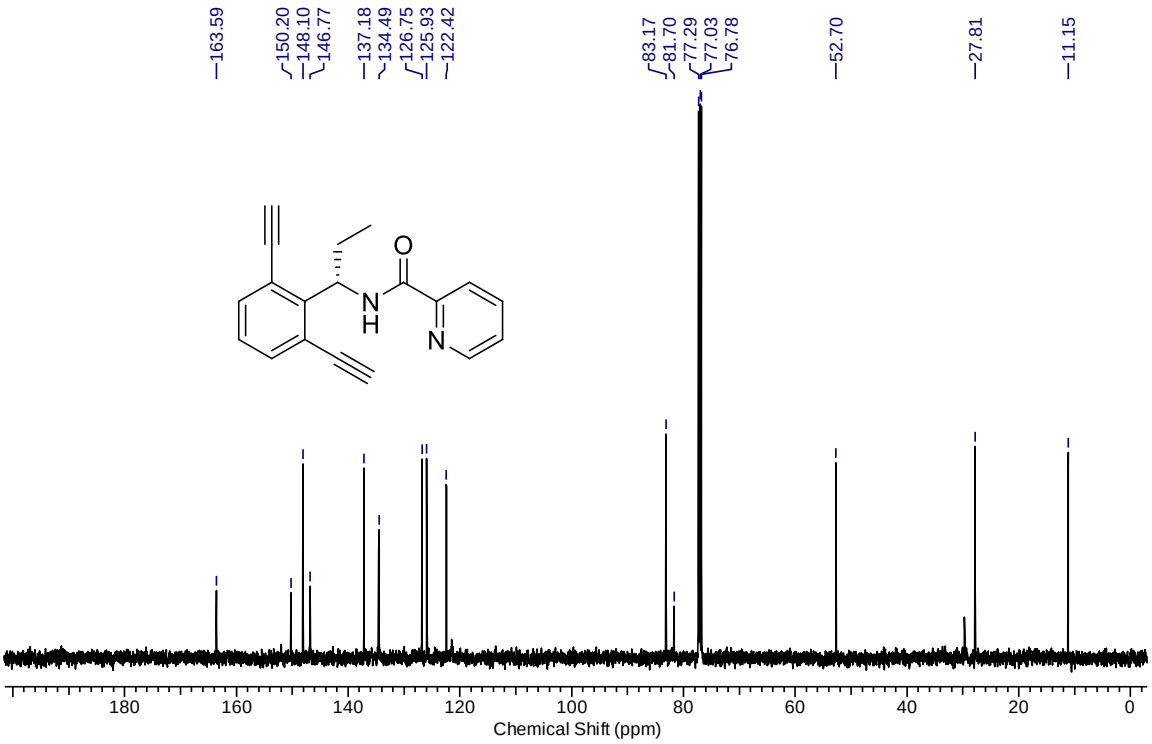

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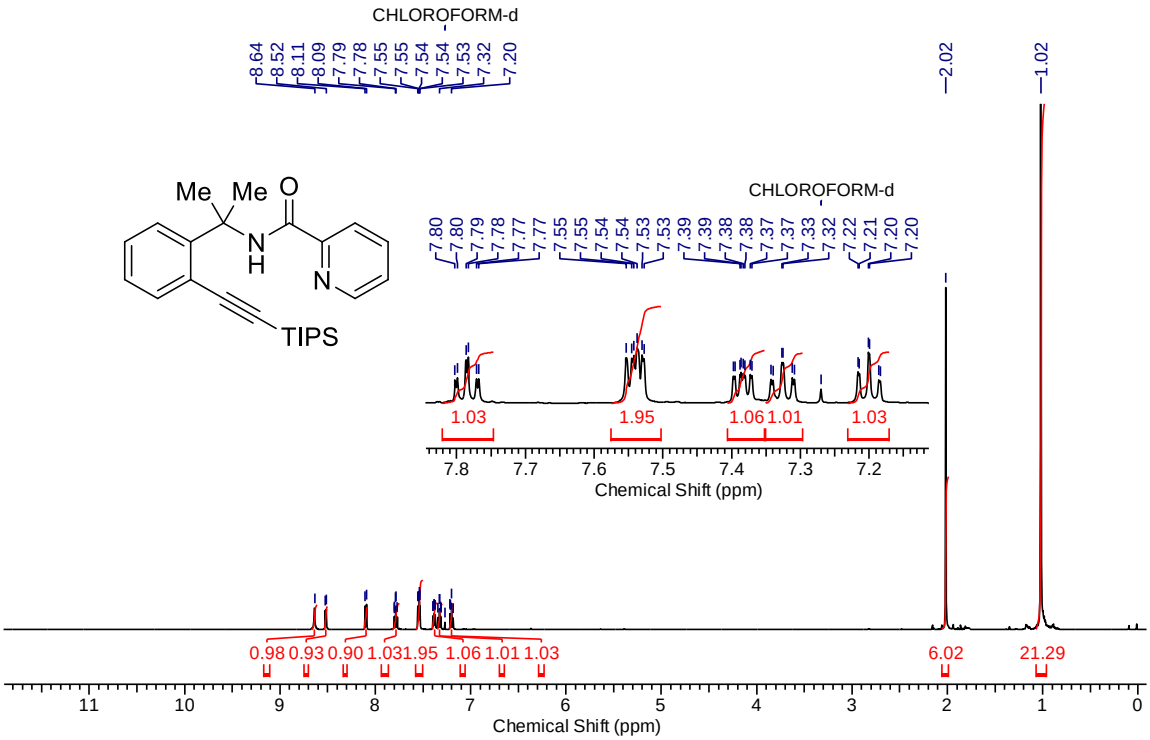

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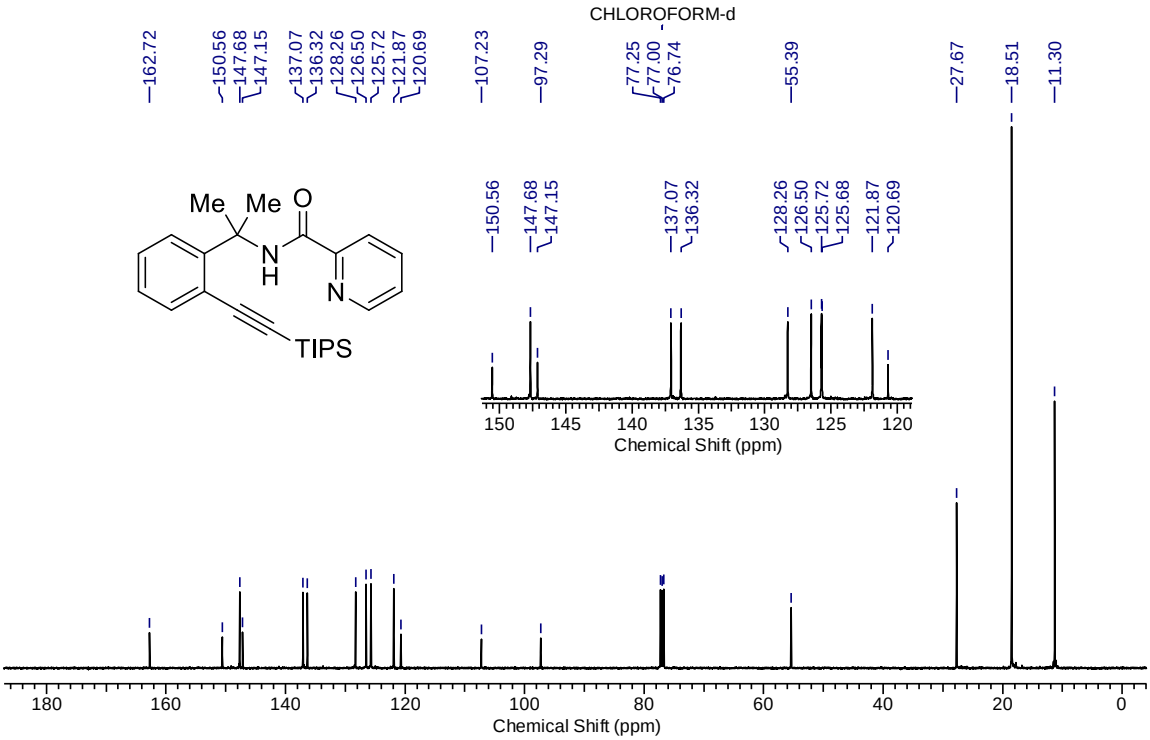

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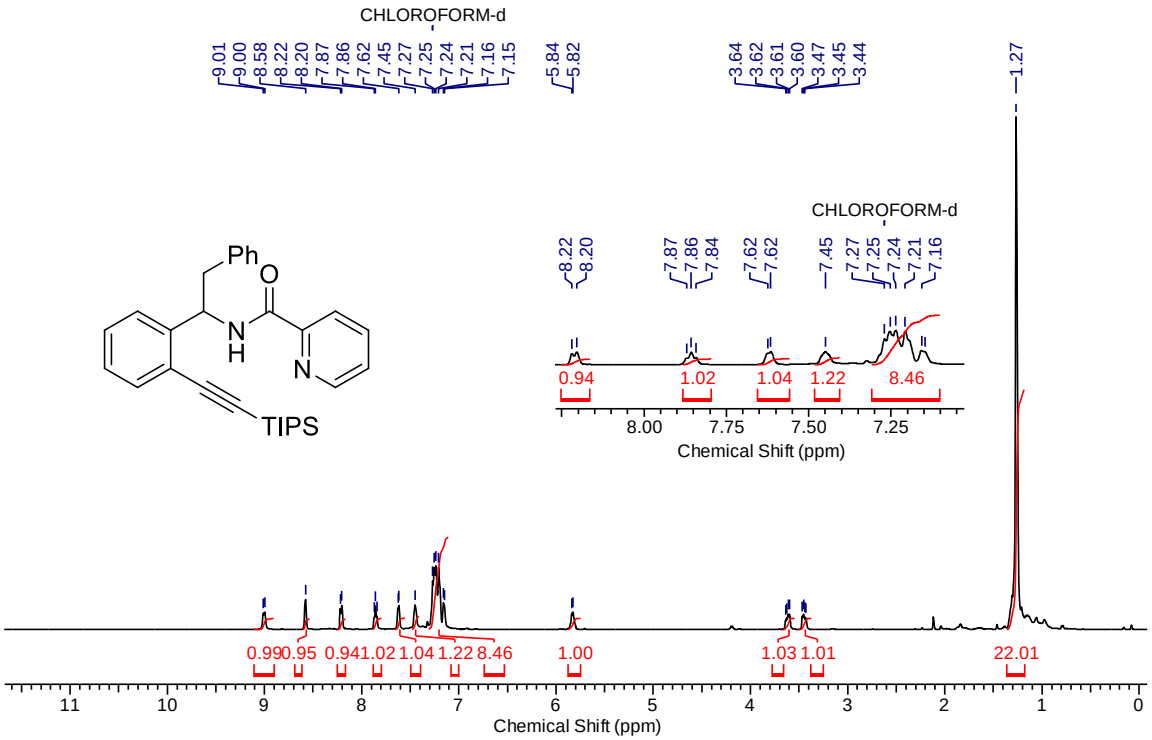

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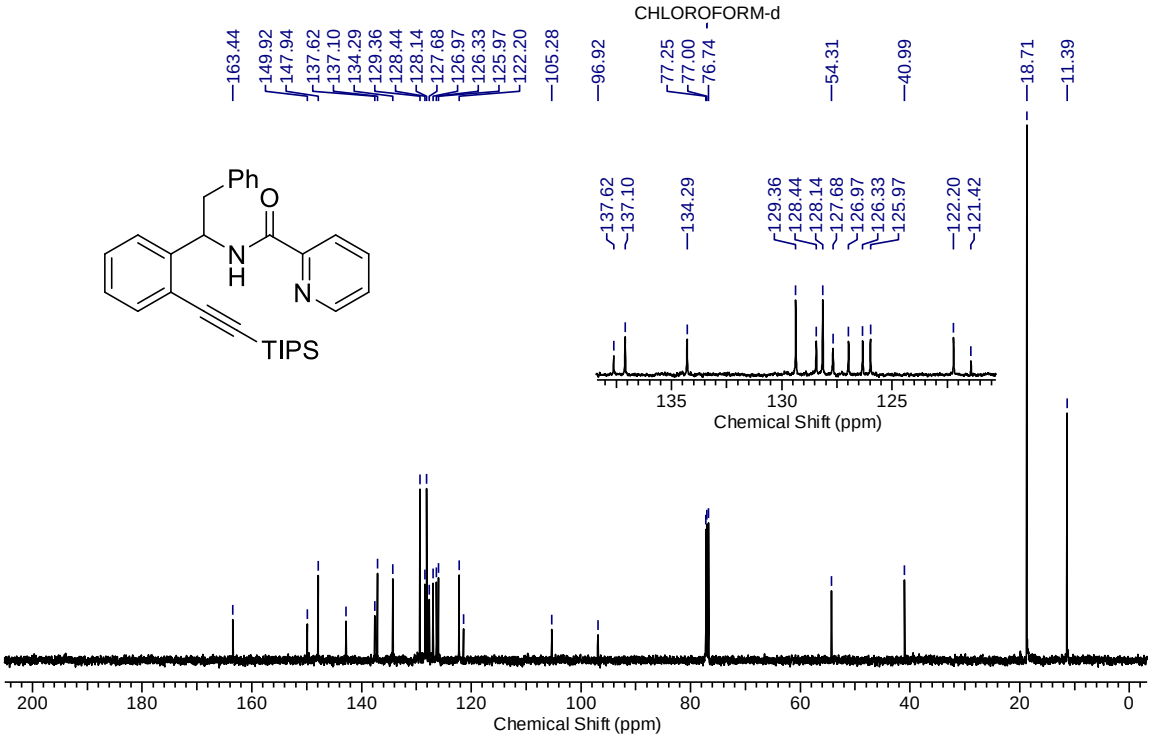

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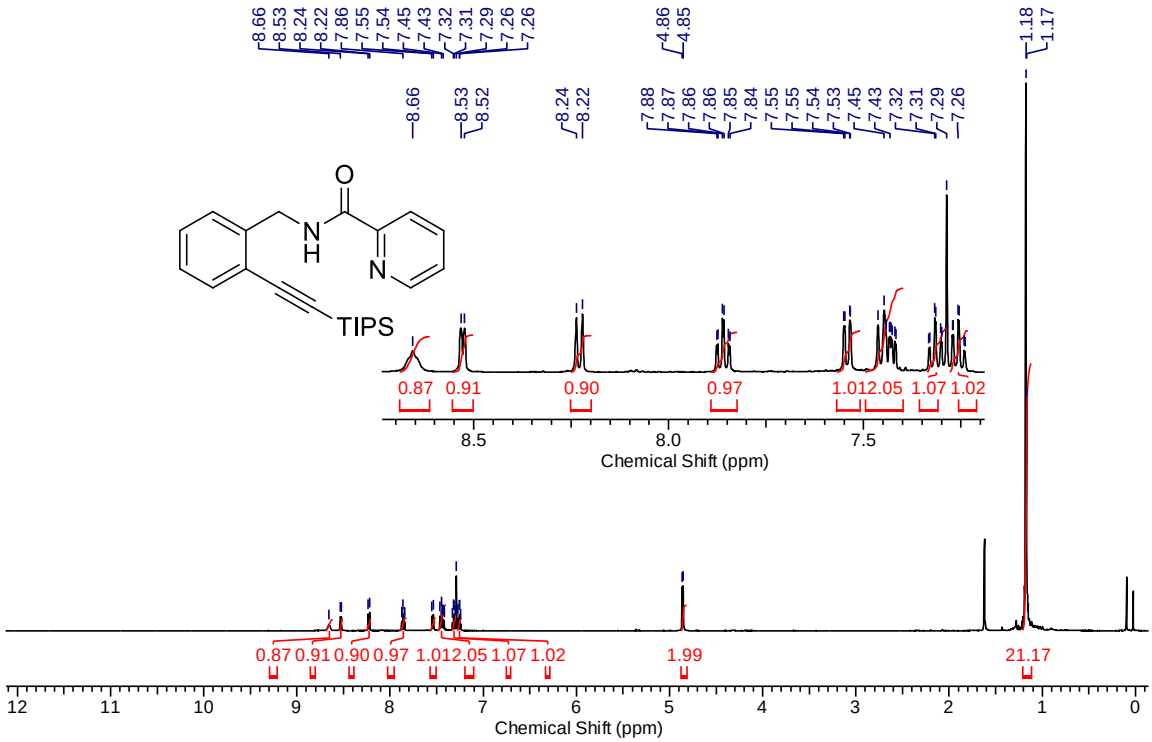

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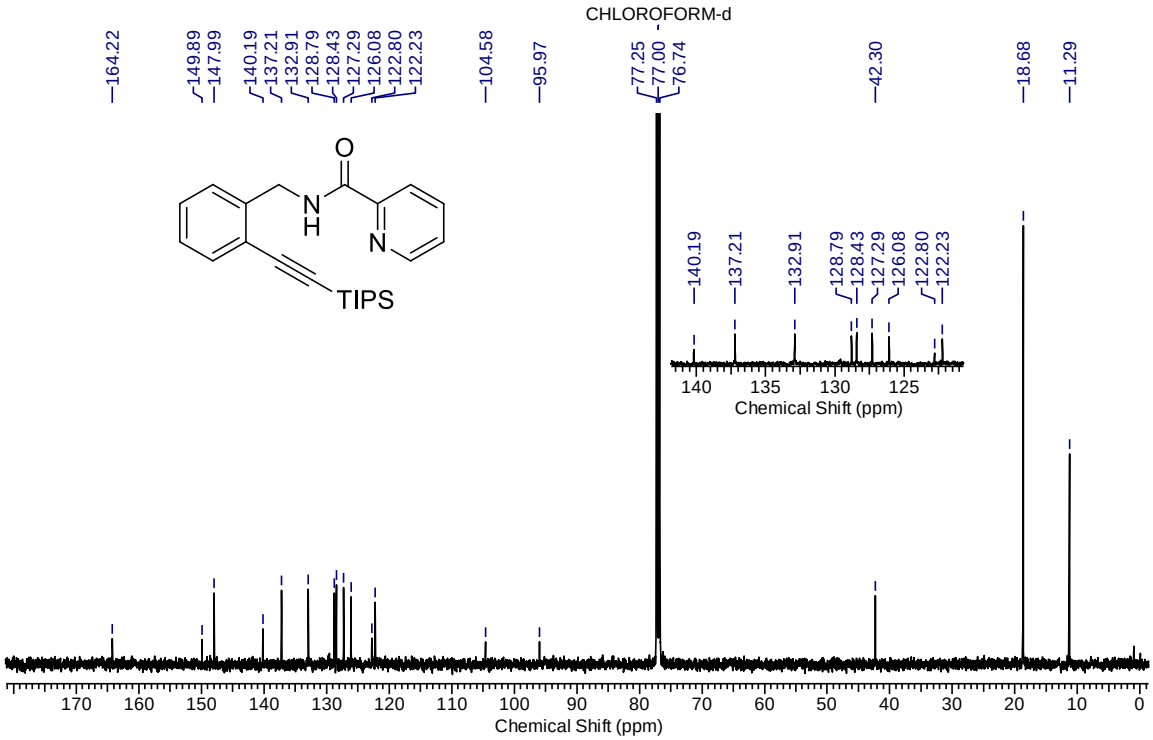

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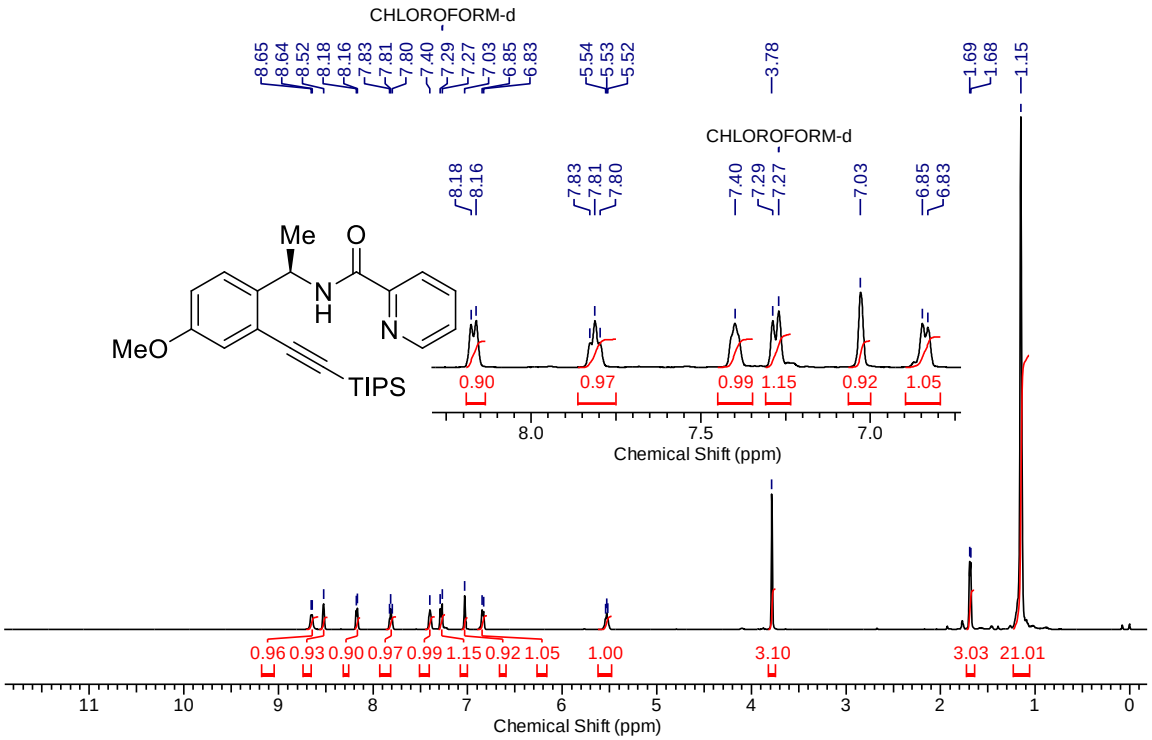

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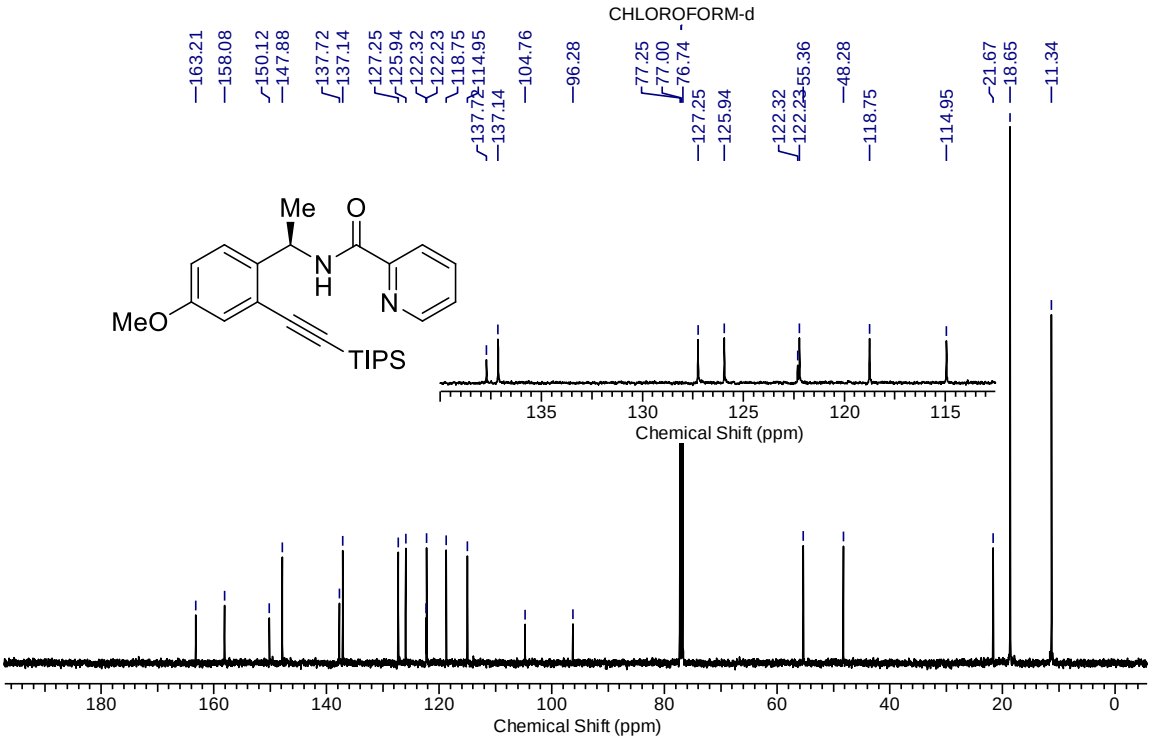

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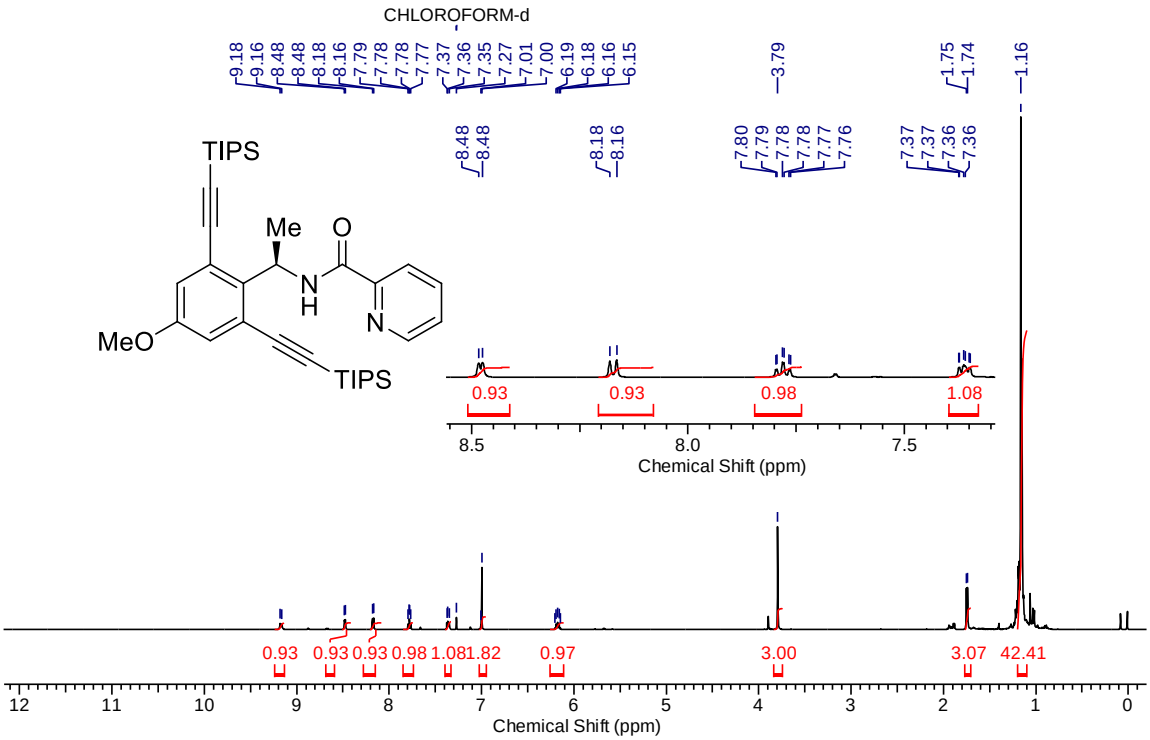

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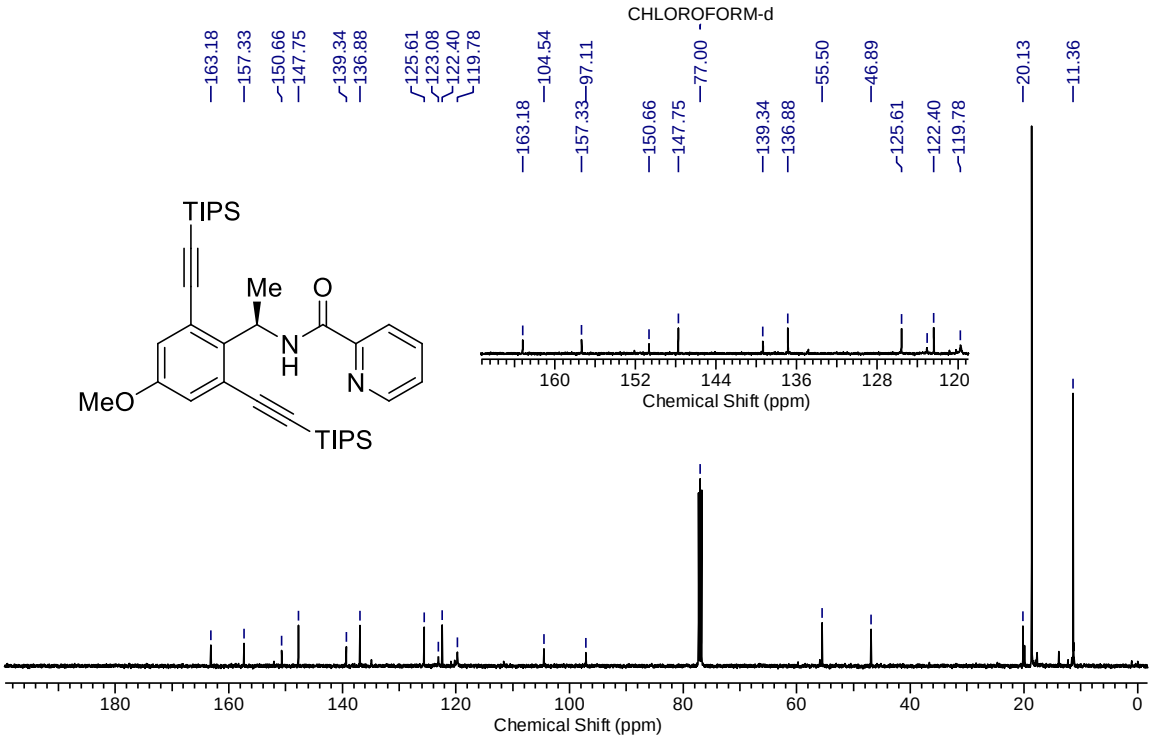

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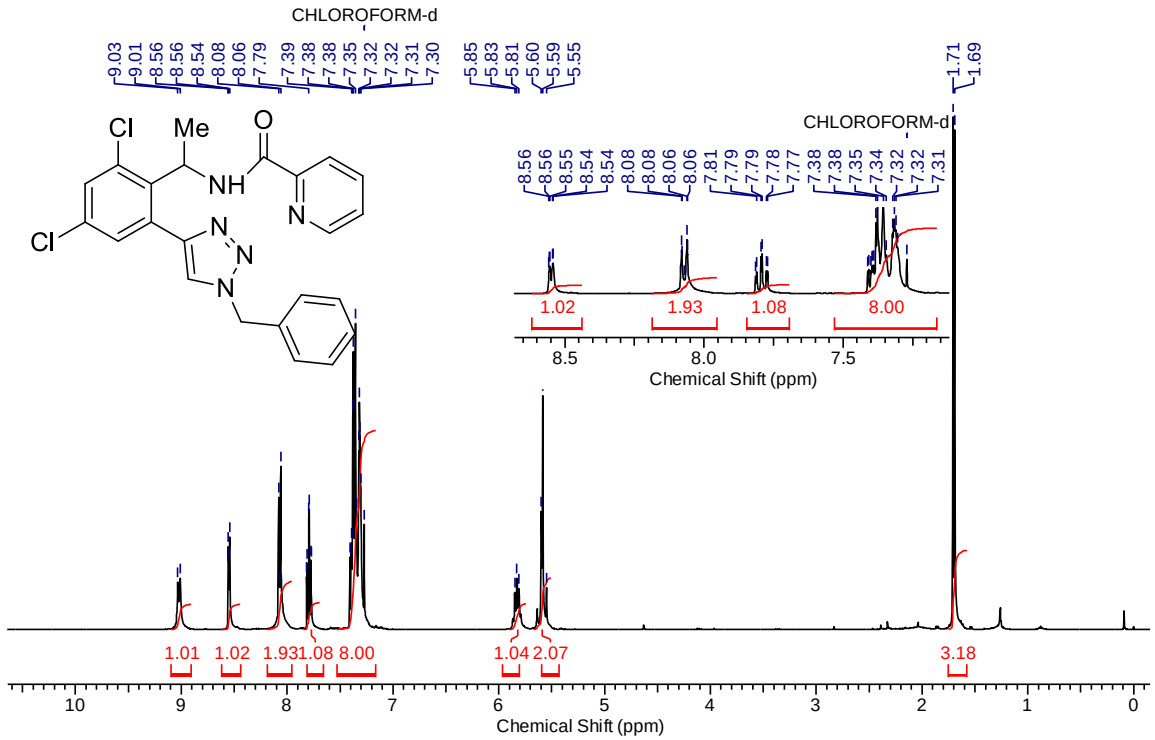

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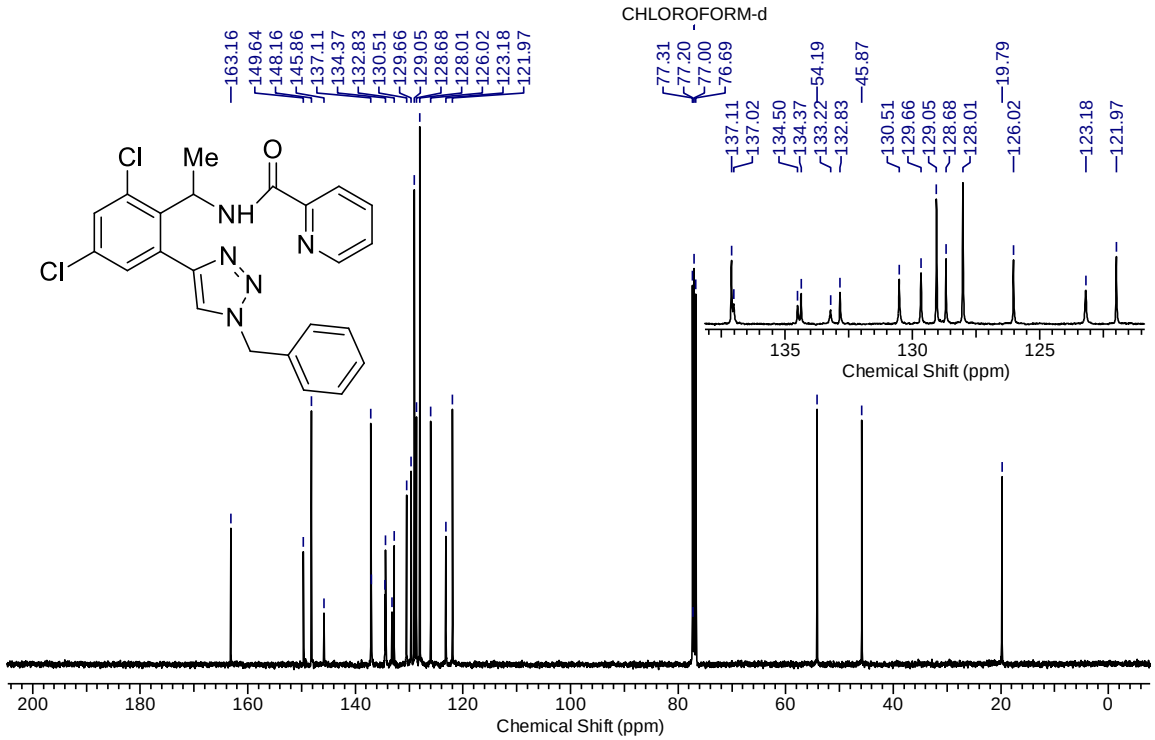

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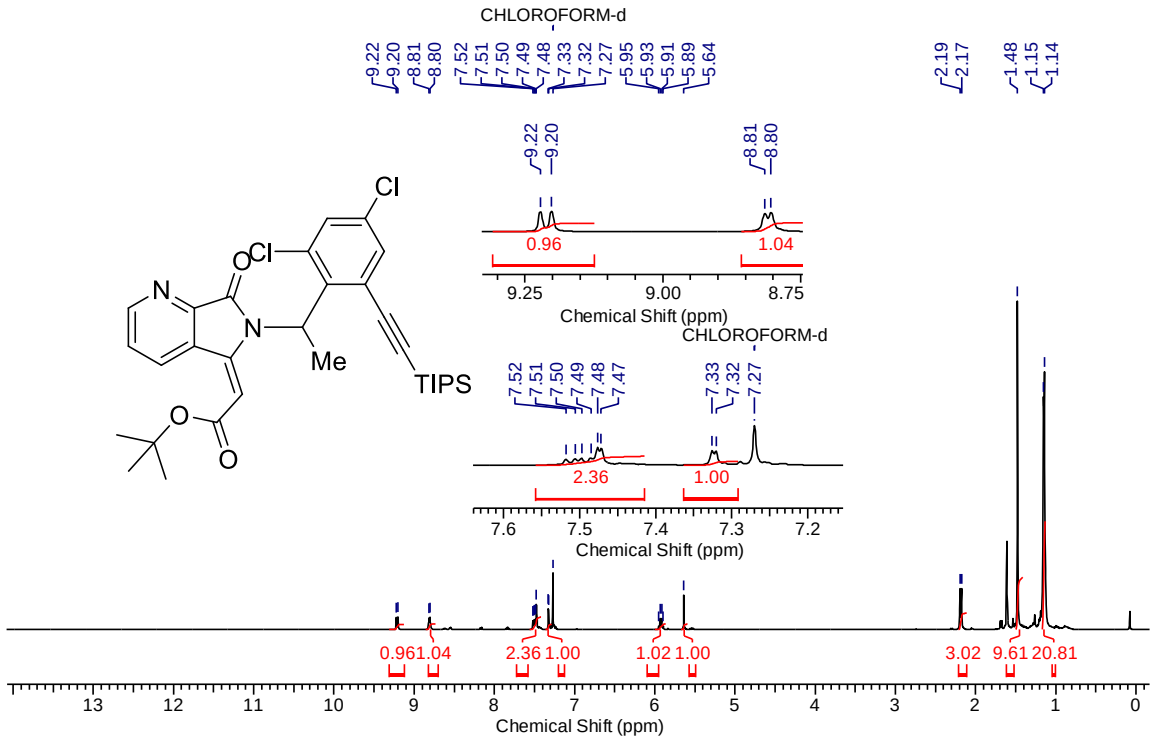

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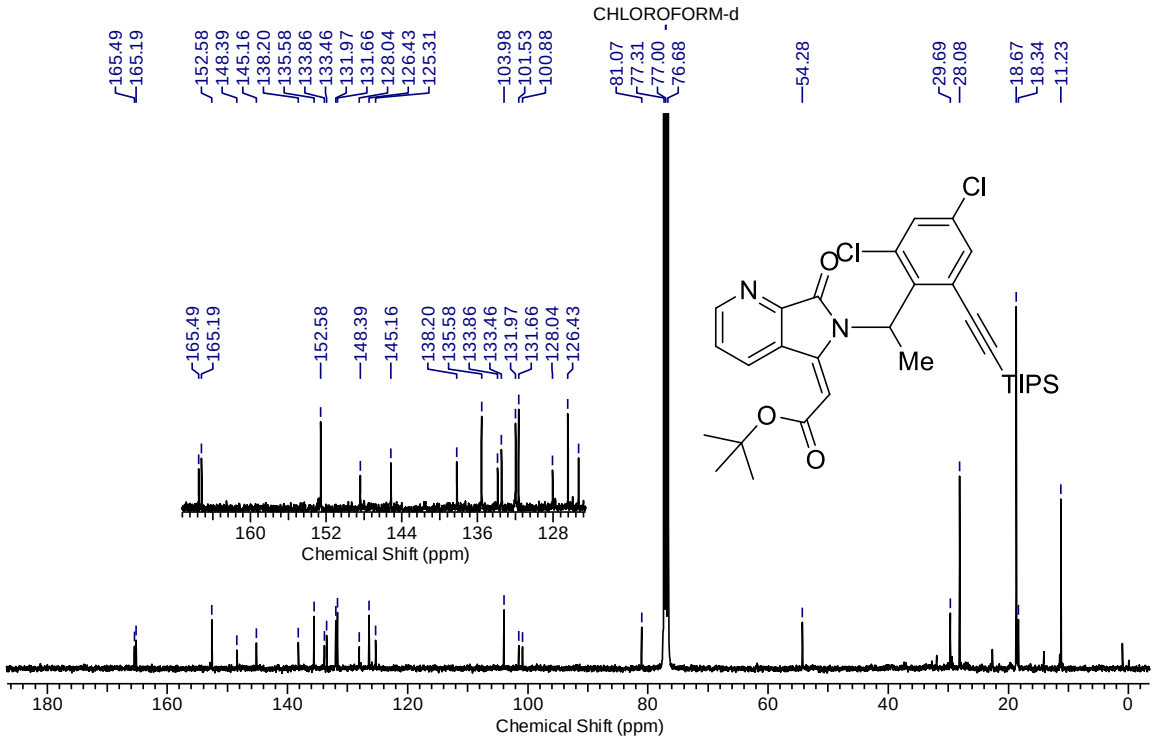
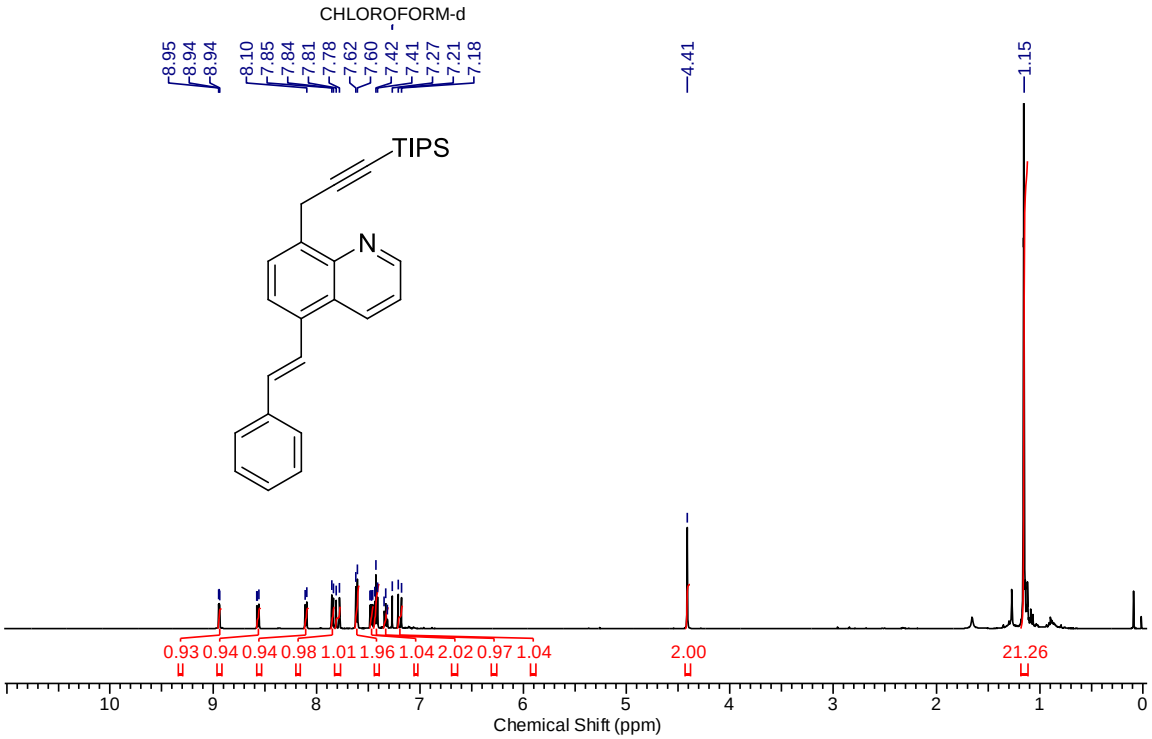


^{13}C NMR

Chapter-4



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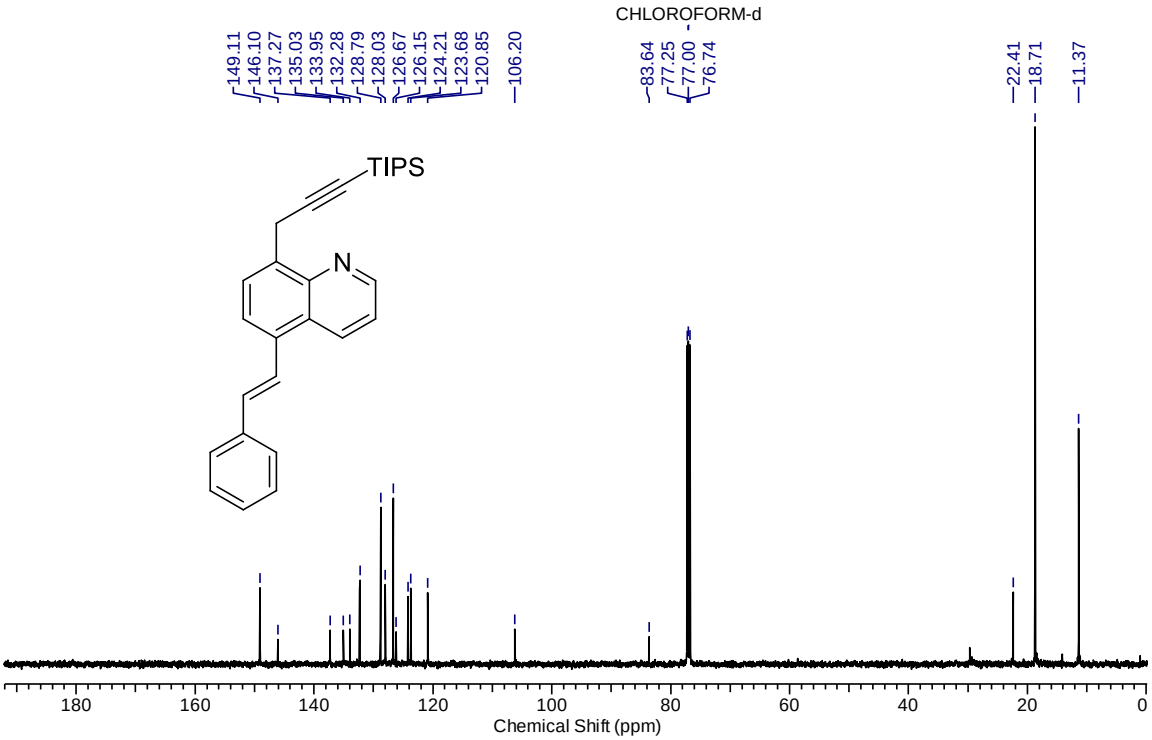

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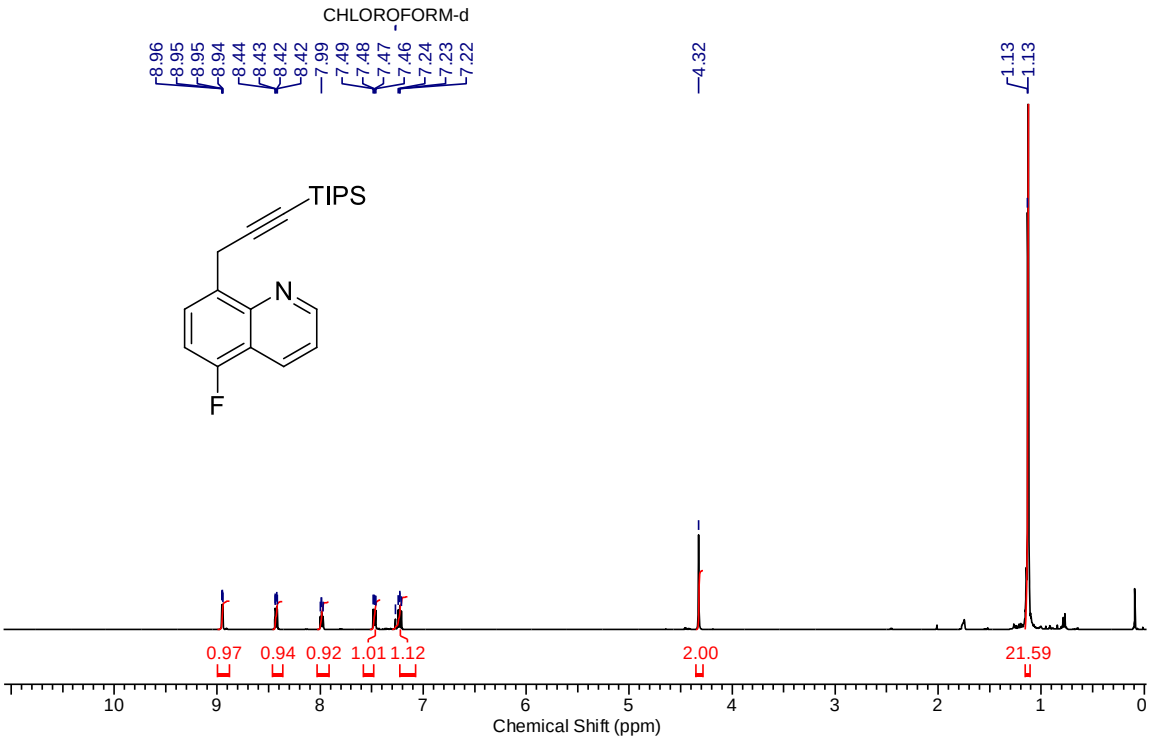

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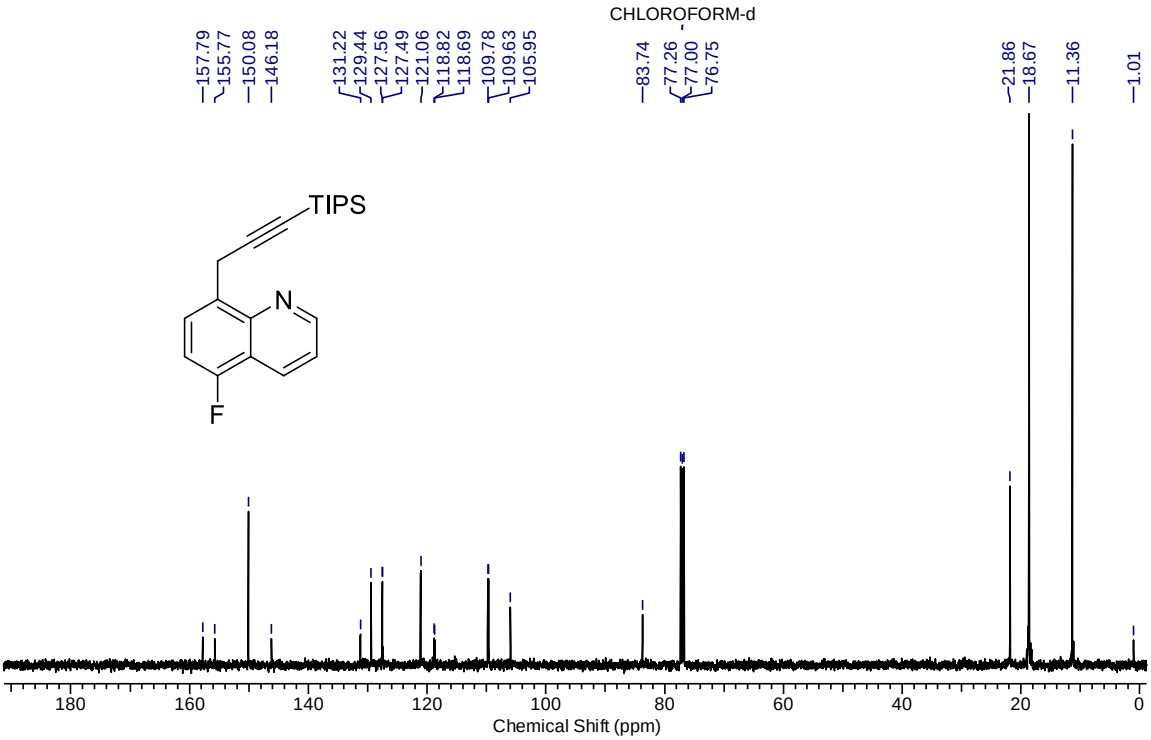

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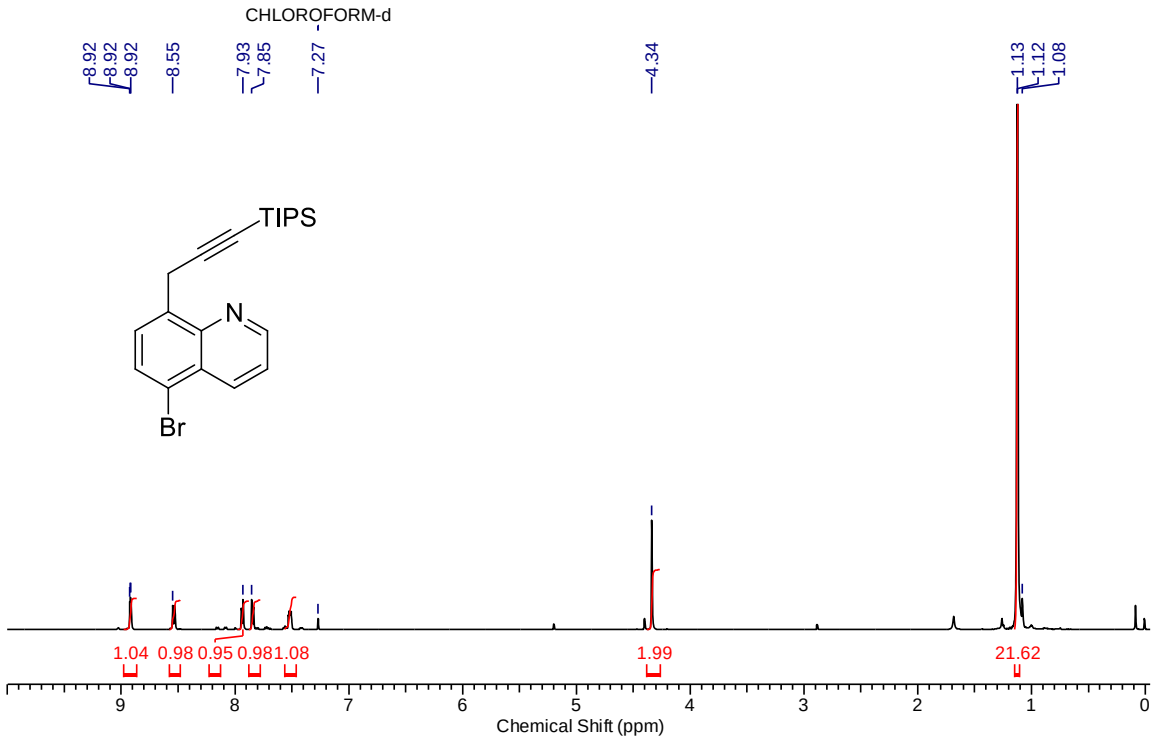

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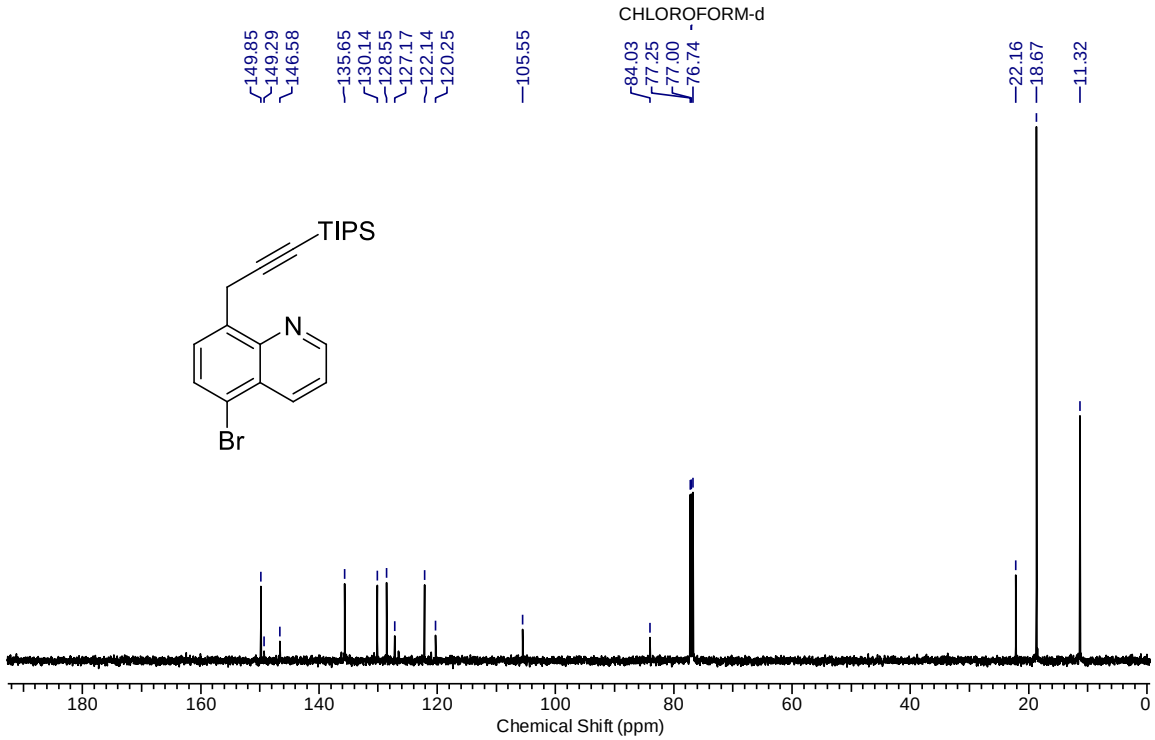

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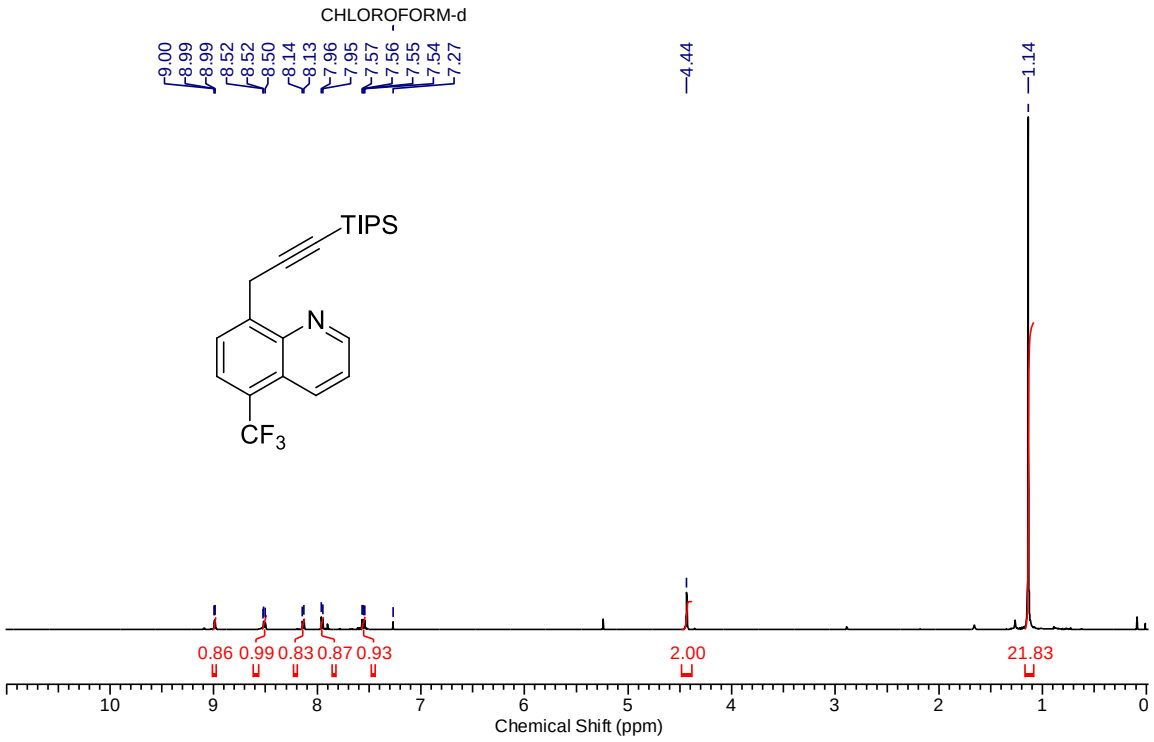

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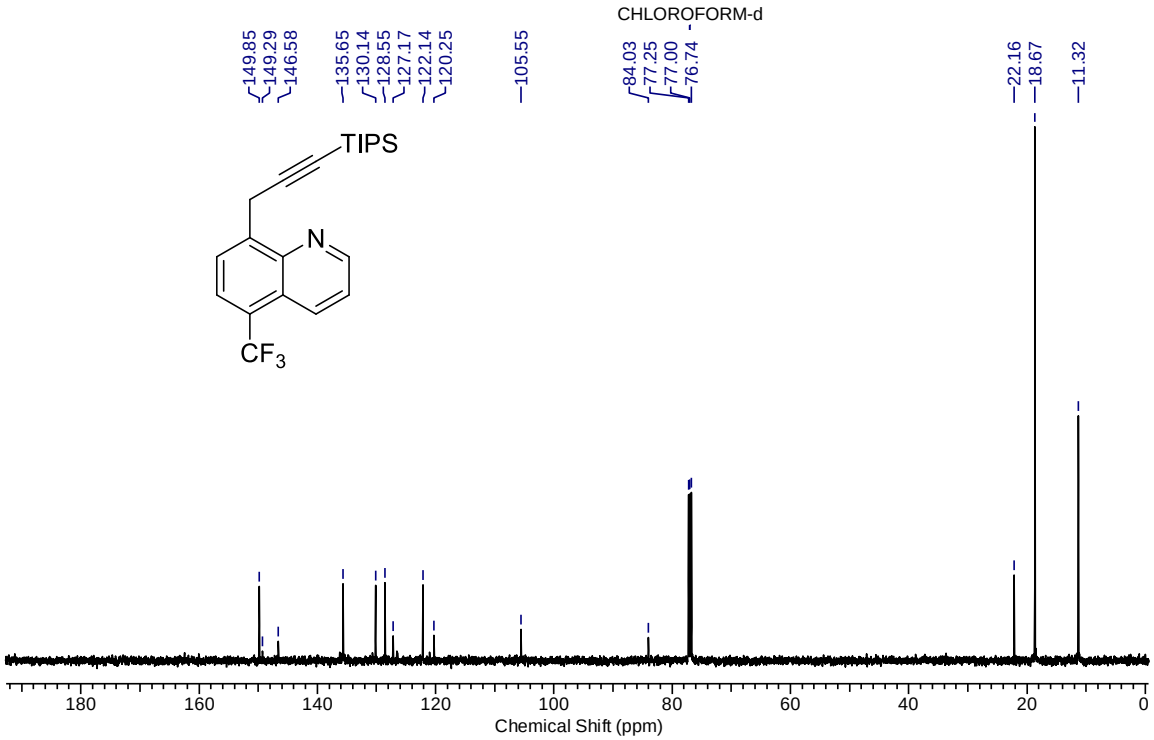

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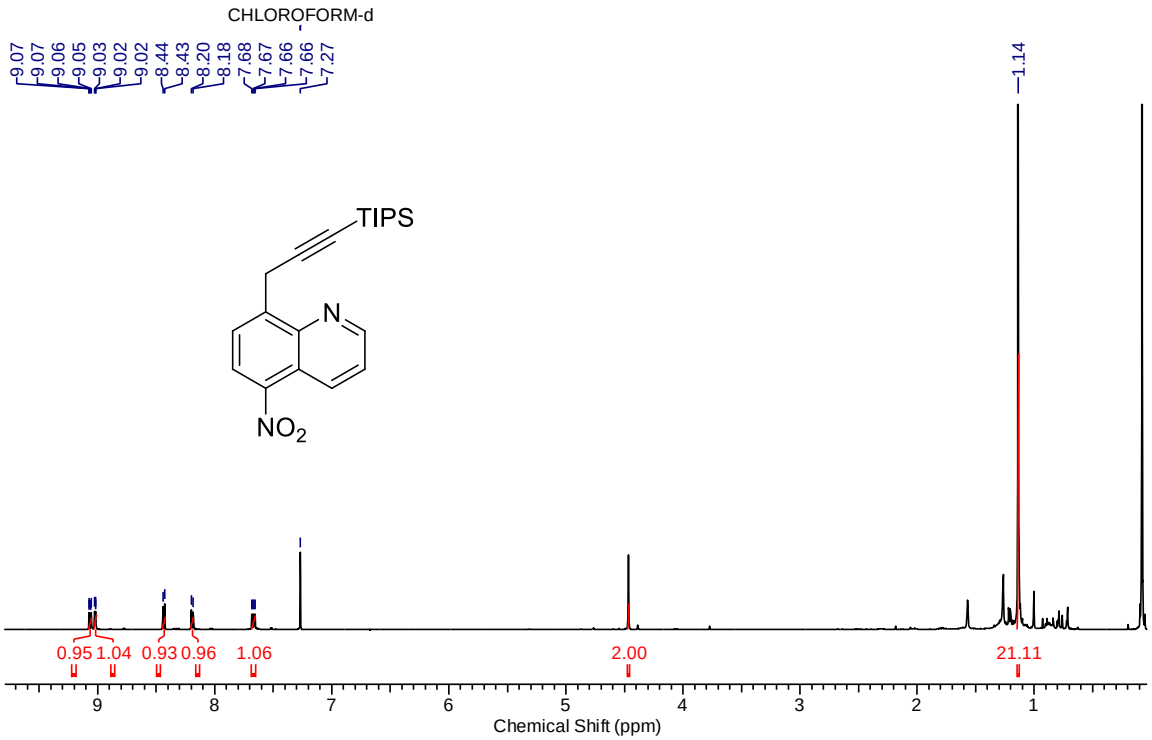

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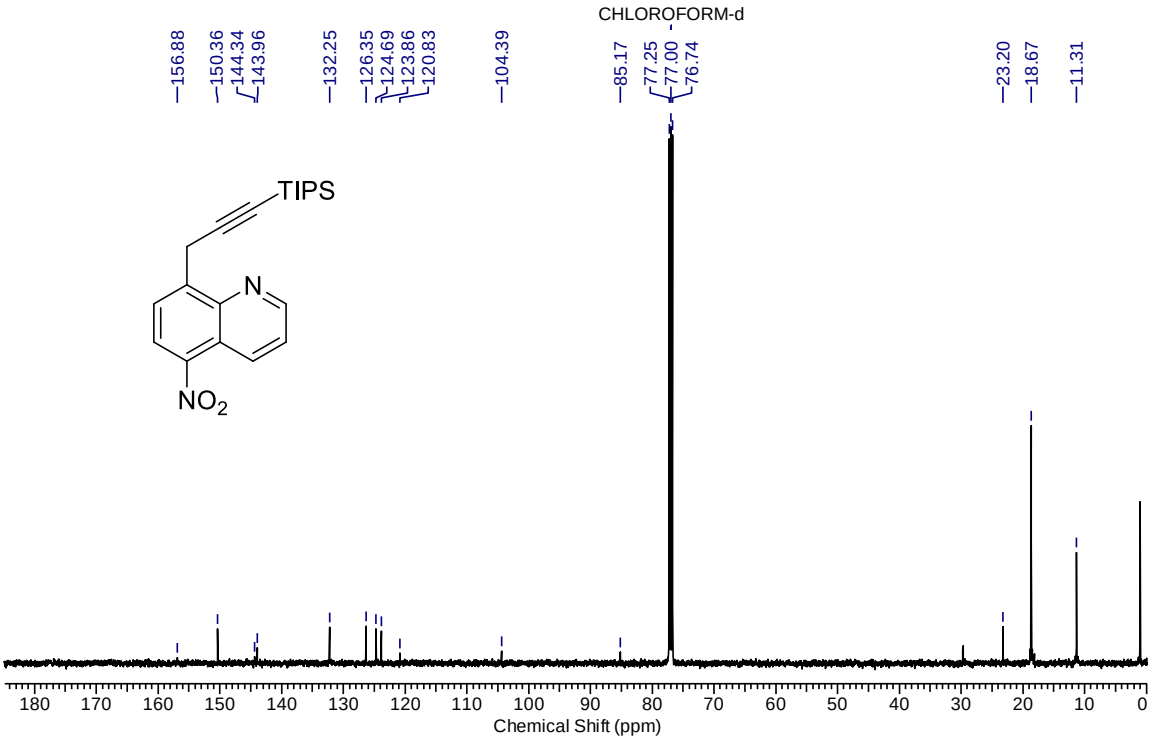
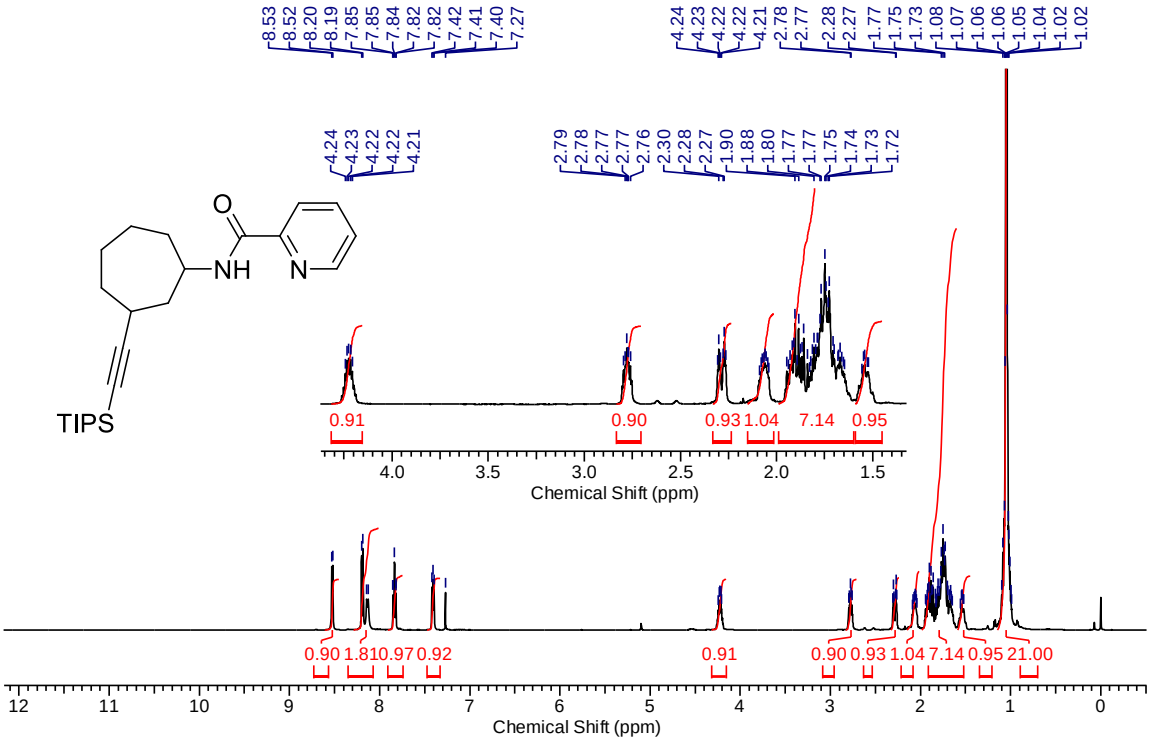


^{13}C NMR

Chapter-5



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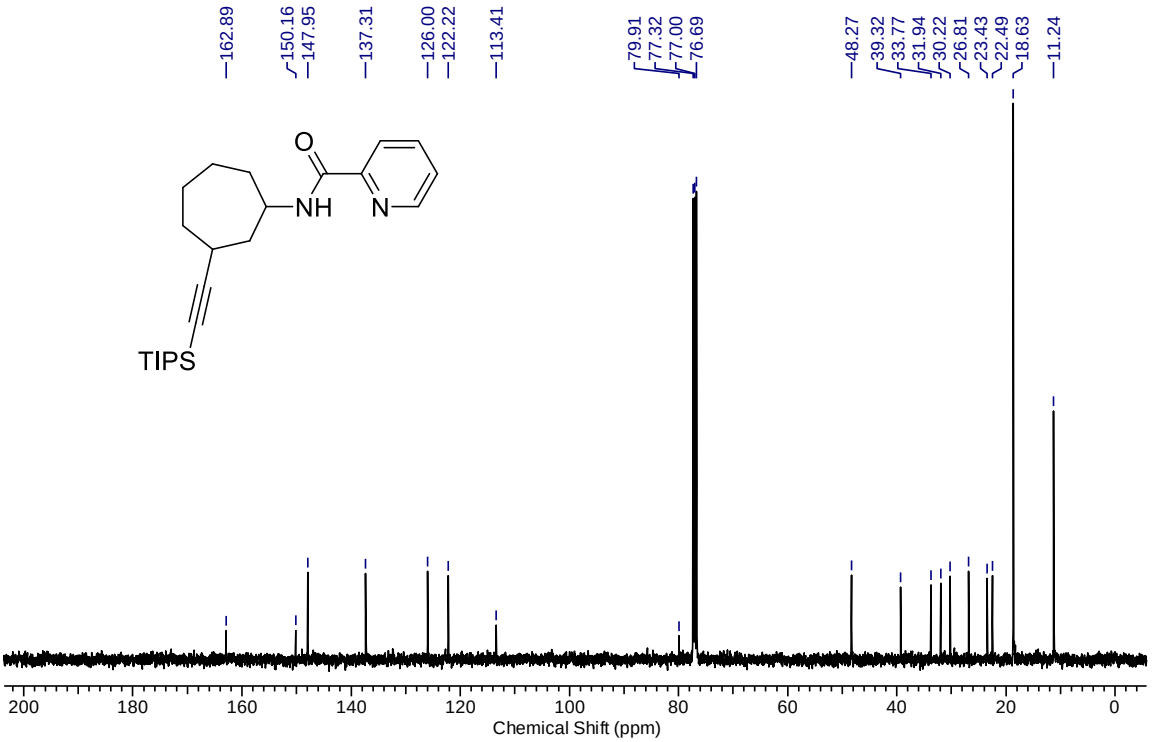

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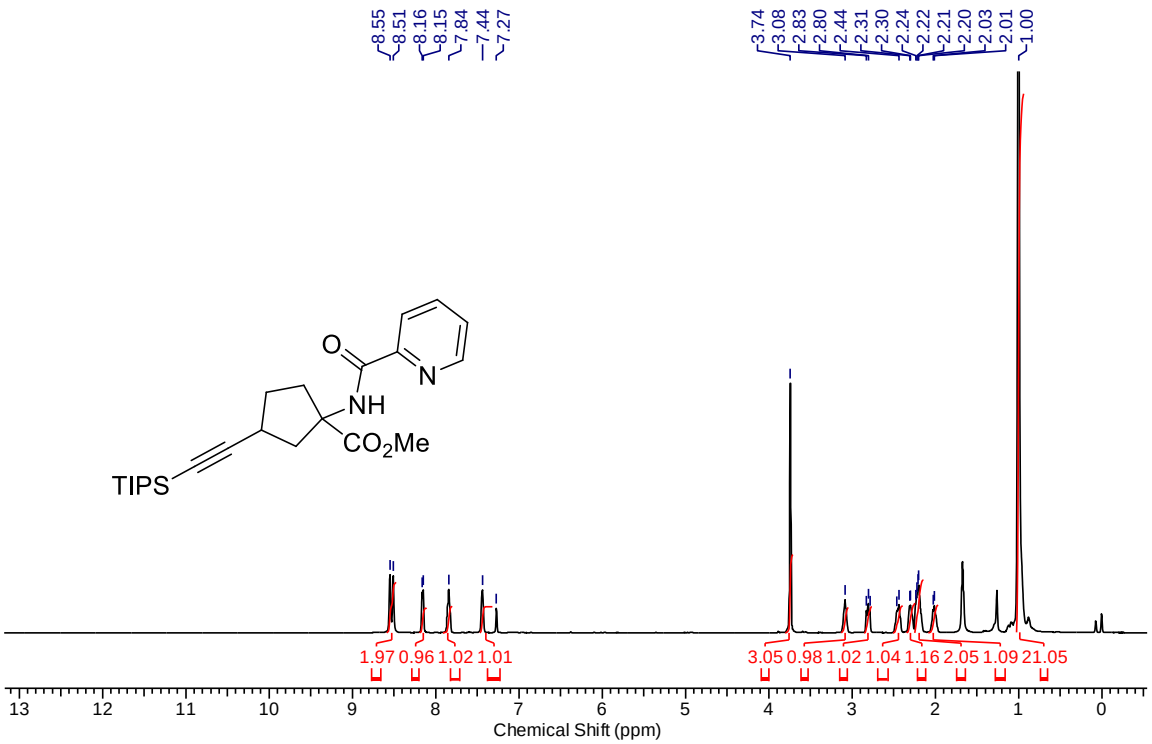

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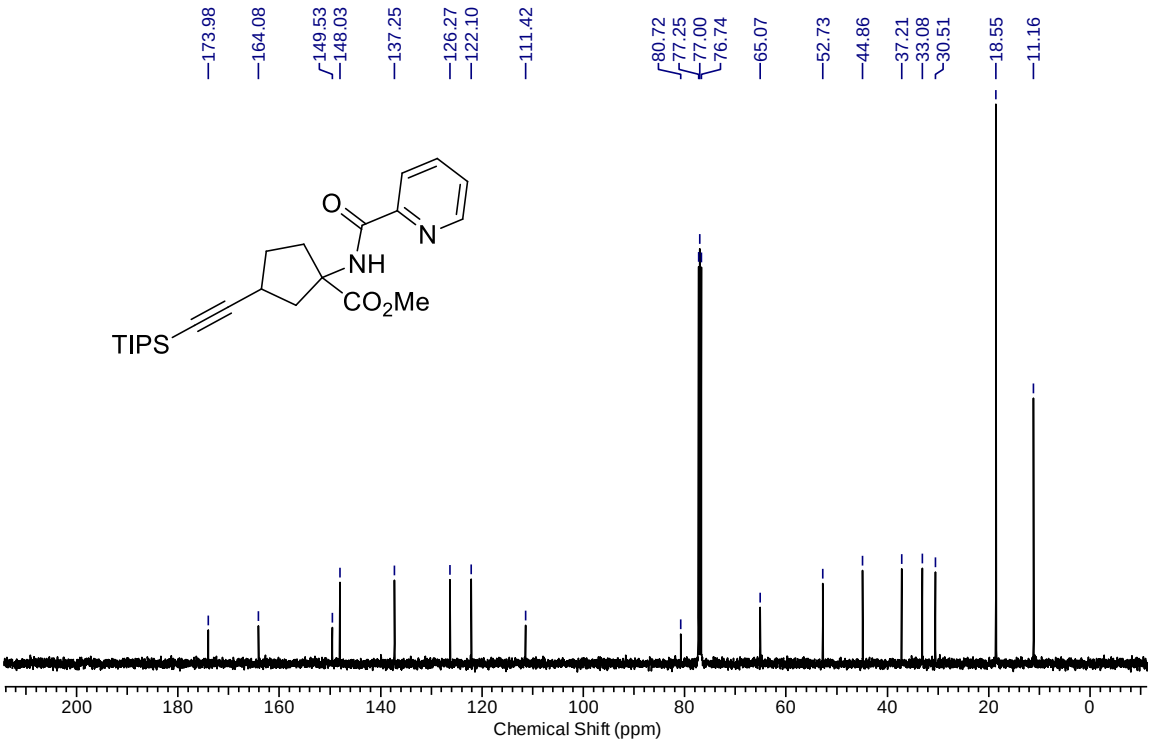

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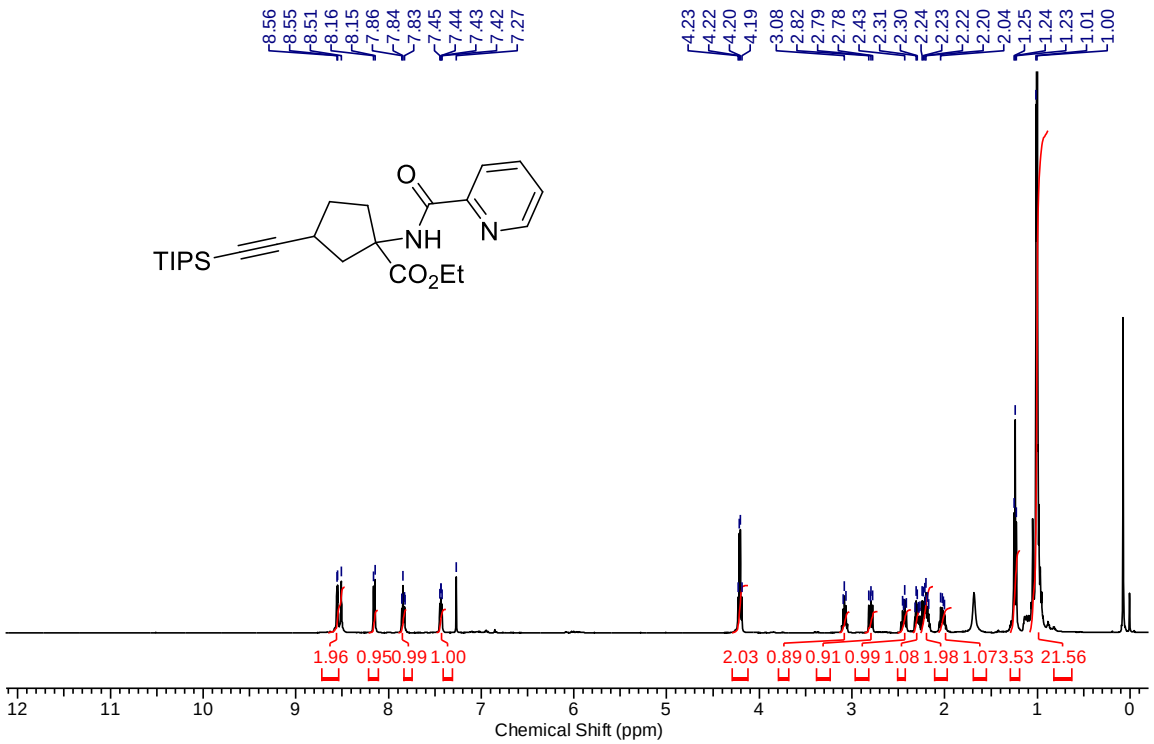

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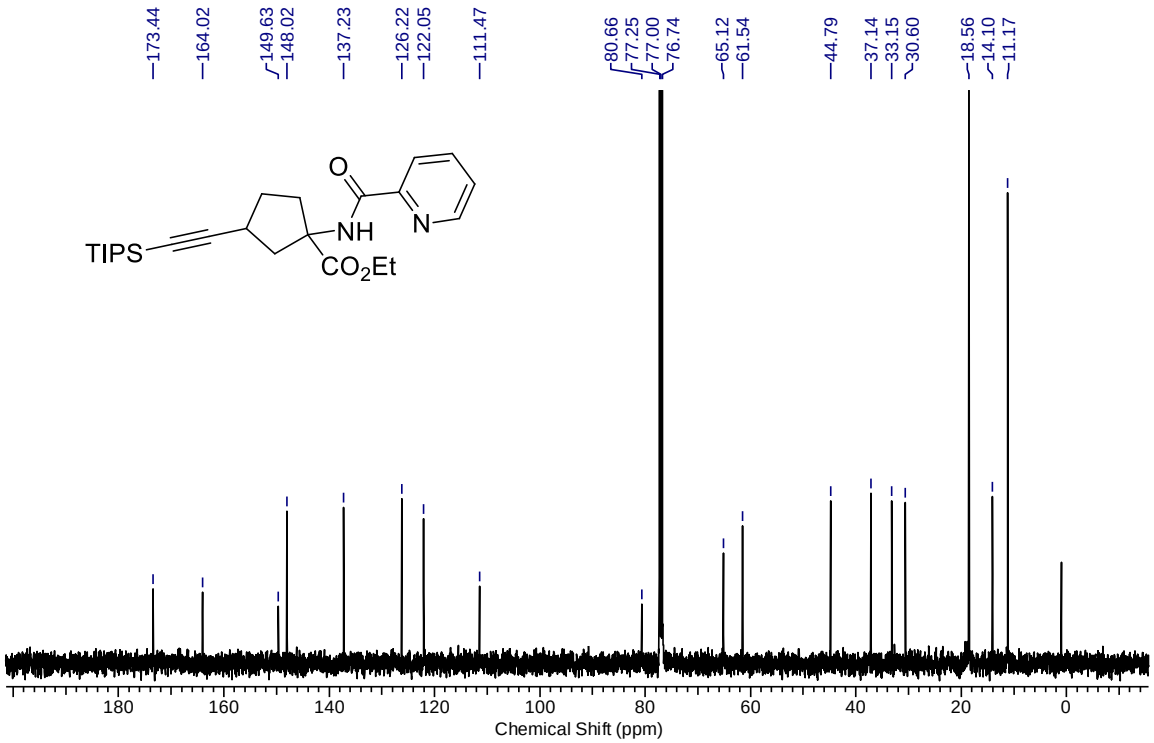

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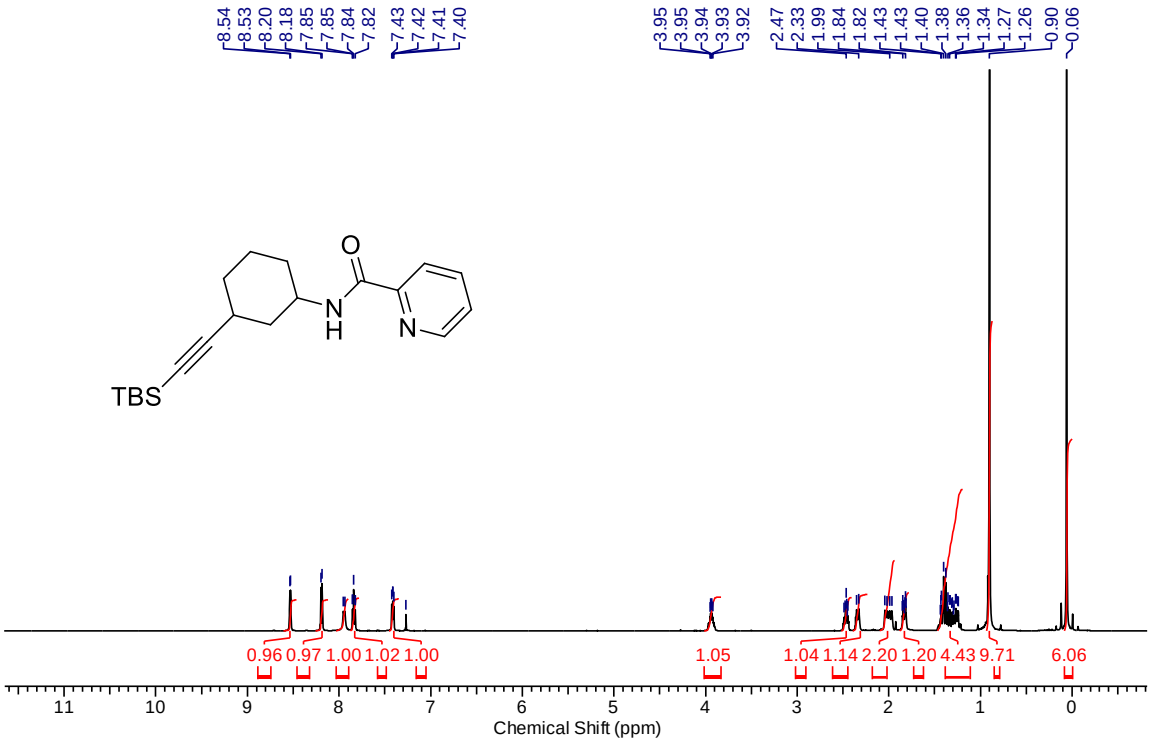

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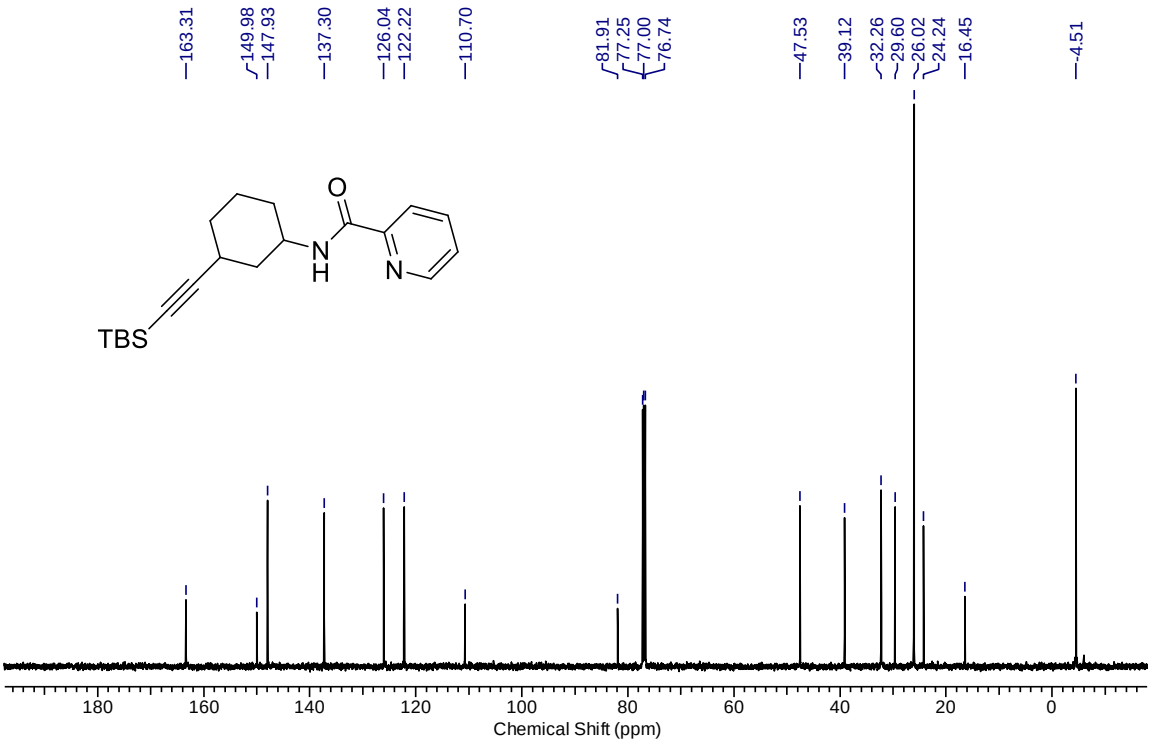

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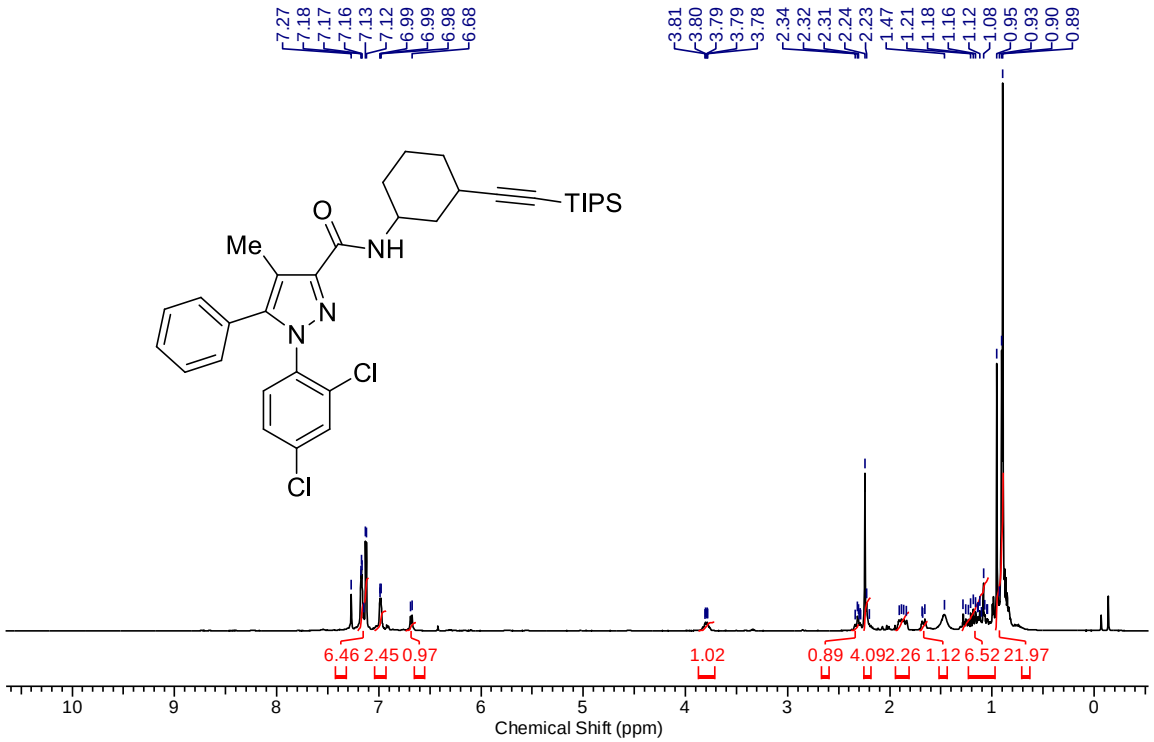

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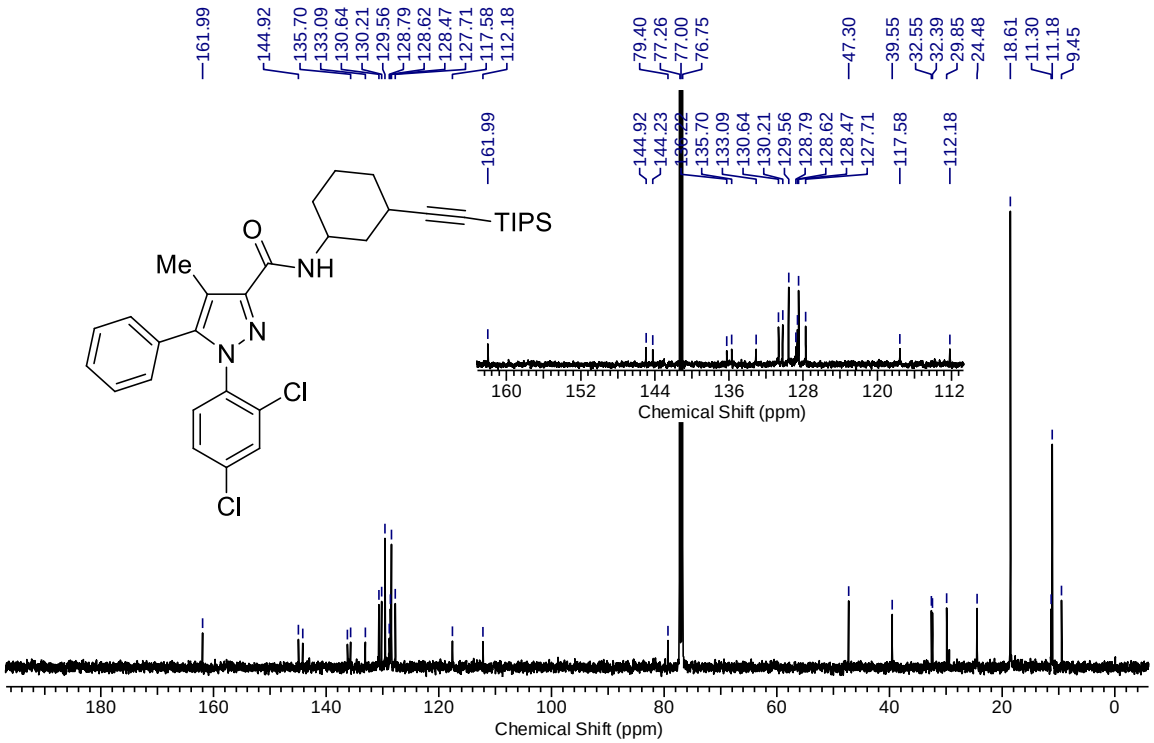

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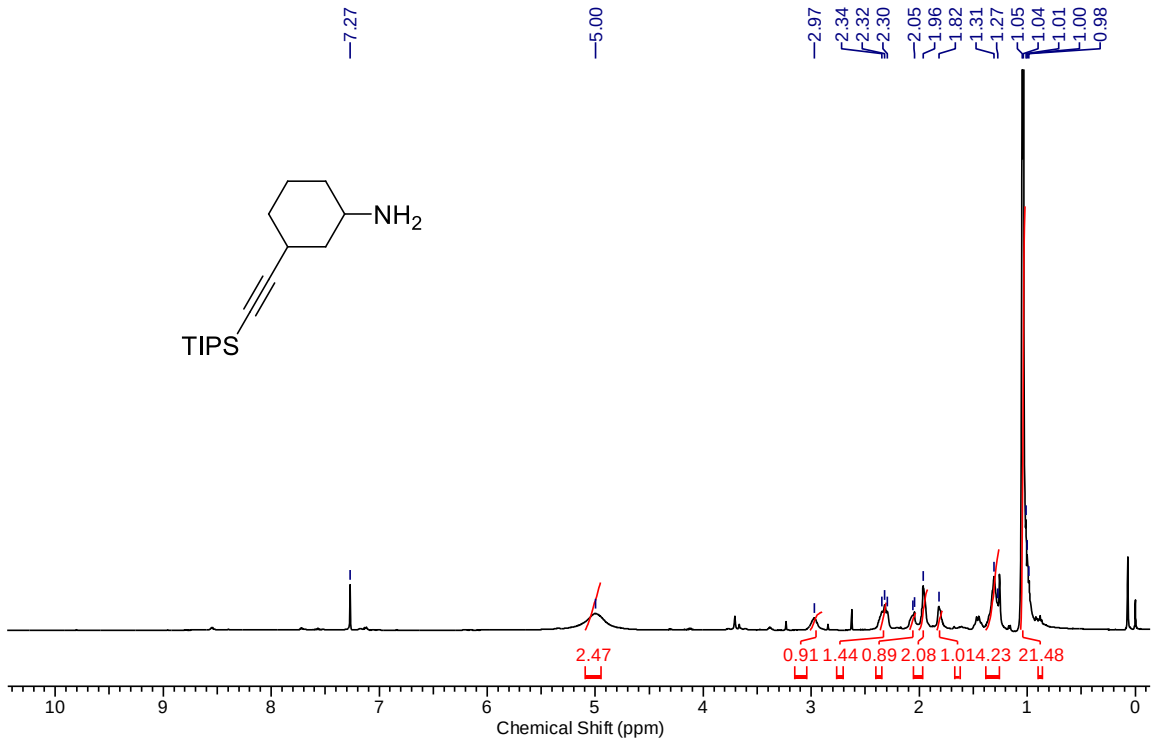

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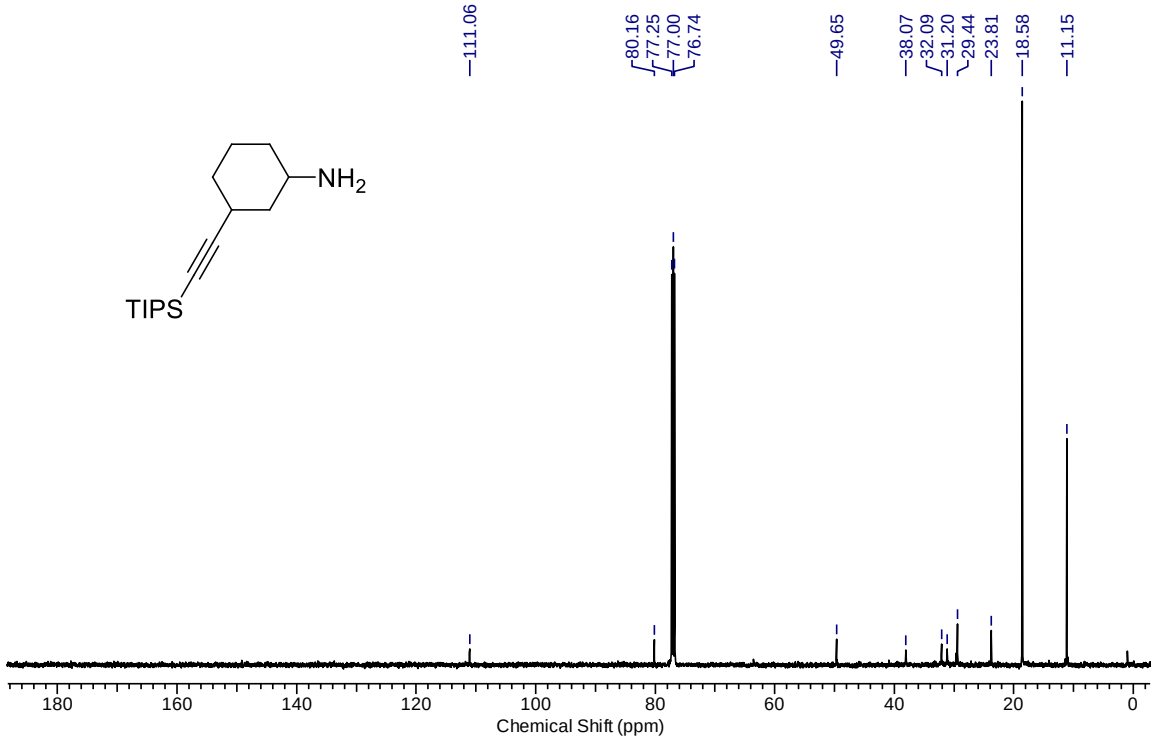

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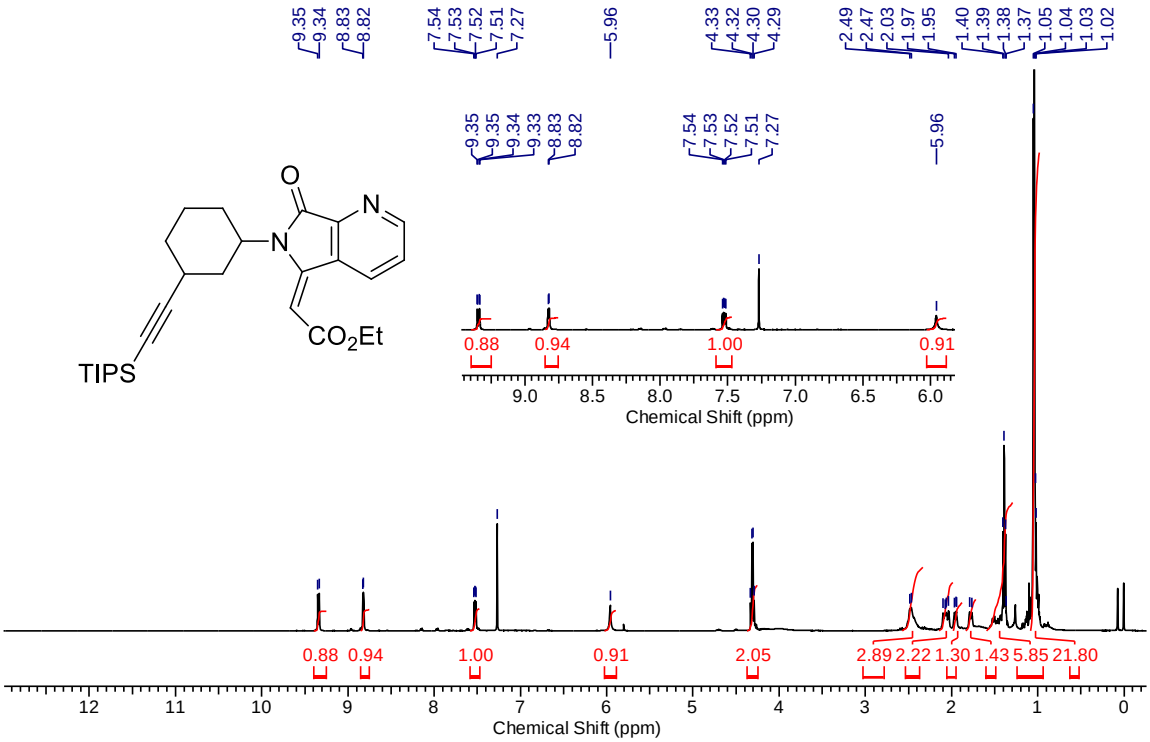

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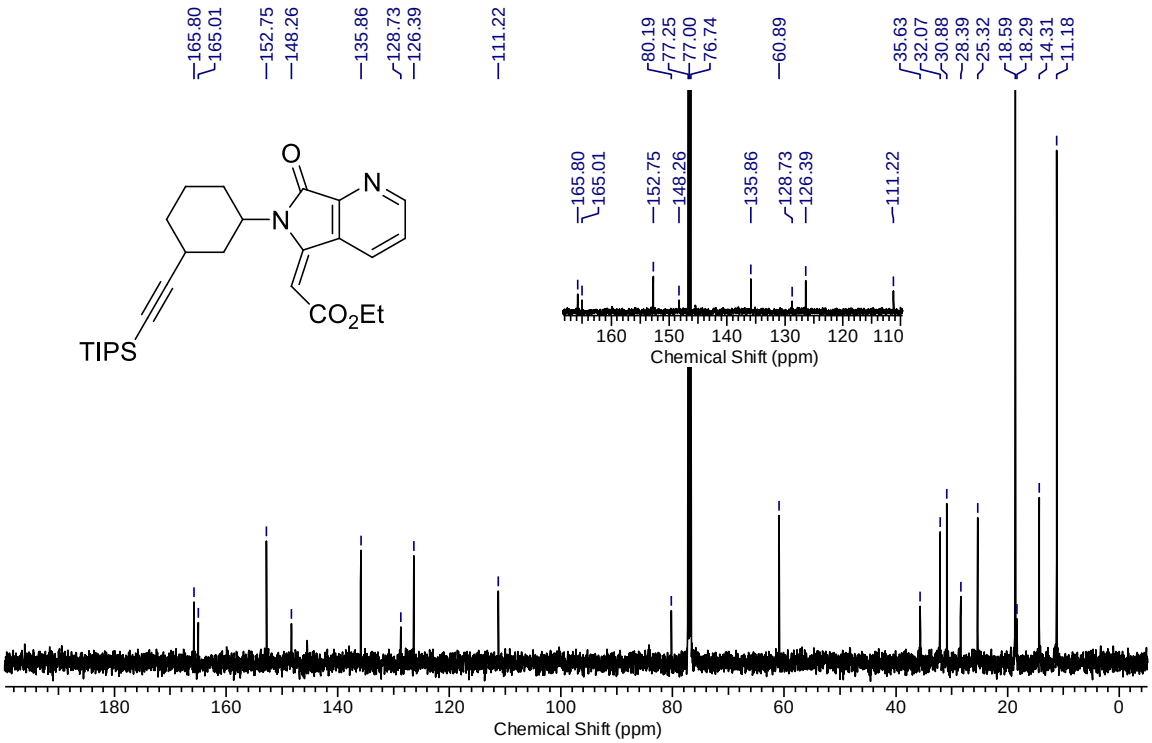

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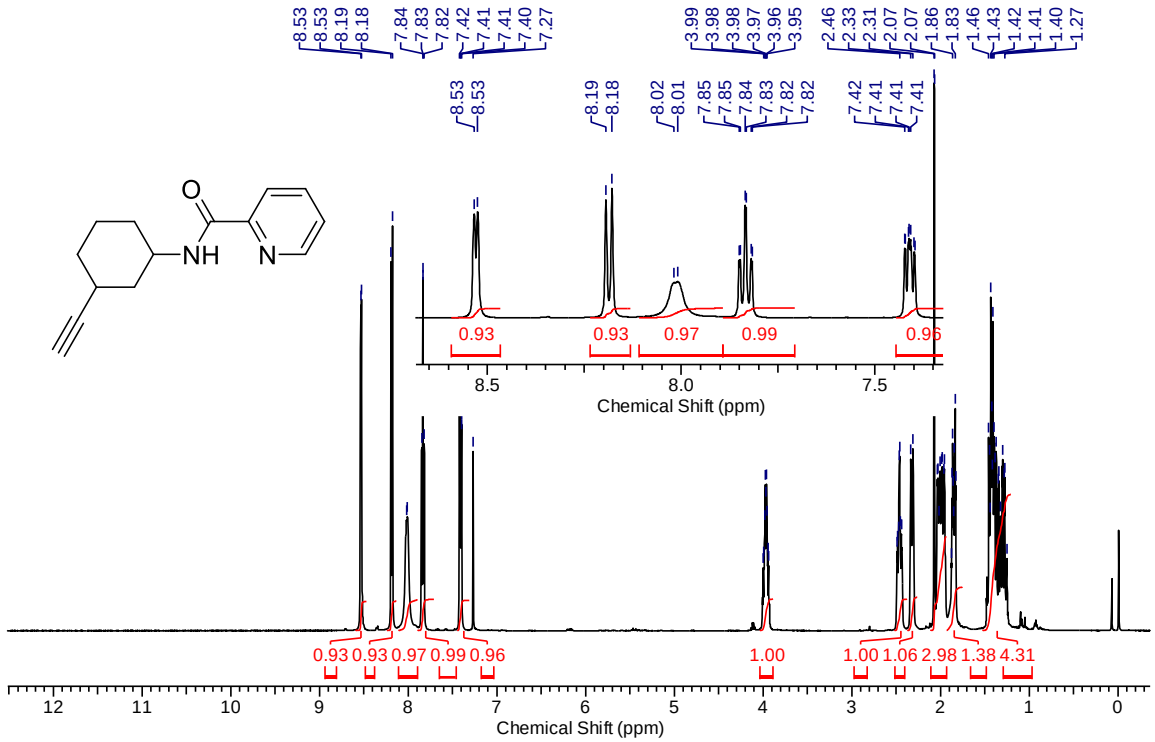

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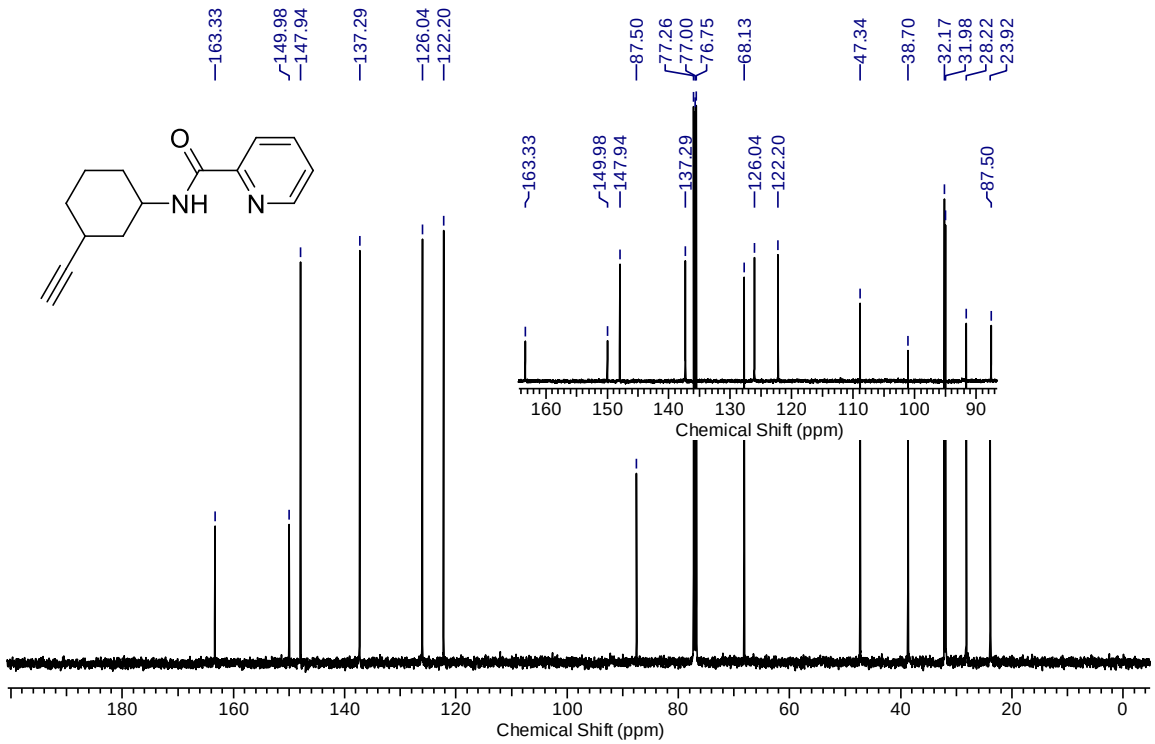

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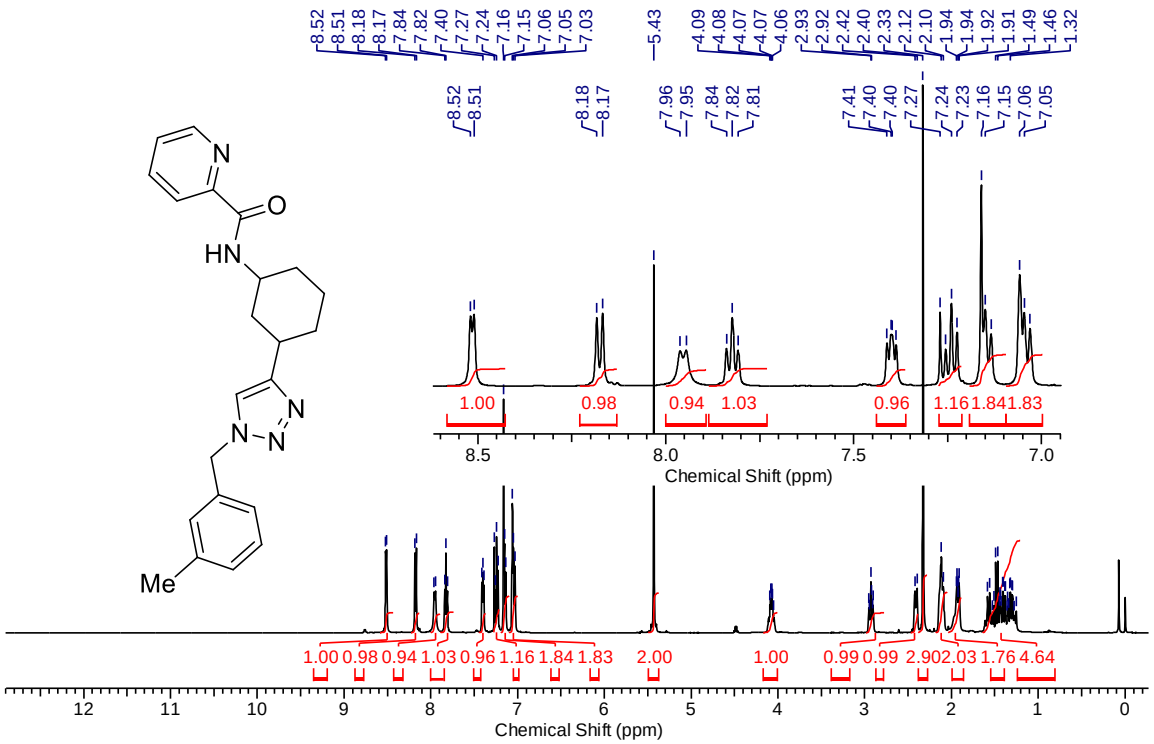
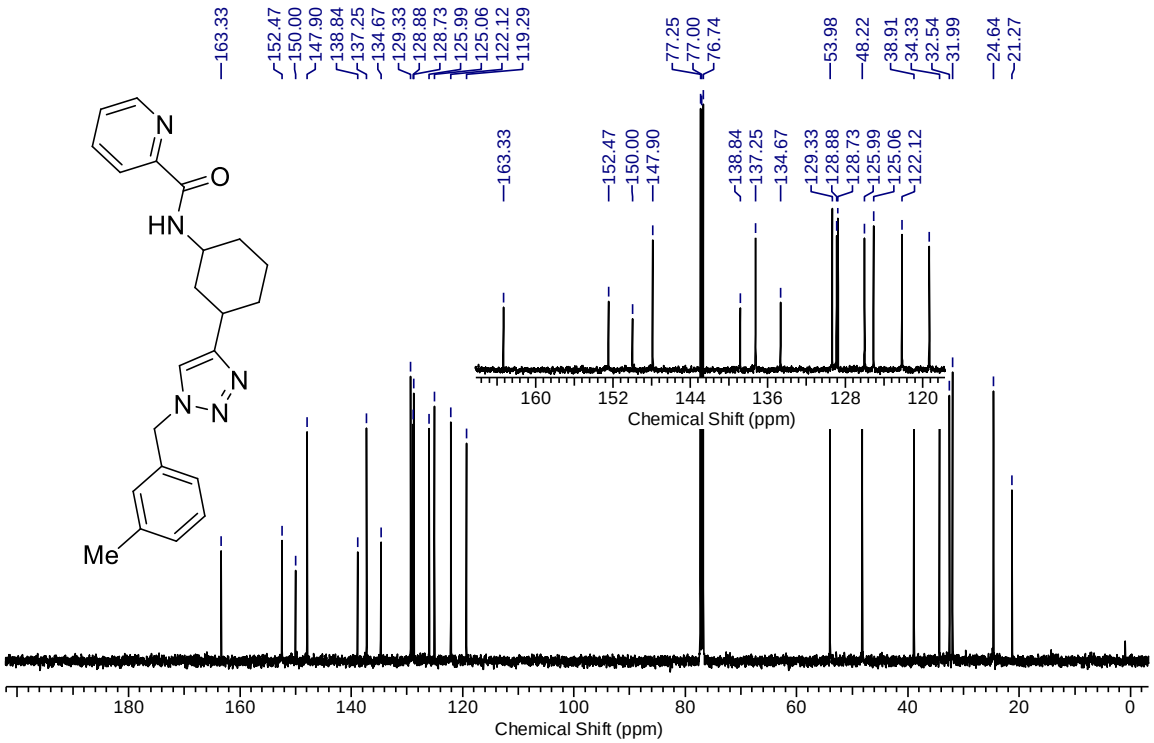
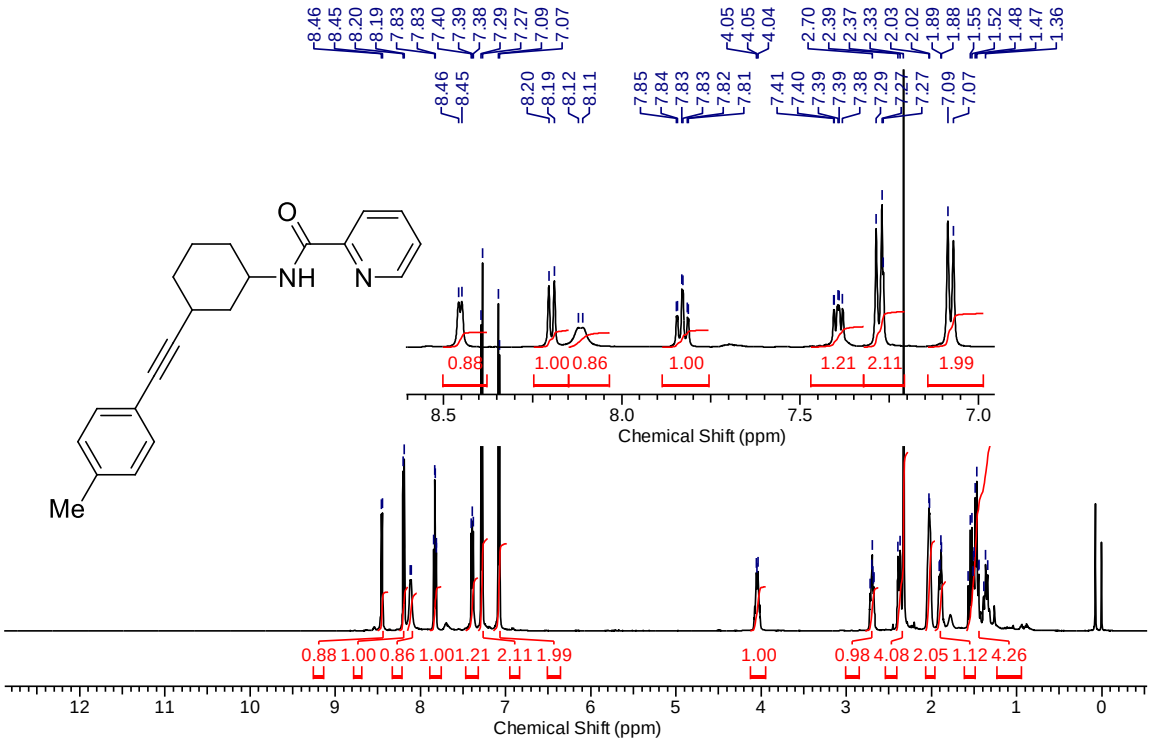


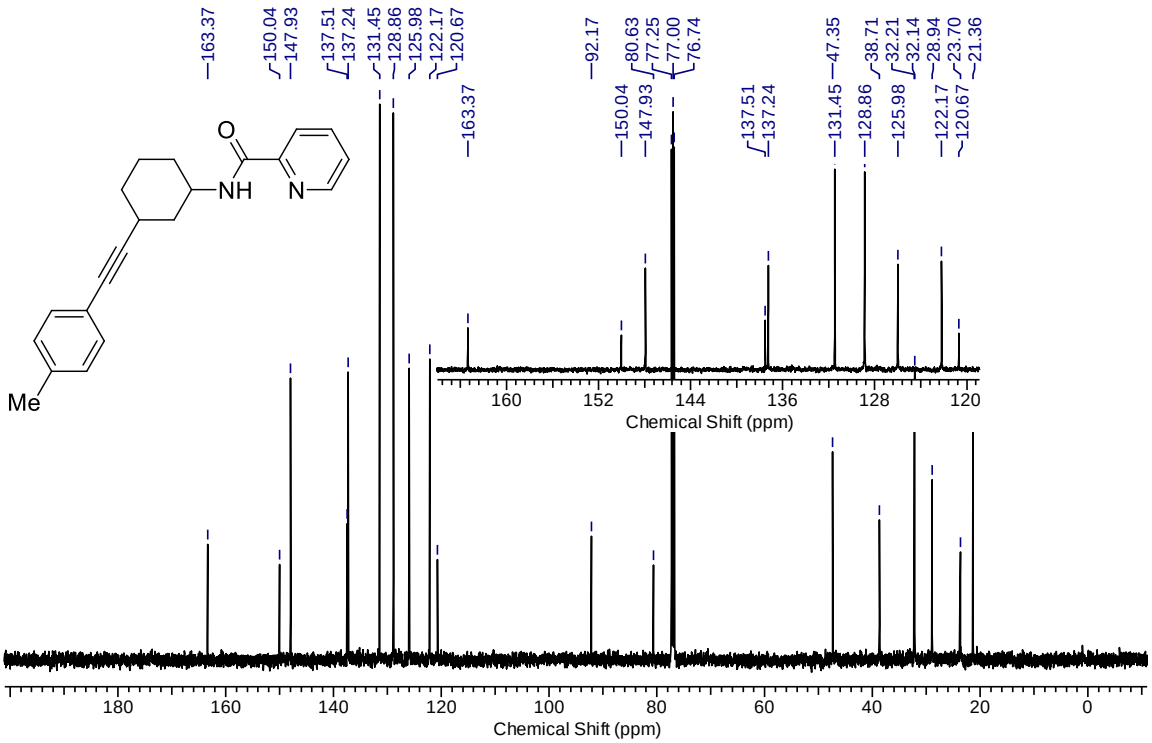
^{1}H NMR



^{13}C NMR



^{1}H NMR



^{13}C NMR

CURRICULUM VITAE

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Academic qualification

Present status

From December 2013 to till date working as Ph.D. Scholar with Dr. E. Balaraman at CSIR- National Chemical Laboratory. I will be completing my doctoral work by August 2018.

Educational Qualification:

Transition-metal catalyzed C-H bond alkynylation.

(Expected to be complete by August-2018)

CSIR-Senior Research Fellow, Registered with AcSIR-New Delhi at CSIR-National Chemical Laboratory, Pune, India.

M. Sc., General Chemistry with First Class (69%), Pune University - Pune, India, 2011-2013.

B. Sc., Chemistry, Physics, Mathematics, First Class with Distinction (84%), Pune University - Pune, India, 2008-2011.

Research Experience

1) CSIR-Junior Research Fellow for PhD from 3rd December 2013 on the topic "Transition-metal catalyzed C(sp^2)-H bond alkynylation" with **Dr. E. Balaraman** at CSIR-National Chemical Laboratory, Pune.

3) CSIR-Senior Research Fellow for PhD from 3rd December 2015 on the topic "Transition-metal catalyzed C(sp^3)-H bond alkynylation"with **Dr. E. Balaraman**at CSIR-National Chemical Laboratory, Pune.

Pre-Synopsis done on 10h April 2018, PhD is expected to be complete in August 2018.

Duration: 3rd December 2013 to till date.

Symposia Attended

National conferences: 1 (Participation)
2 (Poster presentation)
International conferences: 1 (Participation)

Details of Publications:

1. Pd(II)-Catalyzed *gamma*-C(sp^3)-H Alkynylation of Amides: A selective functionalization of R chain of amides $R^1C(O)NHR$. **Landge**, **V.G.;** Parveen, A.; Nandakumar, A.; Balaraman E. ***Chem. Commun.,*** **2018**, *54*, 7483.
2. Manganese catalyzed ligand enabled selectivity *N*-alkylation of Amines with Alcohols. **Landge**, **V.G.;** Mondal, A.; Jaiswal, G.; Kumar, V.; Nandakumar A.; Balaraman, E. Communicated, 2018
3. Cobalt-Catalyzed Acceptorless Dehydrogenative Coupling of Amino alcohols with alcohols: Direct Access to Pyrrole, Pyridine and Pyrazine Derivatives. Midya, S. P.; **Landge**, **V. G.;** Sahoo, M. K.; Rana J.; Balaraman, E. ***Chem. Commun.,*** **2018**, *54,* 90.
4. Phosphine-free cobalt pincer complex catalyzed *Z*-selective semihydrogenation of unbiased alkynes. **Landge**, **V. G.;** Pitchaimani, J.; Midya, S. P.; Subaramanian, M.; Madhu, V.; Balarama E. ***Catal. Sci. Technol.,*** **2018**, *8*, 428.
5. A unified strategy for silver-, base-, and oxidant free direct arylation of C–H bonds. Sahoo, M. K.; Midya, S. P.; **Landge, V. G.;** Balaraman, E. ***Green Chem.,*** **2017**, *19*, 2111.
6. Iron-based nanocatalyst for the acceptorless dehydrogenation reactions. Jaiswal, G.; **Landge**, **V.G.**; Jagadeesan, D.; Balaraman, E.; ***Nature Commun.,*** **2017***, 8,* 2147.
7. Nickel-catalyzed *N*-vinylation of heteroaromatic amines *via* C-H bond activation. **Landge, V. G.;** Rana, J.; Subaramanian, M.; Balaraman, E. ***Org. Biomol. Chem.,*** **2017**, *15*, 6896.
8. Expedient cobalt-catalyzed C–H alkynylation of (enantiopure) benzylamines **Landge**, **V. G.;** Midya, S. P.; Rana, J.; Shinde, D. R.; Balaraman, E. ***Org. Lett.,*** **2016**, *18*, 5252.

Highlights:

- Cited in Organic Chemistry Portal-2017 (Benzene Derivatives: The Mohr Synthesis Of Ilicicolinic Acid)
- http://www.organic-chemistry.org/Highlights/2017/19June.shtm

9. Cobalt-catalyzed bis-alkynylation of amides via double C-H bond activation. **Landge**, V. G.; Jaiswal, G.; Balaraman, E. ***Org. Lett.*, 2016**, *18*, 812.
10. Sustainable iron-catalyzed direct imine formation by acceptorless dehydrogenative coupling of alcohols with amines. Jaiswal, G. **Landge**, **V.G.;** Jagadeesan, D. Balaraman, E. ***Green Chem.*, 2016**, *18*, 3232.
11. Nickel-catalyzed direct alkynylation of C(sp^2)-H bonds of amides: An "inverse Sonogashira strategy" to ortho-alkynylbenzoic acids. **Landge, V. G.;** Shewale, C. H.; Jaiswal, G.; Sahoo, M. K.; Midya, S. P.; Balaraman, E.; ***Catal. Sci. Technol.*, 2016**, *6,* 1946.
12. Reversed reactivity of anilines with alkynes in the Rhodium-catalysed C–H activation/carbonylation tandem. Midya, S. P.; Sahoo, M. K.; **Landge, V. G.;** Rajamohanan, P. R.; Balaraman, E.; ***Nature Commun.*, 2015**, *6,* 8591.
13. Transition-metal catalysed hydrogen transfer annulation strategy to heterocyclic scaffolds. Nandakumar, A.; Midya, S. P.; **Landge, V. G.;** Balaraman, E.; ***Angew. Chem. Int. Ed.*, 2015**, *54,* 11022.
14. Well-defined palladium(II) complexes for ligand enabled C(sp^3)-alkynylation. **Landge, V.G.;** Sahoo, M. K.; Midya, S. P.; Jaiswal, G.; Balaraman, E. ***Dalton Trans.*, 2015**, *44,* 15382.

Details of Patents:

1. A Novel 2-pyraimidyl aniline derivatives, process for preparation and thereof. Ekambaram Balaraman; **Vinod Gokulkrishna Landge,** Akash Mondal *Ind. Pat.* **2017**, Application No. 201711034640.
2. Novel phosphine free cobalt complexes acceptorless dehydrogenative annulation of Aminoalcohols with alcohols. Ekambaram Balaraman; Siba Prasad Midya; **Vinod Gokulkrishna Landge** *Ind. Pat.* **2017**, Application No. 201711031330.
3. Catalytic process for the formation and/or hydrogenation of esters including lactones by phenanthroline based pincer complexes. Ekambaram Balaraman;

Siba Prasad Midya; **Vinod Gokulkrishna Landge** *US. Pat.* **2015**, Application No. 15/549827.

4. Catalytic hydrogenation of CO_2 to methanol by single-site Ru(II)- pincer-type catalysts. Ekambaram Balaraman; **Vinod Gokulkrishna Landge;** Siba Prasad Midya; Manoj Kumar Sahoo; Garima Jaiswal *US. Pat.* **2014**, Application No. 15/549827.
5. Direct C (sp^3)-H alkynylation of *N*-heterocyles: a chelation assisted Pd catalysis. Ekambaram Balaraman; **Vinod Gokulkrishna Landge** *US. Pat.* **2014**, Application No. 15/543714.