Thesis

Exploration for Distal C–H Functionalization of Aliphatic and Aromatics by Pd Catalysis

Submitted in partial fulfillment of the requirements

of the degree of

Doctor of Philosophy

of the
Indian Institute of Technology, Bombay, India
and
Monash University, Australia

by

Sandeep Yadavrao Pimparkar

Supervisors:

Prof. Debabrata Maiti (IIT Bombay)

Prof. David Lupton (Monash University)

The course of study for this award was developed jointly by
Monash University, Australia and the Indian Institute of Technology, Bombay
and was given academic recognition by each of them.
The programme was administrated by The IITB-Monash Research Academy

(Year 2019)

Declaration

I declare that this written submission represents in my own words and where others ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhere to all principal of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea, data, fact & source in my thesis submission. I do understand that any violation of above will cause disciplinary action by the institutes/s and can evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Notice 1

Under the Copyright Act 1968, this thesis must be used only under the normal conditions of scholarly fair dealing. In particular no results or conclusions should be extracted from it, nor should it be copied or closely paraphrased in whole or in part without the written consent of the author. Proper written acknowledgement should be made for any assistance obtained from this thesis.

Notice 2

I certify that I have made all reasonable efforts to secure copyright permissions for third-party content included in this thesis and have not knowingly added copyright content to my work without the owner's permission.

Student Name: Sandeep Yadavrao Pimparkar

IITB ID: 144034004

Monash ID: 26852845

Thesis Approval Sheet

The thesis entitled **"Exploration for Distal C-H Functionalization of Aliphatic and Aromatics by Pd Catalysis"** by Sandeep Yadavrao Pimparkar (IITB Roll no: 144034004, Monash ID: 26852845) is approved for the degree of **DOCTOR OF PHILOSOPHY.**

.....	.....
External Examiner	Internal Examiner
.....	.....
Prof. Debabrata Maiti	Prof. David W. Lupton
Supervisor	Supervisor

.....

Chairperson

Date:

Place: IITB Monash Research Academy,

IIT Bombay,

Powai. Mumbai-400076.

Declaration

I declare that this written submission represents in my own words and where others ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhere to all principal of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea, data, fact & source in my thesis submission. I do understand that any violation of above will cause disciplinary action by the institutes/s and can evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Date:

Sandeep Y. Pimparkar

(IITB Roll No: 144034004)

(Monash ID: 26852845)

Acknowledgment

I owe my deepest gratitude to my family, without their unconditional support and encouragement, I could not have come this far.

It is my pleasure to express my deepest gratitude to my Ph. D. advisors Prof. Debabrata Maiti and Prof. David W. Lupton for giving me wonderful opportunity work under their supervision. I am grateful for their constant encouragement, support and insightful suggestions during my work. Their enthusiasm, inspiration and dedication to science have greatly influenced me and my overall development of research career and will undoubtfully benefit me throughout my life.

Apart from my supervisors, I am also grateful to Prof. Gautam K. Lahiri and Prof. Joel Hooper for being part of my annual progress committee and their evaluations and valuable suggestions during my annual progress seminars.

I am thankful to IITB Monash Research academy, Department of Chemistry, IIT Bombay and Monash University, Australia for the Ph. D. position offered, and infrastructure provided. I am also thankful to IITB Monash Research academy for financial assistance during my tenure, Department of Chemistry-Central Facility, SAIF, IIT Bombay for instrumental facility.

I sincerely thanks to all graduated senior Ph. D. students Dr. Naveen Togati, Dr. Sujoy Rana, Dr. Soham Maity, Dr. Tuhin Patra, Dr. Atanu Modak, Dr. Argha Deb, Dr. Arun Maji, Dr. Soumitra Agasti, Dr. Sukdev Bag, Dr. Uttam Dutta, senior and current postdoc students Dr. Rahul Watile, Dr. Santosh Kumar Sahoo, Dr. Rajesh Kancherla, Dr. Milan Bera, Dr. Kapileshwar Seth, Dr. Ramasamy Jayarajan, Dr. Srimanta Guin, Dr. Ramakrishna Kankanala, Dr. Tapas Kumar Achar, Dr. Anjana Ramesh, Dr. Sadhan Jana for mentoring, teaching and encouraging during my studies. I am also thankful to former & present lab members Sheuli Sasmal, Pravas Dolui, Jyotiprasad Biswas, Jayabrata Das, Sandip Porey, Chandrashekar HB, Tapas Pal, Soumya Kumar Sinha, Trisha Bhattacharya, Sukumar Pradhan, Sudip Maiti, Nupur Goswami, Gaurav Prakash, Argha Saha, Avijit Hajra, Santanu Singha, Anirban Mondal, Aniruddha Dey, Semanti Mukherjee,

Ehtasimul Hoque, Arka Chakraborty, Minal Wagh, Prakriti Kalra, Satyadip Pal, Kishan Daud, Arup Mondal, Vikas Kumar Singh, Aishanee Sur, Suman Bhowmic for making my workplace amazing. I am also thankful to lab members of Prof. David Lupton's lab Jhi Ametvoski, Adam Ametvoski, Rachel Gillard, Lydia Scott, Jared E. M. Fernando, Darcy Williamson, Simon Cromwell, Andrzeb Zieba, Jing Cao, Xuan Nguyen, Venkatachalam Pitchumani, Alexander Wright, Song Bae at Monash University for great working atmosphere during my stay at Monash University, Australia.

Outside of work zone I would like to thank all my Ph. D. batchmates, my friends Dr. Prashant, Dr. Ganesh Wagh, Dr. Varoon Singh, Sweetij, Rahul, Vishal, Shrikant, Dattatray, Kiran, Arvind & Yogesh for supporting me through.

I am greatly thankful to my father Yadavrao, mother Bharati, sister Surekha, wife Ujjwala giving me all strength throughout the journey and twin boys Prasanna and Prafulla for making my journey cheerful.

I also convey my profound gratefulness to all my friends, seniors and juniors who made my journey possible and helped in every need. I also gratefully acknowledge all the non-teaching staff of Department of Chemistry IIT Bombay, School of Chemistry, Monash University and all the instrument operators for their helps in different ways.

Sandeep

Content

Chapter 1

Introduction and Scope of Thesis

Chapter 2

Chelation assisted palladium catalysed arylation of aliphatic carboxylic acid derivatives

Chapter 3

Ligand enabled chelation assisted C(sp^3)–H alkynylation of aliphatic carboxamides

Chapter 4

Palladium catalyzed distal *para* C(sp^2)–H cyanation of arene by U-shaped template

List of abbreviations

°C	Degree Celsius
atm	Atmosphere
Ar	Aryl
Ar	Aryl
^{i}Pr	Iso propyl
^{t}Bu	Tertiary butyl
Cy	Cyclohexyl
cat.	Catalyst
acac	Acetylacetonate
calcd.	Calculated
dba	Dibenzylidineacetone
DCM	Dichloromethane
DMF	Dimethyl Formamide
DG	Directing group
DMSO	Dimethyl Sulfoxide
DCE	Dichloroethane
DTBP	Di-tertiary-butyl peroxide
equiv.	Equivalent
ESI MS	Electrospray Ionization Mass Spectrometry
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
etc.	Et cetera
et al.	Etalii
EtOH	Ethanol
EWG	Electron-withdrawing group
EDG	Electron-donating group
GC	Gas chromatography
h	Hour
HRMS	High resolution mass spectrometry

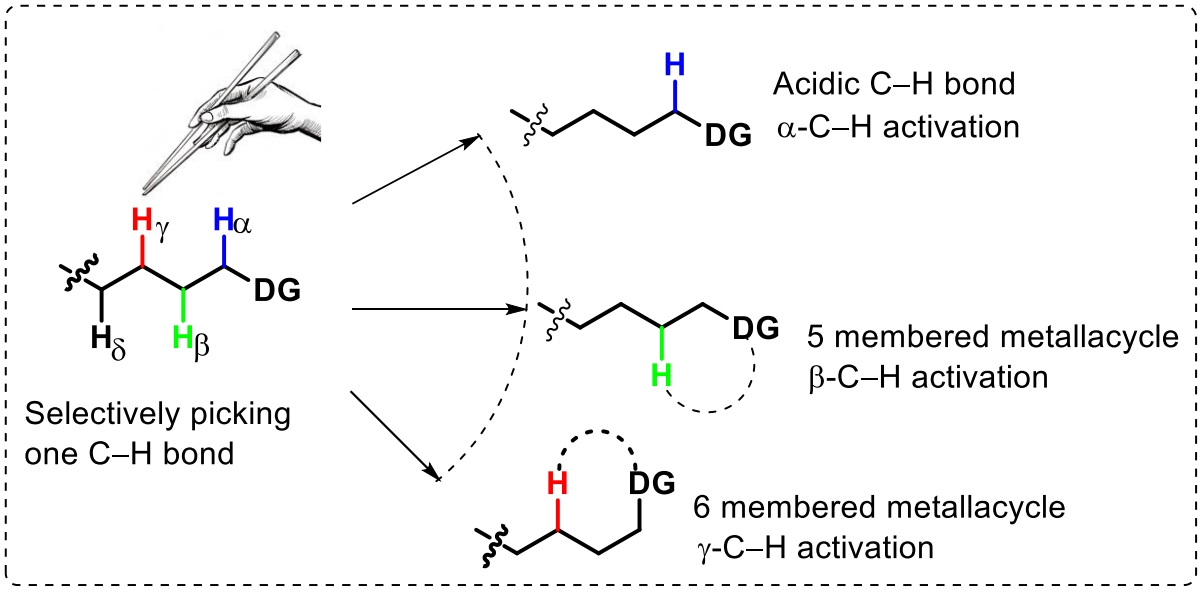
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
IR	Infrared spectroscopy
KIE	Kinetic isotope effect
L	Ligand
MeOH	Methanol
mL	Milli liter
MS	Molecular sieves
mmol	Milli mole
M.P.	Melting point
NMR	Nuclear Magn
NMP	N-methylpyrrolidone
OAc	Acetate
OMe	Methoxy
Ph	Phenyl
phen	1, 10-phenanthroline
rt	Room temperature
SET	Single electron transfer
***t*-BuOH**	Tertiary butyl alcohol
TFA	Trifluoroacetic acid
***t*-Amy-OH**	Tertiary amyl alcohol
TFT	Trifluorotoulene
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TFE	Trifluoroethanol
XRD	X-Ray Diffraction

Chapter 1

Introduction and Scope of Thesis

1.1 Introduction:

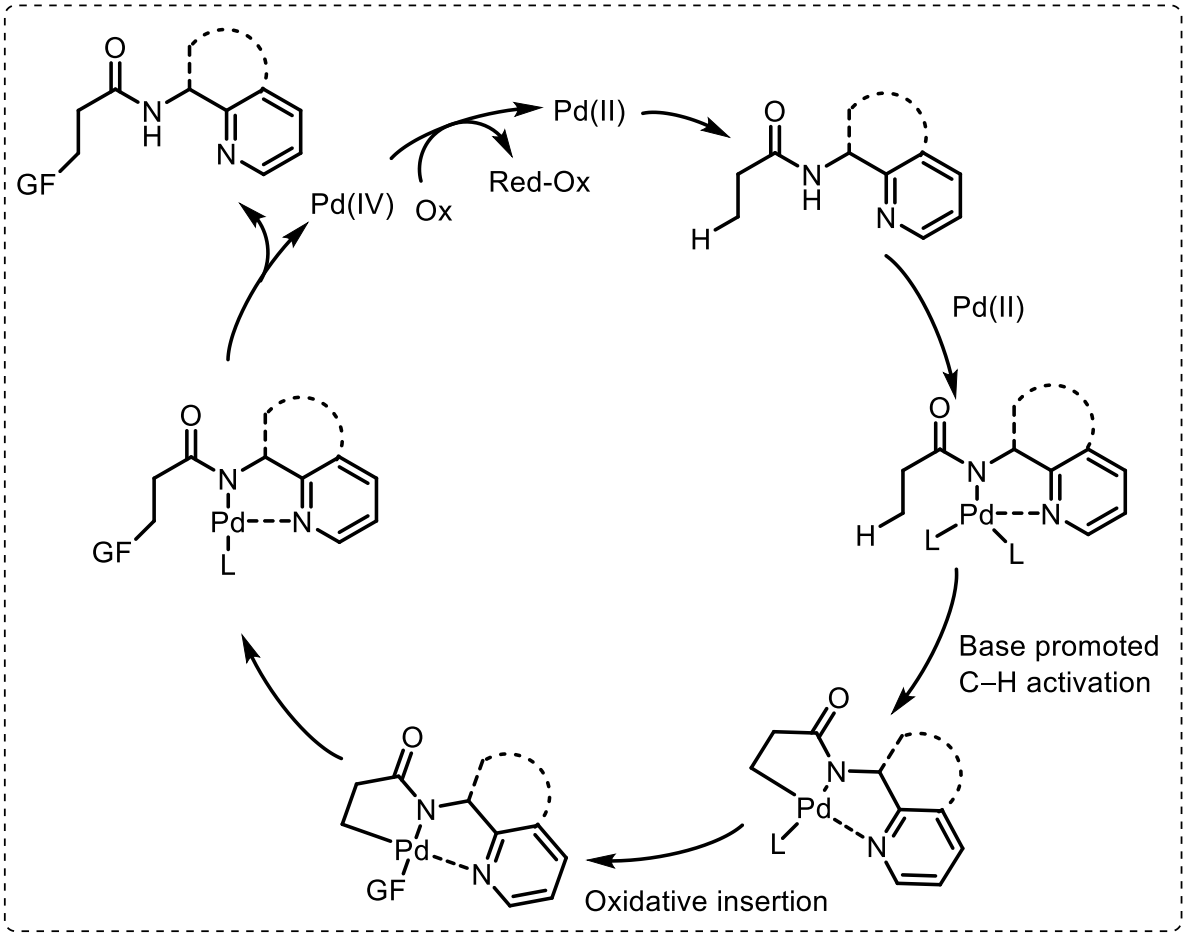
Alkanes are one of the major available feedstock materials to us, in the form of petrochemicals and in synthetic terms they are refered as aliphatic motifs. They range from methane to C_nH_{n+2} alkane. We have always keen to utilize such a abundant material by various synthetic transformation. The strategic functionalization of unactivated aliphatic C–H bonds has potency to open newer avenues for synthesis of material, agrochemicals, pharmaceuticals, natural products[1] but, when one thinks to convert them to valuable product in various functionalities, one has to face many challenges. First, availability of C–H bond-presence of many similar active sites in molecule makes it unselective towards a reaction. Second, high bond dissociation energy makes it difficult cleave and reattach with other functional group. Over the decade, many research groups around globe started to utilize such material in form of aliphatic substrate for C–H activation strategy by using a directing group approach in assisted with various transition metal as catalyst. (Scheme **1**) Due to this we have witnessed various α, β, γ & δ distal functionalization.[2]



Scheme 1: Schematic representation for aliphatic C–H activation

1.2 Background

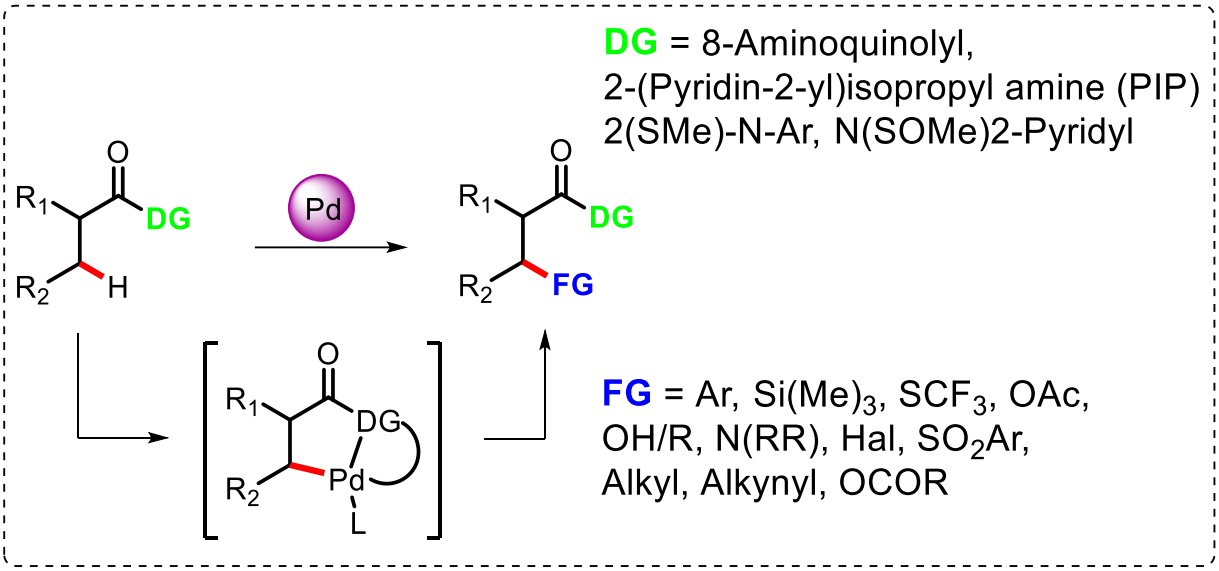
In past decade substantial progress has been made for α C–H functionalization. Proximal position from directing group or a functional group poses its electronic character allowing α C–H bond to be more acidic and many functionalization of acids, amine, amides are known to us via organo-catalysis and metal catalysis. Avenging further distal β-C–H bond needed newer approach during this development. In the past decade synthetic community has witnessed new paradigm for aliphatic C–H activation via transition metal catalysis to access the farther places on aliphatic substrates and to synthesize complex functionalities. One such successful example was directing group assisted aliphatic β-C–H activation where 5 membered metallacycle was favored (Scheme **1**).



Scheme 2: General mechanism for β-C–H functionalization

In a general term, suitable directing group in aliphatic substrate chelates with metal first and forms intermediate **A**, a pre-activation intermediate. Later base/oxidant abstract the aliphatic proton to form C–H activated adduct **B**. Oxidative addition of coupling partner increase Pd oxidation state and subsequent reductive elimination releases product. Later metal re-oxidised by oxidant for next catalytic cycle. (Scheme **2**)

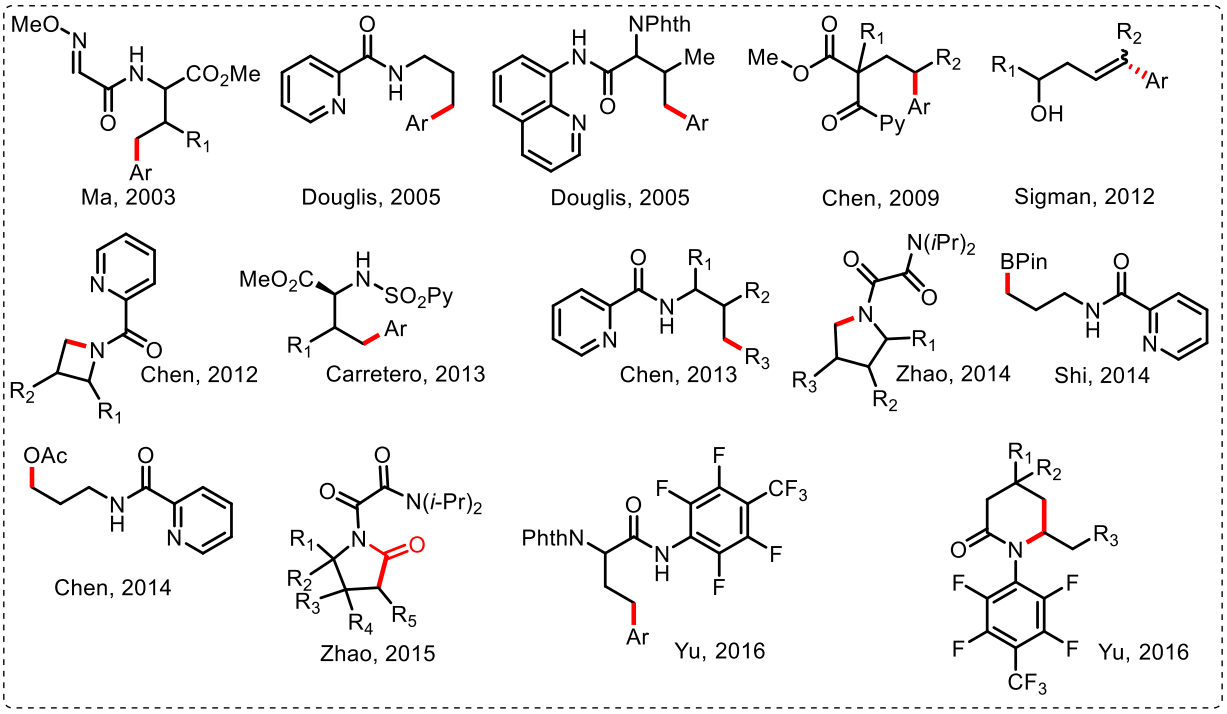
For this transformation in past decade number of monodentate (pyridyl based), bidentate (aminoquinoline based) directing groups has been utilized to chelate with transition metals. 8-aminoquinoline (8-AQ) as bidentate directing group introduced by Daugulis in various β-selective transformation for arylation, alkylation and later same directing group was used for arylation, silylation, hydroxylation, acetoxylation, amination, halogenation, sulfonation and few other has proved efficacy to form desired 5 membered metallacycle.[3] 2(Pyridine-2-yl)isopropelamine (PIP) served as bidentate auxiliary for various β selective reactions developed by Shi. 2-Picolinic acid also served as bidentate auxillary for β selective functionalization of aliphatic amines. Scarcity of these type of functionalizations at more distal positions can be concluded to involvement of less favored palladacycle intermediate. By forming 5 membered metallacycle only β position of aliphatic systems can be accessed, but to access immediate farther γ-C–H bond one must look after more reliable route to access 6 membered metallacycle in similar systems[3].



Scheme 3: Overview of β C–H functionalization

1.2.1. Chelation assisted palladium catalysed arylation of aliphatic carboxylic acid derivatives

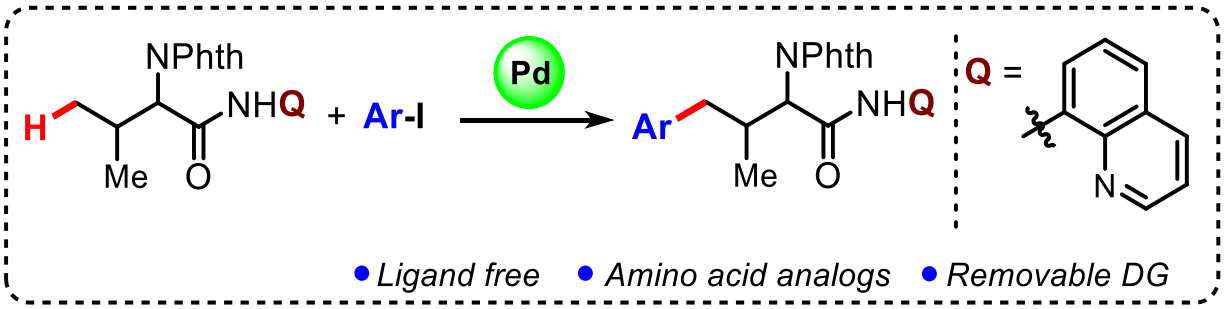
Introducing aryl group on C(sp^2) or C(sp^3) carbon or nitrogen centres always been a widely studied functionalisation as it can lead to various biaryls which are synthetically, pharmaceutically, and medicinally important core structures. Two aryls can be coupled via many synthetic and catalytic routes by Suzuki coupling, Negishi coupling, Kumada coupling, Still coupling, Buchwald-Hartwig cross coupling, Ullmann reaction, and we have seen tremendous outgrowth in this arena.[4a] In past few decades these reactions have changed the aspect of chemistry by transforming into valuable target motifs ranging from pharmaceutical, medicinal, material, fine chemical industries and showed wide array of applications. Although β-selective arylation were known via few directing groups by transition metal catalysis[4] but utilising aryl coupling by distal γ-C(sp^3) –H activation was still unknown in past decade.



Scheme 4: Summary of γ-C(sp^3) –H functionalization with directing groups

2nd chapter of this thesis present earlier methods, pitfalls and current work developed for γ-selective C(*sp*^{3}) –H activation. To summarise various functionalisation are known at γ-C(*sp*^{3}) –H bond by utilising different directing groups. If metal can change its co-ordination preference, it is possible to intervein into 6 membered metallacycle and which will subsequently result in γ-C–H activation. In the view of similar attempt Ma in 2003 reported arylation of amino acid derivatives and later Dougulis reported arylation of aliphatic amines by using 2-picolyl as directing group. Similar directing group was used by Chen in 2009 & 2013 for arylation and for alkylation, Shi in 2014 for borylation, Chen in 2014 for acetoxylation of aliphatic amines. Along with that Sigman in 2012 developed methodology for enantioselective arylation of aliphatic alcohols. Chen in 2012, Zhao in 2014, 2015 found a way to synthesize cyclic lactums by intramolecularly activating γ-C–H bond. Carretaro in 2013 reported arylation of aliphatic amines by using pyridyl sulfonyl as directing group for first time. Recently in 2016 Yu reported method for γ–C–H arylation & olefination of aliphatic acids by using 4-CF_3-(C_6F_4)-NH_2 as directing group. Most of these methods required a ligand to accelerate the reaction but we developed method which no

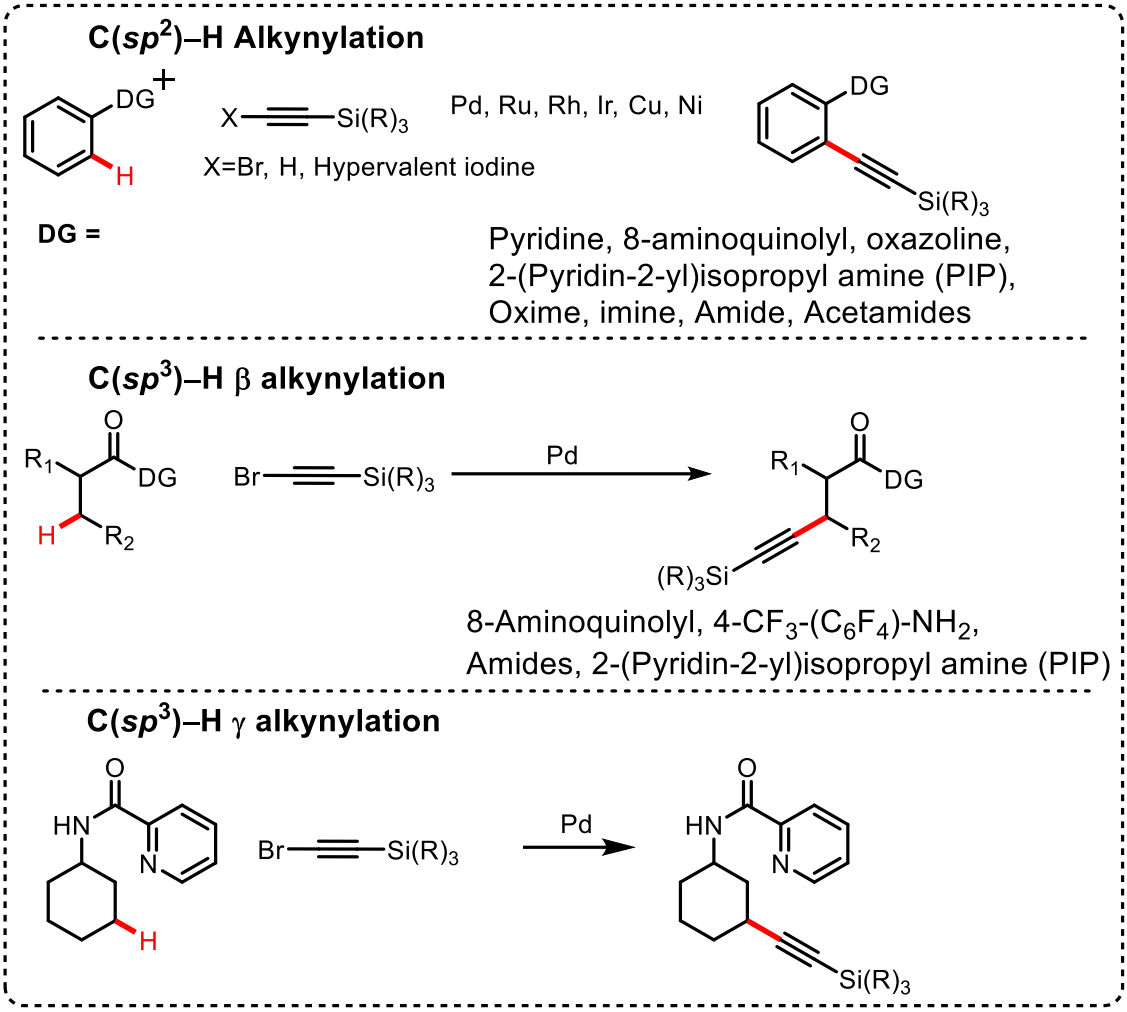
longer required external ligand and method was successful to different substituted aryl iodides and for this reaction amino acids analogs reacted efficiently with aryl iodide. Study also included control experiments to prove role of oxidant and predicted the reaction mechanism.[4]



Scheme 5: Overview of present work

1.2.2. Ligand enabled chelation assisted C(sp^3)–H alkynylation of aliphatic carboxylic acids

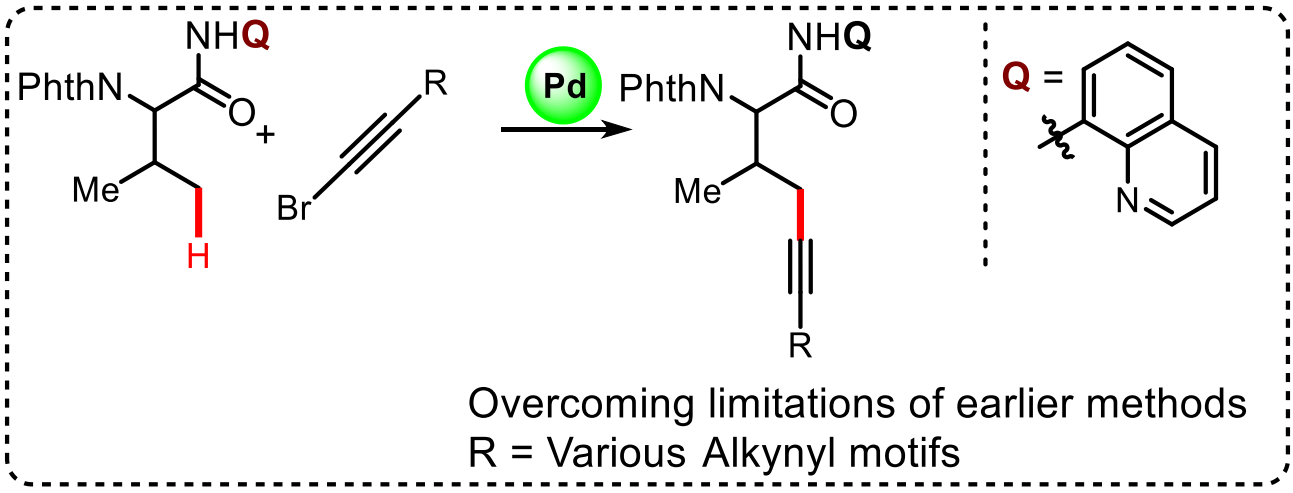
Alkynes are one of the most important structural motifs found in natural products, pharmaceuticals and materials. Synthetically Alkynes can be modified into many functionalities and can lead a platform for various complex motifs useful in various arena of chemistry for metathesis, cycloaddition, natural product synthesis and beyond. Past several decade have witnessed efficient strategies to synthesize functionalised alkynes via transition metal catalysis including a) oxidative coupling of aryl with terminal alkynes b) palladium/copper catalysed Sonogashira coupling reaction between terminal alkynes and aryl halides c) oxidative coupling of aryl and alkyl C-H bonds with alkynylhalides.[5]



Scheme 6: Summary of C(sp^2) & C(sp^3) Alkynylation reactions

Although many methods are known to us for alkyne insertion into various C(sp^2)–H bonds of aryl-heteroaryls using various directing groups like 8-aminoquinoline, oxaxoline, PIP, 2-picolyl, NHAc, imine, oximes by using preactivated substrates, preactivated alkynes but till date no method is available to insert alkyne into γ C(sp^2)–H bonds of carboxylic acids (Scheme **5**). So far in literature β selective alkynylation has been developed by Chatani (8-aminoquinolyl DG), Yu (4CF_3(C_6F_4)-NH DG), Shi (PIP DG) and only one example is available for γ selective alkylation of aliphatic amines by 2-picolyl as directing group reported by Balaraman *et al* in early 2018. 3rd chapter of this thesis conclude the study for γ selective C(sp^3)–H alkynylation of amino acid analogs, carboxylic acid amides via

chelation assisted strategy by utilising aminoquinoline as directing group under palladium catalysis.[5]



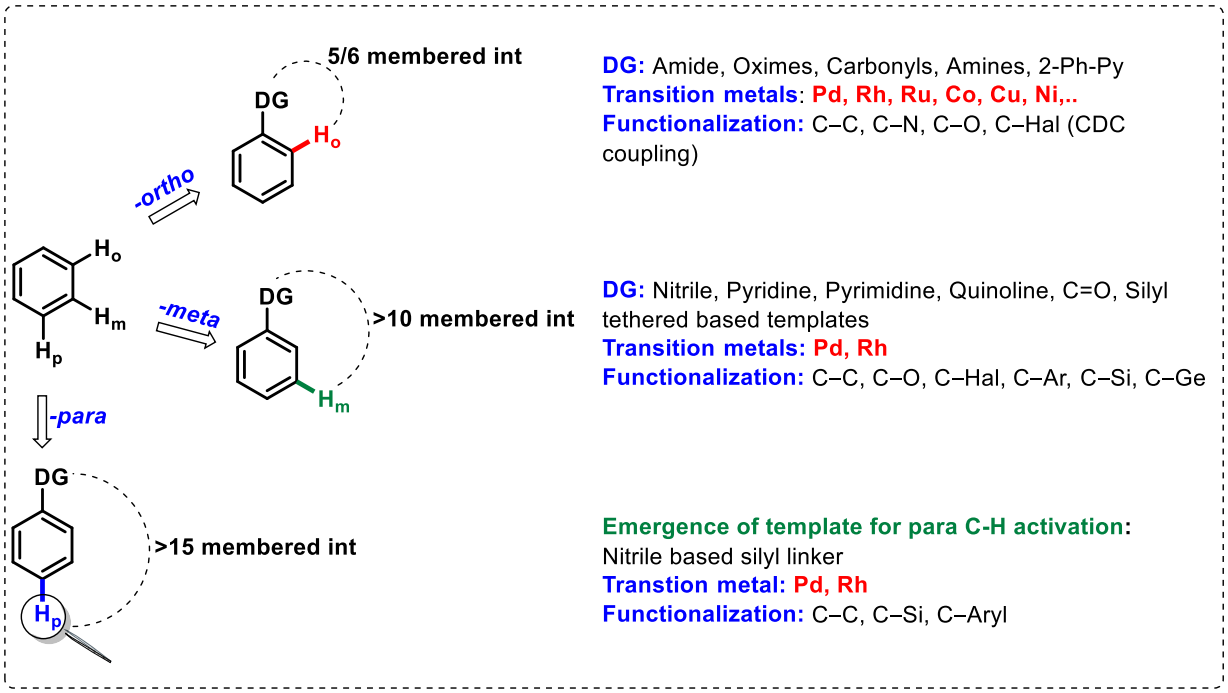
Scheme 7: Overview of present work

1.2.3. Palladium catalyzed distal *para* C(sp^2)–H cyanation of arene by U-shaped template

Unlike, cross coupling reactions in organic synthesis has played vital role in development of modern-day chemistry which allowed us to synthesize complex molecules. Traditional methods to couple two reactants together poses several challenges. Work on the basis of transition metal catalysts in the 70's by pioneers Heck, Noyori and Suzuki led the foundation of homogeneouns catalysis and current synthetic catalytic chemistry. Third row precious transition metals served standard as most robust, versatile catalytic systems for today's pool of enormous application in organic synthesis. One majorly studied reaction of all time now is transformation via C–H activation. In principal as its name suggests C–H activation refers to activating C–H bond for possibly functionalization by taking advantage of catalysis.[1]

Ortho C(sp^2)–H bond activation is widely known to us today. Site selectivity is always a critical challenge for C–H activation reaction. Since the two decades and more, various groups around the globe have solved this problem by introducing directing group on the

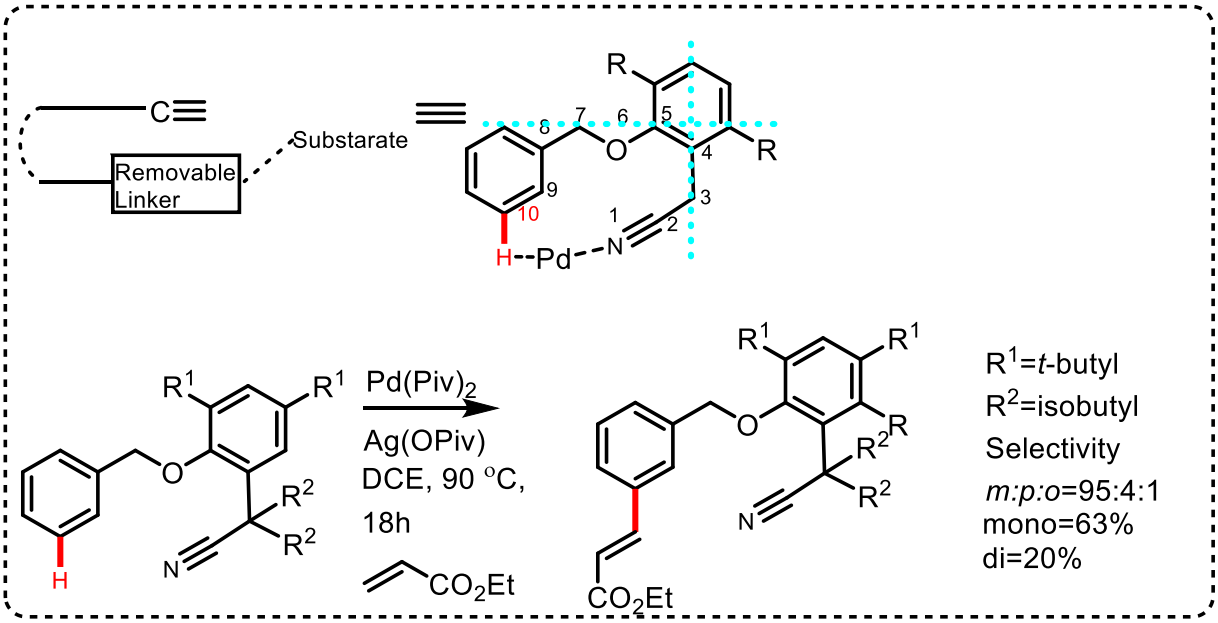
arenes to facilitate the chelation of transition metal and subsequent activating the specifically *ortho* C–H bond which is present in close proximity. This strategy is now well diversified with various directing groups that include amides, anilides, aldehydes, ketones, carboxylates to give olefinated, arylated, hydroxylated, alkenylated arenes and heteroarenes (Scheme **8**). It has been always a difficult task to approach the 'distal' C–H bond due to instability of macrocyclic transition states or limitation of 5 or 6 membered transition states.



Scheme 8: Summary of proximal, distal C–H activation

Yu et al in 2012 overruled this limitation by employing a strategy of template assisted distal C–H activation by taking advantage of nitrile template to chelate Pd catalyst to reach the distal *meta* C–H bond and subsequently further functionalization. (Scheme **9**). To overcome the limitation of traditional directed C–H activation, linear 'end-on' coordinating template was proposed to accommodate a macrocyclic cyclophane like pre-transition state.[6a] Later same group reported mechanistic investigation report which proved that reaction proceeded through four major steps: C–H activation (concerted metalation deprotonation pathway)-a rate as well as regioselectivity determining step, alkene insertion, *β*-hydride elimination and reductive elimination.[6b] Having all proof in hand that

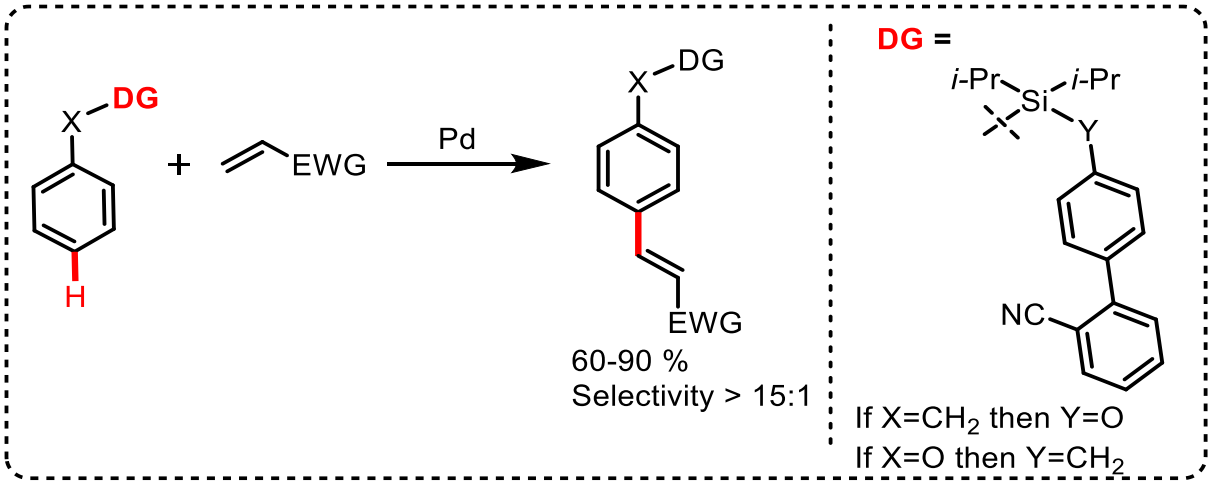
nitrile can act as a weakly coordination site, various templates were reported based on nitrile directing templates. Inspired from this, *meta* C–H activation was achieved by using new silyl-based nitrile directing template by Tan and coworker.



Scheme 9: Design of first -meta selective '-end-on' template

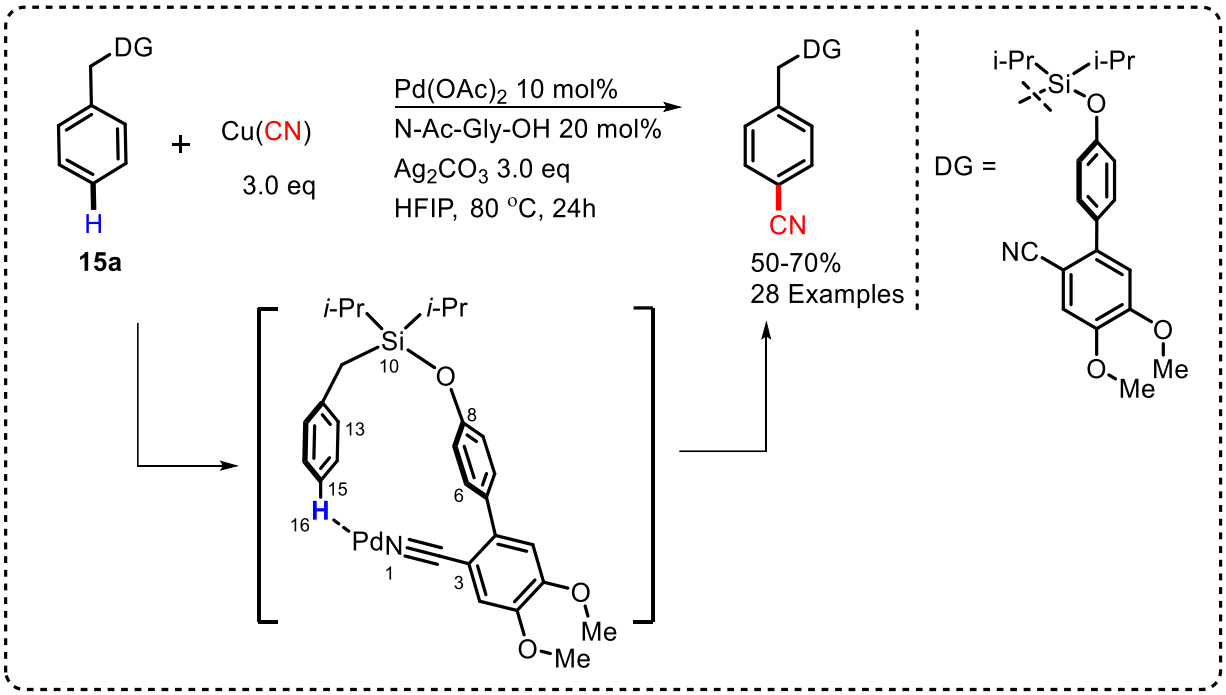
Maiti and coworker disclosed new sulfone-based arene nitrile template which proved useful for *meta* selective homo-diolefination and hetero-diolefination using Pd(II) catalyst.[6c] This methodology gave access to successful sequential olefinations in a regio-selective manner providing a novel route for the synthesis of hetero-dialkenylated products which are difficult to access using conventional methods. To improve efficiency of *meta* selective reaction Maiti et al reported various new directing group based on pyridyl, pyrimidine, sulfonyl-quinoline to introduce various functionalization like olefination, acetoxylation, alkylation, alkynylation, acetoxylation, hydroxylation.

Maiti et al for the first time developed a strategy based on nitrile template which now can deliver metal at *para*-position of aromatic ring with the help of D-shaped template.[6d-e] The template designed utilized Thorpe-Ingold effect to introduce strain in system but keeps flexible in such a way that co-ordination site can undermine *ortho*- and *meta*- position and selectively reaches *para*- position to deliver the metal at *para* C(sp^2)–H bond.



Scheme 9: *para*-selective olefination of toluene & phenol derivatives.

Cyano or nitrile group are used for wide variety of functional group interconversion in synthetic chemistry. It can be converted to corresponding acid, benzyl alcohols, ester by using synthetic routes and which can lead to different functionality in single motifs. Currently over 30 nitrile-containing pharmaceuticals are prescribed for a diverse variety of medicinal conditions with 20 in queue for clinical development. Also, few drugs molecules like Etravirine (Anti-HIV agent), Periciazine (Antipsychotic and neuroleptic), Vildagliptin (Antidiabetic drug), Fadrozole monohydrochloride (One of the first nonsteroidal aromatase inhibitors for treatment of breast cancer), Tanaproget (Nonsteroidal contraceptives), Etravirin, Dapivirin, Rilpivirin, Lersivirin (New class of anti-HIV drugs) and Citalopram (Selective serotonin transport inhibitor) has cyano/nitrile group.[7] Since there are adequate methods reported about *ortho*- selective cyanation of aromatics by various directing groups like amides, oximes, indoles, 2-phenyl pyridines, aromatic phosphonate esters, vinylic amides, tert-amines[8] but there is no study or report for distal C–H activation for cyanation reaction. 4th chapter of this thesis presents the template assisted *para*- selective approach for cyanation of toluene, optimization studies and exploring tolerance of methodology with respect to substituents on ring, mechanistic aspects & post synthetic application.



Scheme 10: Overview of current work

1.2.4. References:

1) For selective examples on C(sp^2)–H & C(sp^3)–H functionalization see: a) Phipps, R. J.; & Gaunt, M. J. *Science* **2009**, *323*, 1593-1597. b) Feng, Y.; & Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958-961. c) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463-466. d) Xie, Y.; Yang, Y. Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2012**, *14*, 1238-1241. e) Ren, Z.; Mo, F.; Dong, G.; *J. Am. Chem. Soc.* **2012**, *134*, 16991-16994. f) Ménard, G.; & Stephan, D. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 4409-4412. g) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135-12141. h) Gigant, N.; Bäckvall, J.-E. *Chem. Eur. J.* **2013**, *19*, 10799-10803. i) Hussain, N.; Frensch, G.; Zhang, J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3693-3697. j) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602-13605. k) Maity, S.; Agasti, S.; Earsad, A. M.; Hazra, A. Maiti, D.; *Chem. Eur. J.* **2015**, *21*, 11320-11324. l) Xu, Y.; Yan, G.; Ren, Z. Dong, G. *Nat. Chem.* **2015**, *7*, 829-834. m) Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Sci.* **2016**, *7*, 976-

983. n) Li, M.; González-Esguevillas, M.; Berritt, S.; Yang, X.; Bellomo, A.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 2825-2829. o) Liu, Y.; Yang, K.; Ge, H. *Chem. Sci*. **2016**, *7*, 2804-2808. p) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. q) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. r) White, M. C. Science **2012**, *335*, 807.

2) For selective examples on aliphatic C–H functionalization see: a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155. b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965-3972. c) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689-9714. d) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030-6032.

3) For selective examples on *β*-C–H functionalization see: a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542-9543. b) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc*. **2011**, *133*, 8070-8073. c) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187-4192. d) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc*. **2014**, *136*, 898-901 e) Tobisu, M.; Chatani, N. *Science* **2014**, *343,* 850. f) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc*. **2014**, *136*, 1789-1792. g) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944-3946. h) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 3496-3499.

4) For selective examples on directed γ-C–H functionalization see: a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Chem. Rev. 2002, 102, 5, 1359-1470. b) Fan, M.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12152-12155. c) Li, Q.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Adv. Synth. Catal.* **2014**, *356*, 1544-1548. d) Pasunooti, K. K.; Banerjee, B.; Yap, T.; Jiang, Y.; Liu, C.-F. *Org. Lett.* **2015**, *17*, 6094-6097. e) Li, M.; Yang, Y. Zhou, D.; Wan, D.; You, J. *Org. Lett.* **2015**, *17*, 2546-2549. f) Wang, P.-L.; Li, Y.; Wu, Y.; Li, C.; Lan, Q.; Wang, X.-S. *Org. Lett.* **2015**, *17*, 3698-3701. g) Han, J.; Zheng, Y.; Wang, C.; Zhu, Y.; Shi, D.-Q.; Zeng, R.; Huang, Z.-B.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 9297-9306. h) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.*

2015, *6*, 4610-4614. i) Hyde, A. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 177-180. j) Huang, D. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 5757-5761. k) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3-6. l) Franzoni, I.; Guenee, L.; Mazet, C. Chem. Sci. **2013**, *4*, 2619-2624. m) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830-6833. n) Zhou, X.-L.; Wang, V; Zhang, D.-W.; Liu, P.; Wang, C.-M.; Gong, L.-Z. *Org. Lett.* **2015**, *17*, 5120-5123. o) Jiang, H.; He, J.; Liu, T.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2055-2059.

5) For selected examples on C(sp^2) & C(sp^3) alkynylation see a) Liu, Y-H.; Liu, Y.-J.; Yan, S.-Y.; Shi, B.-F. *Chem. Commun.,* **2015**, *51*, 11650. b) Diederich, F.; Stang P. J.; Tykwinski, R. R. *Acetylene Chemistry: Chemistry, Biology and Material Science*, Wiley-VCH, Weinheim, **2005.** c) Anastasia L.; Negishi, E. *Chem. Rev.,* **2003**, *103*, 1979. d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev*., **2004**, *104*, 3079. e) Liu, C.; Zhang, H.; Shi W.; Lei, A.-W. *Chem. Rev*. **2011**, *111*, 1780 f) Brand, J. P.; Waser, J. *Chem. Soc. Rev.*, **2012**, *41*, 4165. g) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.,* **2011**, *111*, 2937. h) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci*., **2013**, *4*, 4187. i) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.-J.; Chen, F.-J. Shi, B.-F. *Angew. Chem., Int. Ed.,* **2013**, *52*, 13588. j) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.,* **2011**, *133*, 12984–12986. j) Al-Amin, M.; Arisawa, M.; Shuto, S.; Ano, Y.; Tobisu, M.; Chatani, N. *Adv. Synth. Catal.,* **2014**, *356*, 1631–1637. k) Wang, B.; Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.*, **2014**, *16*, 6260–6263. l) Wang, B.; He, G.; Chen, G. *Sci. China: Chem.*, **2015**, *58*, 1345–1348. m) Liu, T.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Angew. Chem., Int. Ed.,* **2017**, *56*, 10924–10927. n) He, J.; Wasa, M.; Chan, L. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.,* **2013**, *135*, 3387–3390. o) Ye, X.; Xu, C.; Wojtas, L.; Akhmedov, N. G.; Chem, H.; Shi, X. *Org. Lett*., **2016**, *18*, 2970–2973. p) Fu, H.; Shen, P.-X.; He, J.; Zhang, F.; Li, S.; Wang, P.; Liu, T.; Yu, J.-Q. *Angew. Chem., Int. Ed.*, **2017**, *56*, 1873–1876. q) Landge, V. G.; Parveen, A.; Nandakumar, A.; Balaraman, E. *Chem, Commun.*, **2018**, *54*, 7438.

6) a) Leow, D.; Li, G.; Mei, T.-S.; & Yu, J.-Q. *Nature*, **2012**, *486*, 518–522. b) Yang, Y. F.; Cheng, G. J.; Liu, P.; Leow, D.; Sun, T. Y.; Chen, P.; Zhang, X.; Yu, J. Q.; Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344–355. c) Bera, M.; Maji, A.; Sahoo, S. K.;

Maiti, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 8515–8519. d) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. *J. Am. Chem. Soc.* **2015**, *137*, 11888. e) Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A, Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751 –7755

7) a) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shoo, B. C. *J. Med. Chem.* **2010**, *53*, 7902. b) Hyland, J. C.; O'Connor, C. *J. Chem. Soc. Perkin Trans. 2, 1973*, 223-227. c) Swain, C. *J. Am. Chem. Soc.* **1947**, *69*, 2306. d) Das, B.; Reddy, C.; Kumar, D.; Krishnaiah, M.; Narender, R. *Synlett* **2010**, 391. e) Finholt, A. E., Jacobson, E. C.; Ogard, A. E.; Thompson, P. *J. Am. Chem. Soc.* **1955**, *77*, 4163. f) Rappoport, Z. *The Chemistry of the Cyano Group*, Interscience Publishers, New York, **1970**. g) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, *4*, 277. h) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298. i) Dalton, J.R.; Regen, S. L. *J. Org. Chem.* **1979**, *44*, 4443. j) Chinchilla, R.; Najera, C. *Chem. Rev.,* **2014**, *114*, 1783-1826.

8) For selected examples of Pd, Ru, Rh, co-catalyzed directed C(sp^2)–H cyanation, see: a) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714. b) Sato, N.; Suzuki, M. *J. Heterocycl. Chem.* **1987**, *24*, 1371. c) Nair, V.; Purdy, D. F.; Sells, T.B. *J. Chem. Soc. Chem. Commun.* **1989**, 878. d) Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118. e) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. e) Jia, X. F.; Yang, D. P.; Zhang, S. H.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. f) Jia, X.F.; Yang, D. P.; Wang, W. H.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009**, *74*, 9470. g) Mishra, A.; Vats, T. K.; Deb, I. *J. Org. Chem.* **2016**, *81*, 6525. h) Chaitanya, M.; Anbarasan, P. *Org. Lett.* **2015**, *17*, 3766. i) Gong, T. J.; Xiao, B.; Cheng, W.-M.; Sun, W.; Xu, J.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 10630. j) Yu, D.-G.; Gensch, T.; Azambuja, F.; Vasquez-Cespedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722. k) Mcmanus, J. B.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 2880. l) Shu, Z.; Ji, W.; Wang, X.; Zhou, Y.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 2186. *Angew. Chem.* **2014**, *126*, 2218. m) Zhang, Y.-H.; Shi, B.-F. Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072 n) Liu, L.-Y. Yeung, K.-S.; Yu, J.-Q *Chem. Eur. J.*, **2019**, *25*, 2199-2202.

Chapter 2

Chelation Assisted Palladium Catalysed Arylation of Aliphatic Carboxylic Acid Derivatives

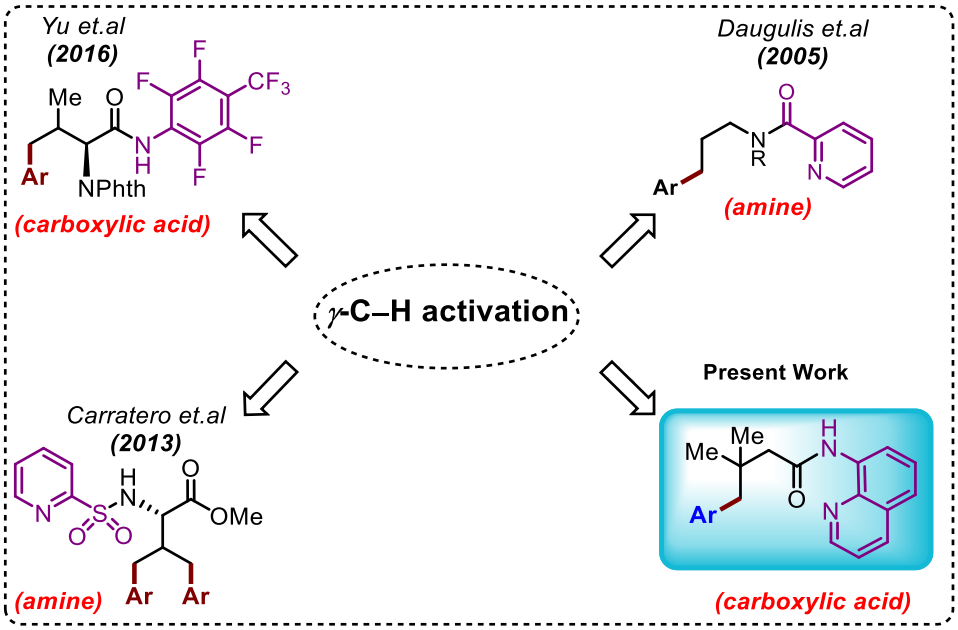
Abstract:

A palladium (II)-catalyzed protocol for highly regioselective remote γ-C–H arylation of aliphatic carboxylic acid has been developed. 8-aminoquinoline as intramolecular bidentate chelator was found to be suitable for this γ-C–H arylation. Various aryl iodides were compatible in regioselective mono-arylated products with a negligible diarylation. Functional group tolerance, easy-to-handle reaction conditions make this method attractive.

2.1 Introduction

A series of success stories over the decades serve as representative paradigms in aliphatic C(sp^3)–H activation which reflect the immense applicative potential for envisioning a C–H bond as an ideal functional core. This has allowed a superior scope of selective functionalization at sp^2/sp^3 carbon centres in the presence of an organometallic catalyst in complex molecular environment[1] but still activation of a sp^3 carbon centre is quite problematic due to its high bond dissociation energy (415 kJ/mol for C–H bond of methane) and abundance of C–H bonds in molecule. Asserting the compliance of such a bond, with absence of a polarizable π-electron cloud and a low-lying σ^* orbital, to undergo a metal-catalysed cleavage is seemingly tedious. A series of strategies implemented over the years has thus helped in the formidable task of making this inert class of C–H bonds participate actively in chemical transformations. One among these strategies allowing the formation of a carbon-carbon bond at an unactivated alkyl C–H centre is by use of a metal-catalysed chelation approach. Formation of a five-membered metallacycle has led to a highly selective β-C–H functionalization. Bidentate 8-aminoquinoline directing group in this regard has been beneficial which can be corroborated by recent literature reports.[1g, 2] Successful β-C–H arylation/alkylation *via* chelation approach in presence of a variety of metal salts has been demonstrated by Chatani, Ge and others.[1d, 3] A wish to farther the scope of this protocol into taming more distal C–H bonds, *viz.* γ-C–H bonds, to undergo functionalization was foreseeable. Progress on γ-C–H functionalization is thus endeavoured by various research groups.[4] γ-C–H arylation of amine by 2-picolinic acid auxiliary was performed by Daugulis *et. al* (Scheme **1**).[2a-b] Pioneering reports by Corey on the γ-C–H functionalization of *N*-phthaloyl-α-amino amides as well as by Chen hold immense significance concerning their utility in drug research and development.[5] Seminal work by Carratero in performing remote C(sp^3)–H arylation on dipeptides by using an *N*-(2-pyridyl)sulphonamide based chelating model is noteworthy.[6] Yu developed a method by promoting the effective use of ligand controlled strategy towards highly site selective arylation at both sp^2 and sp^3 carbon centres.[7] This was demonstrated in a one-pot sequential diarylation of alanine derivatives using a C=O-NHAr$_F$ (Ar$_F$ = C_6F_4-(4-CF_3)) auxiliary at the γ-C–H bond.[8] γ-C–H arylation using amino acid as the

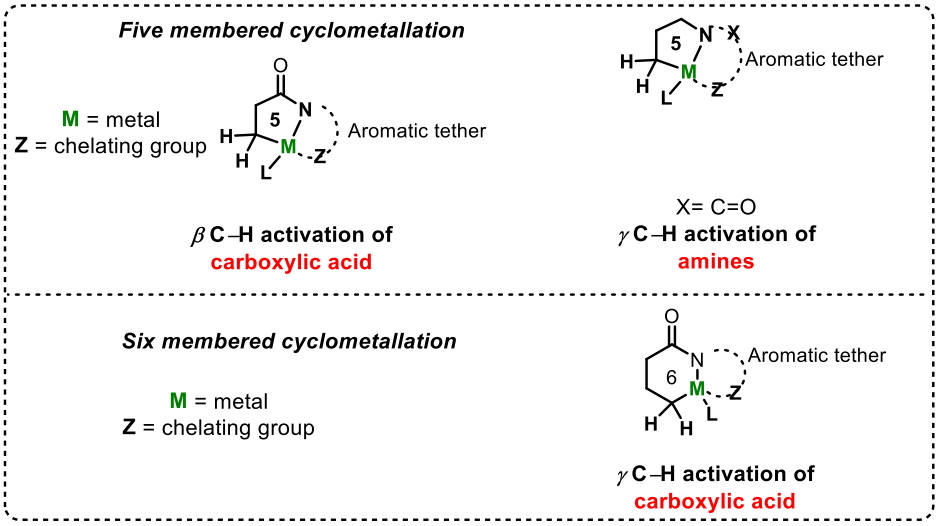
directing group had been also reported which was brought in by changes in the design of the ligands used.[9] In the meantime Yu made a successful attempt towards the distal γ-C–H arylation of carboxylic acid derivatives using $CONHAr_F$ directing group.[10] Arylation was performed selectively at the γ-position of valine, leucine and iso-leucine derivatives. An intricate tuning of ligand helped to overcome the necessity of the sterically bulky phthalimido group, which was primarily required to attend the required metallated intermediate. During this time, I was developing a novel route to activate the remote aliphatic γ-C–H bond of carboxylic acids. After many unsuccessful attempts I was able to fine tune reaction condition for selectively arylation at the remote γ-position of aliphatic carboxylic acids using 8-aminoquinoline as bidentate chelating auxiliary with help of palladium(II) catalyst in which both amine and quinoline nitrogen chelate with the metal.



Scheme 1: Directing group approach for γ-C(sp^3)–H arylation

2.2 Results and Discussion

γ-C–H activation of amines requires a five membered metallacycle, the same in case of carboxylic acids would precede a six membered cyclometallation pathway (Scheme **2**).

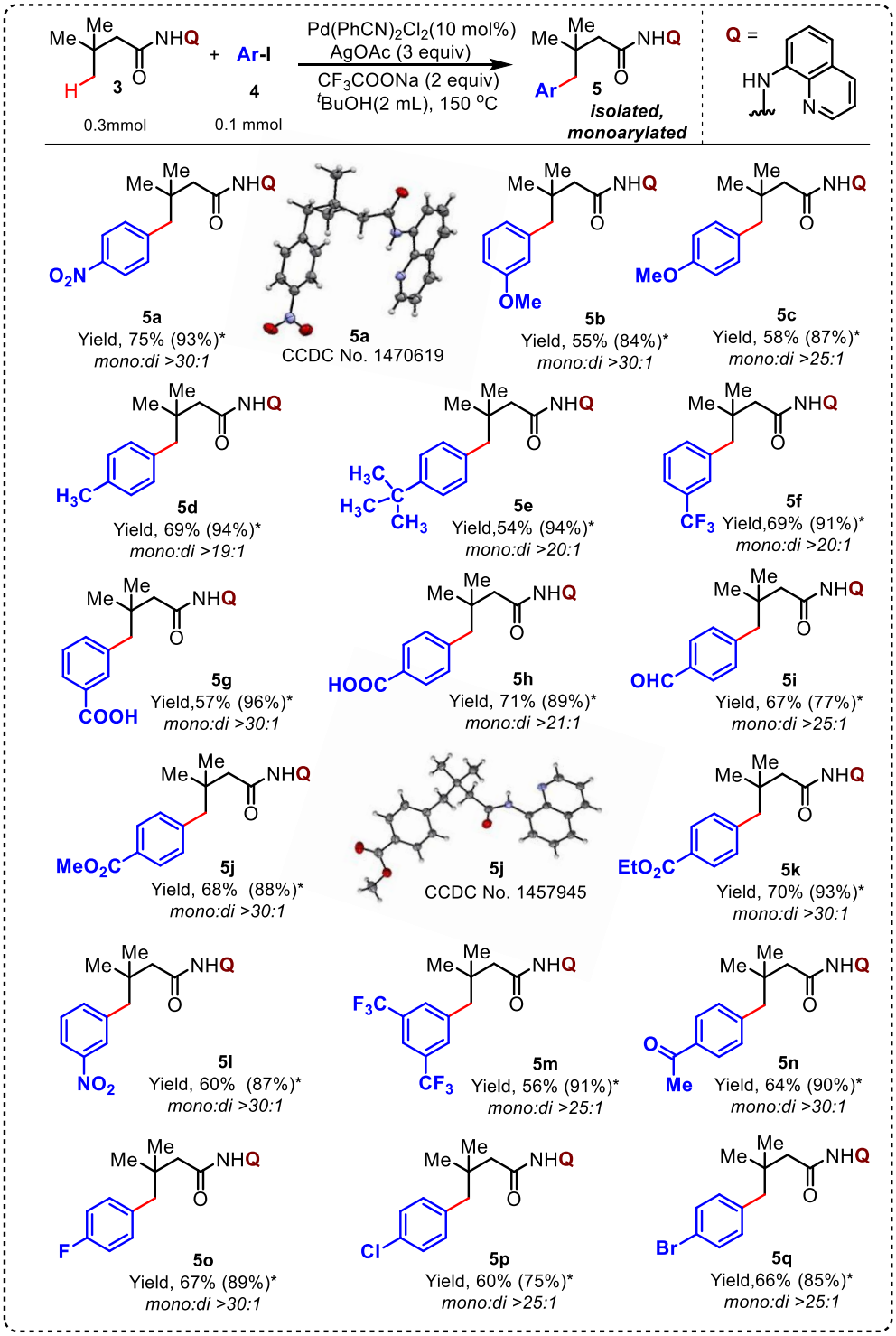


Scheme 1: Formation of metallacycle for β- & γ-C–H activation.

The metal pre-catalyst would undergo an increase in its oxidation state by two while forming the metallacycle. This will require a donor group in the intermediate metallacycle which could stabilize the higher oxidation state of the metal. Use of exogenous ligands was shown to be useful for this type of transformation in earlier reports.[10] In this case, bidentate 8-aminoquinoline was first tethered to a linear *n*-butyl carboxylic acid through an amide linkage that would provide an active chelation assistance with palladium. Unfortunately, this yielded β-arylated products exclusively. Later, I tethered *tert*-butylacetic acid with 8-aminoquinoline via amide linkage for arylation with 4-nitroiodobenzene as arylating source in presence of $Pd(OAc)_2$ as catalyst and AgOAc as oxidant. Interestingly, regioselective γ-arylation was observed (NMR yield, 50%) with a near exclusive formation of mono-arylated product (*mono*:*di*>30:1). With these initial results at hand, detailed optimization of the reaction condition was carried out. A sequential screening of the palladium salts and the oxidants resulted in $Pd(PhCN)_2Cl_2$ and AgOAc as the perfect catalyst-oxidant combination for the reaction. Use of a bulky polar hydroxylic solvent like *t*-BuOH was found to be beneficial for the reaction. Presence of a bulky anion like trifluoroacetate was useful for the reaction. Inclusion of exogenous

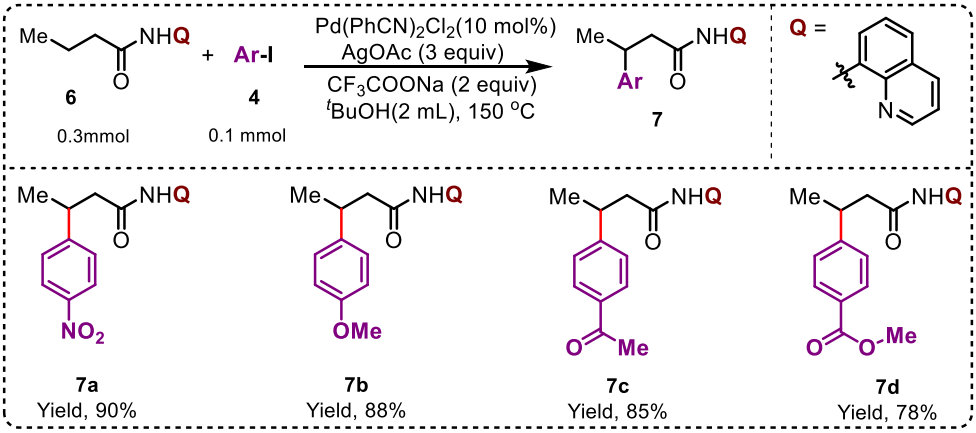
ligand failed to provide any additional improvements on the reaction condition. Moreover, γ-arylation of carboxylic acids was unknown in absence of any ligands till date and therefore had remained as a challenge.[10] However, a prudent choice of the directing group has allowed this target to be achievable. The reaction condition employed in this study completely nullified the requirement of any exogenous ligands. This ensured an enhanced atom-economical catalytic conversion and an easier reaction condition without any compromise of the yield and mono-selectivity. Bidentate chelation by the tethered 8-aminoquinoline ensured an apt placement of the palladium catalyst to maintain the required six-membered metallacycle (Scheme **2**). Presence of this directing group provided a strong coordination mode that helped in stabilizing the intermediary high oxidation states of palladium. Addition of exogenous bulky ligand therefore did not help in improving the yield as much since it may hinder the intramolecular chelation by the 8-aminoquinoline group.[11] This led to a facile activation of the remote γ-C–H bond of the aliphatic carboxylic acid and the imminent γ-arylation with impressive mono-selectivity. With the optimized condition, I went on to contemplate the scope of the substrates (Scheme **3**). Both electron-donating and electron-withdrawing aryliodides were found to be effective for the regioselective γ-arylation in moderate to good yields. Electron rich arene containing substituents like 3-methoxy (**5b**), 4-methoxy (**5c**), 4-methyl (**5d**) as well as 4-*tert*-butyl groups (**5e**) underwent successful γ-arylation with an excellent ratio in favour of mono-arylated products relative to diarylation. Aryliodides containing electron-withdrawing groups such as trifluoromethyl, carboxyl, formyl, esters and keto groups were also found to be effective (**5f-5n**). Fluorine containing aryl groups have been found to be important in agrochemicals and pharmaceuticals. Notably, 4-fluorophenyliodide gave mono-arylated product (**5o**) with excellent selectivity and moderate yields when subjected to the above reaction condition. Parallel to this, other halogens like chloro and bromo substituted phenyliodides also provided γ-mono-arylated products with enhanced selectivity (**5p & 5q**). However, iodo derivatives of heteroaryl, phenol and benzyl alcohols failed to undergo the arylation reaction as suitable coupling partners. Initial attempts for arylation with *n*-butylamides had led to the exclusive formation of β-arylated products with a variety of aryl iodides (Scheme **4**, **7a**-**7d**).

However, substrates with a β-alkyl/aryl substituent (Scheme **5**, **9a**-**9l**) showed high γ-regioselectivity for arylation.



Scheme 2: Arylation of carboxylic acid derivatives

Substrates like isovaleric acid were also tested which yielded mono-γ-arylated products (**9f**-**9i**). Further, using the initially obtained β-arylated products, γ-arylation was performed. Gratifyingly, exclusive formation of mono-γ-arylated products were obtained (**9j**-**9l**). Interestingly, γ-cyclization was obtained for mesitoic acid amide which proceeded via intramolecular cyclization (**9m**). Examination of the carboxylic acid scope was then carried out with *N*-protected amino acids such as L-valine and L-isoleucine despite the

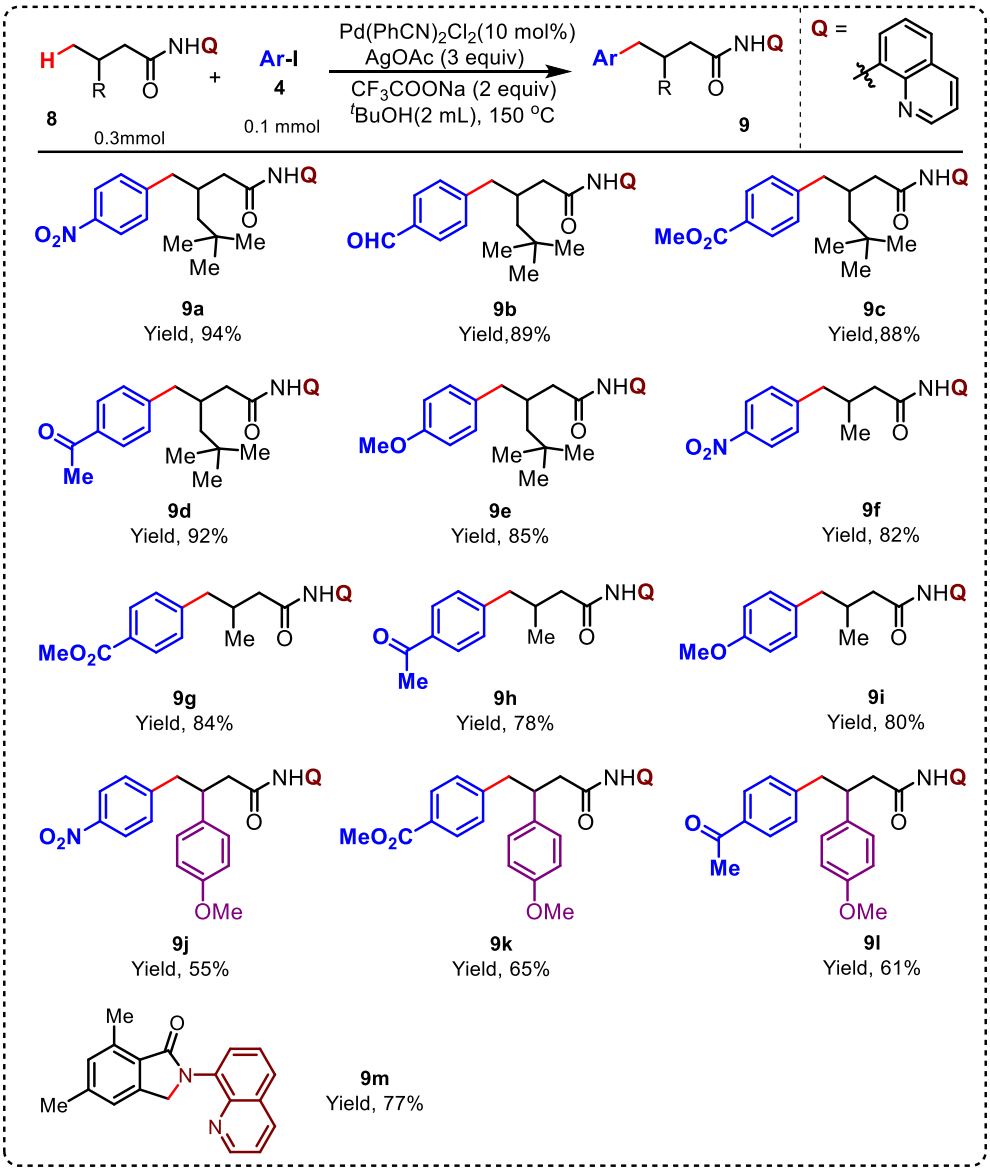


Scheme 3: β-arylation with linear carboxylic acids.

presence of a β-hydrogen, both the amino acids yielded successful γ-arylation in good to excellent yields (Scheme **6**, **11a**-**11h**). Careful ^{1}H-NMR analysis revealed that products were formed in good diastereomeric ratio. Aryliodides with electron-donating or electron-withdrawing substituents underwent the transformation with exceptional mono-selectivity.

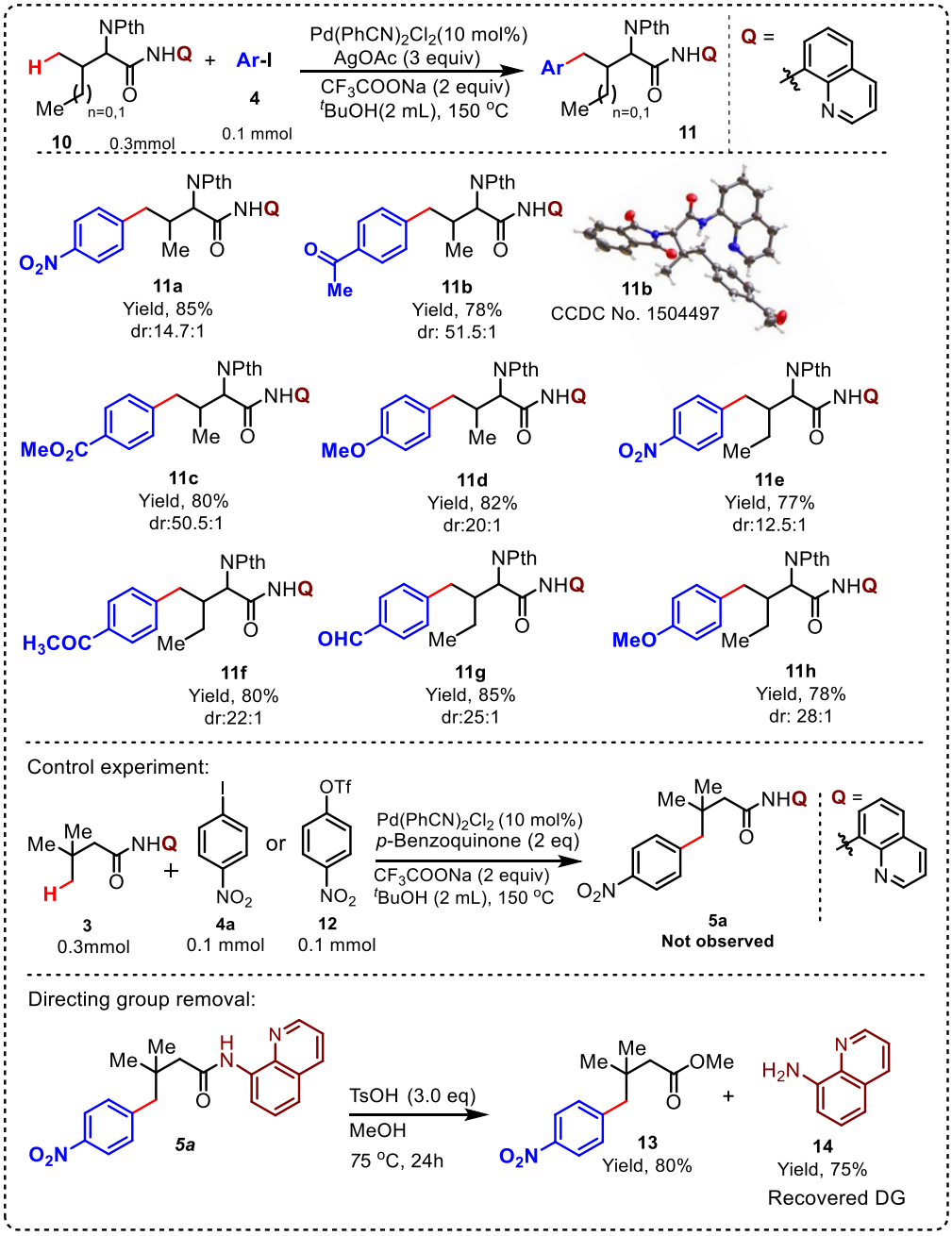
To gain more insight into the plausible reaction mechanistic pathway control experiments were performed to understand the role of AgOAc. In independent set of reactions, replacement of AgOAc either by air, oxygen or N_2 did not give corresponding product. Replacing AgOAc with *p*-benzoquinone as an oxidant with 4-nitroiodobenzene (**4a**) as coupling partner did not yield any product. Also replacing 4-nitroiodobenzene (**4a**) with 4-nitrophenyltriflate (**12**) and using *p*-benzoquinone as the oxidant failed to produce **5a**. Thus, arylhalide is a potent arylating source for this protocol. (Scheme **7**). Moreover, AgOAc exhibits a dual role by probably acting as halide scavenger as well as oxidant. Further application of the protocol was demonstrated by facile removal of the 8-aminoquinoline directing group by *p*-toluenesulphonic acid in MeOH at reflux conditions

which furnished the corresponding aliphatic methoxy ester (Scheme **7**, **13**) in 80% yield along with recovery of the 8-aminoquinoline moiety (**14**) in 75% yield.



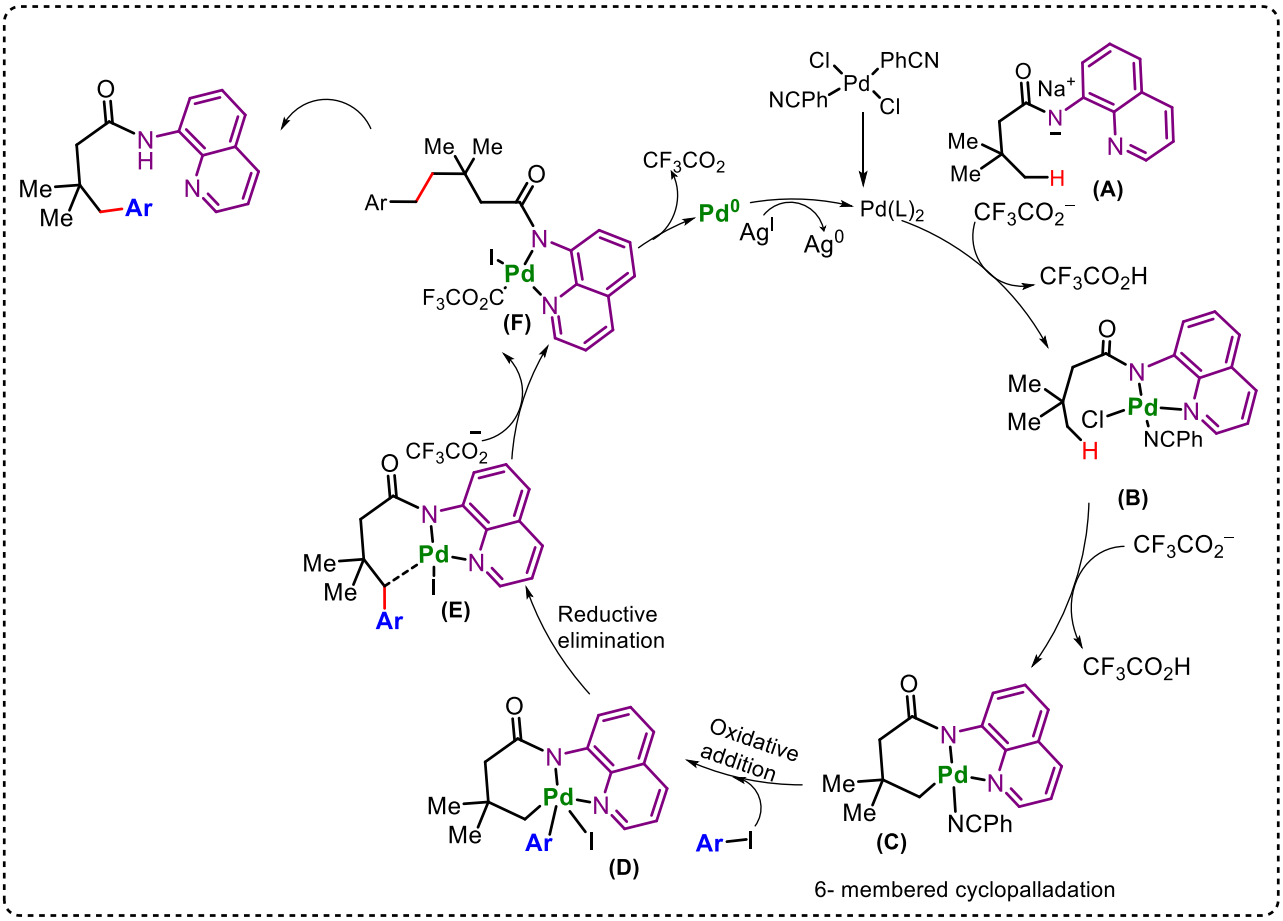
Scheme 4: Scope of various β unprotected carboxylic acids for γ-C–H arylation

Based on previous literature reports for understanding of reaction mechanism, reaction proceeds via abstraction of N-H proton on amide to chelate with metal (Scheme **8**, **A**). Later amino group from bidentate 8-aminoquinoline chelates with metal forming (**B**) which in presence of sodium trifluoroacetate abstracts *sp*^{3} C–H proton on substrate forming 6 membered C–H activation complex (**C**) which was proved by X-Ray diffraction technique



Scheme 5: Scope of N-protected amino acids for γ-C–H arylation, control experiment and synthetic utility.

of single crystal in similar analogous study in my research group after publishing this work. The complex (**C)** can undergo oxidative addition with aryl iodide to form Pd(II) complex (**D**) which on reductive elimination transfers aryl group to substrate and subsequently releasing the arylated product. Reduced palladium upon oxidation by Ag regenerate in its Pd(II) state completing mechanistic cycle.



Scheme 7: Plausible reaction mechanism

2.3 Conclusion:

In summary, this chapter described a palladium-catalyzed protocol for selective γ-C–H arylation of carboxylic acids. This strategy utilizes the chelation potential of 8-aminoquinoline for the site selective C–H activation of carboxylic acids. Prudent application of a suitable directing group has eliminated the necessity of expensive exogenous ligands for γ-C–H arylation rendering the protocol as cost effective and economical. A possible reaction mechanism predicted about the protocol gives the understanding about the reactivity.

2.4 Experimental details

2.4.1 General Consideration

2.4.1.a. Reagent information:

Unless otherwise stated, all the reactions were carried out in screw cap reaction tube under air atmosphere with magnetic stirring. Palladium salts were purchased from Alfa Aesar and used directly. All oxidants were purchased from Alfa Aesar. All the solvents were bought from MERCK and used directly. All the other reagents were purchased from commercial source and used as received. For column chromatography silica gel (60-120 mesh and 100-200 mesh) was supplied from SRL Co. During elution hexane and ethyl acetate mixture was used. Thin layer chromatography was performed on EMD Chemicals Si 60 F_{254}. TLC plates (silica gel 60F_{254}) supplied from MERCK.

2.4.2.b. Analytical information:

All isolated compounds were characterized by ^{1}H, ^{13}C NMR spectroscopy, HR-MS, FT-IR. Unless otherwise stated, all Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 and 500 MHz instrument. The references used for NMR is tetramethylsilane (TMS) for ^{1}H and ^{13}C NMR. ^{1}H NMR data are reported in units, parts per million (ppm) and were recorded relative to the signals for residual chloroform (7.26 ppm). ^{13}C NMR data were obtained with ^{1}H decoupling and were recorded relative to the signals for residual chloroform (77.36 ppm). NMR yield was calculated using 1,3,5-trimethoxybenzene (TMB) as the internal standard. GC yield was calculated by using n-Decane as internal standard. High-resolution mass spectra (HRMS) were recorded on a micro-mass ESI TOF (time of flight) mass spectrometer.

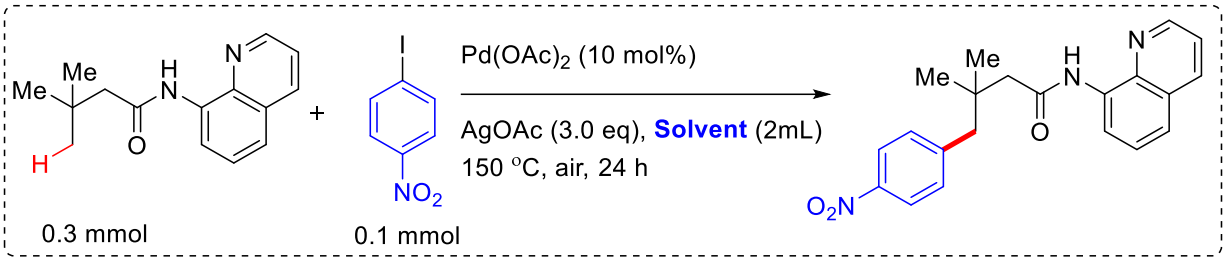
2.4.3.c. Description of reaction tube:

Pictorial description of reaction tube for arylation of amide: Fisherbrand Disposable Borosilicate Glass Tubes (16*125mm) with Threaded End (Fisher Scientific Order No. 1495935A) [left hand side]; Kimble Black Phenolic Screw Thread Closures with Open Tops (Fisher Scientific Order No. 033407E) [right hand side, top]; Thermo Scientific National PTFE/Silicone Septa for Sample Screw Thread

Caps (Fisher Scientific Order No. 03394A) [right hand side, bottom].

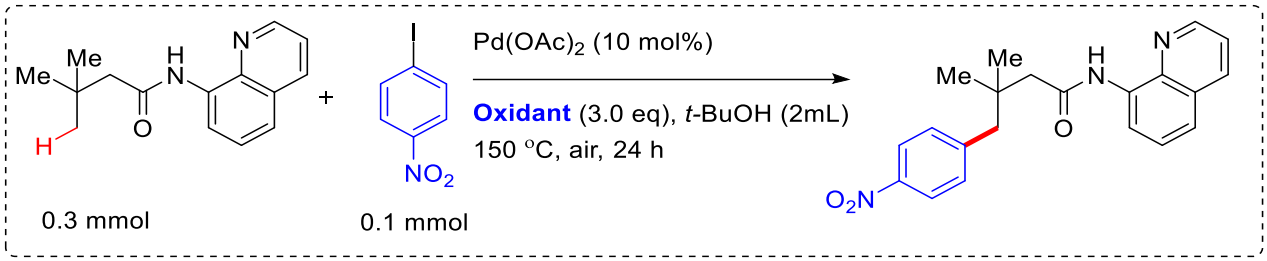
2.4.2. Optimization details

Table 1: Optimization of solvents



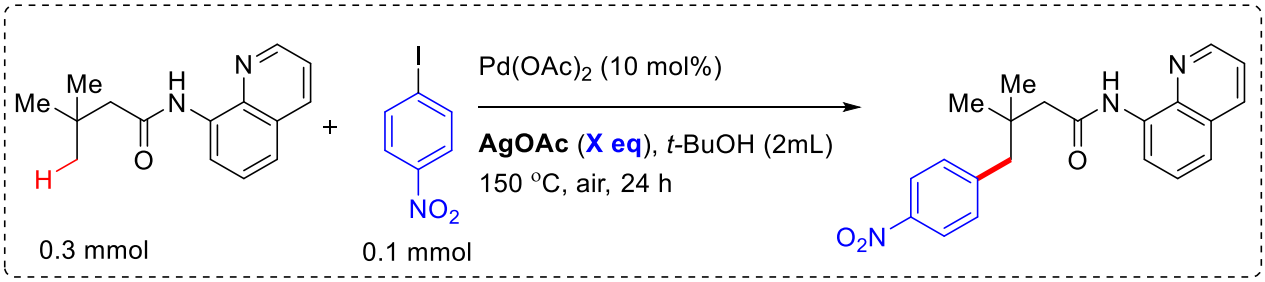
Entry	Solvent	NMR Yield (%)
1.	HFIP	40
2.	*iso*-amyl alcohol	18
3.	CF_3CH_2OH	32
4.	hexane-1-ol	17
5.	1,4 butanediol	12
6.	**^{t}BuOH**	**50**
7.	EtOH	13
8.	^{i}PrOH	35
9.	DCE	5
10.	MeOH	21
11.	*tert*-amyl alcohol	30
12.	Trifluorotoluene	--
13.	Cyclohexane	--
14.	Toluene	05
15.	2-methyl THF	--
16.	Benzene	--
17.	THF	--
18.	1,4-dioxane	25
19.	DMF	5

Table 2: Oxidant optimization:



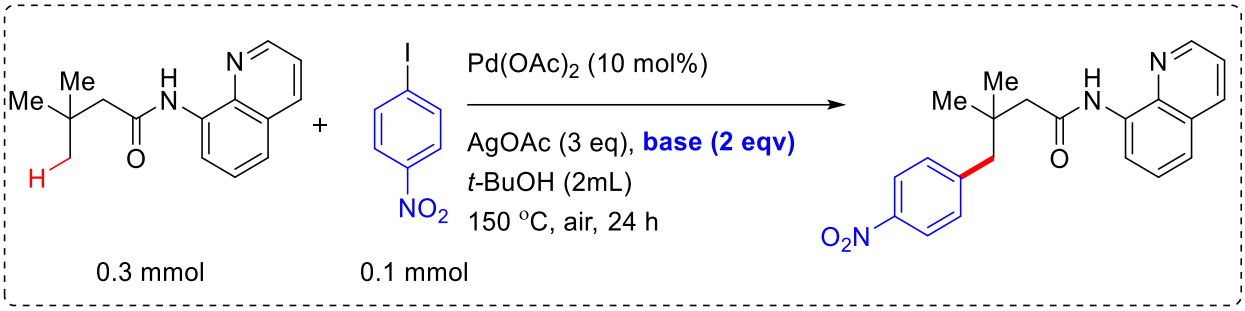
Entry	Oxidant	NMR Yield (%)
1.	AgI	20
2.	**AgOAc**	**50**
3.	Ag_2CO_3	45
4.	$AgNO_3$	20
5.	Ag_2SO_4	15
6.	AgOTf	25
7.	Benzoquinone	--
8.	CuO	14
9.	CuOAc	32
10.	CuCl	--
11.	CuF_2	20
12.	$Na_2S_2O_8$	--
13.	DDQ	--

Table 3: Oxidant amount optimization:



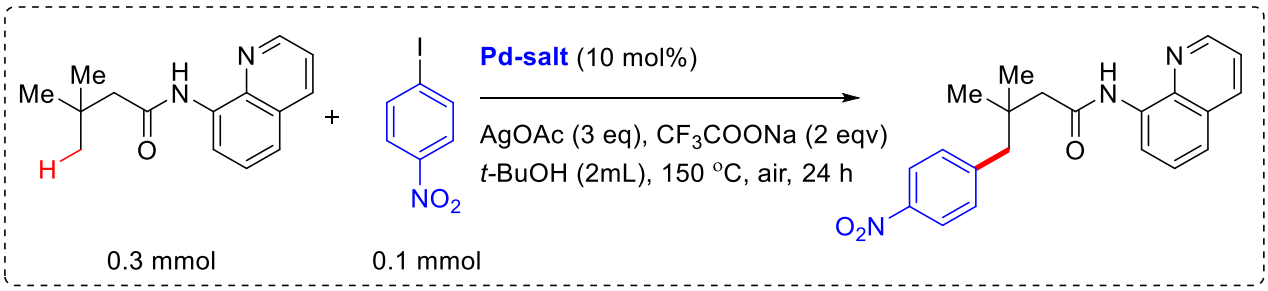
Entry	AgOAc (X eqv.)	NMR Yield (%)
1.	1.0	45
2.	2.0	50
3.	2.5	52
3.	**3.0**	**57**
4.	3.5	48
5.	4.0	40
6.	4.5	35

Table 4: Base optimization:



Entry	Base	NMR Yield (%)
1.	CsF	62
2.	K_2CO_3	45
3.	$NaHCO_3$	30
4.	KOAc	68
5.	**CF_3CO_2Na**	**70**

Table 5: Pd-salt optimization:



Entry	Pd-salt	GC Yield (%)
1.	$Pd(OAc)_2$	70
2.	$Pd(OPiv)_2$	55
3.	$PdCl_2$	50
4.	***trans*-$Pd(PhCN)_2Cl_2$**	**75**
5.	$Pd(CH_3CN)_2Cl_2$	60
6.	$Pd(TFA)_2$	62
7.	$PdSO_4$	30

Table 6: Ligand optimization:

Entry	Ligand	NMR Yield (%)

1.	Ac-Gly-OH	14
2.	Ac-Ile-OH	41
3.	Ac-Val-OH	43
4.	Boc-Val-OH	45
5.	PPh_3	44
6.	1,10-Phenanthroline	51
7.	TMEDA	27
8.	Li-Yu's *t*-butyl quinoline	69
9.	BINAM	33
10.	**Without ligand**	**75**

2.4.3. General procedures

2.4.3.a. General procedure for preparation of N-pthalimide protected amino acid: [1]

A solution of amino acid (10 mmol), phthalic anhydride (12 mmol), NEt_3 (12 mmol) and toluene (10 mL) was refluxed for 12-24 h in a round-bottomed flask. After completion of reaction solvent was removed under vacuum and ethyl acetate was added then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1-2 at 0 °C. The mixture was extracted with EtOAc (30 mL × 3). The combined organic layers was washed with brine, dried with MgSO4, filtrated and concentrated affording the crude product which was purified by flash column chromatography (silica gel, hexane/EtOAc 3/1 to 1/1) to give pure product as a white solids which was further used to prepare corresponding acid chlorides by usual procedure and further to prepare amide as per procedure 2.4.3.b

2.4.3.b. General procedure for preparation aliphatic 8-aminoquinoline amide (3), (6), (8, 8') and (10, 10') : [2,3]

In a clean oven dried 100 mL round bottomed flask equipped with stir bar, 8-aminoquinoline (10 mmol) was taken and evacuated and purged with N_2. Later dry dichloromethane was added. Subsequently NEt_3 (10 mmol) was added via syringe and reaction mixture was cooled to 0 ^oC. Now, corresponding aliphatic acid chloride (10 mmol) in dichloromethane was added dropwise. Reaction mixture was allowed to stirred

for 12 h and upon completion of reaction (monitored by TLC, complete consumption of 8-aminoquinoline), was quenched with saturated NH_4Cl and extracted in ethyl acetate thrice (3 X 50 mL). Organic layer was dried over Na_2SO_4 and solvent was removed under *vacuum* and purified with column chromatography by eluent as petroleum ether/ethyl acetate (5:95 v/v).

[1] Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi *Angew. Chem., Int. Ed.* **2013**, *52*, 13588-13592.
[2] M. Wasa, K. M. Engle, J.-Q. Yu *J. Am. Chem. Soc*. **2009**, *131*, 9886.
[3] For preparation of compound **12:** D. E. Frantz, D.G. Weaver, J. P. Carey, M. H. Kress, U. H. Dolling *Org. Lett,* **2002**, *4*, 4717-4718.

2.4.3.c. General procedure for palladium-catalyzed γ-arylation of carboxamides:

In a clean, oven–dried screw cap reaction tube containing magnetic stir-bar, 3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (0.3 mmol), iodoarene (0.1 mmol), $Pd(PhCN)_2Cl_2$ (10 mol %, 0.01 mmol), AgOAc (3 eqiv. 0.3 mmol), CF_3CO_2Na (2 eqiv. 0.2 mmol) were weighed. Solid reagents were weighed before the liquid reagents. Then ^{t}BuOH (2.0 mL) was introduced in the reaction tube through syringe and the tube was tightly closed by screw cap fitted with rubber septum. Finally, the reaction tube was placed in a preheated oil bath at 150 °C to stir vigorously (900 rpm) for 24 h. After completion, the reaction mixture was cooled to room temperature and filtered through celite with aid of ethyl acetate (15 mL). This filtrate was concentrated under reduced pressure and purified by column chromatography through silica gel using petroleum ether/ethyl acetate as eluent.

2.4.3.d. General procedure for removal of 8-aminoquinoline directing group:

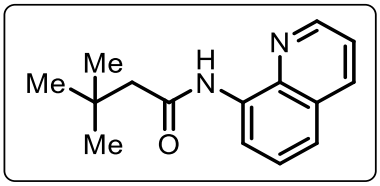
In a clean, oven–dried screw cap reaction tube containing magnetic stir-bar arylated

product **5a** (1 mmol) and *p*-Toluenesulfonic acid monohydrate (3 mmol) was added. To this 2 mL of methanol was added. Reaction was allowed to stir for 24 h at 75 °C. After completion (TLC monitoring) reaction was cooled, filtered through Celite and evaporated under vacuum and purified with column chromatography by eluent as petroleum ether/ethyl acetate (5:95 v/v) to give **13** in 80% along with recovered 8-aminoquinoline **14** in 75% yield.

2.5 Characterization data:

3,3-Dimethyl-*N*-(quinolin-8-yl)butanamide (3):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky slight brown liquid; isolated yield: 75%



^{1}H NMR (500 MHz, Chloroform-*d*) δ: 9.74 (s, 1H), 8.80 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.77 (dq, *J* = 4.0, 1.5 Hz, 1H), 8.10 (ddd, *J* = 8.2, 1.5 Hz, 1H), 7.50 (t, *J* = 7.9, 1H), 7.44 (d, *J* = 8.2, 1H), 7.40 (ddd, *J* = 8.2, 4.2, 1H), 2.41 (s, 2H), 1.15 (s, 9H).

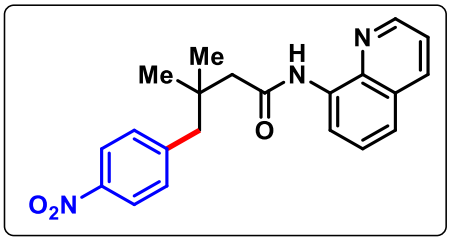
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.86, 148.37, 138.59, 136.54, 134.80, 128.14, 127.62, 121.78, 121.54, 116.52, 52.38, 31.52, 30.14.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{15}H_{18}N_2ONa$ *m/z* 265.1311 and found *m/z* 265.1328

IR (thin film, cm^{-1}): 3354, 2955, 2910, 2865, 1635, 1522, 1400, 1338, 1212, 825, 747, 665.

3,3-Dimethyl-4-(4-nitrophenyl)-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5a):

Eluent: ethyl acetate/petroleum ether (4:96 v/v); appearance: sticky slight brown liquid; isolated yield: 75%



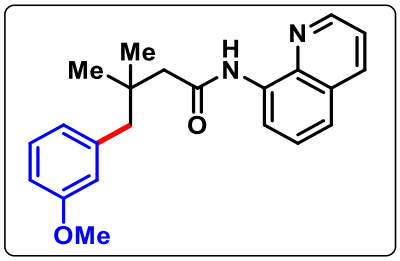
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.80 (m, 2H), 8.16 (dd, *J* = 8.2, 1.1 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 2H), 7.53 (m, 2H), 7.45 (dd, *J* = 8.5, 3.1 Hz, 3H), 2.95 (s, 2H), 2.41 (s, 2H), 1.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.35, 148.53, 147.17, 146.88, 138.64, 136.71, 134.62, 131.92, 128.26, 127.65, 123.31, 121.97, 121.96, 116.75, 49.18, 47.27, 35.42, 27.98.
HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{21}H_{21}N_3O_3Na$ *m/z* 386.1475 and found *m/z* 386.1475.

IR (thin film, cm^{-1}): 3355, 3019, 2961, 2929, 2870, 1679, 1519, 1424, 1345, 1215, 826, 749, 668.

4-(3-Methoxyphenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5b):

Eluent: ethyl acetate/petroleum ether (8:92 v/v); appearance: sticky slight brown liquid; isolated yield: 55%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.83 (d, *J* = 7.5 Hz, 1H), 8.80 (m, 1H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.50 (m, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.85 (m, 2H), 6.79 (m, 1H), 3.79 (s, 3H), 2.79 (s, 2H), 2.45 (s, 2H), 1.16 (s, 6H).

13C NMR (126 MHz, CDCl3) δ: 170.89, 159.48, 148.46, 140.57, 138.68, 136.67, 134.84,

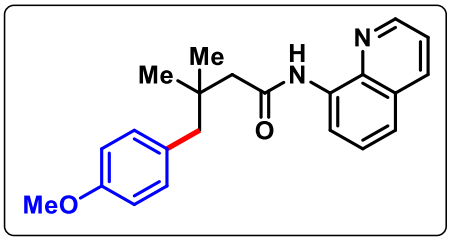
129.00, 128.26, 127.73, 123.72, 121.89, 121.70, 116.97, 116.70, 111.68, 77.61, 77.36, 77.11, 55.45, 49.98, 48.55, 35.24, 27.83.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{22}H_{24}N_2O_2Na$ *m/z* 371.1730 and found *m/z* 371.1727.

IR (thin film, cm^{-1}): 3360, 3010, 2958, 2939, 2870, 1680, 1598, 1526, 1484, 1383, 1261, 861, 825, 755, 669.

4-(4-Methoxyphenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5c):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky slight brown liquid; isolated yield: 58%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.84 – 8.79 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 2.74 (s, 2H), 2.42 (s, 2H), 1.13 (s, 6H).

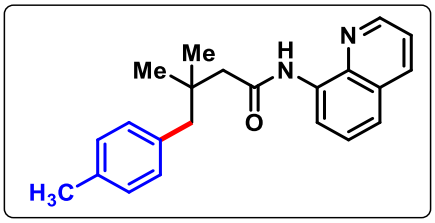
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.96, 158.29, 148.42, 138.64, 136.65, 134.81, 132.05, 130.99, 128.23, 127.69, 121.86, 121.67, 116.67, 113.51, 55.48, 49.82, 47.59, 35.24, 27.62.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{22}H_{24}N_2O_2Na$ *m/z* 371.1730 and found *m/z* 371.1725.

IR (thin film, cm^{-1}): 3356, 3016, 2959, 2939, 2870, 1678, 1611, 1523, 1484, 1389, 1285, 866, 834, 761, 670.

3,3-Dimethyl-*N*-(quinolin-8-yl)-4-(*p*-tolyl)butanamide (Scheme 3, entry 5d):

Eluent: ethyl acetate/petroleum ether (8:92 v/v); appearance: sticky slight brown liquid; isolated yield: 69%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.81 (s, 1H), 8.82 (dd, *J* = 10.4, 2.7 Hz, 2H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.56 (m, 2H), 7.48 (dd, *J* = 8.2, 4.3 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 2.89 (s, 2H), 2.59 (s, 3H), 2.44 (s, 2H), 1.14 (s, 6H).

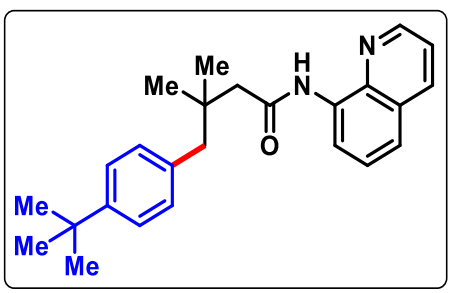
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.74, 148.34, 145.03, 137.31, 135.58, 134.53, 134.03, 131.41, 128.42, 128.28, 127.93, 122.01, 121.93, 117.47, 49.64, 48.00, 35.43, 27.89, 26.92.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{22}H_{24}N_2ONa$ *m/z* 355.1781 and found *m/z* 355.1783.

IR (thin film, cm^{-1}): 3361, 3020, 2971, 2911, 2850, 1668, 1600, 1512, 1475, 1399, 1259, 870, 841, 765, 679.

4-(4-(tert-Butyl)phenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5e):

Eluent: ethyl acetate/petroleum ether (2:98 v/v); appearance: semi solid, Isolated yield: 54%



^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ: 9.77 (s, 1H), 8.84-8.79 (m, 2H), 8.16 (dd, *J* = 8.3, 1.7

Hz, 1H), 7.58 – 7.52 (m, 1H), 7.50 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.32- 7.28 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 2.76 (s, 2H), 2.44 (s, 2H), 1.32 (s, 9H), 1.15 (s, 6H)

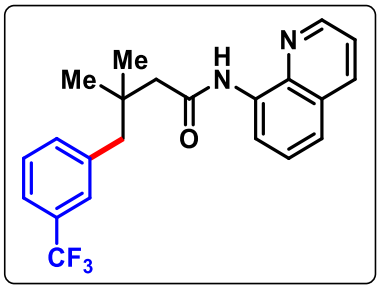
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.05, 149.11, 148.45, 138.71, 136.71, 135.82, 134.89, 130.85, 128.29, 127.78, 125.03, 121.89, 121.69, 116.74, 50.07, 48.26, 35.31, 34.69, 31.76, 27.70.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{25}H_{30}N_2ONa$ *m/z* 395.2250 and found *m/z* 395.2251.

IR (thin film, cm^{-1}): 3361, 3020, 2971, 2911, 2850, 1668, 1600, 1512, 1475, 1399, 1259, 870, 841, 765, 679.

3,3-Dimethyl-*N*-(quinolin-8-yl)-4-(3-(trifluoromethyl)phenyl)butanamide (Scheme 3, entry 5f):

Eluent: ethyl acetate/petroleum ether (1:99 v/v); appearance: sticky slight green liquid; isolated yield: 69%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.81 (s, 1H), 8.82 (m, 2H), 8.17 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.51 (m, 4H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 2.89 (s, 2H), 2.43 (s, 2H), 1.14 (s, 6H).

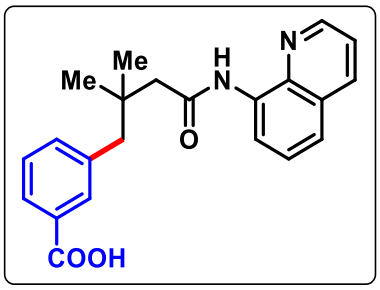
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.58, 148.45, 139.93, 138.57, 136.87, 134.68, 134.57, 130.59, 130.34, 128.56, 128.31, 127.77, 127.69, 127.66, 125.71, 123.55, 123.35, 123.32, 123.29, 123.26, 121.92, 121.89, 116.96, 49.64, 47.72, 35.22, 27.68.

HRMS (ESI-QTOF): $[M +H]^+$ calculated for $C_{22}H_{22}N_2OF_3$ *m/z* 387.1679 and found *m/z* 387.1677.

IR (thin film, cm^{-1}): 3355, 3049, 2961, 2930, 2871, 1681, 1523, 1484, 1384, 1202, 908, 853, 753, 666.

3-(2,2-Dimethyl-4-oxo-4-(quinolin-8-ylamino)butyl)benzoic acid (Scheme 3, entry 5g):

Eluent: ethyl acetate/petroleum ether (15:85 v/v); appearance: sticky slight green liquid; isolated yield: 57%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.81 (s, 1H), 8.83 (dd, *J* = 6.9, 4.2 Hz, 2H), 8.19 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.97 (d, *J* = 6.3 Hz, 2H), 7.83 (d, *J* = 7.4 Hz, 1H), 7.57 (s, 2H), 7.48 (d, *J* = 4.0 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 2.88 (s, 2H), 2.46 (s, 2H), 1.15 (s, 6H).

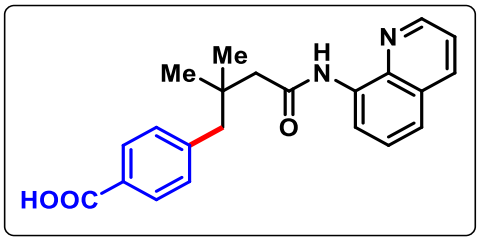
^{13}C NMR (126 MHz, $CDCl_3$) δ: 177.01, 170.78, 148.27, 139.30, 138.29, 137.09, 136.34, 134.39, 132.52, 129.36, 128.90, 128.23, 127.77, 127.60, 121.91, 121.78, 117.39, 49.73, 47.90, 35.16, 27.51.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{22}H_{23}N_2O_3$ *m/z* 363.1703 and found *m/z* 363.1709.

IR (thin film, cm^{-1}): 3361, 3053, 2968, 2939, 2852, 1661, 1522, 1469, 1379, 1215, 944, 856, 741, 670.

4-(2,2-Dimethyl-4-oxo-4-(quinolin-8-ylamino)butyl)benzoic acid (Scheme 3, entry 5h):

Eluent: ethyl acetate/petroleum ether (15:85 v/v); appearance: sticky slight brown liquid; isolated yield: 71%



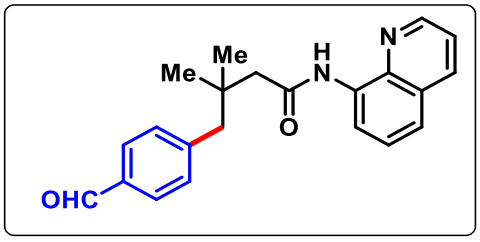
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (s, 1H), 8.1 (m, 2H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.04 (s, 1H), 8.02 (s, 1H), 7.53 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.39 (s, 1H), 7.37 (s, 1H), 2.90 (s, 2H), 2.44 (s, 2H), 1.14 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 172.07, 170.73, 148.55, 145.61, 138.71, 136.80, 134.70, 131.33, 130.08, 128.33, 127.75, 121.95, 116.99, 49.68, 48.12, 35.42, 27.88.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{22}H_{23}N_2O_3$ *m/z* 363.1703 and found *m/z* 363.1706.

IR (thin film, cm^{-1}): 3344, 3058, 2971, 2929, 2854, 1679, 1555, 1473, 1399, 1216, 921, 877, 743, 657.

4-(4-Formylphenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5i): Eluent: ethyl acetate/petroleum ether (8:92 v/v); appearance: sticky slight brown liquid; isolated yield: 67%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.99 (s, 1H), 9.79 (s, 1H), 8.81 (m, 2H), 8.17 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.81 (d, *J* = 7.9 Hz, 2H), 7.53 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 3H), 2.93 (s, 2H), 2.44 (s, 2H), 1.15 (s, 6H).

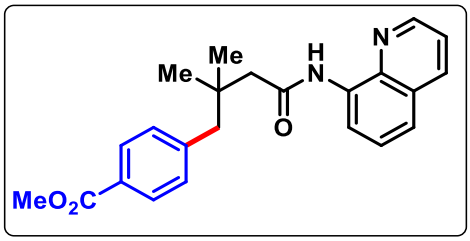
^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.50, 170.58, 148.55, 146.72, 138.72, 136.78, 135.01, 134.73, 131.88, 129.69, 128.33, 127.76, 121.98, 121.93, 116.85, 49.62, 48.07, 35.49, 27.97.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{22}H_{23}N_2O_2$ *m/z* 347.1754 and found *m/z* 347.1751.

IR (thin film, cm^{-1}): 3351, 3055, 2981, 2943, 2864, 1684, 1549, 1481, 1384, 1231, 928, 855, 746, 660.

Methyl 4-(2,2-dimethyl-4-oxo-4-(quinolin-8-ylamino)butyl)benzoate (Scheme 3, entry 5j):

Eluent: ethyl acetate/petroleum ether (8:92 v/v); appearance: sticky slight brown liquid; isolated yield: 68%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.89-8.77 (m, 2H), 8.13 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.46 (m, 2H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 3.89 (s, 3H), 2.86 (s, 2H), 2.41 (s, 2H), 1.12 (s, 6H).

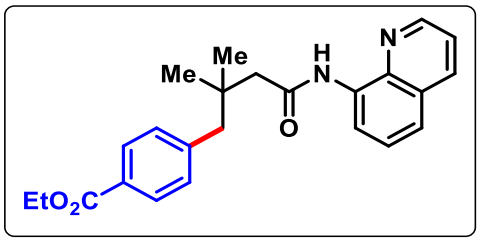
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.55, 167.47, 148.44, 144.60, 138.59, 136.63, 134.68, 131.15, 129.38, 128.31, 128.20, 127.63, 121.87, 121.77, 116.66, 52.25, 49.59, 47.95, 35.28, 27.78.

HRMS (ESI-QTOF): $[M +Na]^+$ calculated for $C_{23}H_{24}N_2O_3Na$ *m/z* 399.1679 and found *m/z* 399.1677.

IR (thin film, cm^{-1}): 3355, 3041, 2971, 2956, 2889, 1687, 1556, 1479, 1371, 1238, 955, 829, 756, 670.

Ethyl 4-(2,2-dimethyl-4-oxo-4-(quinolin-8-ylamino)butyl)benzoate (Scheme 3, entry 5k):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky slight brown liquid; isolated yield: 70%



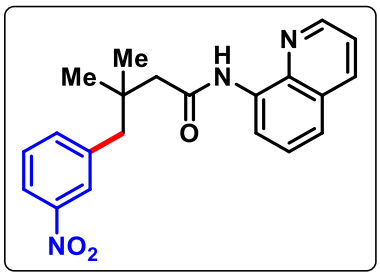
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.81 (s, 1H), 8.84 – 8.80 (m, 2H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.51 (m, 2H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.88 (s, 2H), 2.44 (s, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.73, 167.11, 148.35, 144.55, 139.71, 137.13, 137.03, 136.44, 134.67, 131.19, 129.43, 128.75, 128.38, 127.89, 121.92, 61.15, 49.73, 48.10, 35.39, 27.85, 14.70.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for$C_{24}H_{27}N_2O_2$ *m/z* 391.2016 and found *m/z* 391.2018.

IR (thin film, cm^{-1}): 3359, 3039, 2978, 2961, 2889, 1687, 1541, 1472, 1359, 1288, 940, 850, 756, 666.

3,3-Dimethyl-4-(3-nitrophenyl)-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5l): Eluent: ethyl acetate/petroleum ether (8:92 v/v); appearance: sticky slight brown liquid; isolated yield: 60%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.81 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.13 (t, *J* = 1.9 Hz, 1H), 8.08 (ddd, *J* = 8.2, 2.2, 0.9 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.53 (dt, *J* = 8.3, 7.4 Hz, 2H), 7.45 (m, 2H), 2.95 (s, 2H), 2.42 (s, 2H), 1.14 (s, 6H).

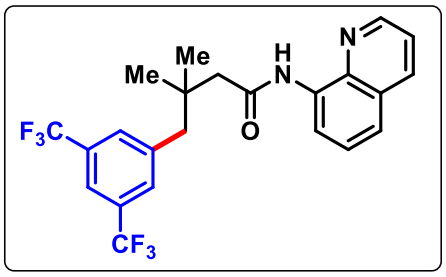
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.37, 148.49, 148.28, 141.09, 138.59, 137.44, 136.79, 134.62, 129.01, 128.28, 127.70, 125.73, 121.95, 121.64, 116.85, 49.37, 47.26, 35.27, 27.76.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for$C_{21}H_{21}N_3O_3Na$ *m/z* 386.1475 and found *m/z* 386.1479.

IR (thin film, cm^{-1}): 3361, 3049, 2965, 2952, 2878, 1665, 1531, 1459, 1389, 1285, 945, 845, 769, 659.

4-(3,5-bis(Trifluoromethyl)phenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5m):

Eluent: ethyl acetate/petroleum ether (1:99 v/v); appearance: sticky slight brown liquid; isolated yield: 56%



^{1}H NMR (500 MHz, $CDCl_3$): δ: 9.82 (s, 1H), 8.1 (m, 2H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.77 (s, 3H), 7.58 – 7.51 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.99 (s, 2H), 2.42 (s, 2H), 1.13 (s, 6H).

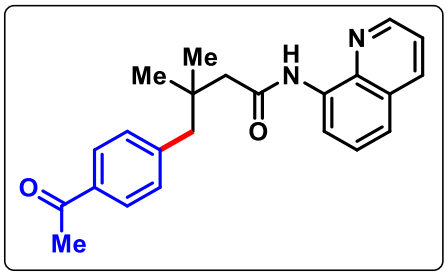
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.24, 148.55, 141.59, 138.68, 136.77, 134.63, 131.78, 131.52, 131.25, 131.19, 131.18, 128.30, 127.73, 124.89, 122.01, 121.99, 120.61, 120.58, 120.55, 120.52, 120.49, 116.86, 49.35, 47.05, 35.26, 27.72.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{23}H_{21}N_2F_6O$ *m/z* 455.1553 and found *m/z* 455.1550.

IR (thin film, cm^{-1}): 3355, 3038, 2948, 2948, 2873, 1667, 1521, 1439, 1359, 1276, 939, 889, 786, 690.

4-(4-Acetylphenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5n):

Eluent: ethyl acetate/petroleum ether (8:92 v/v); appearance: sticky slight brown liquid; isolated yield: 64%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.81 (dd, *J* = 7.4, 1.1 Hz, 1H), 8.78 (m, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.51 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 2.87 (s, 2H), 2.57 (s, 3H), 2.41 (s, 2H), 1.13 (s, 6H).

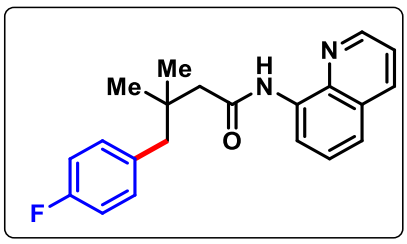
^{13}C NMR (126 MHz, $CDCl_3$) δ: 198.26, 170.52, 148.45, 144.92, 138.61, 136.64, 135.49, 134.69, 131.32, 128.19, 127.63, 121.89, 121.79, 116.67, 49.58, 47.90, 35.31, 27.82, 26.84.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{23}H_{24}N_2O_2Na$ *m/z* 383.1730 and found *m/z* 383.1765.

IR (thin film, cm^{-1}): 3355, 3020, 2961, 2928, 2873, 1678, 1525, 1425, 1385, 1270, 957, 853, 750, 668.

4-(4-Fluorophenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5o):

Eluent: ethyl acetate/petroleum ether (1:99 v/v); appearance: sticky slight green liquid; isolated yield: 67%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.82 (m, 2H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 (m, 2H), 7.51 (m, 2H), 7.46 (m, 2H), 7.40 (m, 1H), 2.89 (s, 2H), 2.43 (s, 2H), 1.13 (s,

6H).

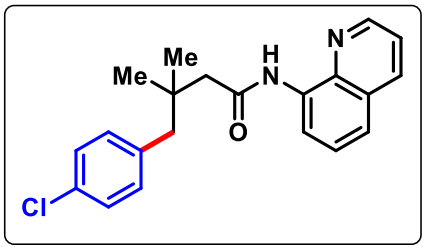
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.02, 162.89, 160.95, 148.22, 138.12, 137.62, 134.64, 134.62, 134.44, 132.55, 132.49, 128.48, 128.05, 122.05, 121.89, 117.83, 115.00, 114.84, 49.53, 47.31, 35.24, 30.05, 27.71.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{21}H_{21}N_2ONaF$ *m/z* 359.1530 and found *m/z* 359.1533

IR (thin film, cm^{-1}): 3354, 3028, 2968, 2918, 2868, 1679, 1531, 1438, 1373, 1291, 988, 855, 753, 669.

4-(4-Chlorophenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5p):

Eluent: ethyl acetate/petroleum ether (1:99 v/v); appearance: sticky slight brown liquid; isolated yield: 60%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.81 (m, 2H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.3 (m, *J* = 8.2, 7.5 Hz, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.25 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 2.79 (s, 2H), 2.40 (s, 2H), 1.12 (s, 6H).

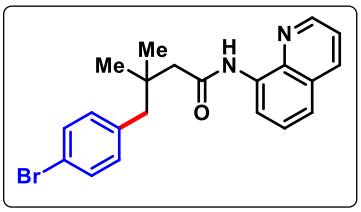
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.73, 148.51, 138.71, 137.49, 136.73, 134.79, 132.51, 132.31, 128.30, 128.28, 127.75, 121.94, 121.82, 116.77, 49.59, 47.38, 35.22, 27.79.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{21}H_{21}N_2ONaCl$ *m/z* 375.1235 and found *m/z* 375.1234.

IR (thin film, cm^{-1}): 3355, 3029, 2962, 2919, 2871, 1675, 1539, 1428, 1381, 1299, 989, 859, 763, 665.

4-(4-Bromophenyl)-3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (Scheme 3, entry 5q):

Eluent: ethyl acetate/petroleum ether (1:99 v/v); appearance: sticky slight brown liquid; isolated yield: 65%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.81 (m, 2H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 16.5, 7.9 Hz, 2H), 7.46 (d, *J* = 4.2 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 2.77 (s, 2H), 2.40 (s, 2H), 1.11 (s, 6H).

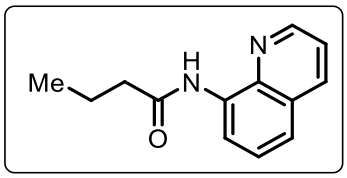
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.69, 148.49, 138.65, 137.98, 136.70, 134.75, 132.90, 131.21, 128.26, 127.71, 121.93, 121.81, 120.39, 116.71, 77.61, 77.36, 77.11, 49.53, 47.37, 35.14, 27.77.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{21}H_{21}N_2OBrNa$ *m/z* 419.0729 and found *m/z* 419.0737.

IR (thin film, cm^{-1}): 3355, 3027, 2965, 2923, 2875, 1685, 1542, 1435, 1399, 1291, 980, 842, 765, 670.

N-(quinolin-8-yl)butyramide (6):

Eluent: Ethyl acetate/Petroleum ether (5:95 v/v); appearance: pale yellow gel; isolated yield: 90%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.78 (m, 2H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.53 (m, 2H), 1.85 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H).

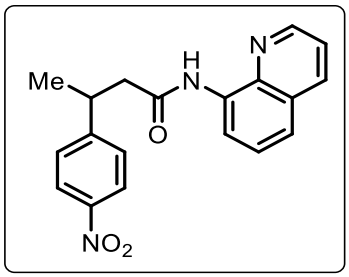
^{13}C NMR (126 MHz, $CDCl_3$) δ: 172.03, 148.31, 138.54, 136.58, 134.74, 128.14, 127.64, 121.77, 121.56, 116.63, 40.36, 19.35, 14.03.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{13}H_{14}N_2NaO$ *m/z* 237.0998 and found *m/z* 237.0957

IR (thin film, cm^{-1}): 3356, 3029, 2961, 2918, 2881, 1689, 1559, 1439, 1400, 1285, 971, 855, 777, 661.

3-(4-nitrophenyl)-N-(quinolin-8-yl)butanamide (Scheme 4, entry 7a):

Eluent**:** Ethyl acetate/Petroleum ether (10:90 v/v); appearance: pale yellow solid; isolated yield: 90%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 8.75 (d, *J* = 4.1 Hz, 1H), 8.70 (dd, *J* = 6.4, 1.9 Hz, 1H), 8.15 (t, *J* = 8.9 Hz, 3H), 7.49 (dd, *J* = 12.0, 7.5 Hz, 4H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.62 (dd, *J* = 14.2, 7.1 Hz, 1H), 2.87 (m, 2H), 1.43 (d, *J* = 6.9 Hz, 3H)

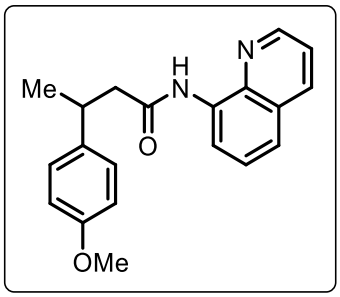
^{13}C NMR (126 MHz, $CDCl_3$) δ: 13C NMR (126 MHz, CDCl3) δ 169.68, 153.91, 148.27, 146.94, 138.24, 137.05, 134.28, 128.27, 128.17, 127.76, 127.25, 124.23, 122.10, 121.96, 117.14, 46.40, 37.08, 21.91.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{19}H_{19}N_3O_3$ *m/z* 336.1343 and found *m/z* 336.1342

IR (thin film, cm^{-1}): 3355, 3036, 2958, 2917, 2888, 1687, 1551, 1451, 1412, 1299, 967, 847, 778, 669.

3-(4-methoxyphenyl)-N-(quinolin-8-yl)butanamide (Scheme 4, entry 7b):

Eluent**:** Ethyl acetate/Petroleum ether (15:85 v/v); appearance: pale yellow solid; isolated yield: 88%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 8.78 (d, *J* = 7.5 Hz, 1H), 8.73 (d, *J* = 4.0 Hz, 1H), 8.07 (m, 1H), 7.47 (m, 2H), 7.38 (dd, *J* = 8.1, 4.0 Hz, 1H), 7.25 (m, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.73 (s, 3H), 3.46 (dd, *J* = 14.4, 7.2 Hz, 1H), 2.84 (dd, *J* = 14.4, 7.0 Hz, 1H), 2.75 (dd, *J* = 14.4, 8.0 Hz, 1H), 1.39 (d, *J* = 7.0 Hz, 3H).

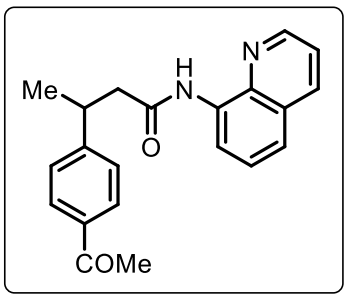
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.61, 158.28, 148.17, 138.38, 138.18, 136.46, 134.59, 128.03, 127.93, 127.50, 121.68, 121.58, 116.63, 114.17, 55.33, 47.30, 36.29, 22.24.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{20}H_{20}N_2NaO_2$ *m/z* 343.1417 and found *m/z* 343.1421

IR (thin film, cm^{-1}): 3354, 3013, 2961, 2933, 2836, 1679, 1523, 1484, 1423, 1386, 1215, 958, 791, 744, 668.

3-(4-acetylphenyl)-N-(quinolin-8-yl)butanamide (Scheme 4, entry 7c):

Eluent**:** Ethyl acetate/Petroleum ether (15:85 v/v); appearance: pale yellow semisolid; isolated yield: 85%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 8.76 (dd, *J* = 4.1, 1.3 Hz, 1H), 8.73 (dd, *J* = 7.1, 1.6 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.52 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 3.57 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.91 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.83 (dd, *J* = 14.6, 7.7 Hz, 1H), 2.54 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H).

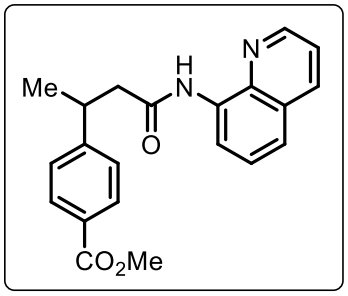
^{13}C NMR (126 MHz, $CDCl_3$) δ: 13C NMR (101 MHz, CDCl3) δ 198.10, 170.23, 151.92, 148.10, 137.23, 135.93, 134.42, 129.15, 128.36, 127.92, 127.51, 125.17, 121.99, 121.88, 117.39, 46.65, 37.24, 26.85, 21.98.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{21}H_{20}N_2NaO_2$ *m/z* 355.1417 and found *m/z* 355.1416.

IR (thin film, cm^{-1}): 3350, 3008, 2959, 2959, 2927, 2871, 1680, 1605, 1526, 1485, 1324, 1267, 1059, 957, 858, 758, 690.

methyl 4-(4-oxo-4-(quinolin-8-ylamino)butan-2-yl)benzoate (Scheme 4, entry 7d):

Eluent**:** Ethyl acetate/Petroleum ether (20:80 v/v); appearance: pale yellow solid; isolated yield: 78%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 8.72 (m, 2H), 8.10 (m, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.46 (m, 2H), 7.38 (d, *J* = 8.2 Hz, 3H), 3.55 (m, 1H), 2.87 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.79 (dd, *J* = 14.6, 7.9 Hz, 1H), 1.41 (d, *J* = 7.0 Hz, 3H).

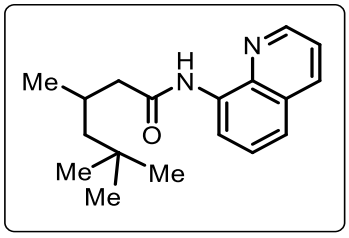
^{13}C NMR (126 MHz, $CDCl_3$) δ: 13C NMR (126 MHz, CDCl3) δ 170.12, 167.28, 151.58, 148.35, 138.47, 136.59, 134.49, 130.25, 128.60, 128.13, 127.59, 127.22, 121.84, 116.74, 52.25, 46.64, 37.12, 21.88.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{21}H_{20}N_2NaO_3$ *m/z* 371.1366 and found *m/z* 371.1352

IR (thin film, cm^{-1}): 3355, 3011, 2962, 2949, 2923, 2877, 1685, 1617, 1523, 1488, 1310, 1259, 1060, 947, 828, 748, 667.

3,5,5-trimethyl-N-(quinolin-8-yl)hexanamide (8):

Eluent: Ethyl acetate/Petroleum ether (10:90 v/v); appearance: slight brown gummy liquid; isolated yield: 78%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 8.80 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.51 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.57 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.36 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.27 (m, 1H), 1.39 (dd, *J* = 14.0, 3.9 Hz, 1H), 1.21 (dd, *J* = 14.0, 6.4 Hz, 1H), 1.09 (d, *J* = 6.5 Hz, 3H), 0.94 (s, 9H).

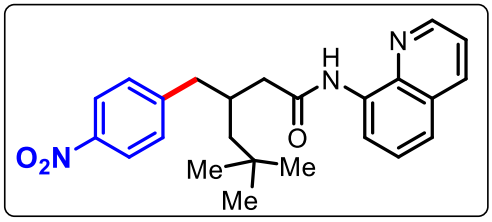
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.73, 148.47, 138.71, 136.72, 134.88, 128.31, 127.81, 121.89, 121.69, 116.84, 51.07, 48.42, 31.48, 30.37, 27.93, 23.11.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{18}H_{24}N_2NaO$ *m/z* 307.1781 and found *m/z* 317.1385.

IR (thin film, cm^{-1}): 3355, 3023, 2961, 2949, 2918, 2867, 1667, 1617, 1528, 1479, 1311, 1269, 1045, 959, 848, 746, 669.

5,5-dimethyl-3-(4-nitrobenzyl)-N-(quinolin-8-yl)hexanamide (Scheme 5, entry 9a):

Eluent: ethyl acetate/petroleum ether (20:80 v/v); appearance: sticky slight brown semisolid; isolated yield: 94%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.72 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 2H), 7.51 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.41 (m, 2H), 2.91 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.66 (dd, *J* = 13.9, 3.8 Hz, 1H), 2.44 (m, 2H), 1.38 (m, 2H), 0.87 (s, 9H).

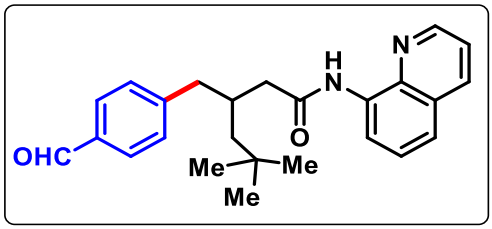
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.85, 149.11, 148.50, 146.74, 138.56, 136.78, 134.59, 130.62, 128.29, 127.71, 123.78, 121.98, 121.92, 116.76, 47.49, 44.75, 42.95, 34.11, 31.41, 30.13.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{24}H_{27}N_3NaO_3$ *m/z* 428.1945 and found *m/z* 428.1911

IR (thin film, cm^{-1}): 3354, 3013, 2961, 2971, 2931, 2869, 1678, 1615, 1530, 1438, 1355, 1279, 1056, 964, 848, 746, 659.

3-(4-formylbenzyl)-5,5-dimethyl-N-(quinolin-8-yl)hexanamide (Scheme 5, entry 9b):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 89%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.90 (s, 1H), 9.73 (s, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.74 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.50 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 2.86 (dd, *J* = 13.4, 6.6

Hz, 1H), 2.75 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.62 (d, *J* = 9.6 Hz, 1H), 2.46 (m, 2H), 1.37 (m, 2H), 0.87 (s, 9H).

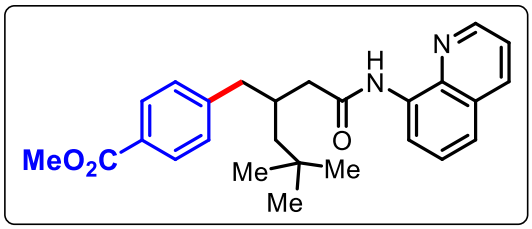
^{13}C NMR (126 MHz, $CDCl_3$) δ: 192.27, 171.03, 148.63, 148.45, 138.57, 136.72, 134.91, 134.67, 130.50, 130.09, 128.26, 127.71, 121.93, 121.79, 116.74, 47.46, 44.83, 43.29, 34.14, 31.39, 30.13.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{25}H_{28}N_2NaO_2$ *m/z* 411.2043 and found *m/z* 411.2048

IR (thin film, cm^{-1}): 3358, 3019, 2949, 2957, 2914, 2857, 1691, 1615, 1523, 1488, 1334, 1212, 1061, 960, 869, 741, 667.

Methyl 4-(4,4-dimethyl-2-(2-oxo-2-(quinolin-8-ylamino)ethyl)pentyl)benzoate (Scheme 5, entry 9c):

Eluent: ethyl acetate/petroleum ether (20:80 v/v); appearance: sticky slight brown semisolid; isolated yield: 88%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 8.79 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.75 (d, *J* = 7.4 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.49 (dd, *J* = 14.5, 8.0 Hz, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 2.83 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.72 (dd, *J* = 13.4, 6.6 Hz, 1H), 2.59 (t, *J* = 8.7 Hz, 1H), 2.44 (m, 2H), 1.36 (d, *J* = 3.5 Hz, 2H), 0.86 (s, 9H).

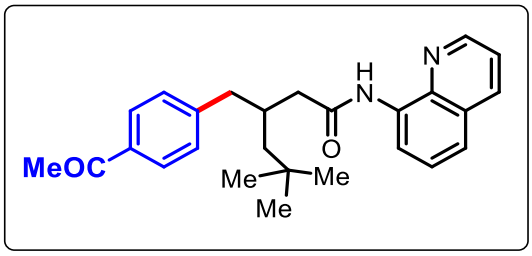
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.14, 167.41, 148.42, 146.63, 138.55, 136.66, 134.69, 129.86, 128.22, 127.69, 121.89, 121.70, 116.71, 52.22, 47.29, 44.82, 43.03, 34.12, 31.35, 30.12.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{26}H_{30}N_2NaO_3$ *m/z* 441.2149 and found *m/z* 441.2145.

IR (thin film, cm^{-1}): 3355, 3015, 2949, 2949, 2935, 2868, 1688, 1623, 1528, 1487, 1315, 1261, 948, 849, 735, 660.

3-(4-acetylbenzyl)-5,5-dimethyl-N-(quinolin-8-yl)hexanamide (Scheme 5, entry 9d):

Eluent: ethyl acetate/petroleum ether (20:80 v/v); appearance: sticky slight brown semisolid; isolated yield: 92%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.71 (s, 1H), 8.79 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.73 (dd, *J* = 7.3, 1.6 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.50 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 2.82 (dd, *J* = 13.5, 6.8 Hz, 1H), 2.75 (dd, *J* = 13.4, 6.8 Hz, 1H), 2.61 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.51 (s, 3H), 2.46 (dt, *J* = 14.0, 4.9 Hz, 2H), 1.37 (d, *J* = 4.5 Hz, 2H), 0.88 (s, 9H).

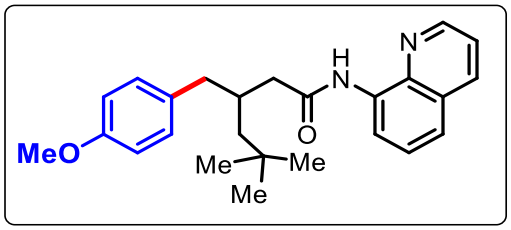
^{13}C NMR (126 MHz, $CDCl_3$) δ: 198.19, 171.16, 148.46, 146.93, 138.60, 136.72, 135.47, 134.71, 130.05, 128.71, 128.28, 127.73, 121.93, 121.78, 116.79, 47.56, 44.86, 43.14, 34.12, 31.41, 30.25, 30.18, 26.78.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{26}H_{30}N_2NaO_2$ *m/z* 425.2199 and found *m/z* 425.2193

IR (thin film, cm^{-1}): 3353, 3011, 2949, 2958, 2919, 2869, 1689, 1625, 1523, 1483, 1320, 1260, 1064, 951, 851, 755, 689.

3-(4-methoxybenzyl)-5,5-dimethyl-N-(quinolin-8-yl)hexanamide (Scheme 5, entry 9e):

Eluent: ethyl acetate/petroleum ether (20:80 v/v); appearance: sticky slight brown semisolid; isolated yield: 85%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.72 (s, 1H), 8.79 (m, 2H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.50 (dt, *J* = 8.1, 4.5 Hz, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 3.73 (s, 3H), 2.68 (m, 2H), 2.54 (m, 1H), 2.47 (m, 1H), 2.40 (dd, *J* = 12.1, 5.7 Hz, 1H), 1.38 (t, *J* = 5.2 Hz, 2H), 0.91 (s, 9H).

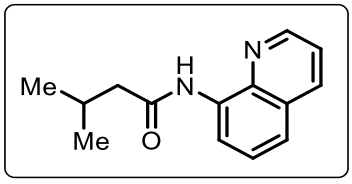
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.52, 158.17, 148.35, 138.60, 136.61, 134.85, 132.99, 130.69, 128.22, 127.71, 121.83, 121.56, 116.68, 113.94, 55.45, 47.44, 44.79, 42.20, 34.45, 31.41, 30.22.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{25}H_{30}N_2NaO_2$ *m/z* 413.2199 and found *m/z* 413.2202

IR (thin film, cm^{-1}): 3353, 3023, 2947, 2951, 2925, 2879, 1679, 1615, 1523, 1468, 1358, 1279, 1046, 959, 849, 794, 656.

3-methyl-N-(quinolin-8-yl)butanamide (8'):

Eluent: Ethyl acetate/Petroleum ether (5:95 v/v); appearance: pale yellow gel; isolated yield: 80%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 8.79 (m, 2H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.43 (d, *J* = 7.2 Hz, 2H), 2.27 (m, 1H), 1.06 (d, *J* = 6.6 Hz, 6H).

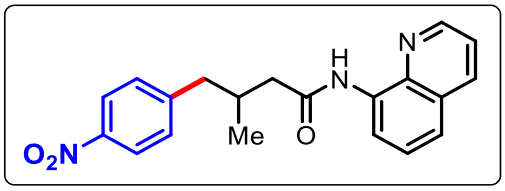
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.66, 148.45, 138.67, 136.69, 134.87, 128.27, 127.77, 121.89, 121.67, 116.73, 47.88, 26.65, 22.89.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{14}H_{16}N_2NaO$ *m/z* 251.1155 and found *m/z* 251.1142

IR (thin film, cm^{-1}): 3353, 3012, 2956, 2947, 2913, 2846, 1656, 1600, 1500, 1446, 1335, 954, 826, 735, 660.

3-methyl-4-(4-nitrophenyl)-N-(quinolin-8-yl)butanamide (Scheme 5, entry 9f):

Eluent: Ethyl acetate/Petroleum ether (15:85 v/v); appearance: pale yellow semisolid; isolated yield: 82%



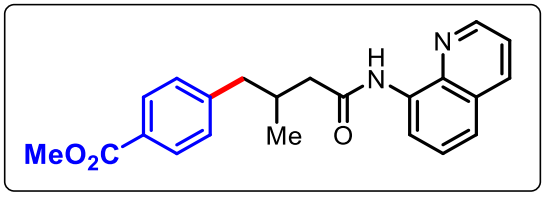
^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.14 (s, 1H), 8.86 (dd, J = 14.9, 5.3 Hz, 2H), 8.39 (s, 1H), 8.11 (d, *J* = 8.7 Hz, 2H), 7.63 (m, 3H), 7.40 (d, *J* = 8.7 Hz, 2H), 2.95 (dd, *J* = 13.3, 5.6 Hz, 1H), 2.66 (dt, *J* = 21.6, 13.1 Hz, 2H), 2.57 (dd, *J* = 16.0, 6.2 Hz, 2H), 1.05 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.34, 148.82, 146.97, 146.76, 139.62, 133.60, 130.42, 128.78, 128.75, 128.71, 123.82, 122.40, 121.75, 119.39, 44.96, 43.07, 32.85, 19.94.
HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{20}H_{19}N_3NaO_3$ *m/z* 372.1319 and found *m/z* 372.1318

IR (thin film, cm^{-1}): 3354, 3028, 2946, 2941, 2928, 2889, 1684, 1698, 1549, 1445, 1394, 1249, 1094, 994, 859, 755, 664.

methyl 4-(2-methyl-4-oxo-4-(quinolin-8-ylamino)butyl)benzoate (Scheme 5, entry 9g):

Eluent: Ethyl acetate/Petroleum ether (15:85 v/v); appearance: pale yellow semisolid; isolated yield: 84%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 8.79 (m, 2H), 8.15 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.51 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 3H), 2.86 (m, 1H), 2.58 (m, 3H), 2.41 (m, 1H), 1.03 (d, *J* = 6.2 Hz, 3H).

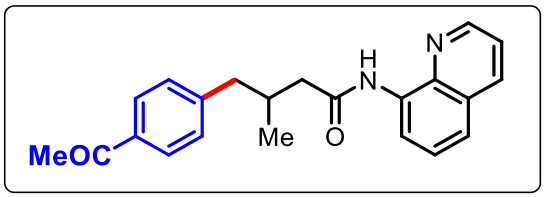
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.07, 167.44, 148.46, 146.25, 138.59, 136.71, 134.67, 129.94, 129.64, 128.33, 128.25, 127.72, 121.93, 121.82, 116.78, 52.29, 45.26, 43.27, 32.84, 19.93.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{22}H_{22}N_2NaO_3$ *m/z* 385.1523 and found *m/z* 385.1520

IR (thin film, cm^{-1}): 3351, 3023, 2965, 2946, 2937, 2891, 1692, 1678, 1546, 1479, 1316, 1297, 1039, 964, 853, 747, 691.

4-(4-acetylphenyl)-3-methyl-N-(quinolin-8-yl)butanamide (Scheme 5, entry 9h):

Eluent: Ethyl acetate/Petroleum ether (20:80 v/v); appearance: pale yellow semisolid; isolated yield: 78%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 8.75 (dd, *J* = 14.1, 5.6 Hz, 2H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 2H), 7.52 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 3.57 (m, 1H), 2.91 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.83 (dd, *J* = 14.6, 7.7 Hz, 1H), 2.54 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H).

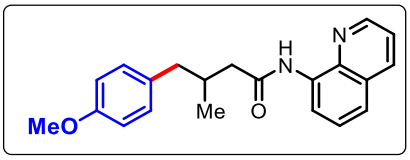
^{13}C NMR (126 MHz, $CDCl_3$) δ: 198.24, 171.08, 148.47, 146.57, 138.58, 136.74, 135.50, 134.63, 129.81, 128.76, 128.25, 127.71, 121.94, 121.87, 116.81, 45.26, 43.26, 32.83, 26.86, 20.00.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{22}H_{22}N_2NaO_2$ *m/z* 369.1573 and found *m/z* 369.1575

IR (thin film, cm^{-1}): 3355, 3009, 2968, 2946, 2931, 2861, 1646, 1623, 1537, 1480, 1320, 1260, 1046, 950, 864, 748, 667.

4-(4-methoxyphenyl)-3-methyl-N-(quinolin-8-yl)butanamide (Scheme 5, entry 9i):

Eluent: Ethyl acetate/Petroleum ether (20:80 v/v); appearance: pale yellow semisolid; isolated yield: 80%



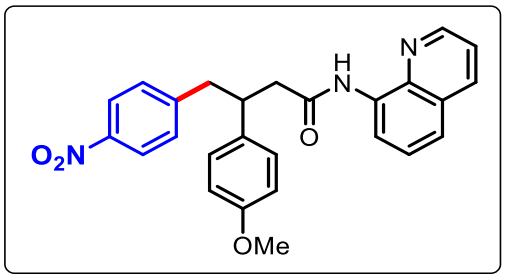
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.79 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.51 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 2.71 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.58 (dd, *J* = 12.9, 4.5 Hz, 1H), 2.54 (dd, *J* = 12.2, 6.4 Hz, 1H), 2.46 (tt, *J* = 6.6, 4.3 Hz, 1H), 2.36 (dd, *J* = 14.1, 7.9 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.49, 158.25, 148.43, 138.66, 136.68, 134.83, 132.70, 130.53, 128.27, 127.75, 121.89, 121.70, 116.76, 114.01, 55.54, 45.32, 42.52, 33.18, 19.95.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{21}H_{22}N_2NaO_2$ *m/z* 357.1573 and found *m/z* 357.1574

IR (thin film, cm^{-1}): 3354, 3011, 2915, 2998, 2966, 2846, 1656, 1623, 1564, 1446, 1364, 1265, 1045, 947, 858, 748, 695.

3-(4-methoxyphenyl)-4-(4-nitrophenyl)-N-(quinolin-8-yl)butanamide (Scheme 5, entry 9j):

Eluent**:** Ethyl acetate/Petroleum ether (20:80 v/v); appearance: pale yellow solid; isolated yield: 55%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.72 (s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.71 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.50 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 3.73 (s, 3H), 3.61 (m, 1H), 3.25 (dd, *J* = 13.3, 5.5 Hz, 1H), 3.01 (dd, *J* = 13.4, 9.4 Hz, 1H), 2.92 (d, *J* = 7.3 Hz, 2H).

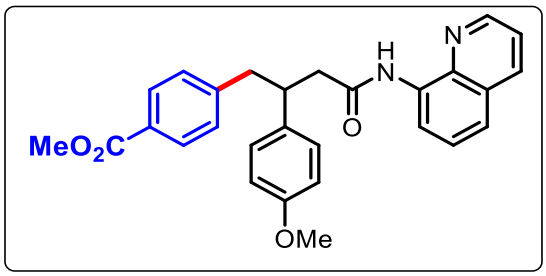
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.04, 148.44, 148.09, 146.75, 136.74, 134.64, 132.25, 130.44, 128.84, 128.25, 127.70, 123.67, 121.99, 116.85, 114.35, 55.50, 44.87, 43.58, 42.96.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{26}H_{24}N_3O_4$ *m/z* 442.1761 and found *m/z* 442.1761.

IR (thin film, cm^{-1}): 3351, 3005, 2951, 2946, 2914, 2846, 1640, 1600, 1511, 1476, 1319, 1274, 1055, 917, 878, 734, 664.

methyl 4-(2-(4-methoxyphenyl)-4-oxo-4-(quinolin-8-ylamino)butyl)benzoate (Scheme 5, entry 9k):

Eluent**:** Ethyl acetate/Petroleum ether (25:75 v/v); appearance: slight brown semisolid; isolated yield: 65%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 7.0, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.49 (dd, *J* =

12.8, 5.5 Hz, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.11 (dd, *J* = 10.6, 8.5 Hz, 4H), 6.76 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 3.61 (dt, *J* = 14.7, 7.3 Hz, 1H), 3.15 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.98 (dd, *J* = 13.4, 8.8 Hz, 1H), 2.89 (dd, *J* = 7.3, 4.3 Hz, 2H).

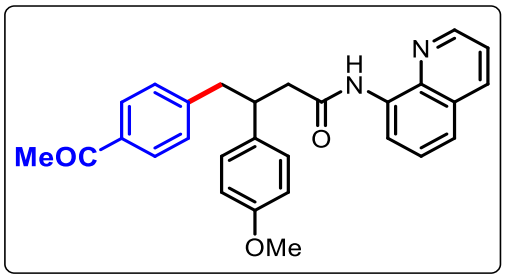
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.20, 167.38, 158.46, 148.28, 145.54, 138.48, 136.56, 135.11, 134.53, 129.68, 129.61, 128.77, 128.12, 127.60, 121.81, 121.71, 116.72, 114.13, 55.37, 52.19, 44.68, 43.49, 43.18.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{28}H_{27}N_2O_4$ *m/z* 455.1965 and found *m/z* 455.1961

IR (thin film, cm^{-1}): 3350, 3002, 2958, 2949, 2937, 2871, 1634, 1676, 1565, 1475, 1324, 1264, 1068, 947, 855, 765, 682.

4-(4-acetylphenyl)-3-(4-methoxyphenyl)-N-(quinolin-8-yl)butanamide (Scheme 5, entry 9l):

Eluent**:** Ethyl acetate/Petroleum ether (20:80 v/v); appearance: pale yellow semisolid; isolated yield: 61%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.70 (dd, *J* = 7.0, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.48 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.13 (dd, *J* = 17.5, 8.4 Hz, 4H), 6.77 (d, *J* = 8.6 Hz, 2H), 3.72 (s, 3H), 3.62 (m, 1H), 3.15 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.99 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.89 (dd, *J* = 7.3, 3.2 Hz, 2H), 2.52 (s, 3H).

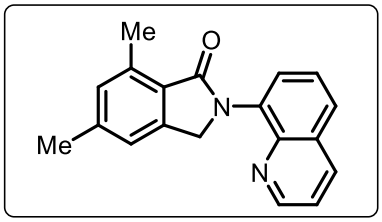
^{13}C NMR (126 MHz, $CDCl_3$) δ: 198.70, 170.69, 158.97, 148.78, 146.34, 138.95, 137.08, 135.85, 135.63, 135.00, 130.27, 129.25, 129.01, 128.61, 128.45, 128.08, 122.31, 122.25, 117.21, 114.64, 55.87, 45.23, 43.93, 43.62, 27.26.

HRMS (ESI-QTOF): $[M + H]^+$ calculated for $C_{28}H_27N_2O_3$ *m/z* 439.2016 and found *m/z* 439.2015

IR (thin film, cm^{-1}): 3355, 3001, 2943, 2934, 2949, 2846, 1688, 1601, 1523, 1446, 1345, 1241, 1079, 946, 874, 750, 690.

5,7-dimethyl-2-(quinolin-8-yl)isoindolin-1-one (Scheme 5, entry 9m):

Eluent: Ethyl acetate/Petroleum ether (30:70 v/v); appearance: pale yellow solid; isolated yield: 55%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.88 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.91 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.82 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.62 (m, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.13 (s, 1H), 7.07 (s, 1H), 5.17 (s, 2H), 2.73 (d, *J* = 15.0 Hz, 3H), 2.44 (s, 3H).

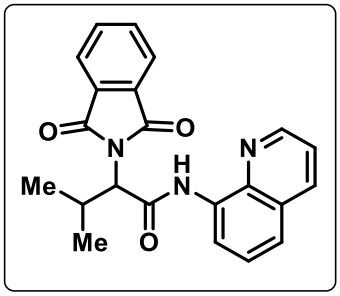
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.05, 150.94, 150.31, 144.83, 143.84, 142.18, 138.30, 136.70, 136.19, 131.23, 129.79, 129.23, 127.65, 126.73, 121.66, 120.97, 53.41, 22.09, 17.66.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{19}H_{16}N_2NaO$ *m/z* 311.1155 and found *m/z* 311.1157

IR (thin film, cm^{-1}): 2951, 2927, 2866, 1700, 1623, 1526, 1321, 1201, 1016, 757, 661.

2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)butanamide (8) or L-valine protected amino acid (10):

Eluent: ethyl acetate/petroleum ether (10:90 v/v); pale yellow solid; isolated yield: 75%



^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.58 (s, 1H), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (m, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.49 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.68 (t, *J* = 11.4 Hz, 1H), 3.22 (m, 1H), 1.22 (s, 3H), 0.98 (s, 3H).

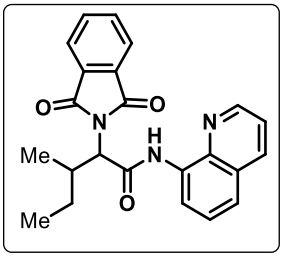
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.48, 167.19, 148.87, 139.03, 136.51, 134.60, 131.92, 128.23, 127.56, 123.99, 122.33, 121.95, 117.34, 63.56, 27.64, 20.77, 19.92.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{22}H_{19}N_3NaO_3$ *m/z* 396.1319and found *m/z* 396.1316

IR (thin film, cm^{-1}): 3349, 3043, 2958, 2946, 2925, 2814, 1680, 1650, 1605, 1576, 1446, 1346, 1245, 1057, 994, 875, 755, 675.

2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)pentanamide (8') or Isoleucine protected amide (10'):

Eluent: ethyl acetate/petroleum ether (10:90 v/v); pale yellow solid; isolated yield: 80%



^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.60 (s, 1H), 8.85 (ddd, *J* = 15.4, 4.2, 1.7 Hz, 1H), 8.76 (m, 1H), 8.13 (m, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.50 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.79 (dd, *J* = 10.8, 9.1 Hz, 1H), 3.07 (ddd, *J* = 4.2, 2.1, 0.9 Hz, 1H), 1.53 (ddd, *J* = 13.6, 7.5, 3.2 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 1H), 0.95 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.54, 167.38, 148.90, 139.07, 136.52, 134.60, 131.95, 128.24, 127.58, 124.00, 122.34, 121.96, 117.39, 62.41, 33.10, 25.99, 16.70, 10.67.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{23}H_{21}N_3NaO_3$ *m/z* 410.1475 and found *m/z* 410.1473

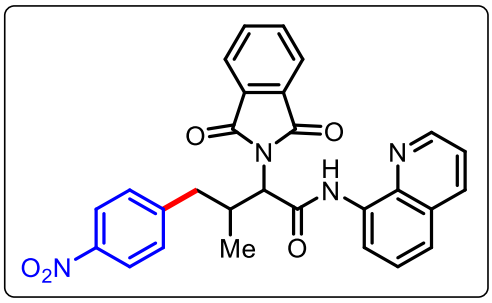
IR (thin film, cm^{-1}): 3300, 3065, 2948, 2965, 2945, 2865, 1675, 1635, 1615, 1575, 1484, 1355, 1254,997, 875, 787, 674.

Table 10: Disteriomer ratio by NMR analysis:

Entry	Major Isomer	Minor Isomer	dr ratio
11a	1	0.07	14.2857
11b	1.03	0.02	51.5
11c	1.01	0.02	50.5
11d	1	0.05	20
11e	1	0.08	12.5
11f	1	0.05	20
11g	1	0.04	25
11h	1.12	0.04	28

2-(1,3-dioxoisoindolin-2-yl)-3-methyl-4-(4-nitrophenyl)-N-(quinolin-8-yl)butanamide (Scheme 6, entry 11a):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight pale yellow semisolid; isolated yield: 85%, **dr: 14: 1**



^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.56 (s, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.70 (dd, *J* = 5.3, 3.7 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.05 (m, 2H), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.47 (m, 5H), 4.89 (d, *J* = 10.6 Hz, 1H), 3.42 (dtd, *J* = 10.4, 6.8, 3.8 Hz, 1H), 3.29 (dd, *J* = 13.4, 3.6 Hz, 1H), 2.56 (dd, *J* = 13.4, 9.8 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 3H).

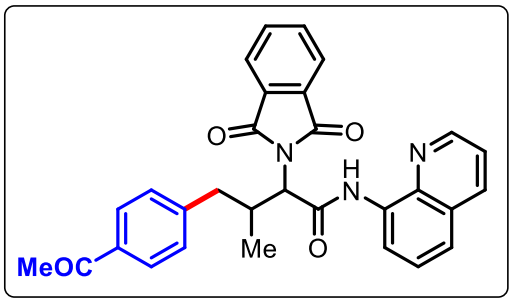
^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.23, 166.42, 148.84, 147.90, 146.77, 138.87, 136.60, 134.78, 134.10, 131.68, 130.45, 128.18, 127.44, 124.08, 123.77, 122.59, 122.03, 117.41, 61.15, 40.85, 34.38, 16.21.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C28H22N4NaO5 *m/z* 517.1482 and found *m/z* 517.1480

IR (thin film, cm^{-1}): 3022, 2920, 2846, 1722, 1635, 1622, 1500, 1485, 1398, 1286, 1225, 1170, 1013, 775, 660.

.4-(4-acetylphenyl)-2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)butanamide (Scheme 6, entry 11b):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 78%, **dr: 51.5:1**



^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.61 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.72 (m, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.50 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 4.88 (d, *J* = 10.7 Hz, 1H), 3.41 (tdd, *J* = 10.3, 6.8, 3.7 Hz, 1H), 3.25 (dd, *J* = 13.4, 3.6 Hz, 1H), 2.53 (s, 3H), 2.50 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H).

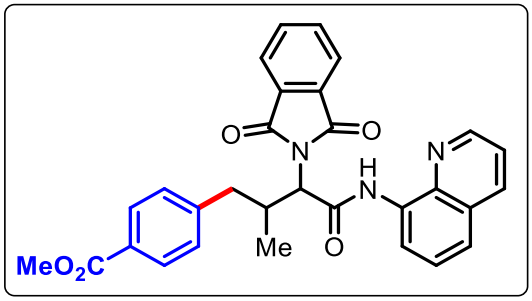
^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.99, 168.14, 166.43, 148.72, 145.60, 138.83, 136.41, 135.42, 134.58, 134.13, 131.61, 129.76, 128.58, 128.06, 127.34, 123.91, 122.35, 121.89, 117.26, 77.48, 77.23, 76.98, 61.38, 40.80, 34.25, 26.69, 16.02.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C30H25N3NaO4 *m/z* 514.1737 and found *m/z* 514.1735

IR (thin film, cm^{-1}): 3025, 2915, 2845, 1718, 1641, 1623, 1530, 1475, 1395, 1276, 1220, 1175, 1023, 746, 668.

methyl 4-(3-(1,3-dioxoisoindolin-2-yl)-2-methyl-4-oxo-4-(quinolin-8-ylamino)butyl)benzoate (Scheme 6, entry 11c):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 80%**, dr: 50.5:1**



^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.63 (s, 1H), 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.74 (m, 1H), 8.13 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.87 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.50 (d, *J* = 4.8 Hz, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 4.88 (d, *J* = 10.7 Hz, 1H), 3.87 (s, 3H), 3.40 (ddt, *J* = 17.0, 6.8, 3.6 Hz, 1H), 3.27 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.49 (dd, *J* = 13.3, 10.3 Hz, 1H), 0.86 (d, *J* = 6.6 Hz, 3H).

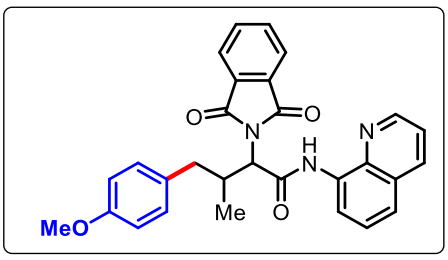
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.27, 167.32, 166.57, 148.84, 145.45, 138.97, 136.53, 134.69, 134.26, 131.75, 129.90, 129.71, 128.42, 128.19, 127.48, 124.02, 122.46, 122.00, 117.39, 61.49, 52.24, 40.92, 34.43, 16.03.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C30H25N3O5 *m/z* 530.1686 and found *m/z* 530.1688

IR (thin film, cm^{-1}): 3021, 2925, 2855, 1718, 1642, 1612, 1531, 1467, 1384, 1281, 1215, 1113, 1013, 750, 668.

2-(1,3-dioxoisoindolin-2-yl)-4-(4-methoxyphenyl)-3-methyl-N-(quinolin-8-yl)butanamide (Scheme 6, entry 11d):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 82%, **dr: 20:1**



^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.67 (s, 1H), 8.84 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.77 (dd, *J* = 5.4, 3.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.51 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 4.87 (d, *J* = 10.7 Hz, 1H), 3.75 (s, 3H), 3.34 (dtd, *J* = 10.3, 6.7, 3.4 Hz, 1H), 3.15 (dd, *J* = 13.5, 3.4 Hz, 1H), 2.39 (dd, *J* = 13.5, 10.1 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H).

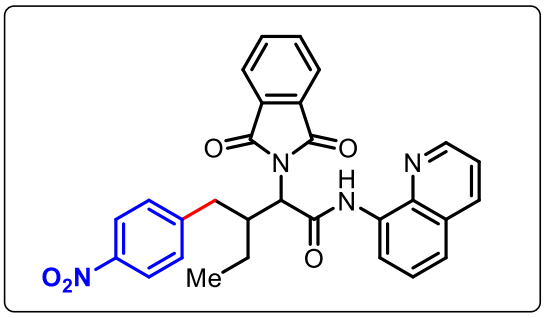
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.34, 166.83, 158.29, 148.82, 139.02, 136.52, 134.61, 134.42, 131.83, 131.80, 130.63, 128.21, 127.51, 123.97, 122.37, 121.97, 117.37, 113.94, 61.75, 55.47, 39.96, 34.71, 16.02.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C29H25N3O4 *m/z* 502.1737 and found *m/z* 502.1736

IR (thin film, cm^{-1}): 3029, 2917, 2865, 1700, 1636, 1600, 1538, 1475, 1398, 1280, 1219, 1099, 1011, 759, 648.

2-(1,3-dioxoisoindolin-2-yl)-3-(4-nitrobenzyl)-N-(quinolin-8-yl)pentanamide (Scheme 6, entry 11e):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 77%, **dr:12.5:1**



^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.60 (s, 1H), 8.85 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.63 (dd, *J* = 6.6, 2.4 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 2H), 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.46 (m, 5H), 5.00 (d, *J* = 10.9 Hz, 1H), 3.47 (m, 1H), 3.06 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.86 (m, 1H), 1.47 (m, 1H), 1.33 (m, 1H), 0.91 (t, *J* = 7.5 Hz, 3H).

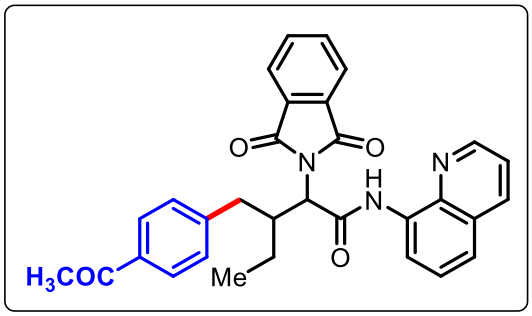
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.38, 166.65, 148.89, 148.16, 146.52, 138.95, 136.60, 134.82, 134.15, 131.77, 130.28, 128.18, 127.41, 124.13, 123.70, 122.67, 122.05, 117.51, 59.65, 39.35, 36.55, 22.36, 9.45.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C29H25N4O5 *m/z* 509.1819 and found *m/z* 509.1810

IR (thin film, cm^{-1}): 3042, 2931, 2835, 1723, 1678, 1635, 1515, 1485, 1345, 1265, 1295, 1114, 1054, 735, 655.

3-(4-acetylbenzyl)-2-(1,3-dioxoisoindolin-2-yl)-N-(quinolin-8-yl)pentanamide (Scheme 6, entry 11f):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 80%, **dr: 20:1**



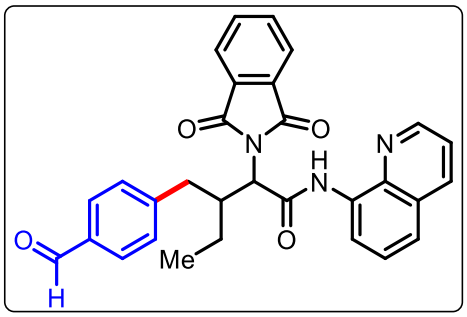
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.65 (s, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.67 (dd, *J* = 6.1, 3.0 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (m, 4H), 7.47 (m, 3H), 7.37 (d, *J* = 8.2 Hz, 2H), 5.00 (d, *J* = 11.0 Hz, 1H), 3.48 (m, 1H), 3.03 (dd, *J* = 13.9, 4.8 Hz, 1H), 2.81 (dd, *J* = 13.9, 8.9 Hz, 1H), 2.47 (s, 3H), 1.45 (m, 1H), 1.31 (dd, *J* = 13.8, 7.1 Hz, 1H), 0.89 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 197.01, 167.37, 165.82, 147.82, 144.93, 137.92, 135.58, 134.33, 133.71, 133.27, 130.79, 128.69, 127.64, 127.17, 126.45, 123.04, 121.49, 121.00, 116.54, 58.71, 38.15, 35.48, 25.74, 21.01, 8.31.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C31H27N3NaO4 *m/z* 528.1894 and found *m/z* 528.1894

IR (thin film, cm^{-1}): 3037, 2956, 2835, 1742, 1697, 1637, 1598, 1454, 1335, 1250, 1245, 1112, 1013, 745, 675.

2-(1,3-dioxoisoindolin-2-yl)-3-(4-formylbenzyl)-N-(quinolin-8-yl)pentanamide (Scheme 6, entry 11g):



Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 85%, **dr: 25:1**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.63 (s, 1H), 9.81 (s, 1H), 8.86 (d, *J* = 2.7 Hz, 1H), 8.65 (dd, *J* = 6.3, 2.4 Hz, 1H), 8.13 (m, 1H), 7.88 (dd, *J* = 5.3, 3.0 Hz, 2H), 7.73 (m, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 13.3, 7.2 Hz, 5H), 5.00 (d, *J* = 11.0 Hz, 1H), 3.49 (d, *J* = 4.6 Hz, 1H), 3.04 (dd, *J* = 13.9, 4.5 Hz, 1H), 2.83 (dd, *J* = 13.8, 8.9 Hz, 1H), 1.49 – 1.41 (m, 1H), 1.31 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H).

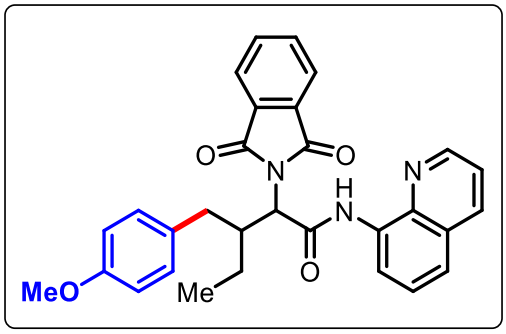
^{13}C NMR (101 MHz, $CDCl_3$) δ: 192.09, 168.38, 166.76, 148.85, 147.63, 138.98, 136.55, 134.74, 134.27, 131.79, 130.15, 130.02, 128.17, 127.43, 124.07, 122.52, 122.01, 117.51, 59.69, 39.24, 36.73, 22.11, 9.34.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C30H25N3NaO4 *m/z* 514.1737 and found *m/z* 514.1732

IR (thin film, cm^{-1}): 3035, 2975, 2845, 1758, 1645, 1613, 1535, 1465, 1375, 1215, 1200, 1053, 747, 666.

2-(1,3-dioxoisoindolin-2-yl)-3-(4-methoxybenzyl)-N-(quinolin-8-yl)pentanamide (Scheme 6, entry 11h):

Eluent: ethyl acetate/petroleum ether (30:70 v/v); appearance: sticky slight brown semisolid; isolated yield: 78%**, dr: 25:1**



^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.68 (s, 1H), 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.73 (m, 1H), 8.14 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.50 (m, 2H), 7.45 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 5.00 (d, *J* = 11.0 Hz, 1H), 3.71 (s, 3H), 3.40 (ddt, *J* = 14.5, 9.7, 4.8 Hz, 1H), 2.94 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.68 (dd, *J* = 14.0, 9.4 Hz, 1H), 1.46 (dtd, *J* = 10.9, 7.5, 3.4 Hz, 1H), 1.27 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H).

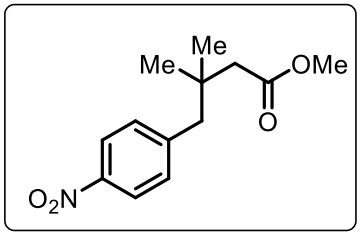
^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.44, 167.11, 158.17, 148.83, 139.06, 136.49, 134.61, 131.88, 130.46, 128.20, 127.49, 123.97, 122.35, 121.96, 117.45, 113.93, 59.74, 55.43, 39.34, 35.24, 21.47, 9.21.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C30H27N3NaO4 *m/z* 516.1894 and found *m/z* 516.1890

IR (thin film, cm^{-1}): 3025, 2945, 2857, 1720, 1647, 1612, 1531, 1467, 1374, 1298, 1223, 1125, 747, 677.

methyl 3,3-dimethyl-4-(4-nitrophenyl)butanoate (Scheme 7, entry 12):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky slight brown semisolid; isolated yield: 80%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 3.70 (s, 3H), 2.80 (s, 2H), 2.19 (s, 2H), 1.01 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 172.73, 146.88, 131.77, 123.41, 51.71, 47.36, 45.30, 34.84, 27.71.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C13H17NNaO4 *m/z* 274.1050and found *m/z* 274.1055

IR (thin film, cm^{-1}): 2850, 1755, 1730, 1633, 1512, 1265, 1220, 1110, 759, 680

2.5. Crystal data:

$C_{21}H_{21}N_3O_3$

Crystal structure for 5a: CCDC 1470619

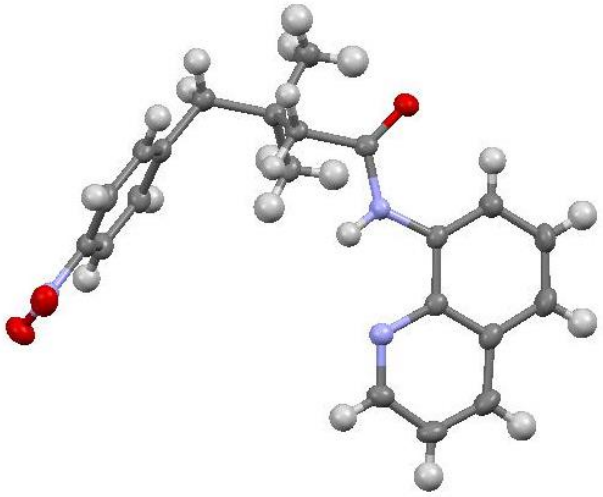


Table 1 Crystal data and structure refinement for C21H21N3O3.	
Identification code	C21H21N3O3
Empirical formula	$C_{21}H_{21}N_3O_3$
Formula weight	363.41
Temperature/K	150
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.2858(8)
b/Å	8.1781(4)
c/Å	16.7542(9)
α/°	90
β/°	110.159(6)
γ/°	90
Volume/Å^3	1837.49(18)
Z	4
ρ_{calc}g/cm^3	1.314
μ/mm^{-1}	0.089
F(000)	768.0
Crystal size/mm^3	0.256 × 0.235 × 0.096
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.022 to 50

Index ranges	-16 ≤ h ≤ 16, -8 ≤ k ≤ 9, -19 ≤ l ≤ 19
Reflections collected	17724
Independent reflections	3233 [R_{int} = 0.1155, R_{sigma} = 0.0535]
Data/restraints/parameters	3233/0/246
Goodness-of-fit on F^2	1.046
Final R indexes [I>=2σ (I)]	R_1 = 0.0562, wR_2 = 0.1392
Final R indexes [all data]	R_1 = 0.0685, wR_2 = 0.1548
Largest diff. peak/hole / e $Å^{-3}$	0.31/-0.32

$C_{23}H_{24}N_2O_3$

Crystal structure for 5j: CCDC 1457945

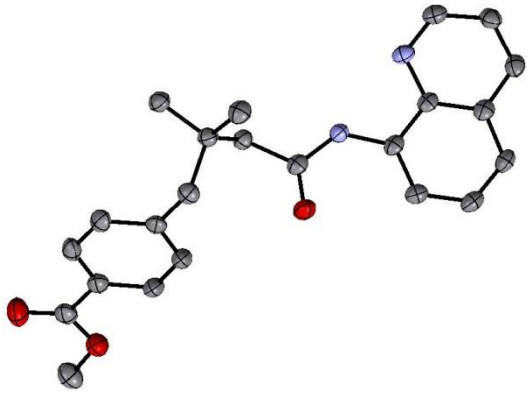


Table 1 Crystal data and structure refinement for C23H24N2O3.	
Identification code	C23H24N2O3
Empirical formula	$C_{23}H_{24}N_2O_3$
Formula weight	376.44
Temperature/K	150
Crystal system	orthorhombic
Space group	Pbca
a/Å	9.583(5)
b/Å	12.840(6)
c/Å	31.602(15)
α/°	90

β/°	90
γ/°	90
Volume/Å^3	3888(3)
Z	8
ρ_{calc}g/cm^3	1.286
μ/mm^{-1}	0.086
F(000)	1600.0
Crystal size/mm^3	0.4 × 0.2 × 0.13
Radiation	MoKα (λ = 0.7107)
2Θ range for data collection/°	6.346 to 50
Index ranges	-11 ≤ h ≤ 11, -15 ≤ k ≤ 15, -37 ≤ l ≤ 37
Reflections collected	24243
Independent reflections	3412 [R_{int} = 0.0739, R_{sigma} = 0.0443]
Data/restraints/parameters	3412/0/256
Goodness-of-fit on F^2	0.990
Final R indexes [I>=2σ (I)]	R_1 = 0.0609, wR_2 = 0.1476
Final R indexes [all data]	R_1 = 0.0780, wR_2 = 0.1645
Largest diff. peak/hole / e Å^{-3}	0.18/-0.22

DM-SYP1-113-2-A_Mo

Crystal structure for 11b: CCDC 1504497

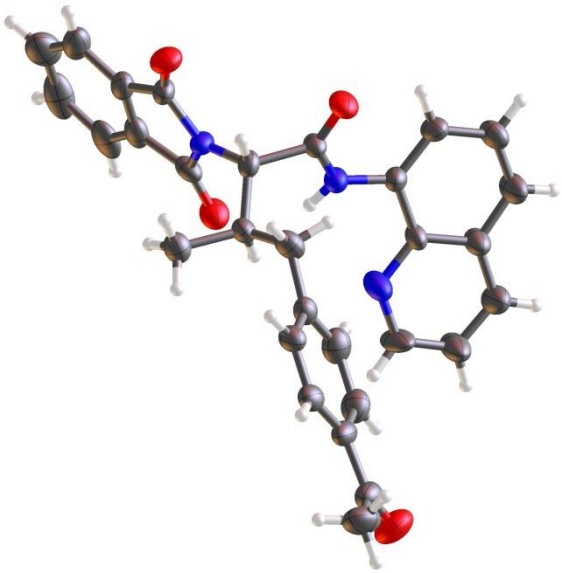
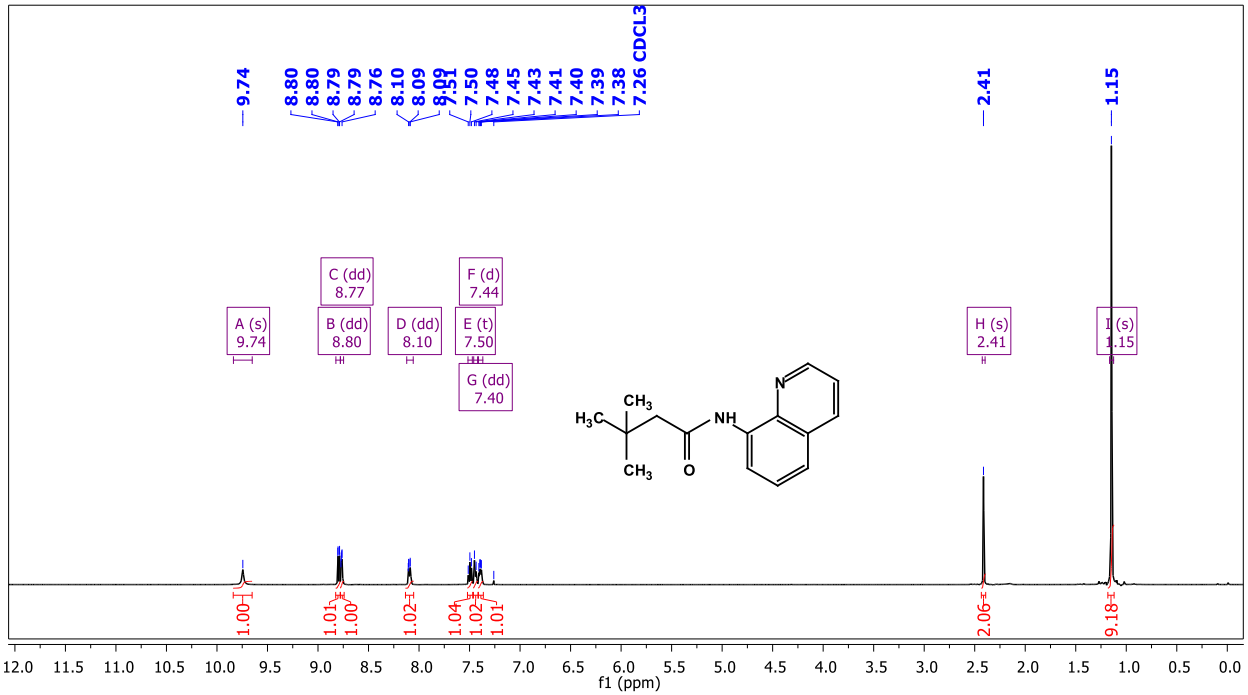


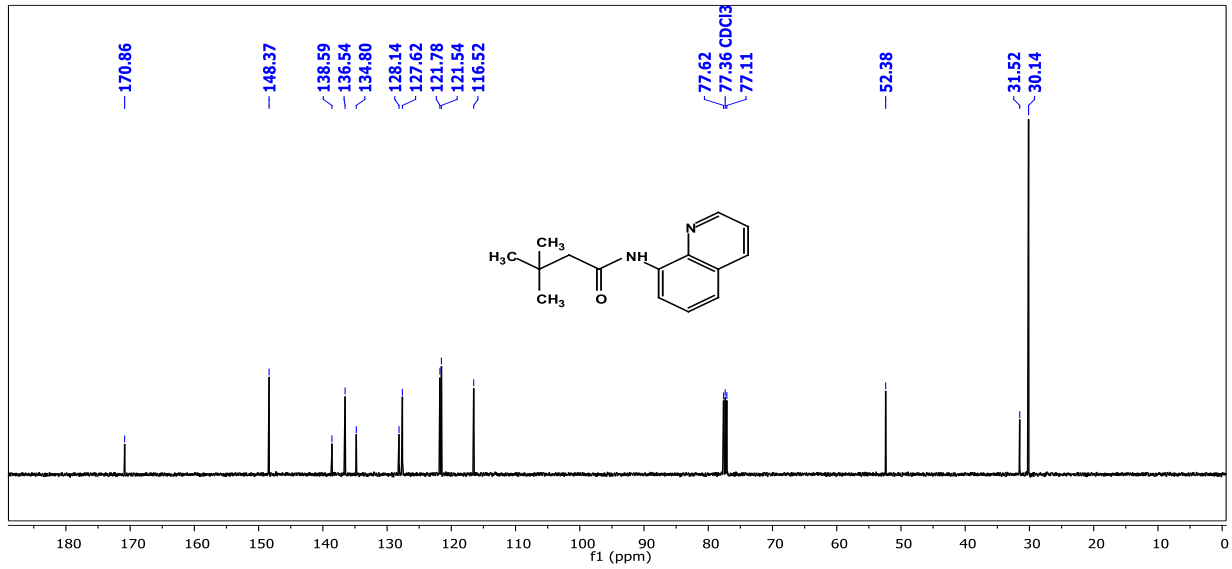
Table 1 Crystal data and structure refinement for DM-SYP1-113-2-A_Mo.	
Identification code	DM-SYP1-113-2-A_Mo
Empirical formula	$C_{30}H_{25}N_3O_4$
Formula weight	491.53
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1$
a/Å	7.8391(6)
b/Å	15.3118(15)
c/Å	12.8177(11)
α/°	90
β/°	97.727(8)
γ/°	90
Volume/Å^3	1524.6(2)
Z	2
ρ_{calc}g/cm^3	1.071
μ/mm^{-1}	0.072
F(000)	516.0
Crystal size/mm^3	0.163 × 0.103 × 0.084
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.206 to 49.996
Index ranges	-9 ≤ h ≤ 9, -18 ≤ k ≤ 18, -15 ≤ l ≤ 15
Reflections collected	15682
Independent reflections	5355 [R_{int} = 0.1040, R_{sigma} = 0.1023]
Data/restraints/parameters	5355/1/337
Goodness-of-fit on F^2	1.283
Final R indexes [I>=2σ (I)]	R_1 = 0.1348, wR_2 = 0.3298
Final R indexes [all data]	R_1 = 0.1753, wR_2 = 0.3770
Largest diff. peak/hole / e Å^{-3}	1.50/-0.96
Flack parameter	-0.1(10)

2.7 Spectra of representative compounds:

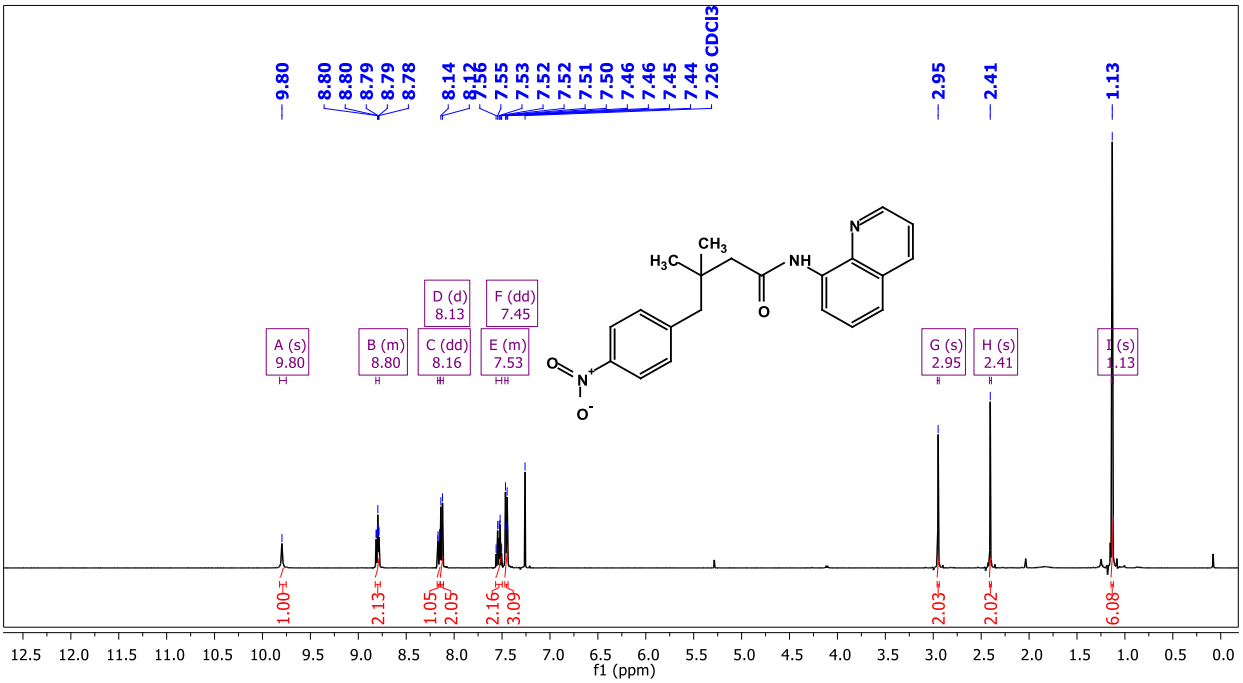
^{1}H Spectra of 3:



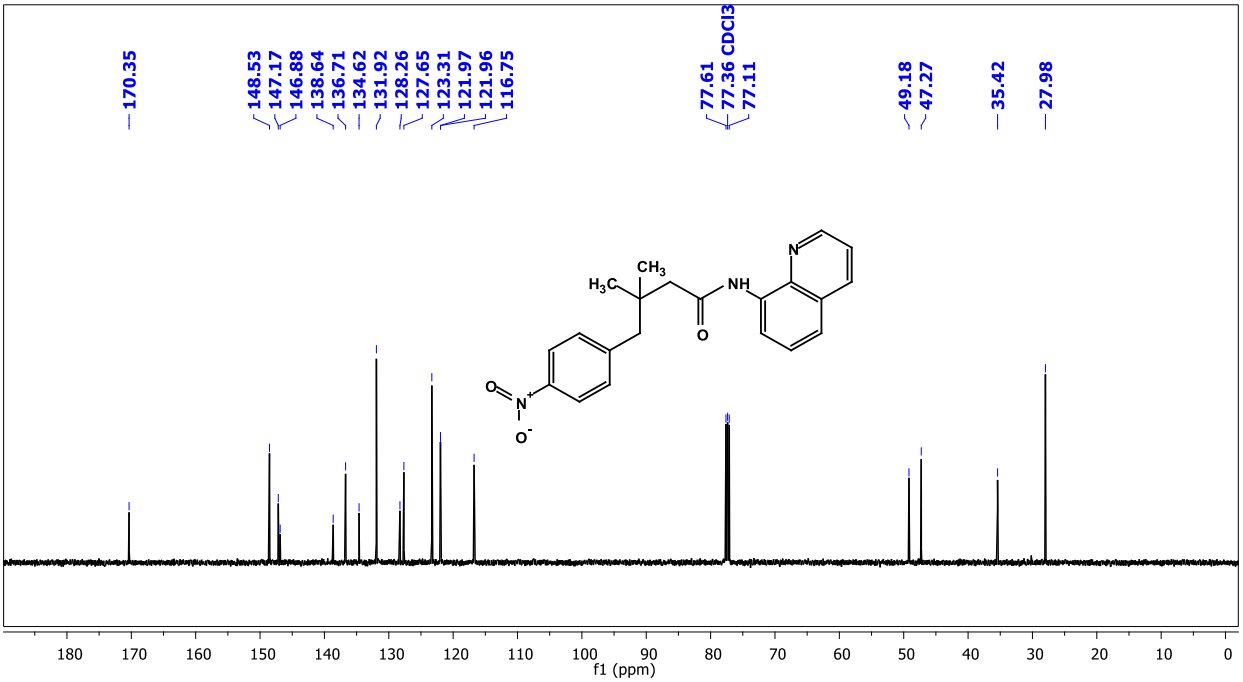
^{13}C Spectra of 3:



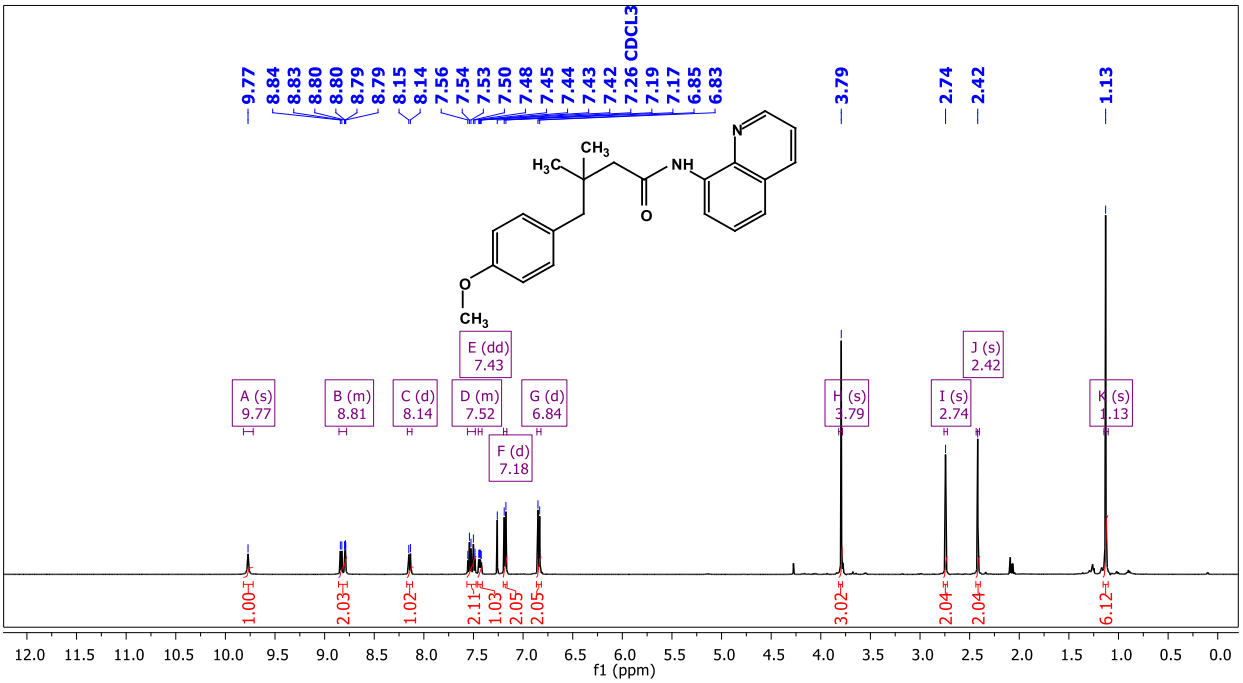
^{1}H Spectra of 5a:



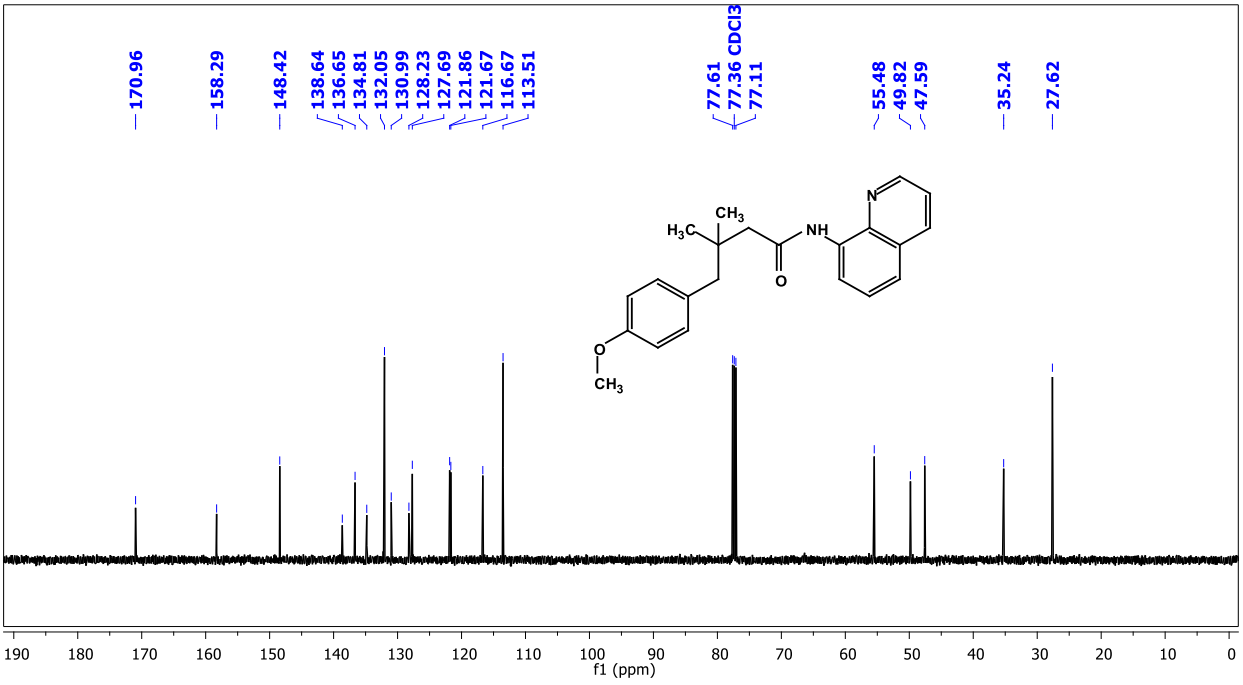
^{13}C Spectra of 5a:



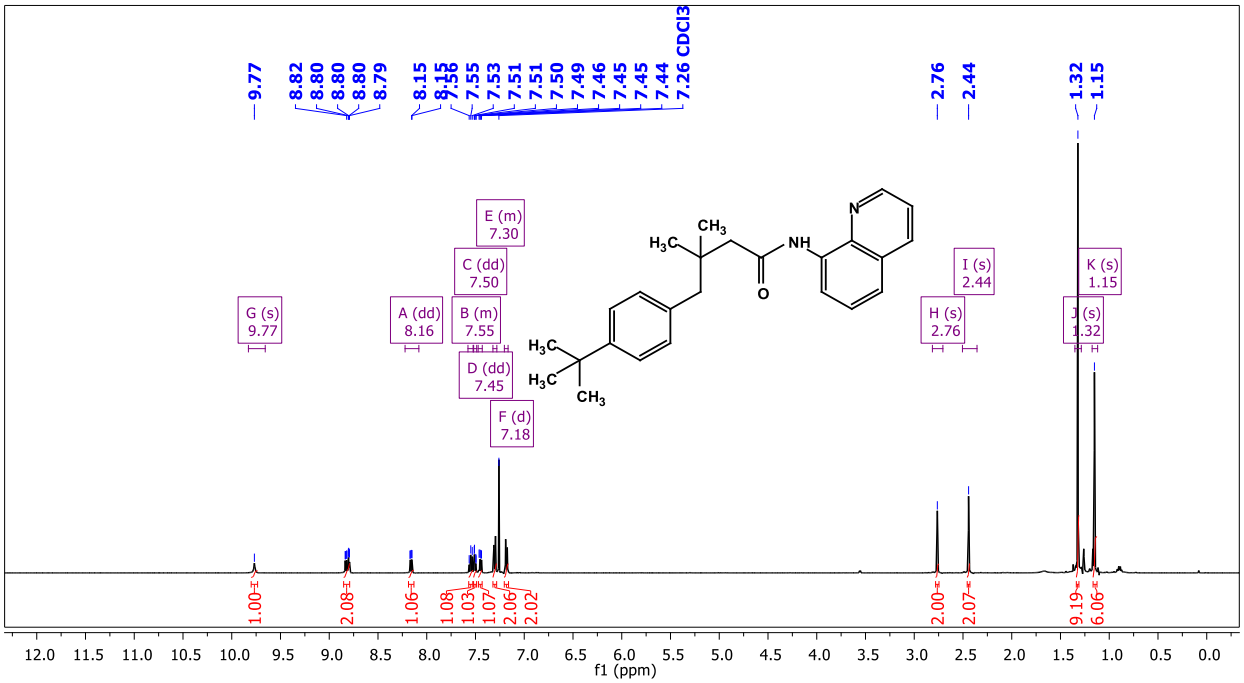
^{1}H Spectra of 5c:



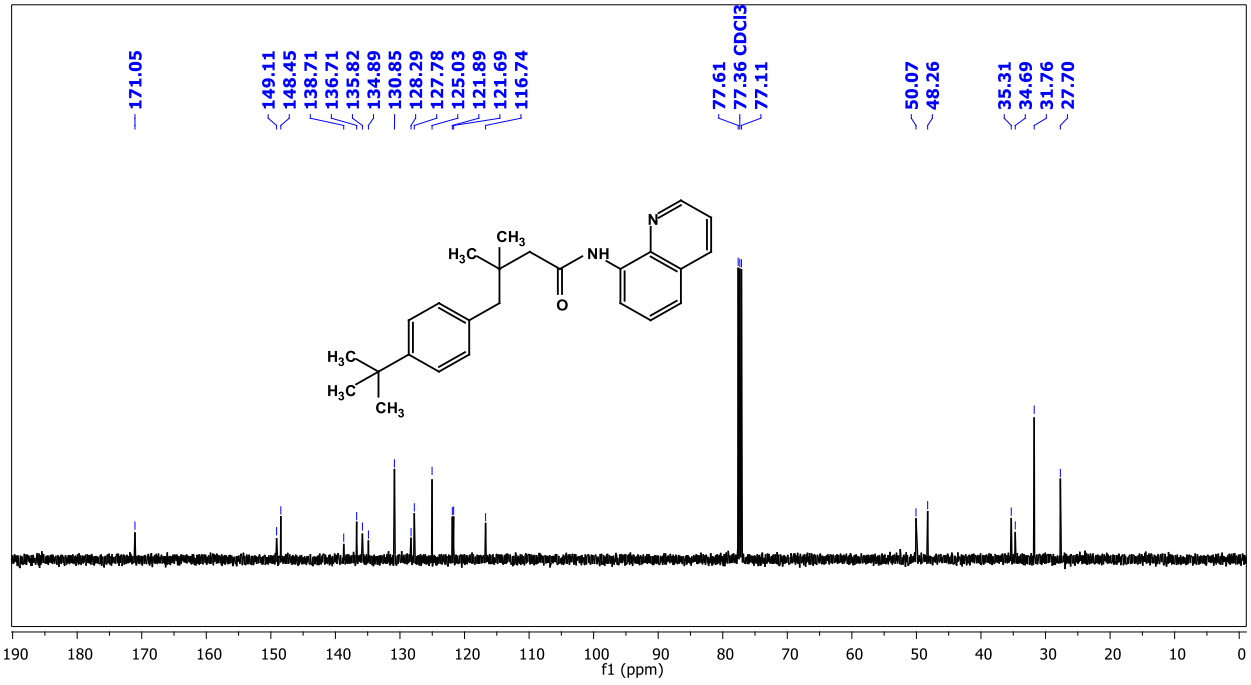
^{13}C Spectra of 5c:



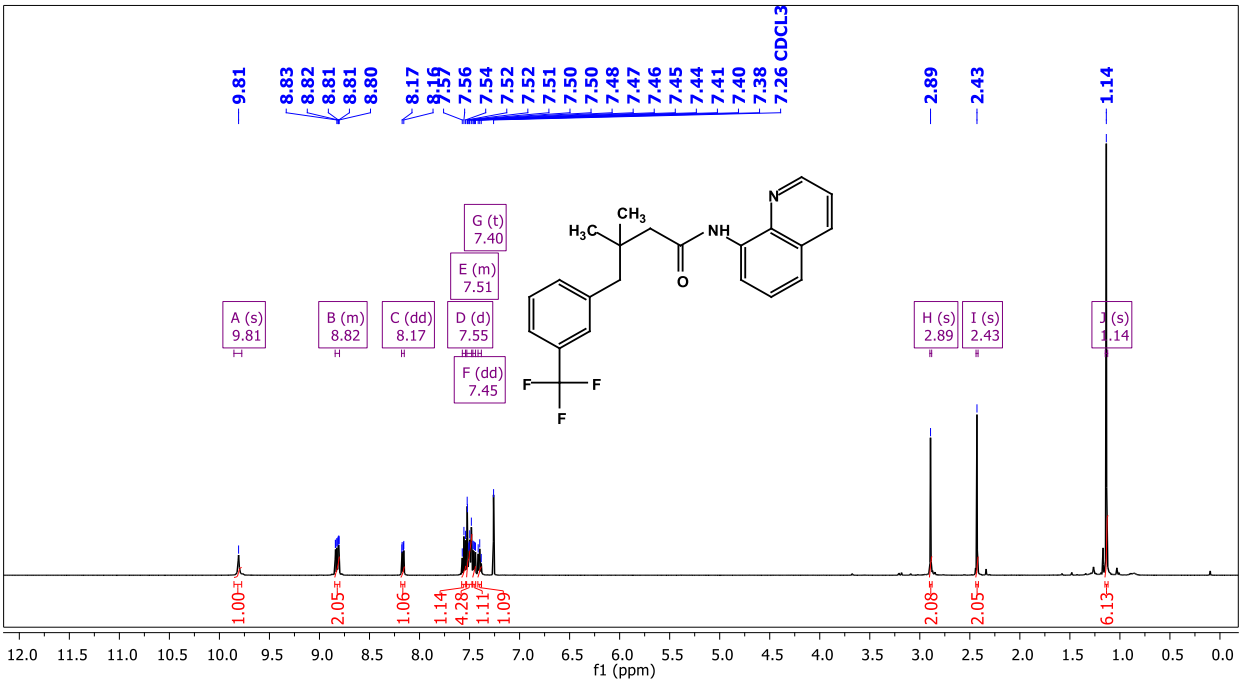
^{1}H Spectra of 5e:



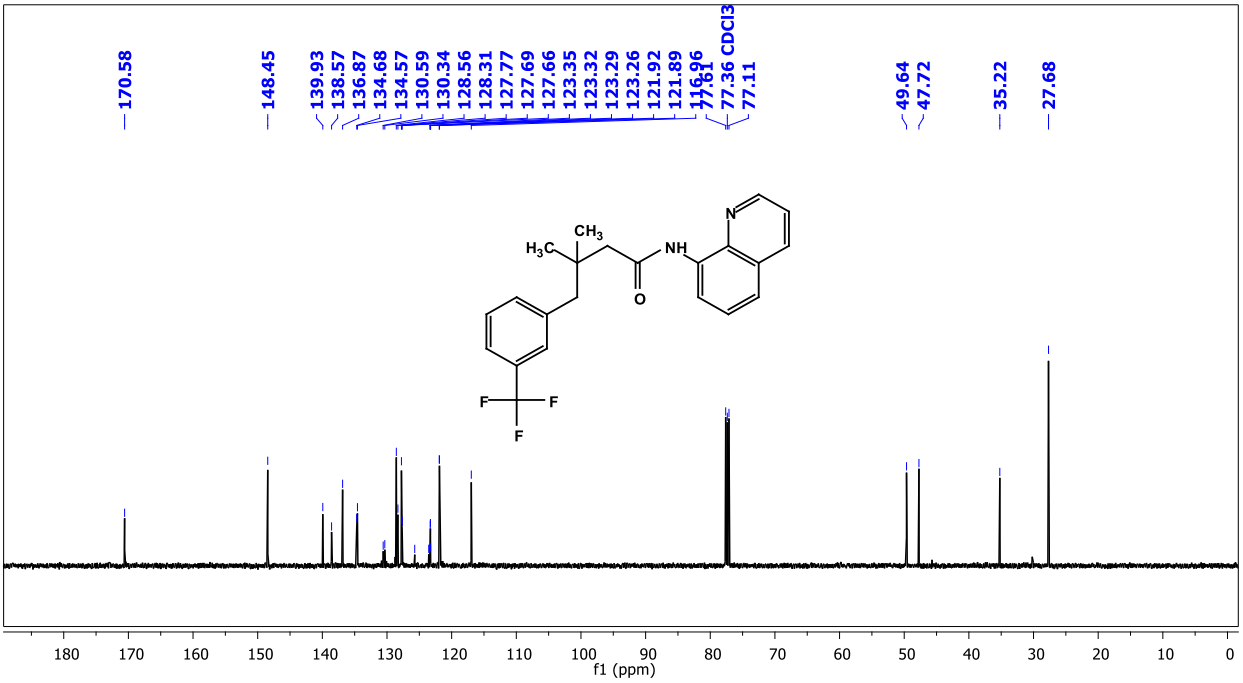
^{13}C Spectra of 5e:



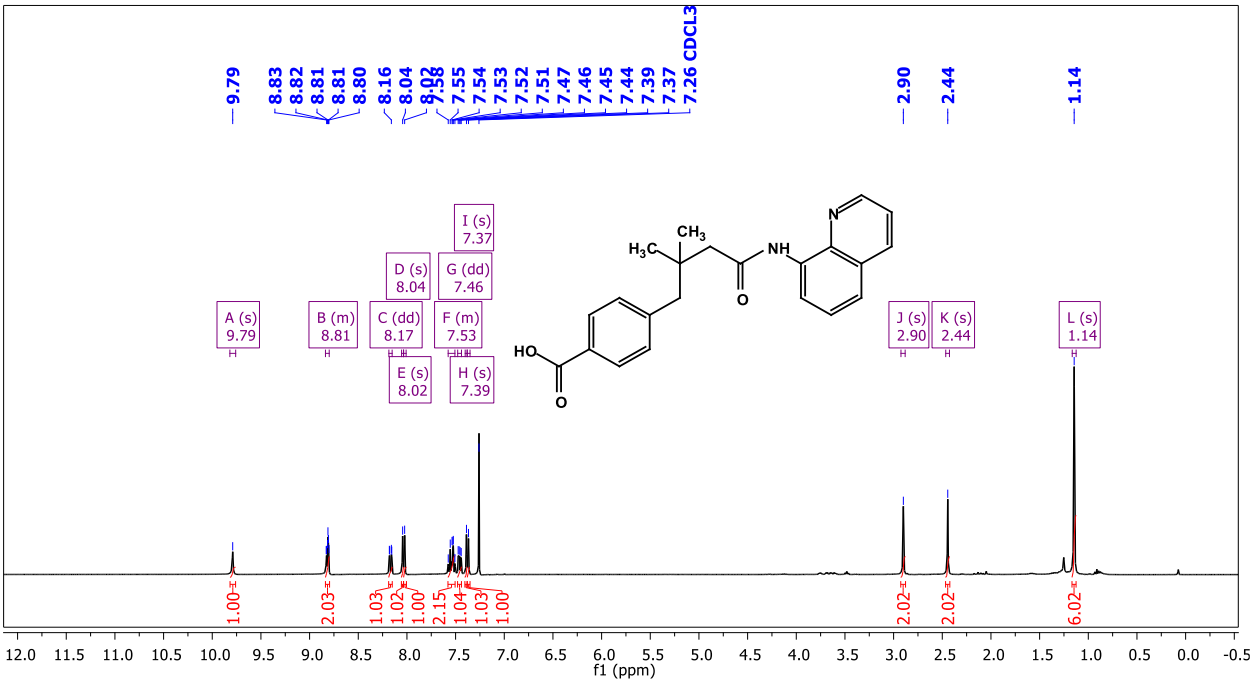
^{1}H Spectra of 5f:



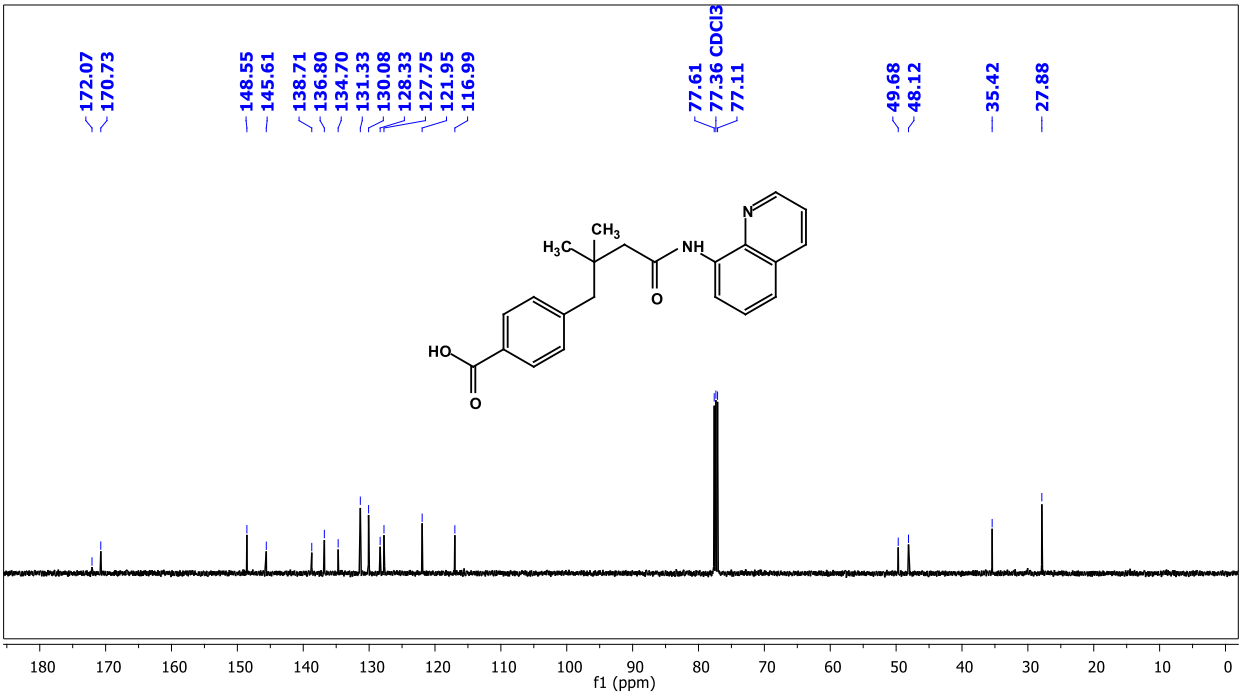
^{13}C Spectra of 5f:



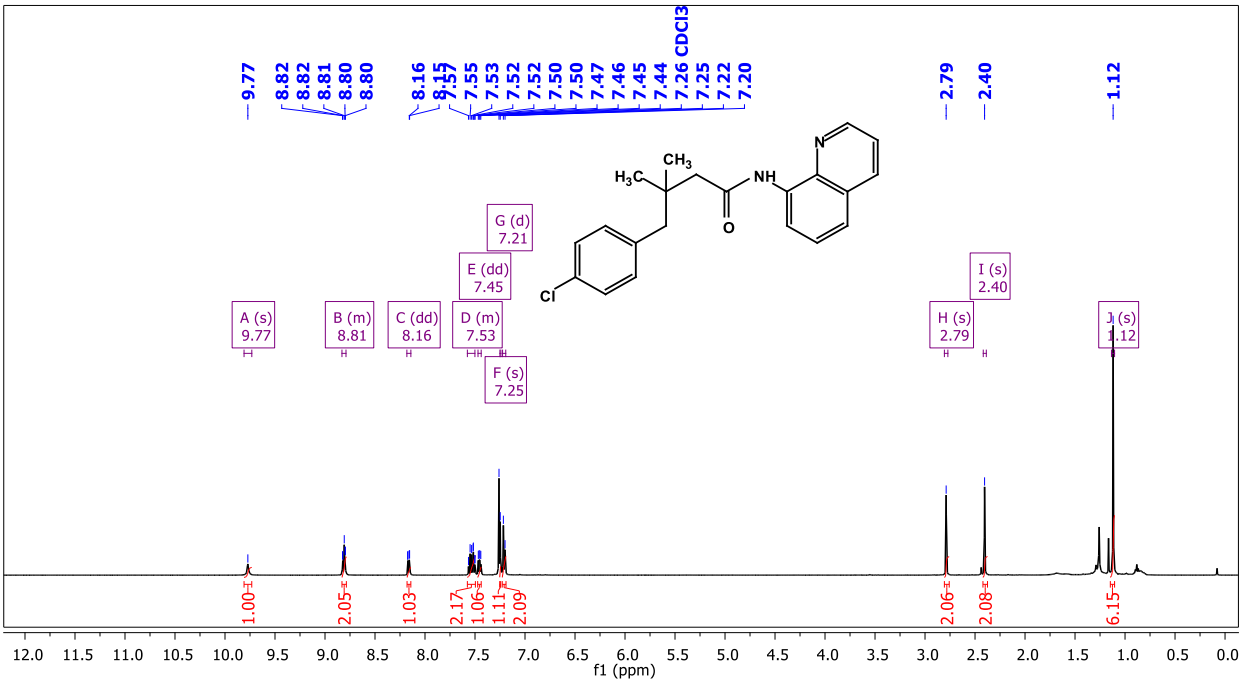
^{1}H Spectra of 5h:



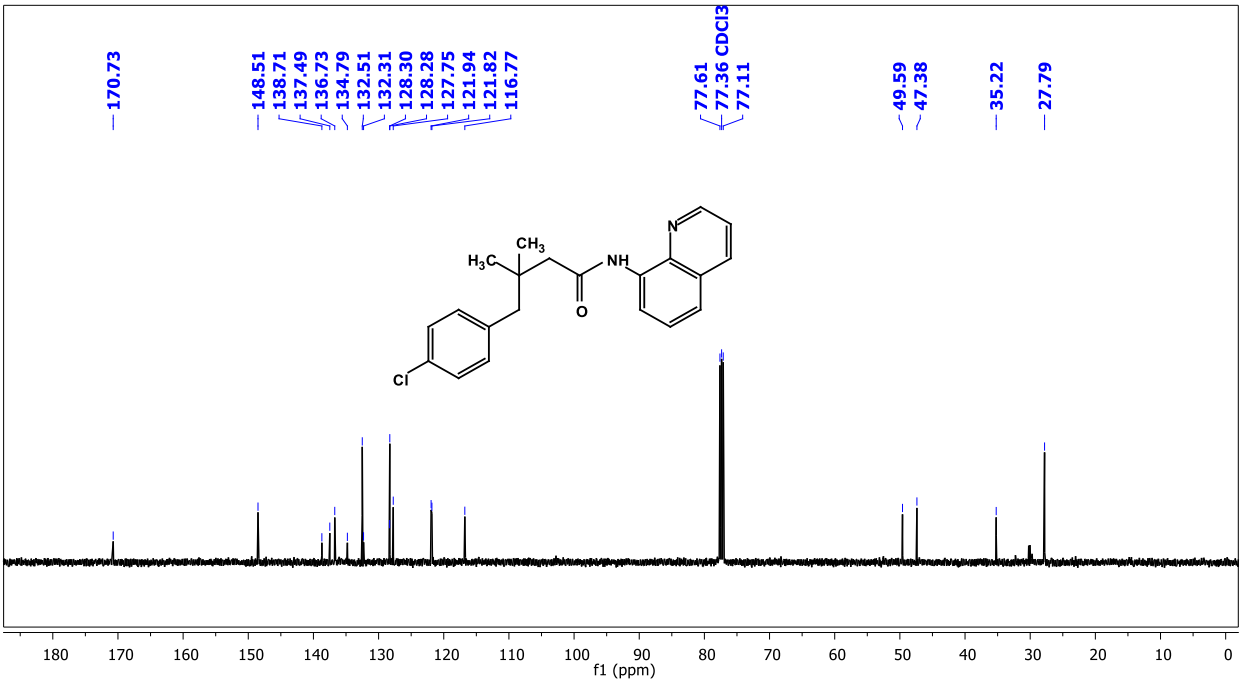
^{13}C Spectra of 5h:



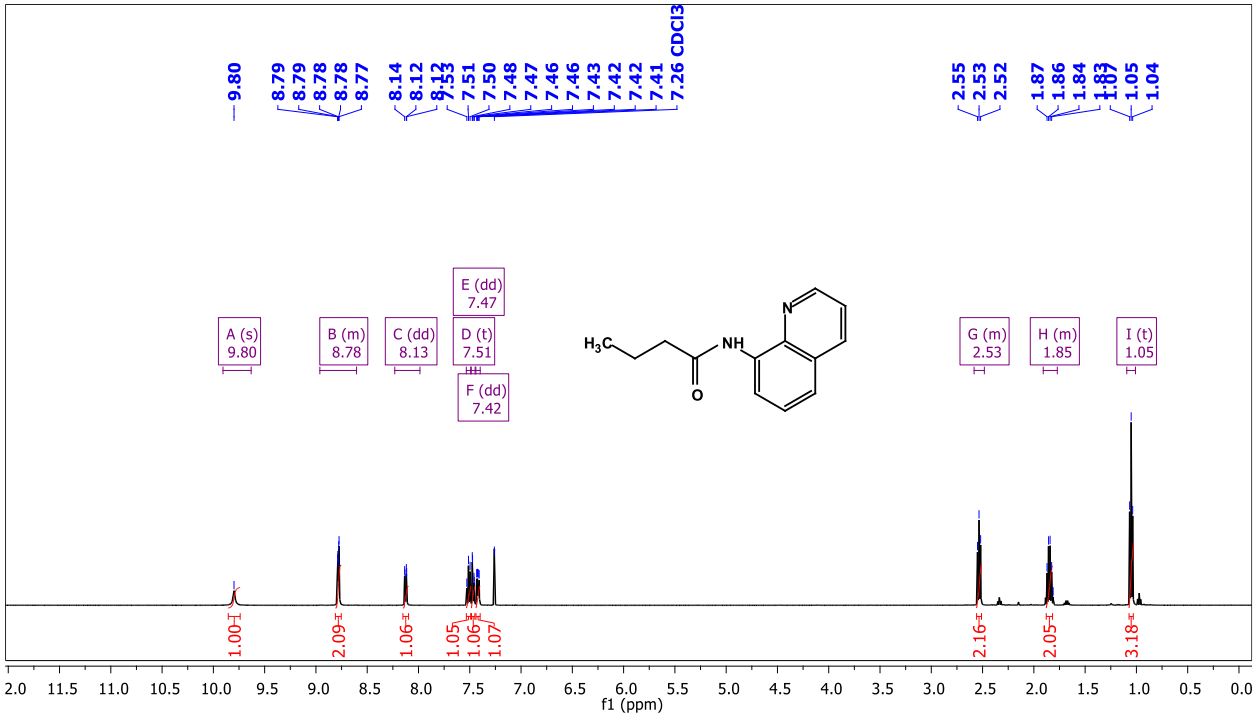
^{1}H Spectra of 5p:



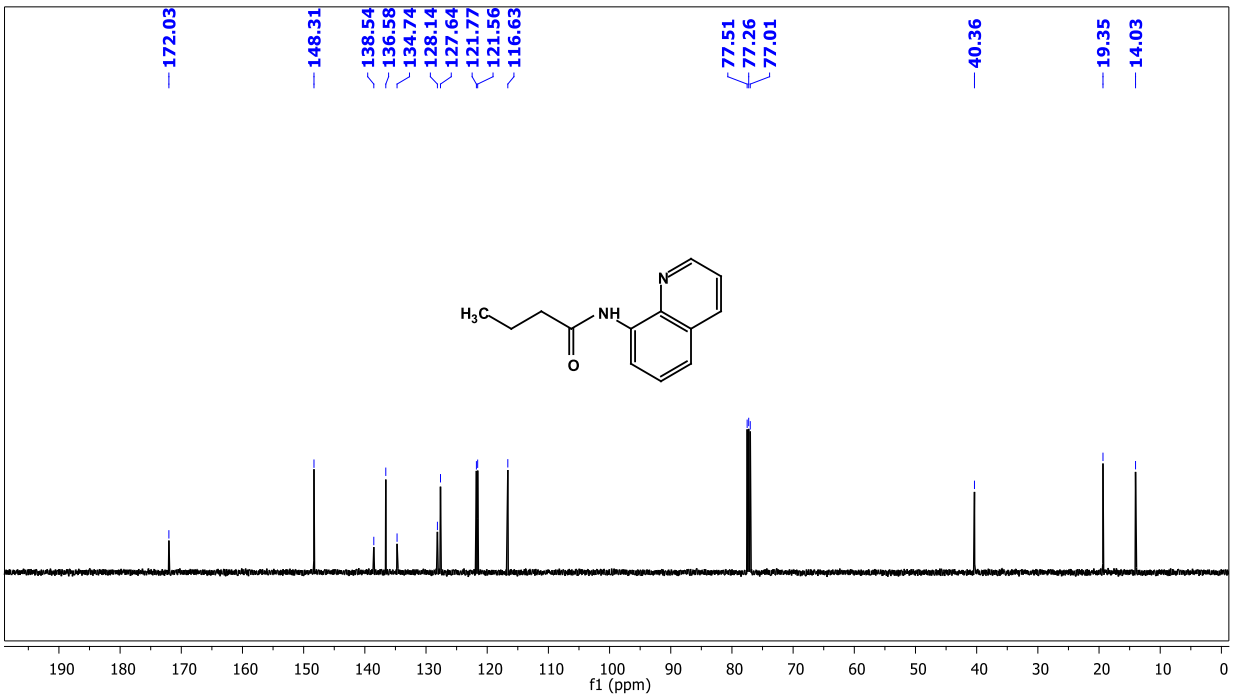
^{13}C Spectra of 5p:



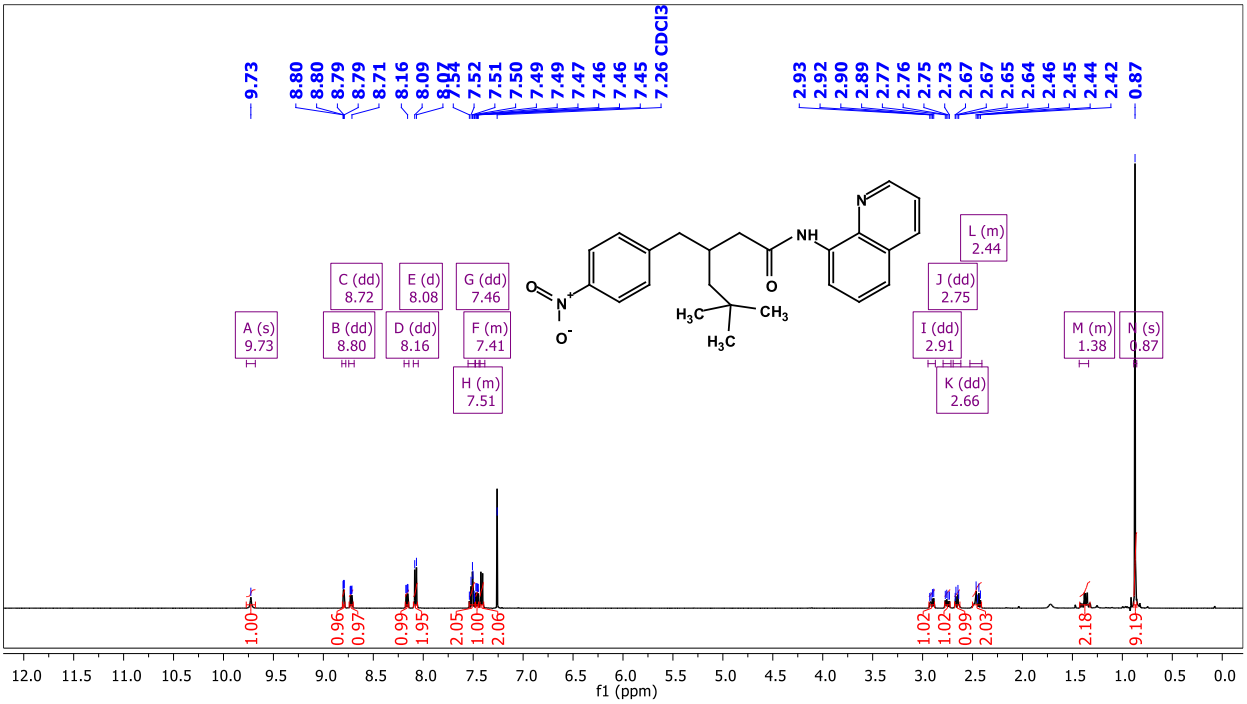
^{1}H Spectra of 6:



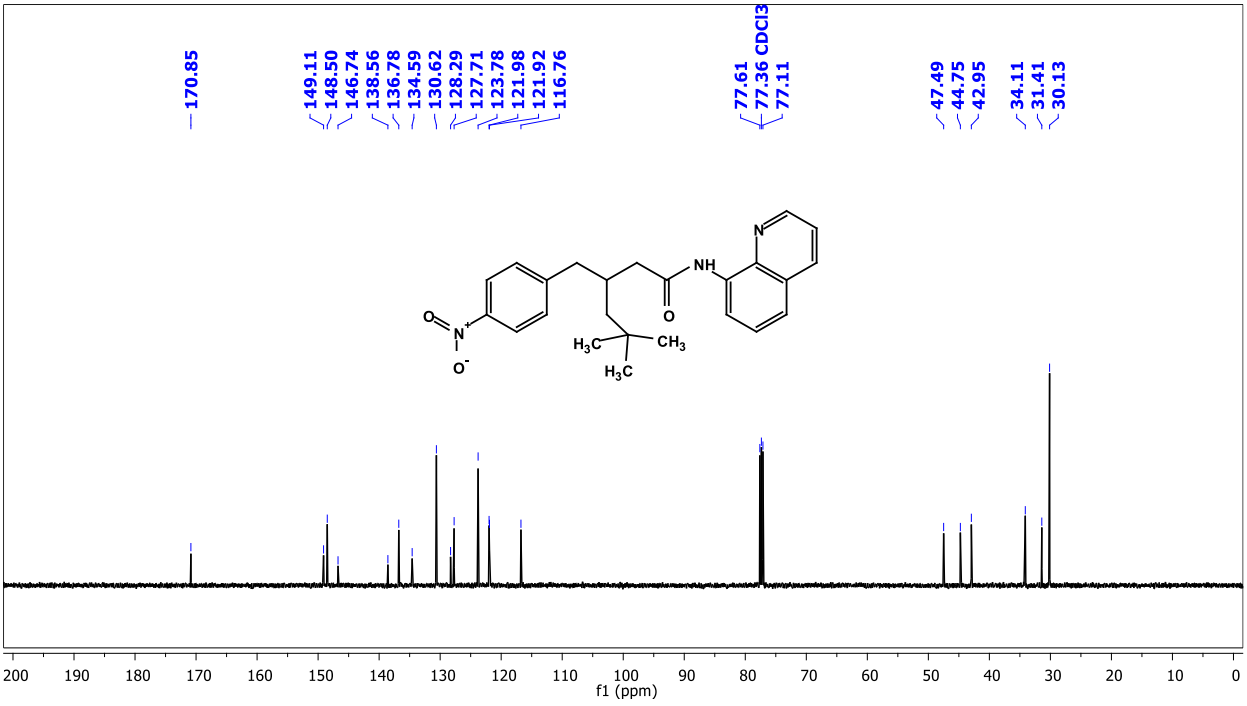
^{13}C Spectra of 6:



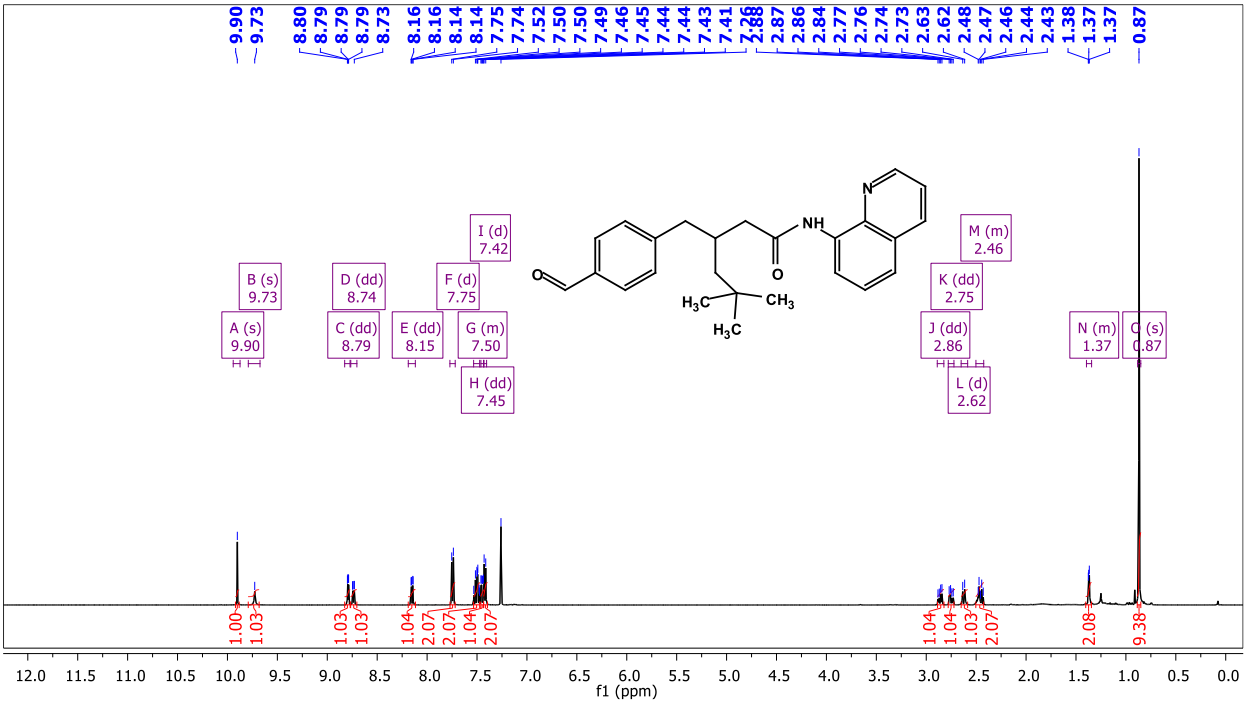
^{1}H Spectra of 9a:



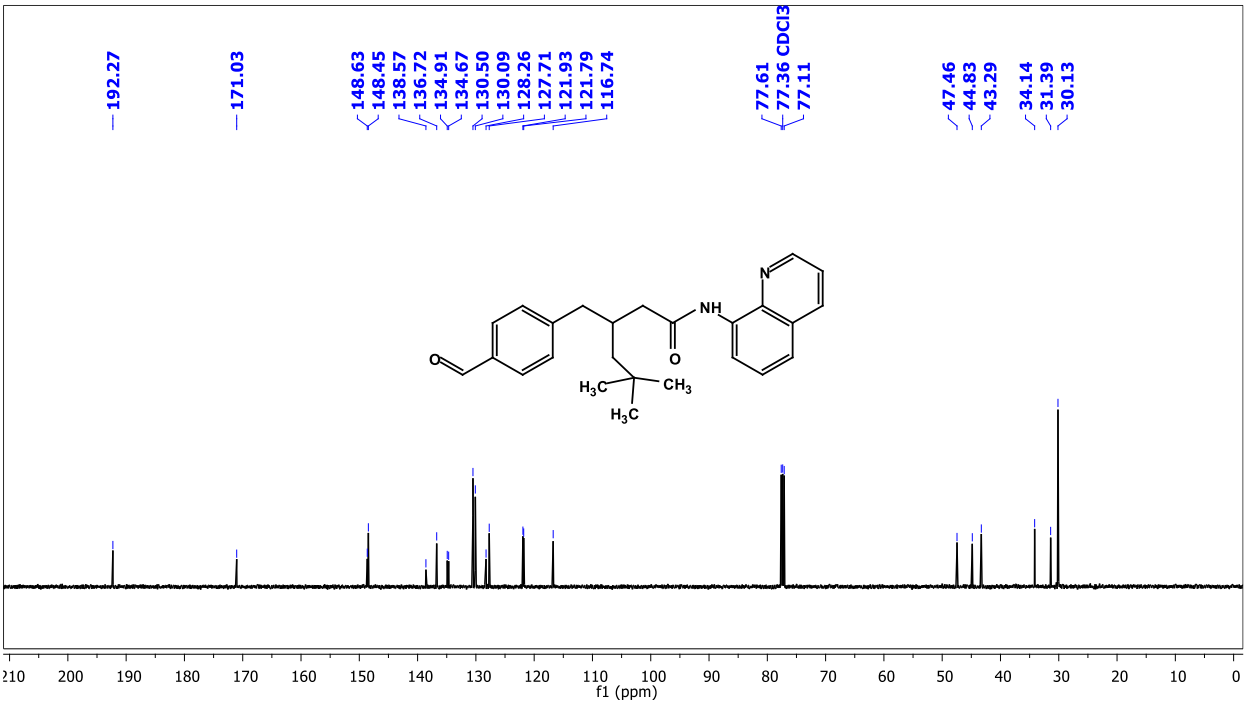
^{13}C Spectra of 9a:



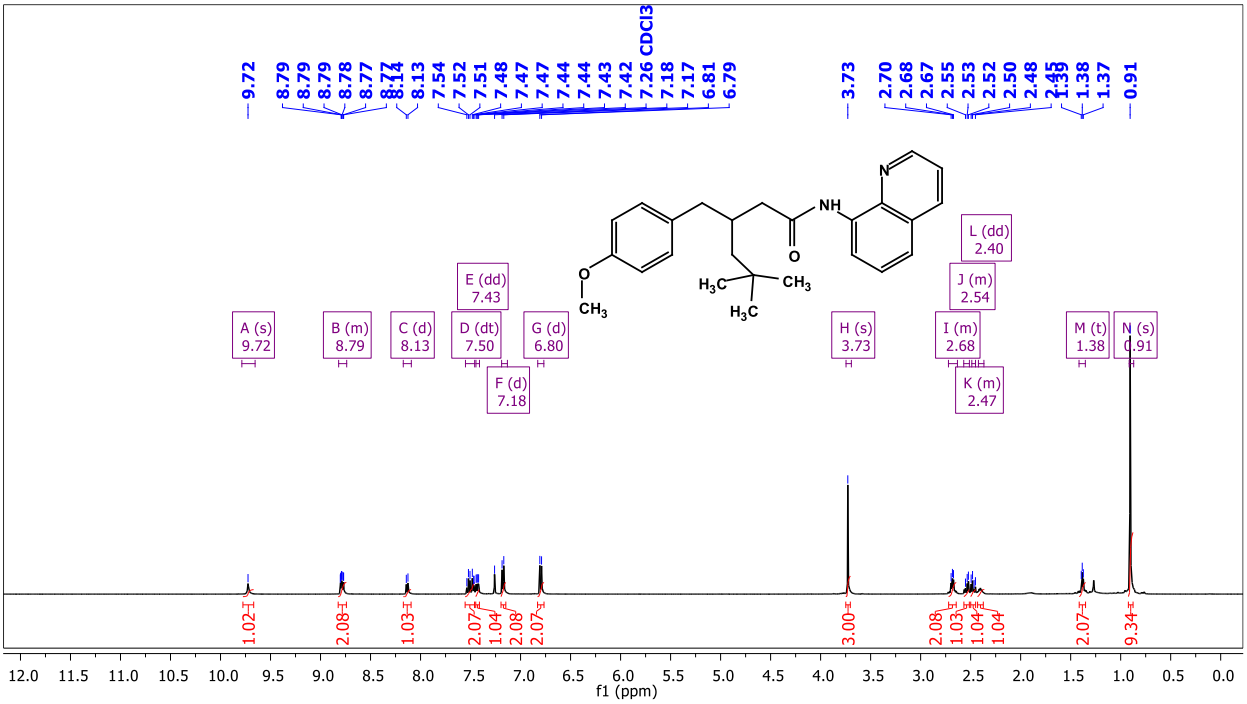
^{1}H Spectra of 9b:



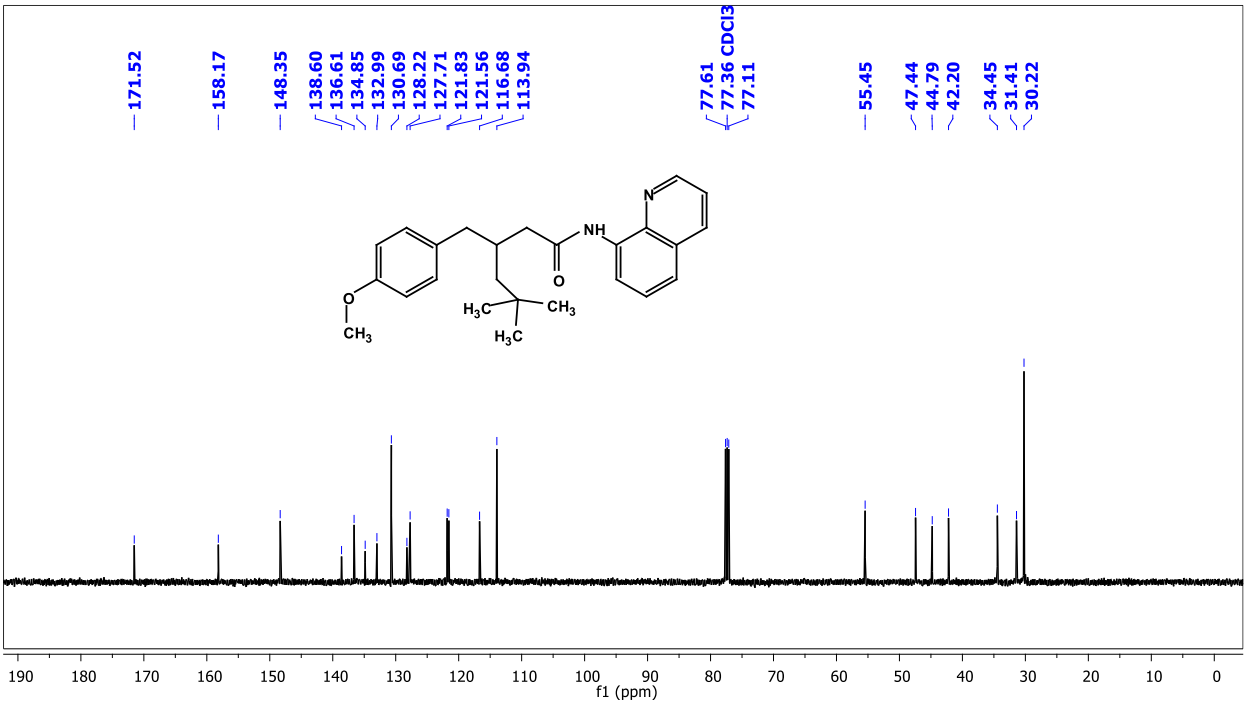
^{13}C Spectra of 9b:



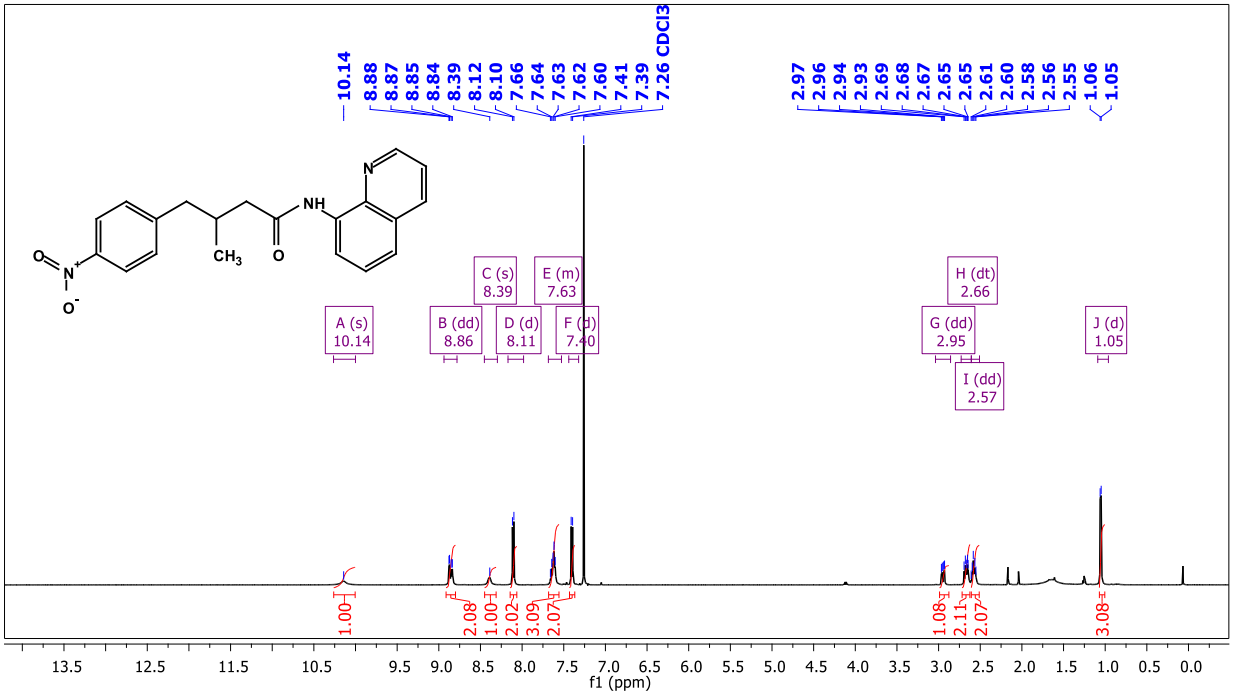
^{1}H Spectra of 9e:



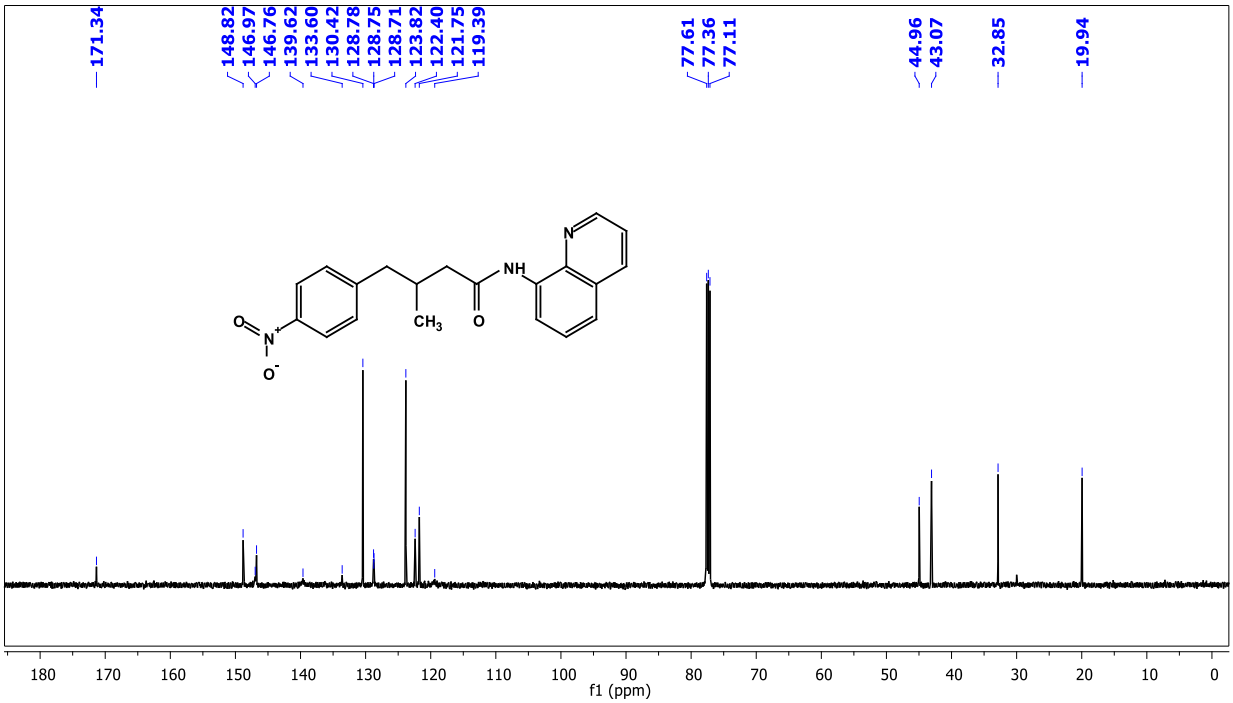
^{13}C Spectra of 9e:



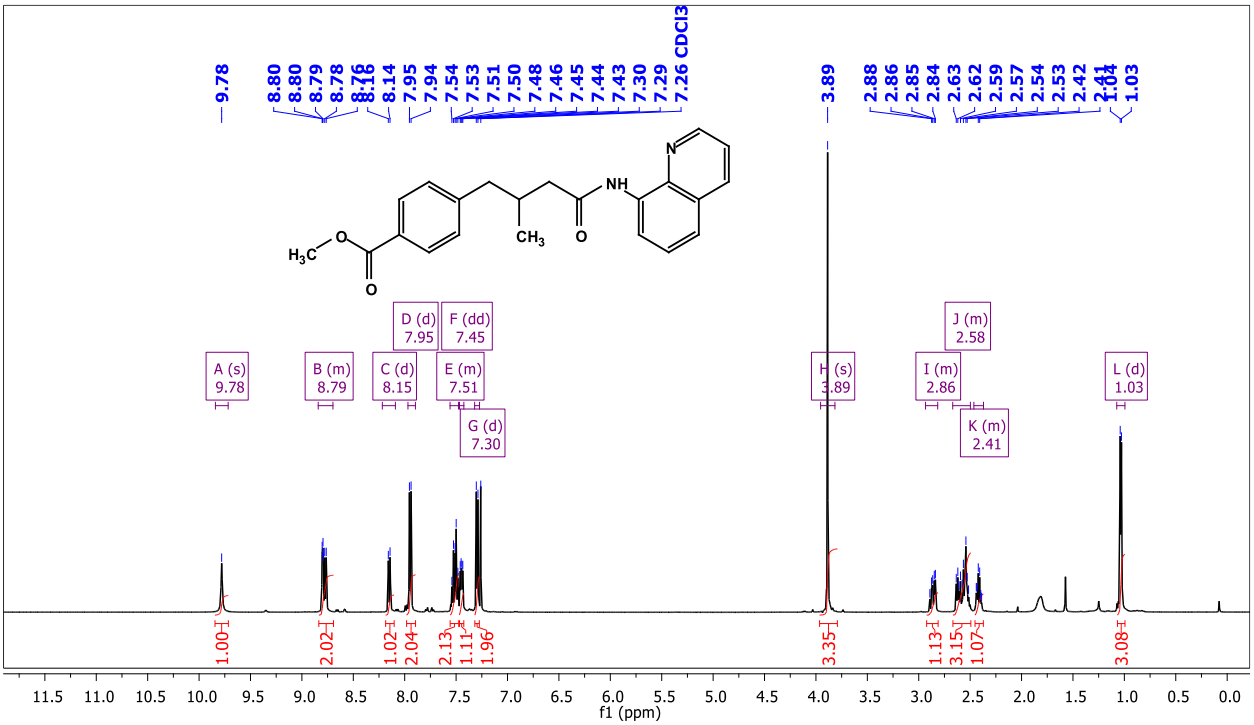
^{1}H Spectra of 9f:



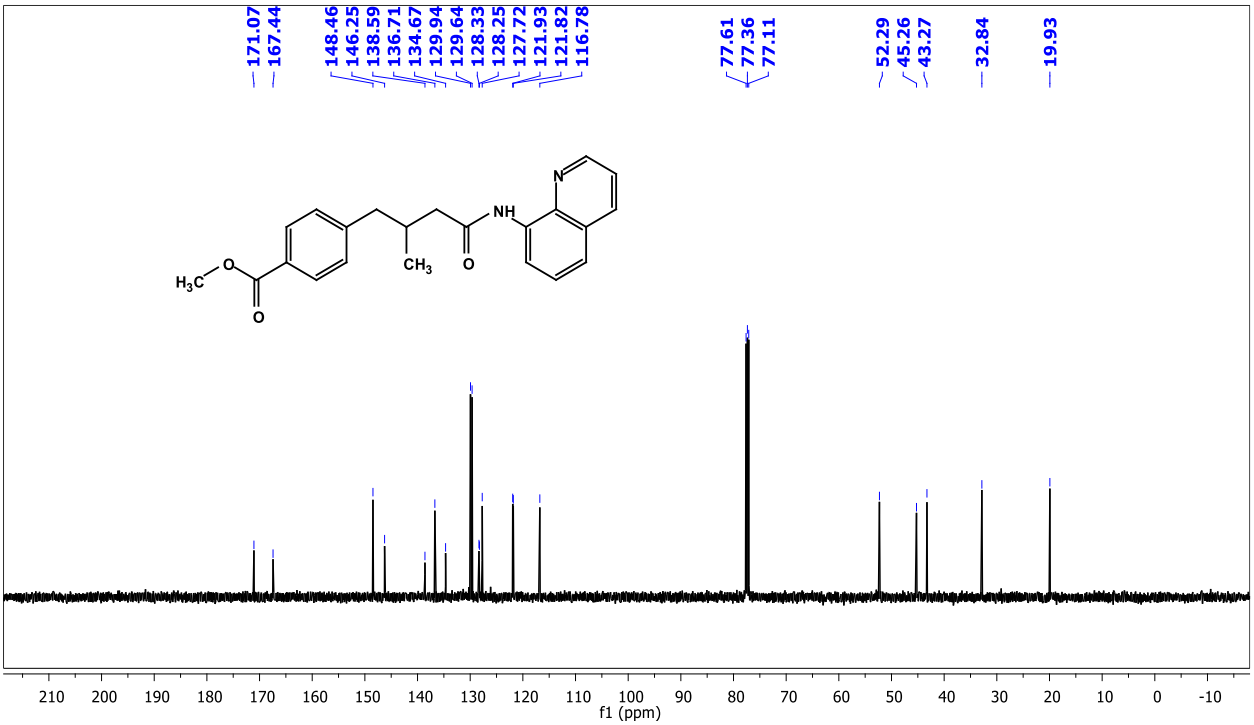
^{13}C Spectra of 9f:



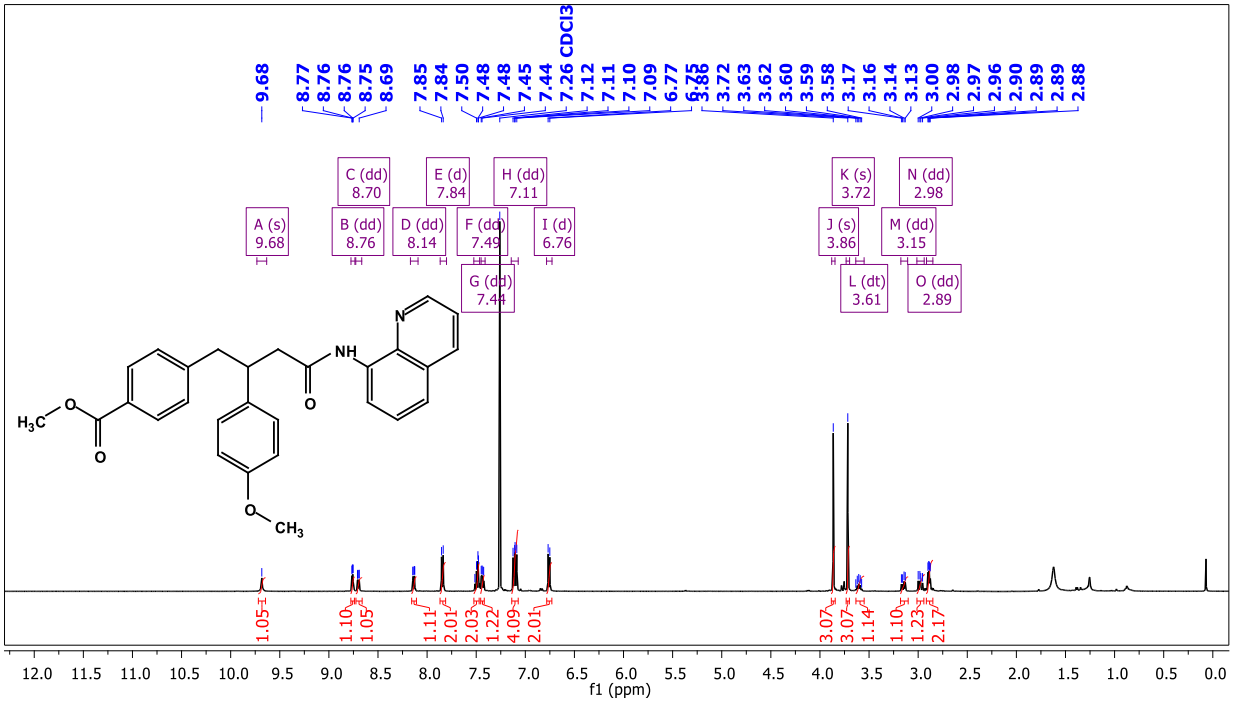
^{1}H Spectra of 9g:



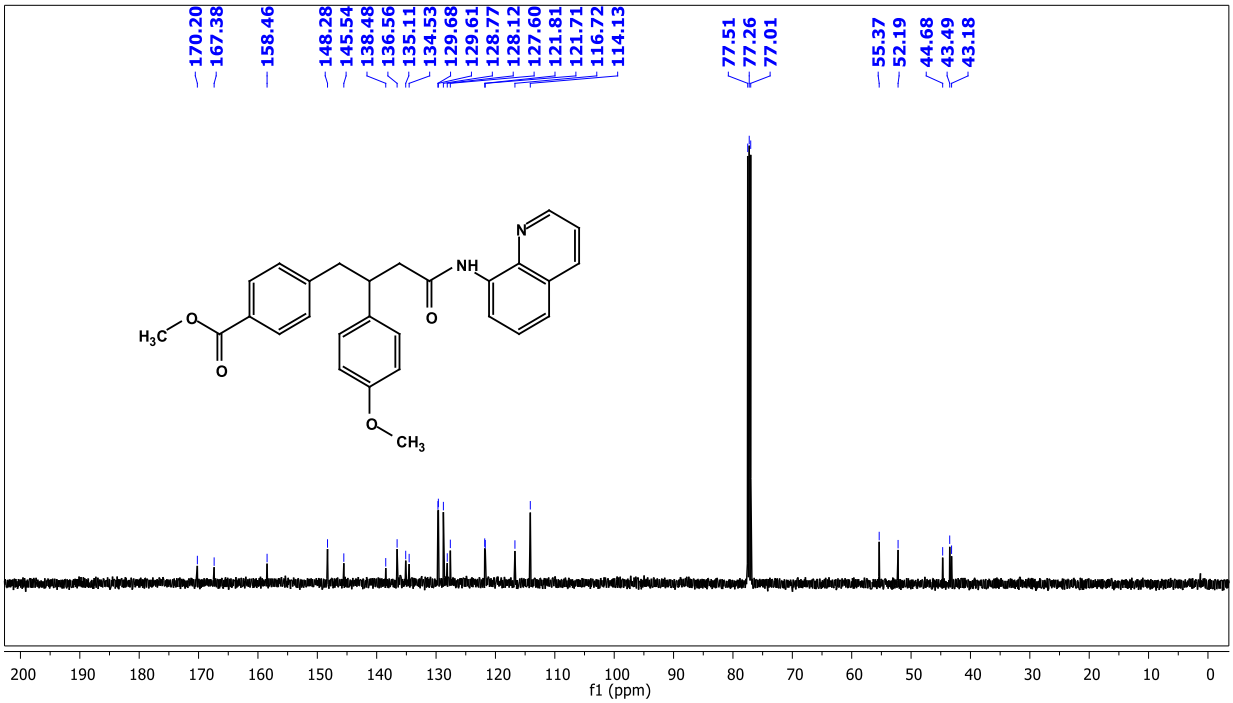
^{13}C Spectra of 9g:


171.07
167.44
148.46
146.25
138.59
136.71
134.67
129.94
129.64
128.33
128.25
127.72
121.93
121.82
116.78
77.61
77.36
77.11
52.29
45.26
43.27
32.84
19.93
N
NH
O
CH3
H3C
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

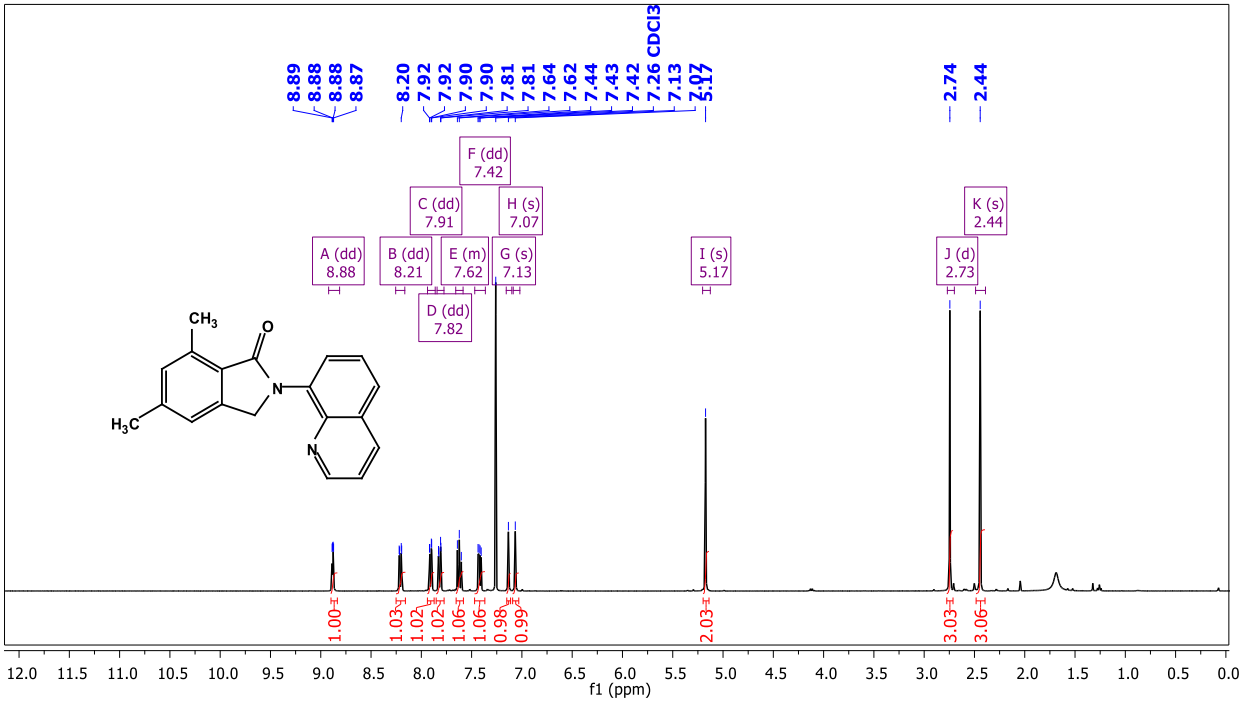
^{1}H Spectra of 9k:



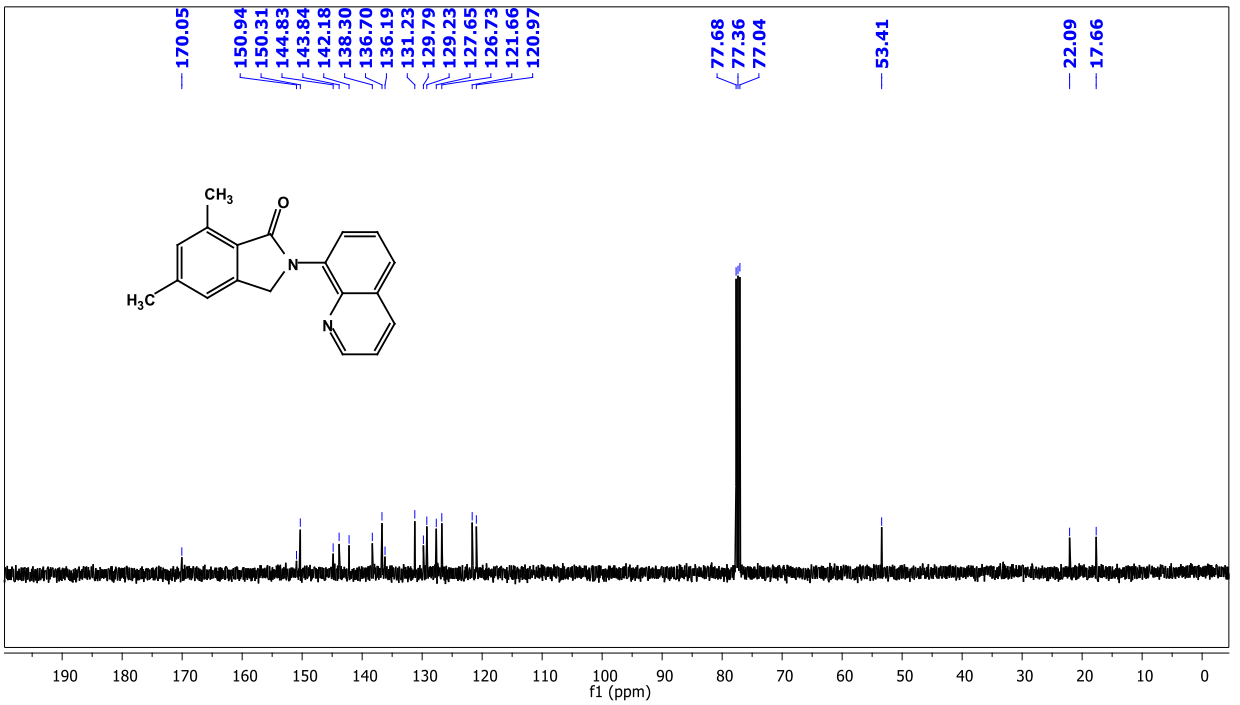
^{13}C Spectra of 9k:



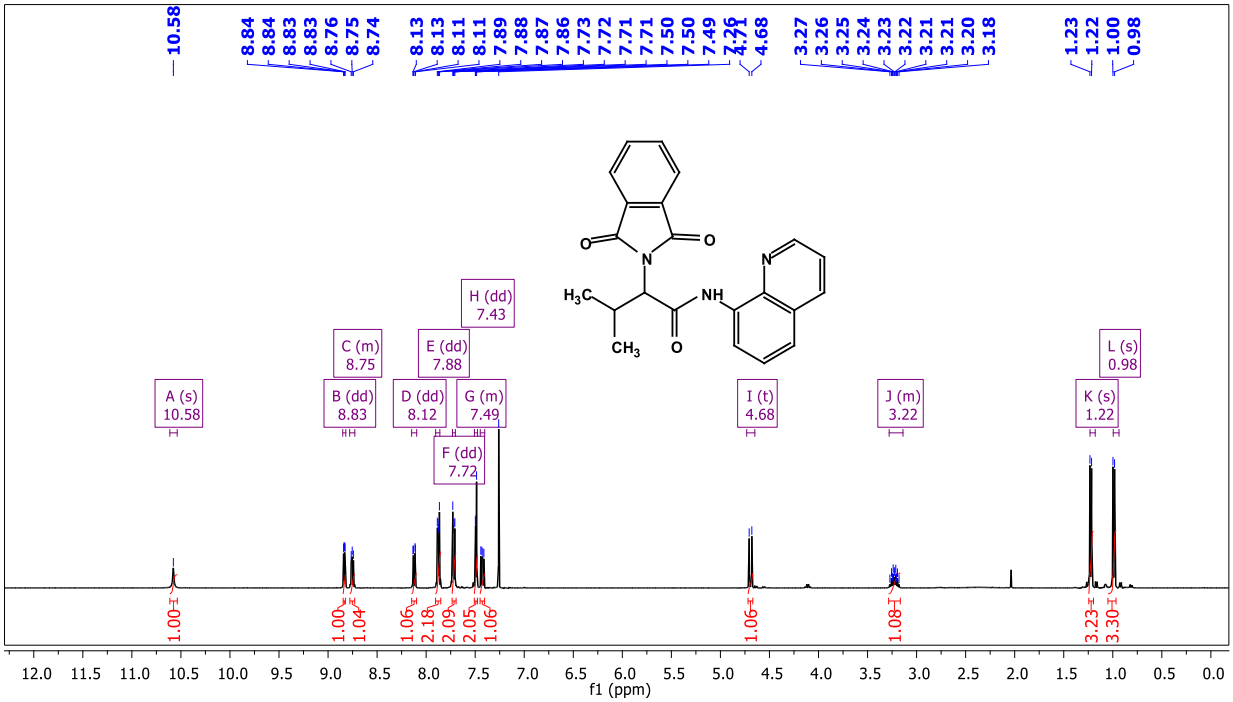
^{1}H Spectra of 9m:



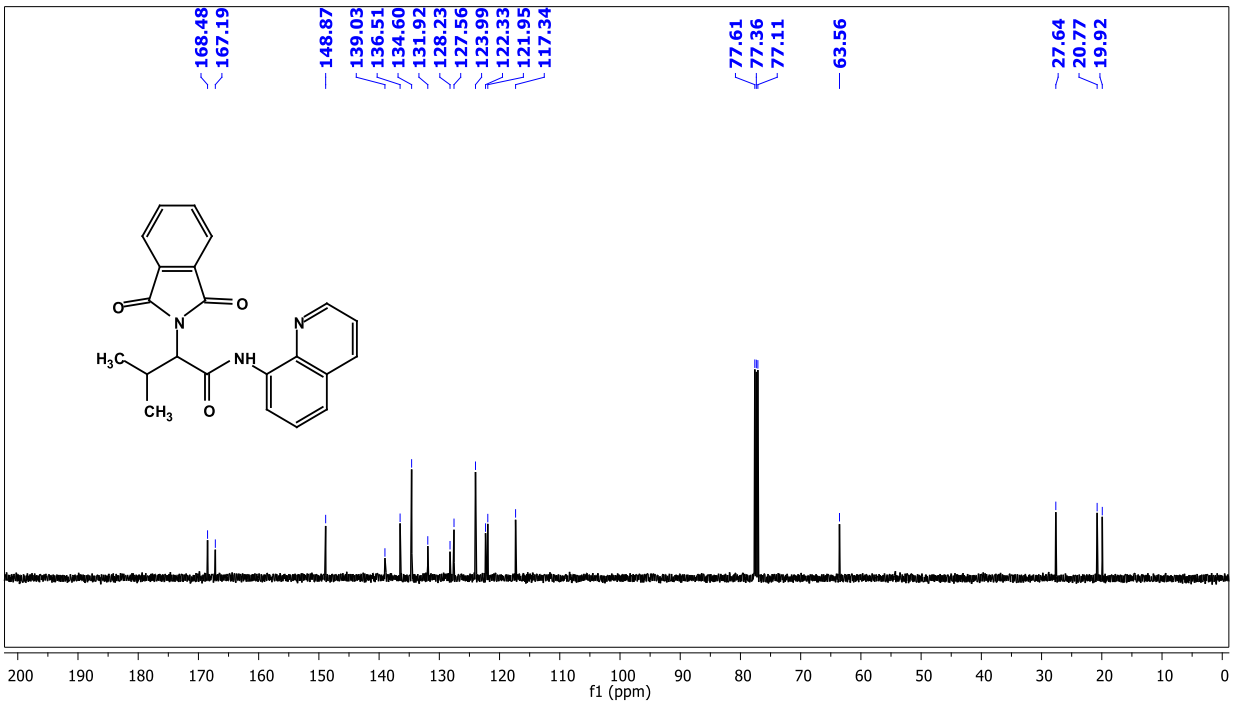
^{13}C Spectra of 9m:



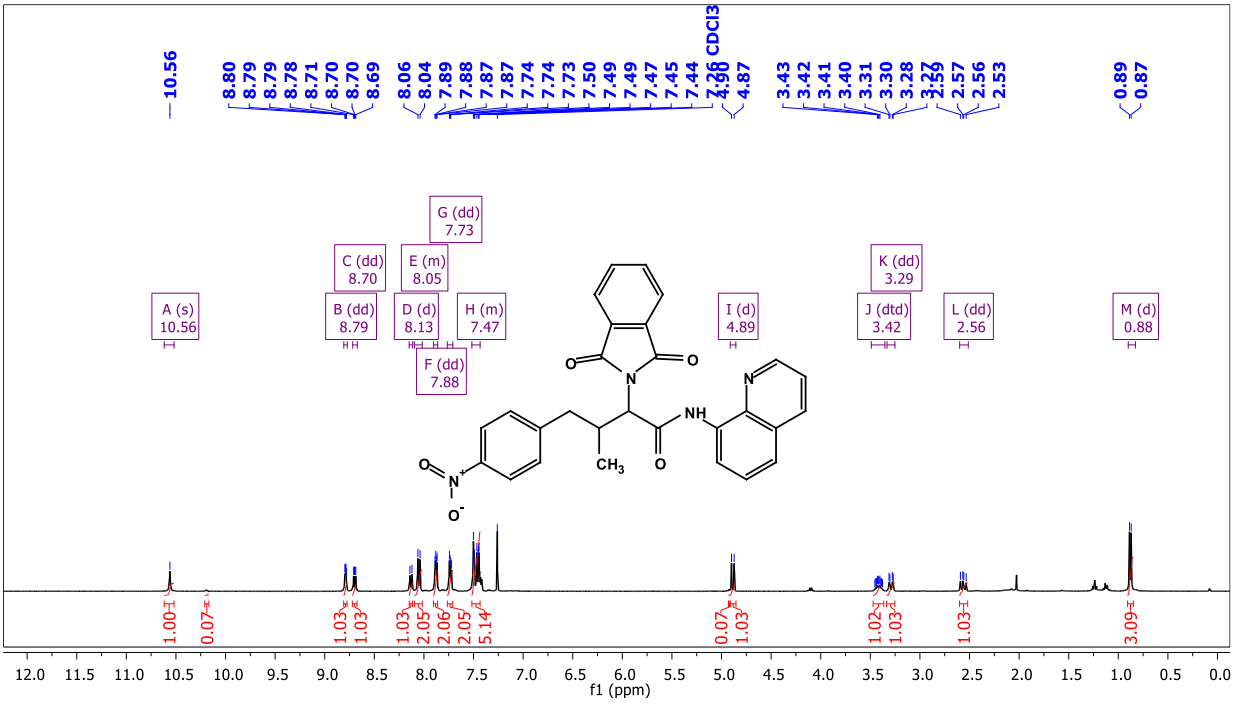
^{1}H Spectra of 10:



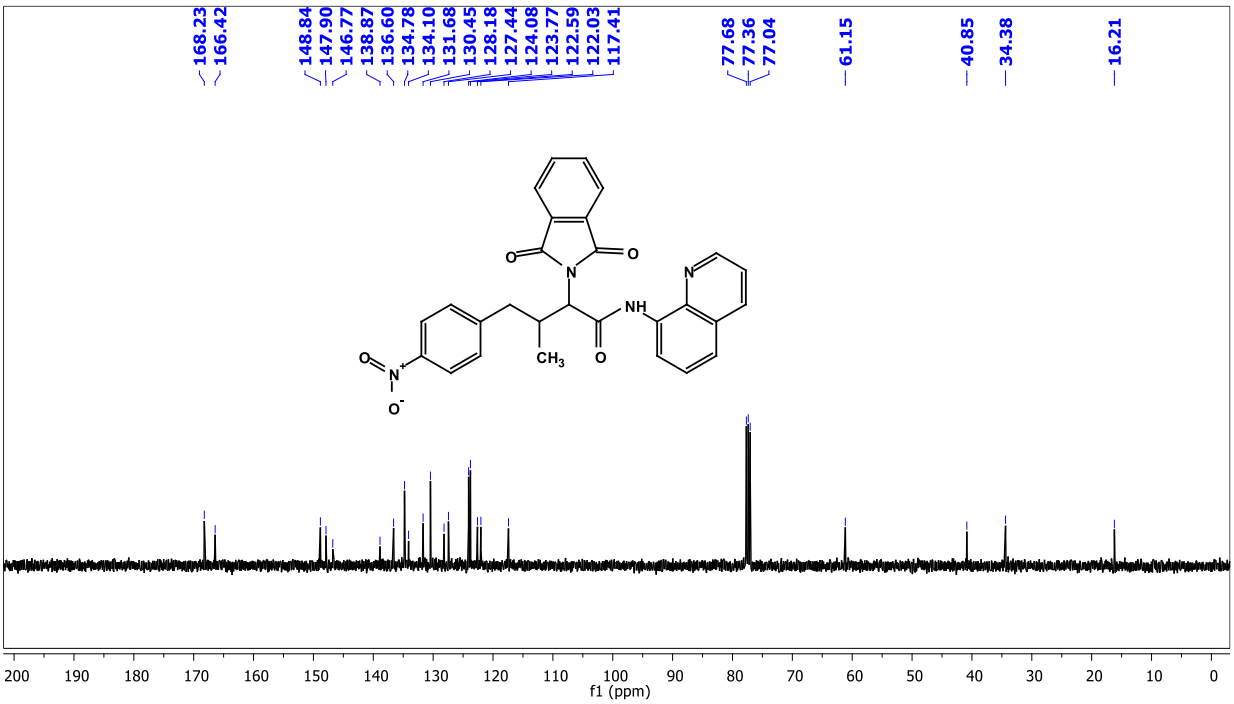
^{13}C Spectra of 10:



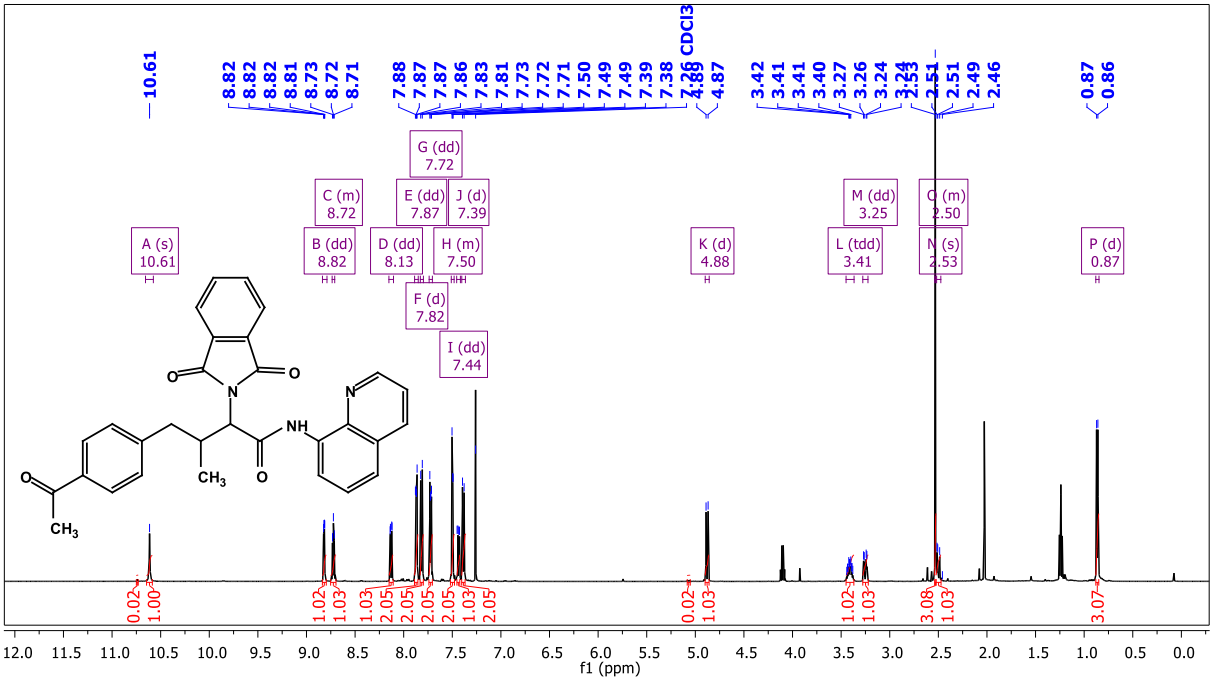
^{1}H Spectra of 11a:



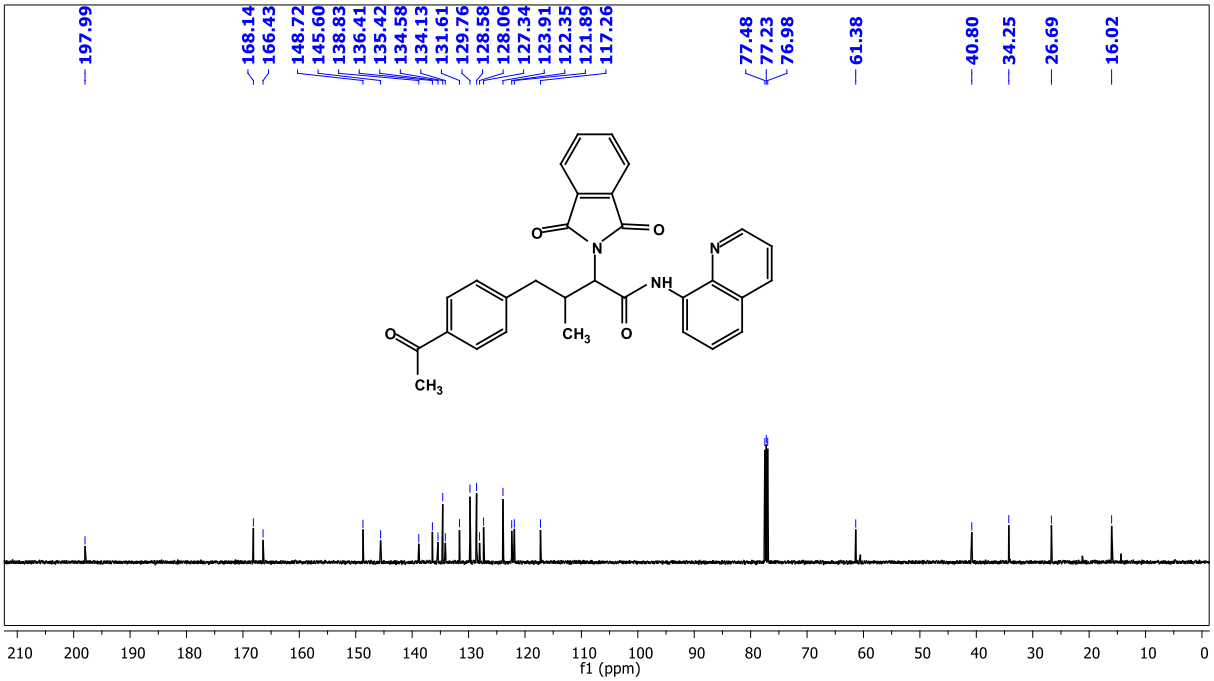
^{13}C Spectra of 11a:



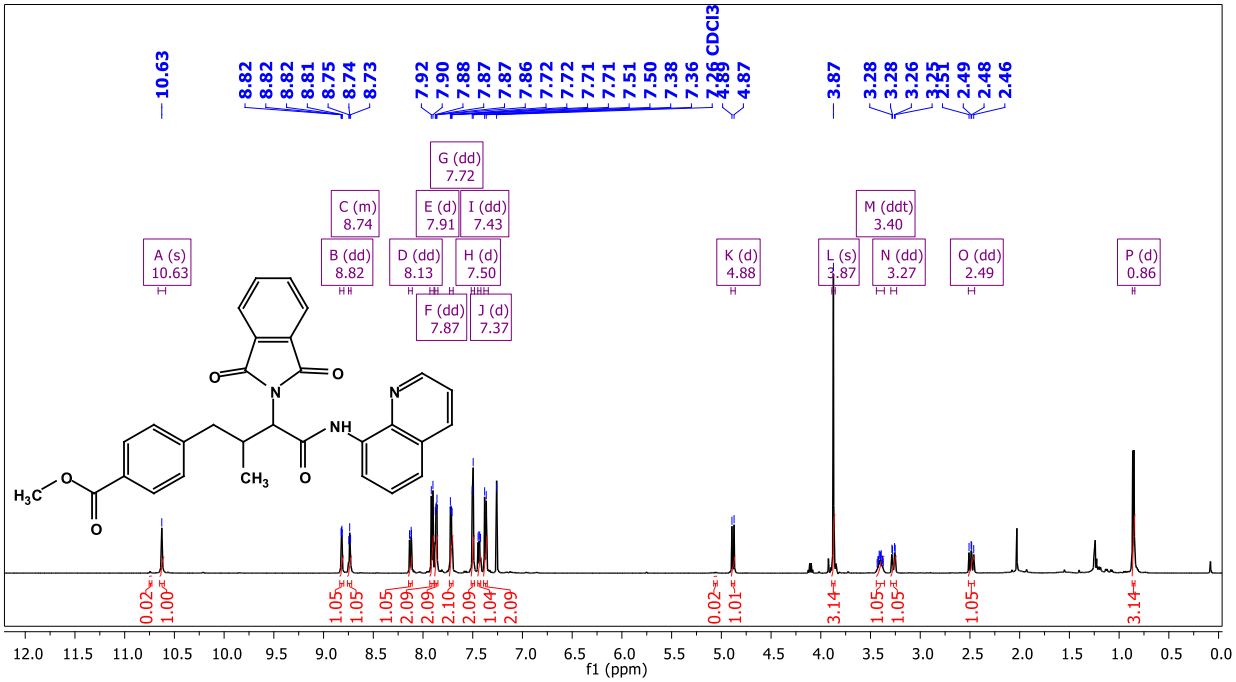
^{1}H Spectra of 11b:



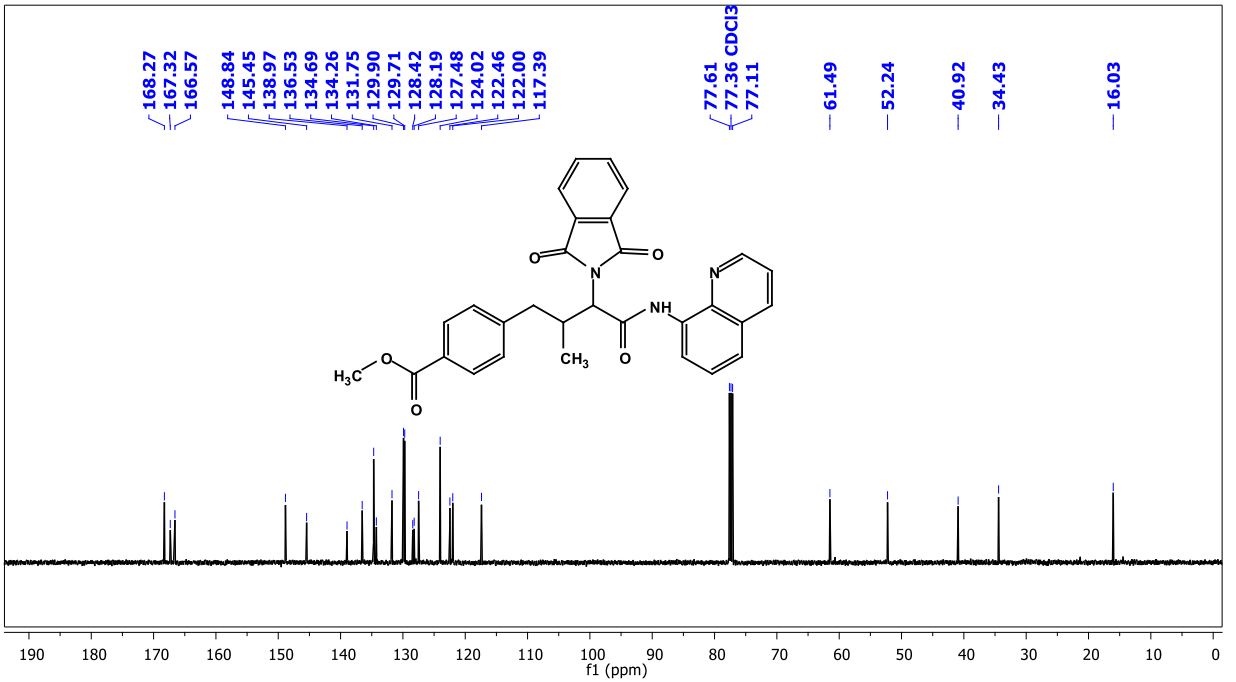
^{13}C Spectra of 11b:



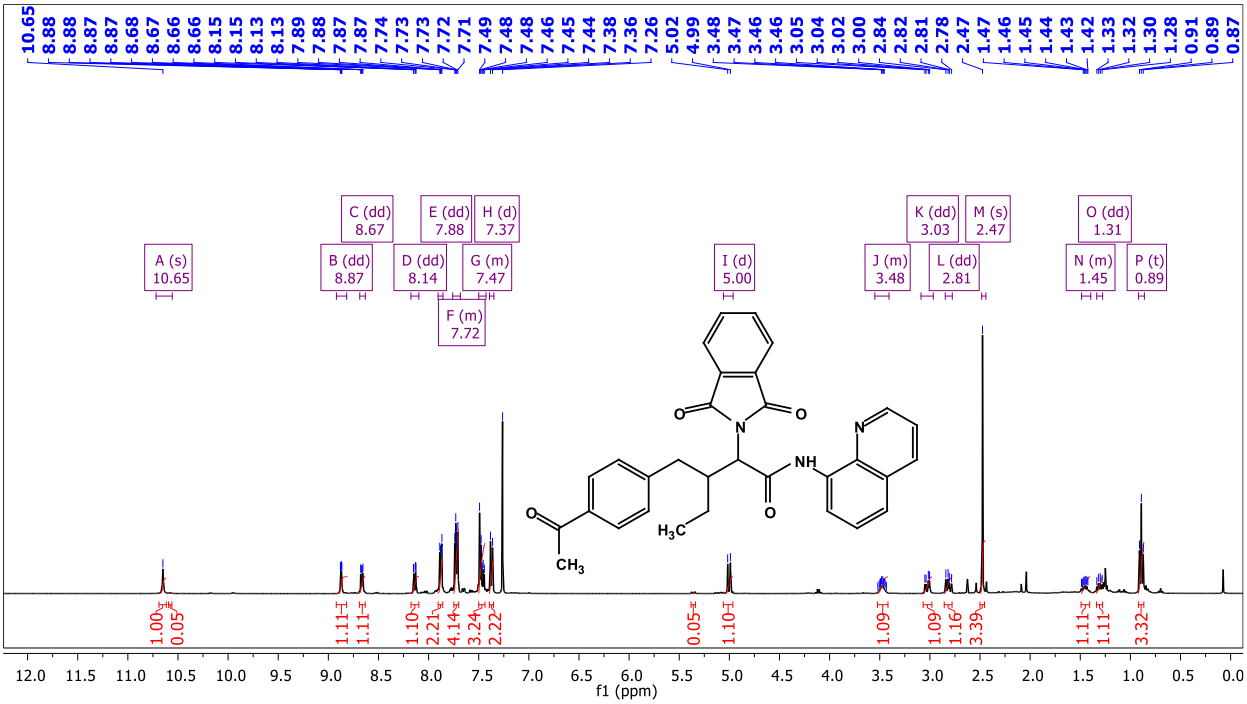
^{1}H Spectra of 11c:



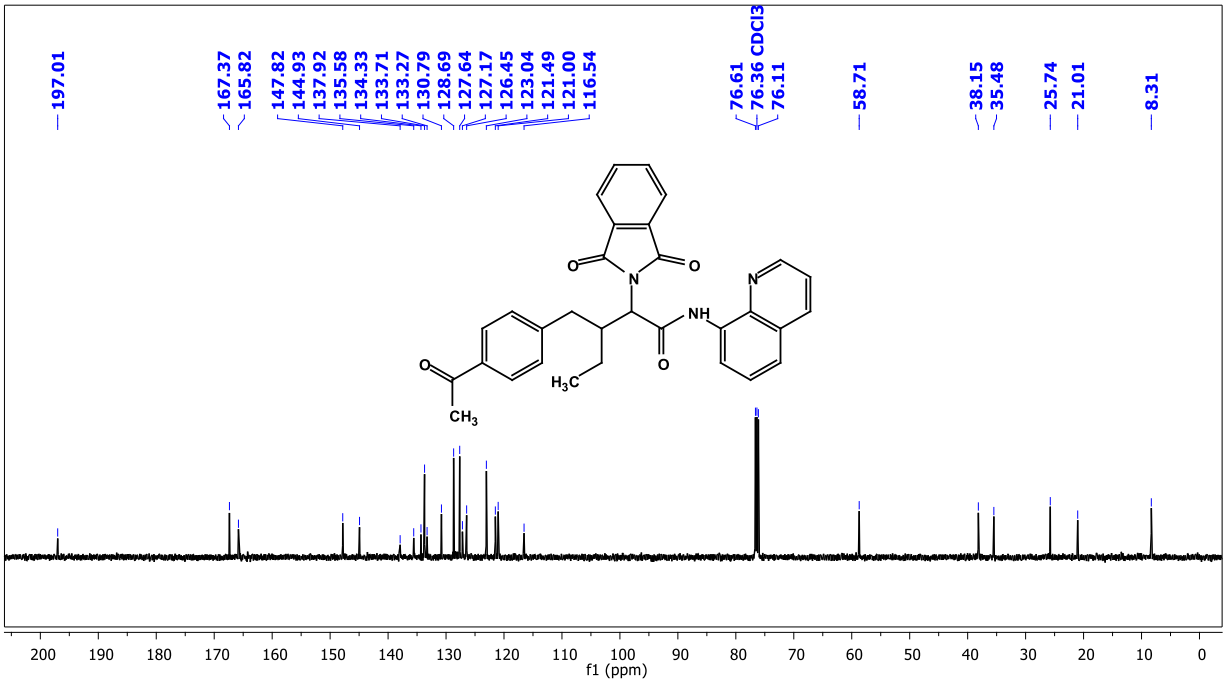
^{13}C Spectra of 11c:



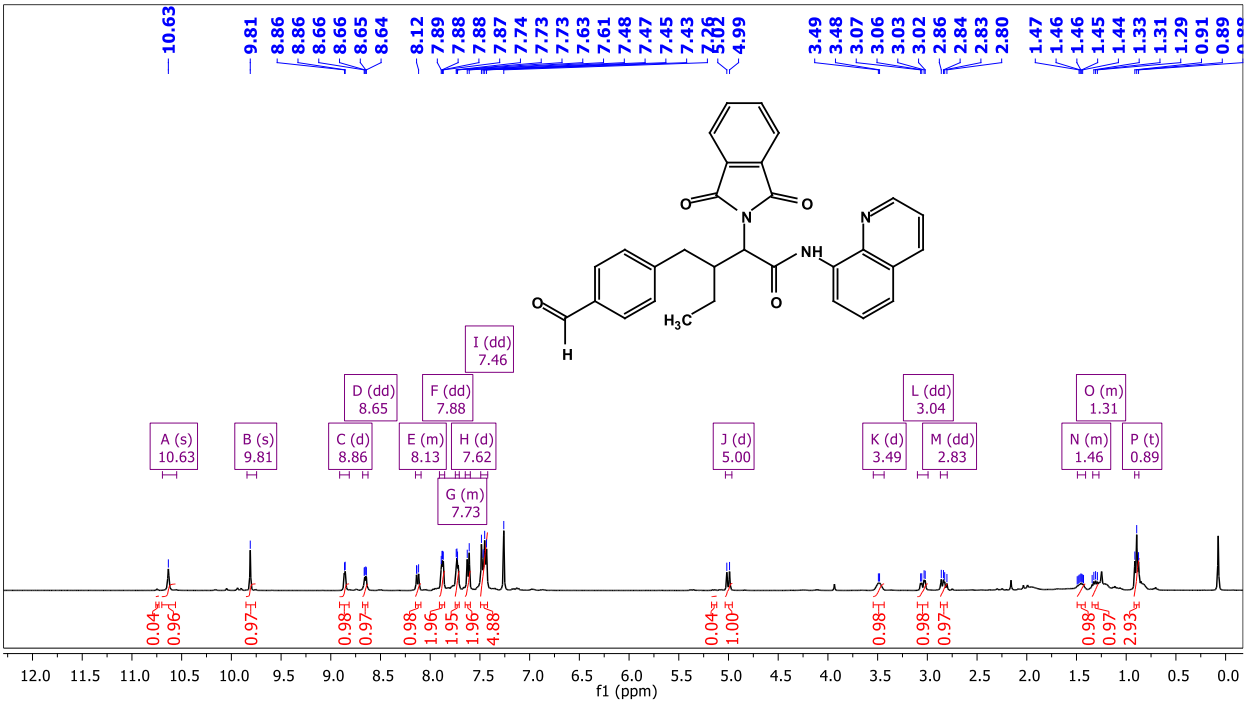
^{1}H Spectra of 11f:



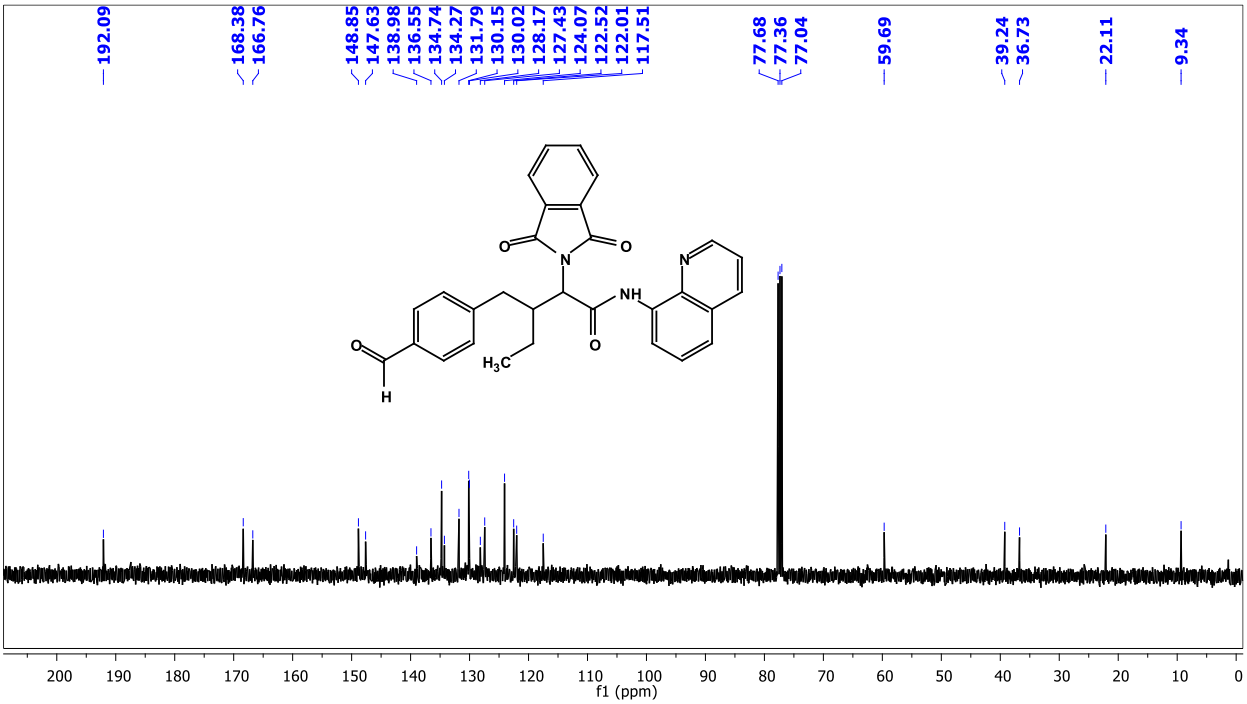
^{13}C Spectra of 11f:



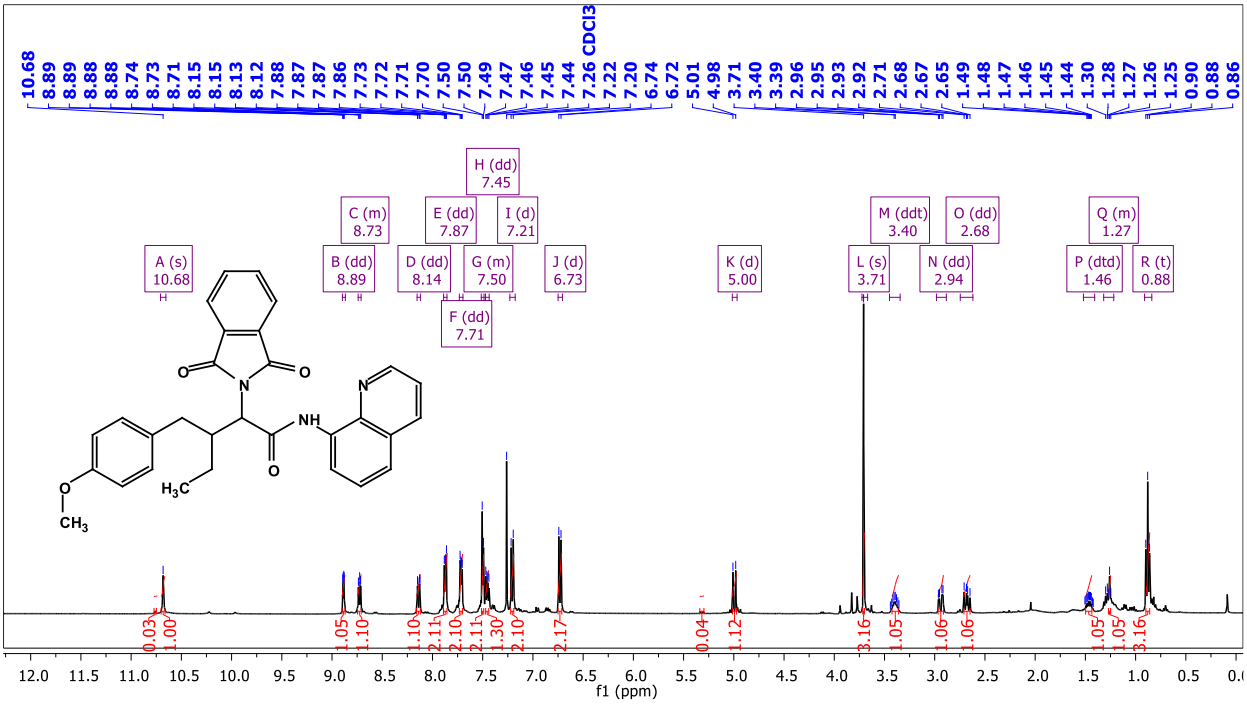
^{1}H Spectra of 11g:



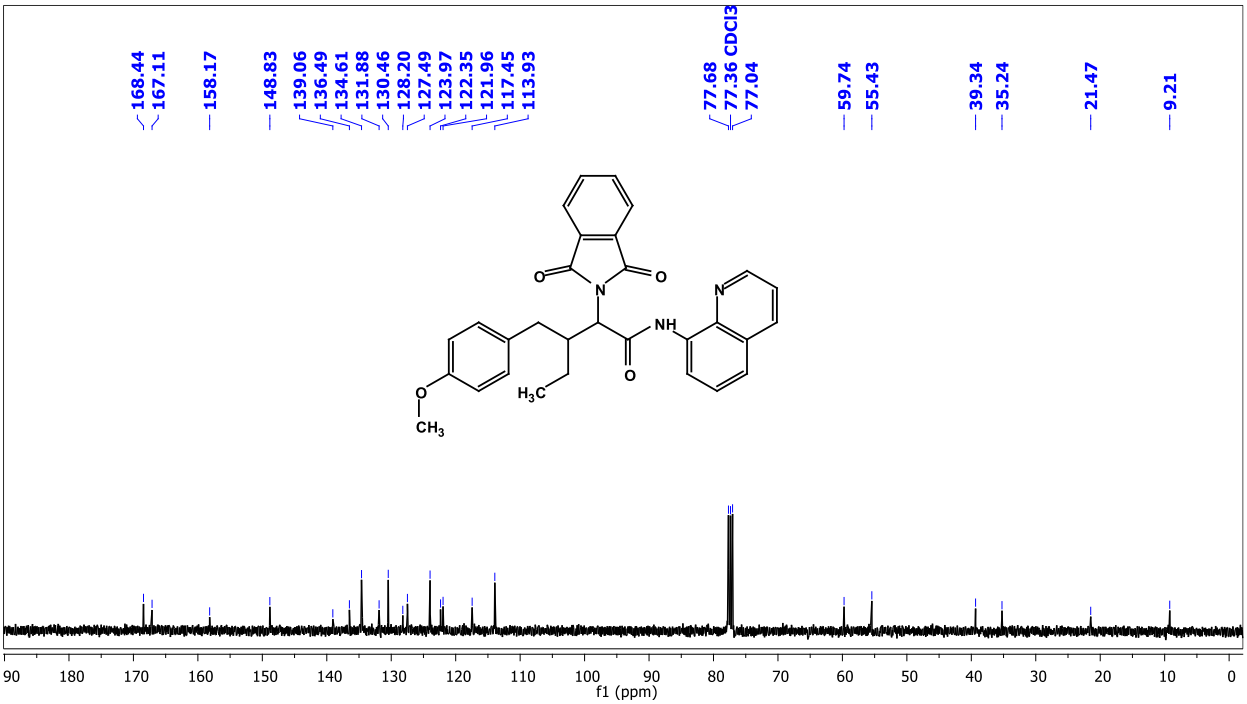
^{13}C Spectra of 11g:



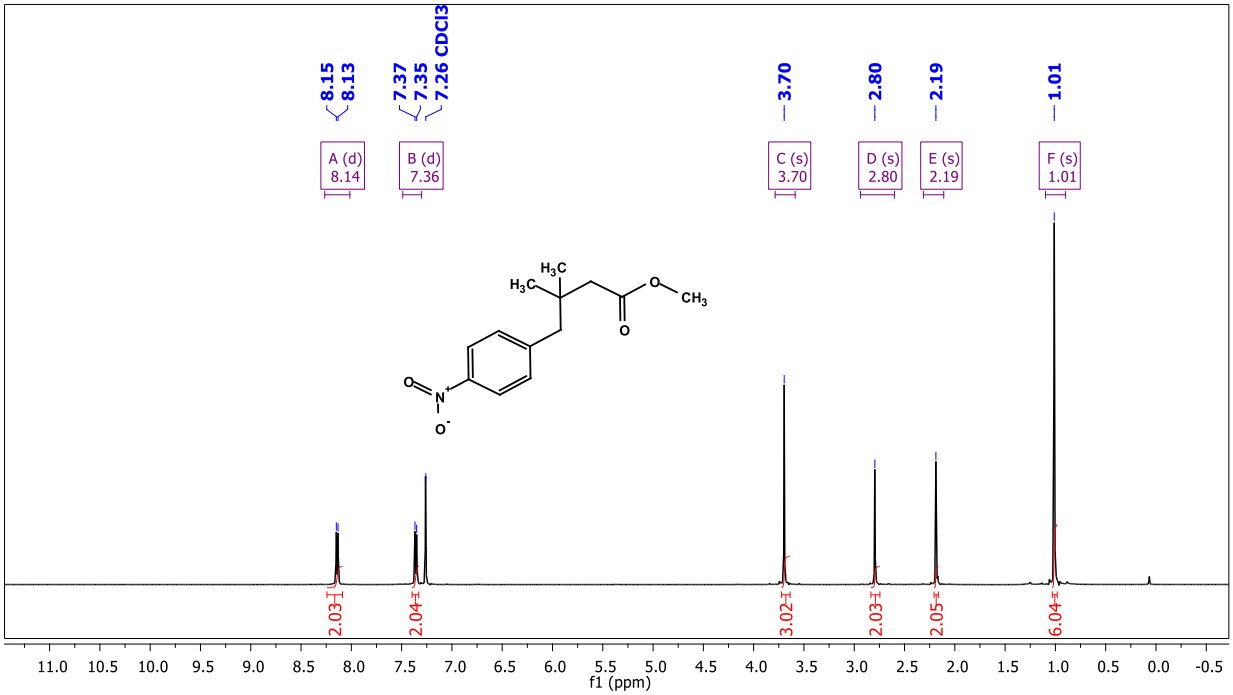
^{1}H Spectra of 11h:



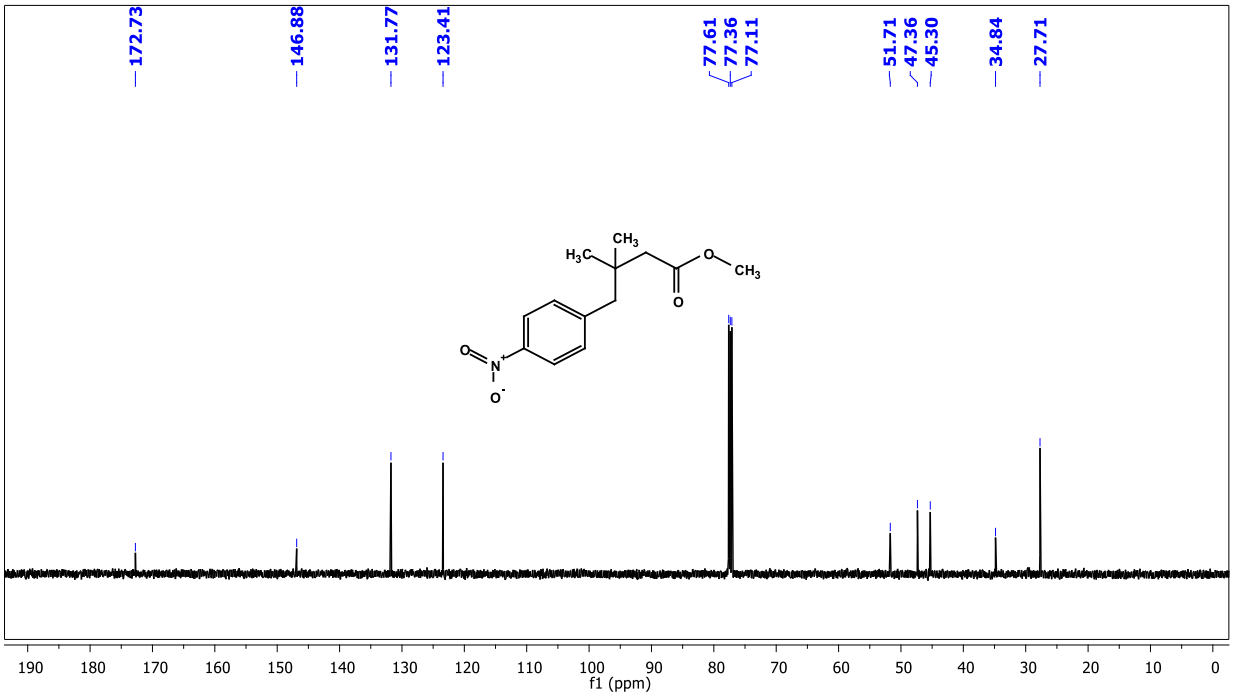
^{13}C Spectra of 11h:



^{1}H Spectra of 12:



^{13}C Spectra of 12:



2.8. References:

1) For selective examples on sp^2/sp^3 C-H functionalization see: a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593(b) Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958(c) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463(d) Xie, Y.; Yang, Y.; Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2012**, *14*, 1238(e) Ren, Z.; Mo, F.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 16991(f) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135(g) Hussain, N.; Frensch, G.; Zhang, J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3693(h) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602(i) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868(j) Maity, S.; Agasti, S.; Earsad, A. M.; Hazra, A.; Maiti, D. *Chem. Eur. J.* **2015**, *21*, 11320(k) Xu, Y.; Yan, G.; Ren, Z.; Dong, G. *Nat Chem* **2015**, *7*, 829(l) Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Sci.* **2016**, *7*, 976(m) Li, M.; González-Esguevillas, M.; Berritt, S.; Yang, X.; Bellomo, A.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 2825(n) Ménard, G.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 4409(o) Gigant, N.; Bäckvall, J.-E. *Chem. Eur. J.* **2013**, *19*, 10799(p) Liu, Y.; Yang, K.; Ge, H. *Chem. Sci.* **2016**, *7*, 2804.

2) For selective examples on Daugulis' 8-aminoquinoline based C–H functionalization see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154(b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965(c) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689(d) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.

3) For selective examples on *β*-C-H functionalization see: (a) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070(b) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187(c) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898(d) Tobisu, M.; Chatani, N. *Science* **2014**, *343*, 850(e) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789(f) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944(g) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem.*

Int. Ed. **2014**, *53*, 3496(h) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.

4) For selective examples on directed γ-C-H functionalization see: (a) Fan, M.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12152(b) Li, Q.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Adv. Synth. Catal.* **2014**, *356*, 1544(c) Pasunooti, K. K.; Banerjee, B.; Yap, T.; Jiang, Y.; Liu, C.-F. *Org. Lett.* **2015**, *17*, 6094(d) Ling, P.; Xiang; Fang, S.; Long; Yin, X.; Song; Chen, K.; Sun, B.; Zheng; Shi, B.; Feng *Chem. Eur. J.* **2015**, *21*, 17503(e) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. *Org. Lett.* **2015**, *17*, 2546(f) Wang, P.-L.; Li, Y.; Wu, Y.; Li, C.; Lan, Q.; Wang, X.-S. *Org. Lett.* **2015**, *17*, 3698(g) Han, J.; Zheng, Y.; Wang, C.; Zhu, Y.; Shi, D.-Q.; Zeng, R.; Huang, Z.-B.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 9297(h) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.* **2015**, *6*, 4610 (j) Huang, D. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 5757(k) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3(l) Franzoni, I.; Guenee, L.; Mazet, C. *Chem. Sci.* **2013**, *4*, 2619(m) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830(n) Zhou, X.-L.; Wang, P.-S.; Zhang, D.-W.; Liu, P.; Wang, C.-M.; Gong, L.-Z. *Org. Lett.* **2015**, *17*, 5120(o) Jiang, H.; He, J.; Liu, T.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2055.

5) B. V. S. Reddy, L. R. Reddy, E. J. Corey, Org. Lett. 2006, 8, 3391 3394.

6) N. Rodriguez, J. A. Romero-Revilla, M. A. Fernandez-Ibanez, J. C. Carretero, Chem. Sci. 2013, 4, 175-179.

7) For selective examples of Yu's work on C-H functionalization see: (a) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864(b) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090(c) Figg, T. M.; Wasa, M.; Yu, J.-Q.; Musaev, D. G. *J. Am. Chem. Soc.* **2013**, *135*, 14206(d) Ye, M.; Edmunds, A. J. F.; Morris, J. A.; Sale, D.; Zhang, Y.; Yu, J.-Q. *Chem. Sci.* **2013**, *4*, 2374(e) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807(f) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042(g) Chen, G.; Shigenari, T.; Jain, P.; Zhang, Z.; Jin, Z.; He, J.; Li, S.; Mapelli, C.; Miller, M. M.; Poss, M. A.; Scola, P. M.; Yeung, K.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**,

1*37*, 3338(h) Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 115

8)He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J. Q. *Science* **2014**, *343*, 1216.

9) Toba, T.; Hu, Y.; Tran, A. T.; Yu, J.-Q. *Org. Lett.* **2015**, *17*, 5966.

10) Li, S.; Zhu, R.-Y.; Xiao, K.-J.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 4317.

11) a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res*. **2009**, *42*, 1074. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (e) Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874 (f) Ackermann, L. *Acc. Chem. Res*. **2014**, *47*, 281.

Chapter 3

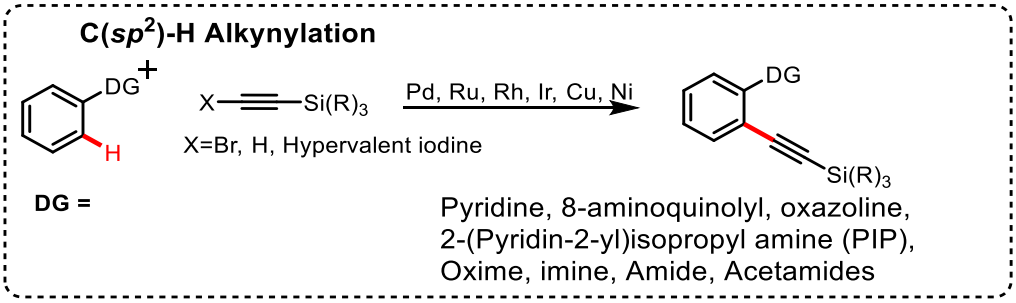
Ligand Enabled Chelation Assisted C(sp^3)–H alkynylation of aliphatic carboxamides.

Abstract:

An efficient protocol for palladium catalysed γ-selective alkynyation of carboxylic acid amide has developed. 8-aminoquinoline as directing group served as chelator for Pd to activate γ-C(sp_3)–H bond. Quinoline based ligand found to be best effective for this transformation rendering its high *mono* vs *di* selectivity. Amino acid analogs with various substituted bromo-alkyne also tolerated making this transformation attractive.

3.1. Introduction

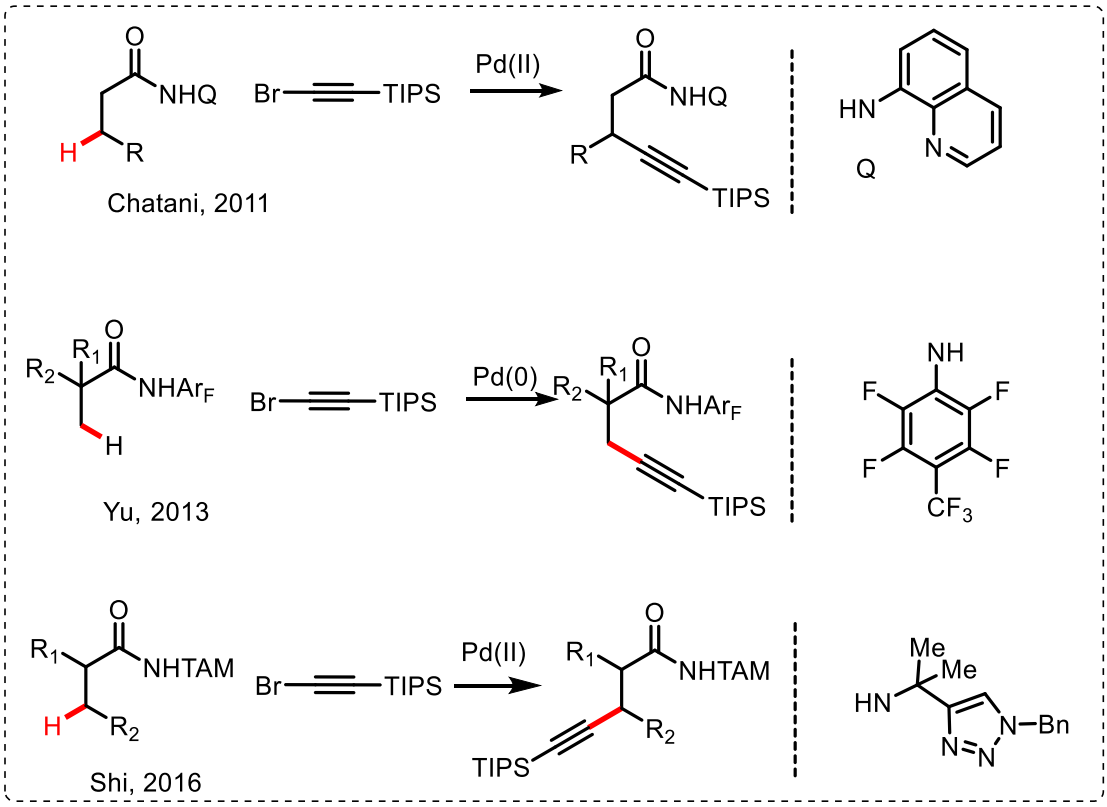
Alkynes are one of most useful synthons in synthetic chemistry in large number of pharmaceuticals, natural products, materials. In recent time various efficient stragtegies has been developed for synthesis of functionalised alkynes. Alkynes can lead to many other functionalities and can serve as platform for various complex motifs in natural product chemistry by enabling cross coupling, methathesis, various cycloaddition reactions and other arenas of chemistry[1]. In the past efficient strategies to synthesize functionalised alkynes via transition metal catalysis including but not limited to a) oxidative coupling of aryl with terminal alkynes b) palladium/copper catalysed Sonogashira coupling reaction between terminal alkynes and aryl halides c) oxidative coupling of aryl and alkyl C–H bonds with alkynylhalides.[2] Till now many methods are developed for alkyne insertion into various C(sp^2)–H bonds but C(sp^2)–H alkyne functionalisation are still less explored. Directing group approach is one of efficient method for C–H activation as it led to cleaner reaction in terms of by-products formed and no pre-activation of substrate required. For alkyne C(sp^2)–H bond functionalisation various directing groups like 8-aminoquinoline, oxaxoline, PIP, 2-picolyl, NHAc, imine, oximes for various transition metals like Rh, Ru, Pd, Ir, Cu and Ni by using preactivated substrates[1,4], preactivated alkynes but till date no method is available to insert alkyne into C(sp^2)–H bonds of carboxylic acids (Scheme **1**).



Scheme 1: Alkynylation by various directing groups

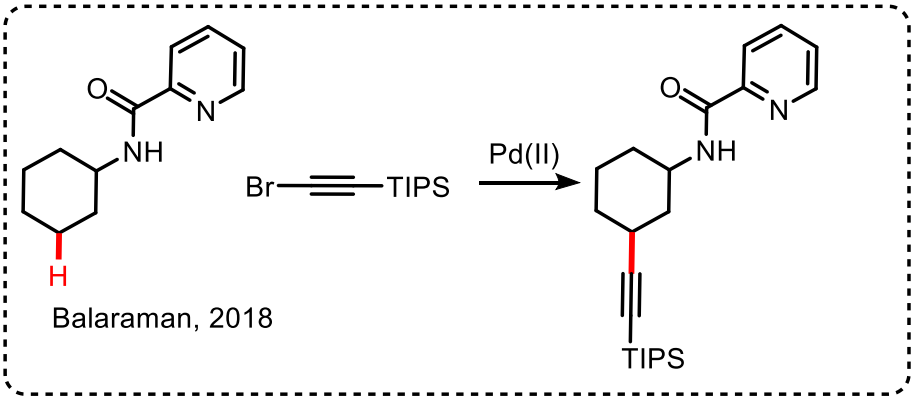
So far in literature β selective alkynylation has been developed by Chatani (8-aminoquinolyl DG) by using Pd(II) in 2011. The reaction worked with various aliphatic

amides under palladium catalysis (Scheme **2**). Later Yu in 2013 used a fluorinated directing group $4CF_3(C_6F_4)$-NH for Pd(0) catalyst. These methods are only able to use



Scheme 2: β-Alkynylations of aliphatic systems

Bromoethynyl triisopropylsilane for alkynylation reaction rendering its limitation. In 2016 Shi reported alkynation of aliphatic amides using TAM as directing group for first time but still this method only used Bromoethynyl triisopropylsilane for reaction and other bromo alkynes were unreactive for these methods.



Scheme 3: γ–alkynation of aliphatic amines

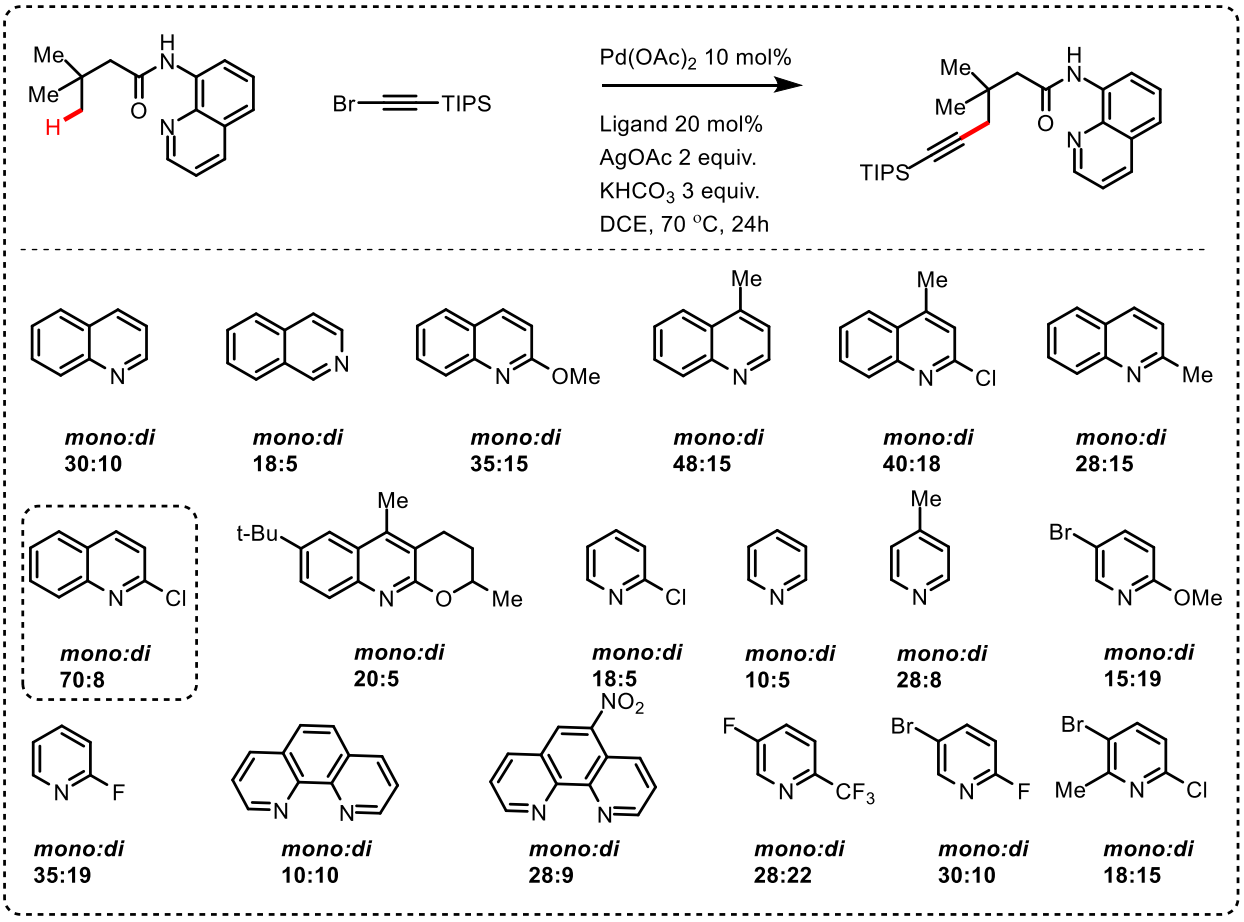
Till now and only one example is available for γ–selective alkylation of aliphatic amines by 2-picolyl as directing group reported by Balaraman et al in early 2018[3i] (Scheme **3**). This reaction used $Pd(OAc)_2$, Ag(OAc) as oxidant and higher temperature 130 ºC. As per earlier methods this transformation was also limited to only Bromoethynyl triisopropylsilane alkyne.

3.2. Result and discussion

To endeavour in this arena and to introduce first γ-selective alkynation of carboxylic acid I started to investigate reaction under model substrate 3,3-dimethylbutryic acid with 8-aminoquinolyl protection as directing group & bromoethynyl triisopropylsilane as alkyne source. Optimisation was started with using $Pd(PhCN)Cl_2$ catalyst, Ag_2CO_3 as oxidant and $NaHCO_3$ as base in t-BuOH as solvent at 80 °C initially gave only 20 % mono and 10% di alkynylated product. After screening various Pd catalyst I concluded that $Pd(OAc)_2$ giving 33% mono and 5% di product. Later oxidant screening revealed AgOAc was among best yields. Different bases were also screened and $KHCO_3$ in 3 equiv. worked best for this transformation. Also, various solvents were screened and temperature was optimised to maximize the mono product yield. Shortening the time for reaction did not help to eliminate di product but rather decreased the yield & starting material was unreacted but still overall yield was limited to 60% mono and 12 % di product. So, I started to screen various quinoline, pyridine, monoprotected amino acid (MPAA) based ligands

but any of MPAA did not give any good results but quinoline based ligands proved efficient. After screening ligands, 2-chloroquinoline was found to be best giving 70% mono and 8% di product.

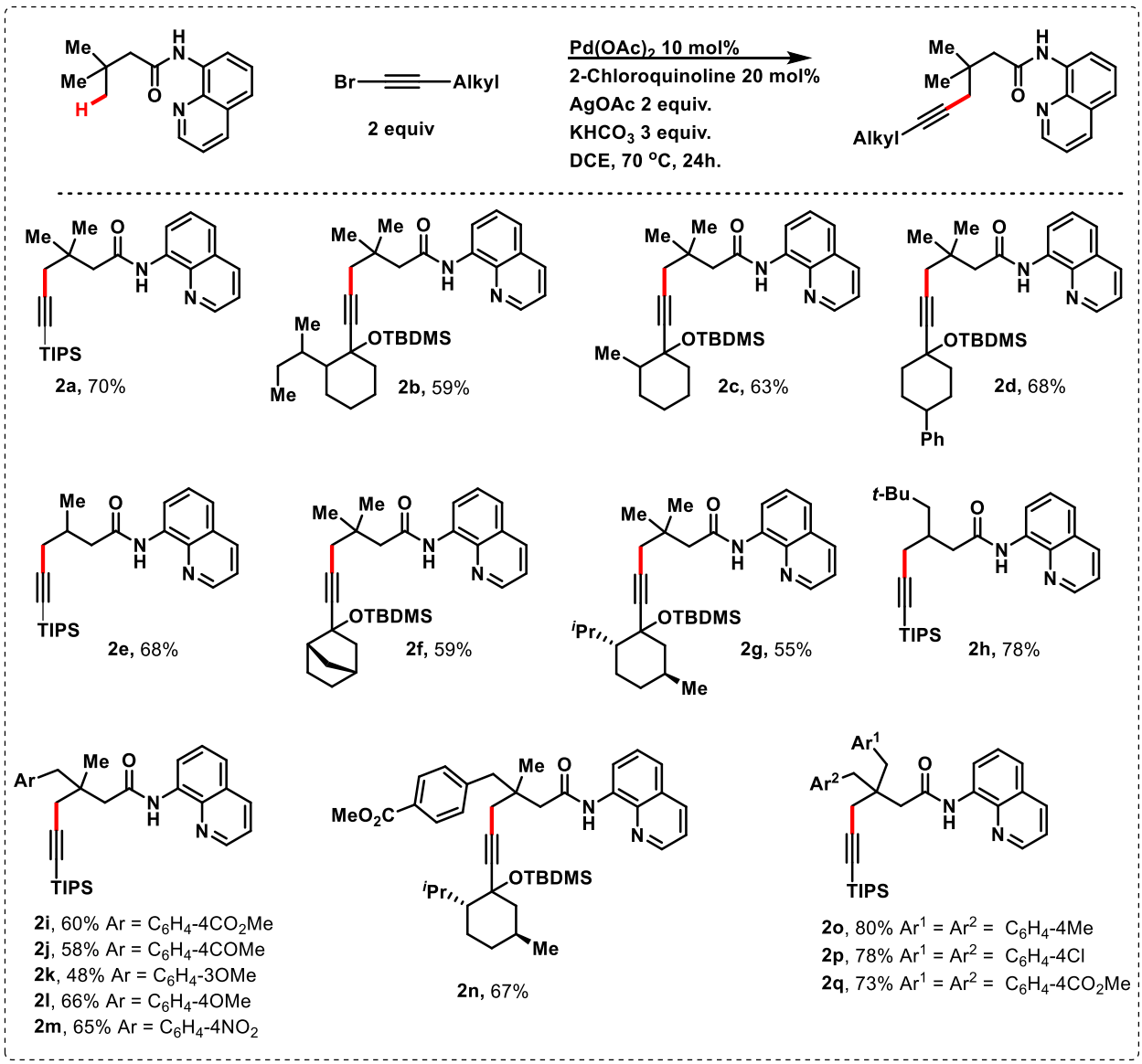
After having better optimized conditions, I started to screen different bromo alkyne for this reaction. With 3,3-dimethylbutrylamide under optimized catalytic conditions TBDMS protected substituted cyclohexylbromoalkyne alkynes reacted in moderate yield giving exclusively *mono* alkynylated product (entry **2b, 2c, 2d, 2g, 2f** Scheme **5**) in 59%, 63%, 68 %, 55% & 59% yield. This might be due to bulkiness around the alkyne which might be rendering for *di* alkynylated product. 8-aminoquinoline protected aliphatic acids like



Scheme 4: Screening of pyridine, quinoline based ligands

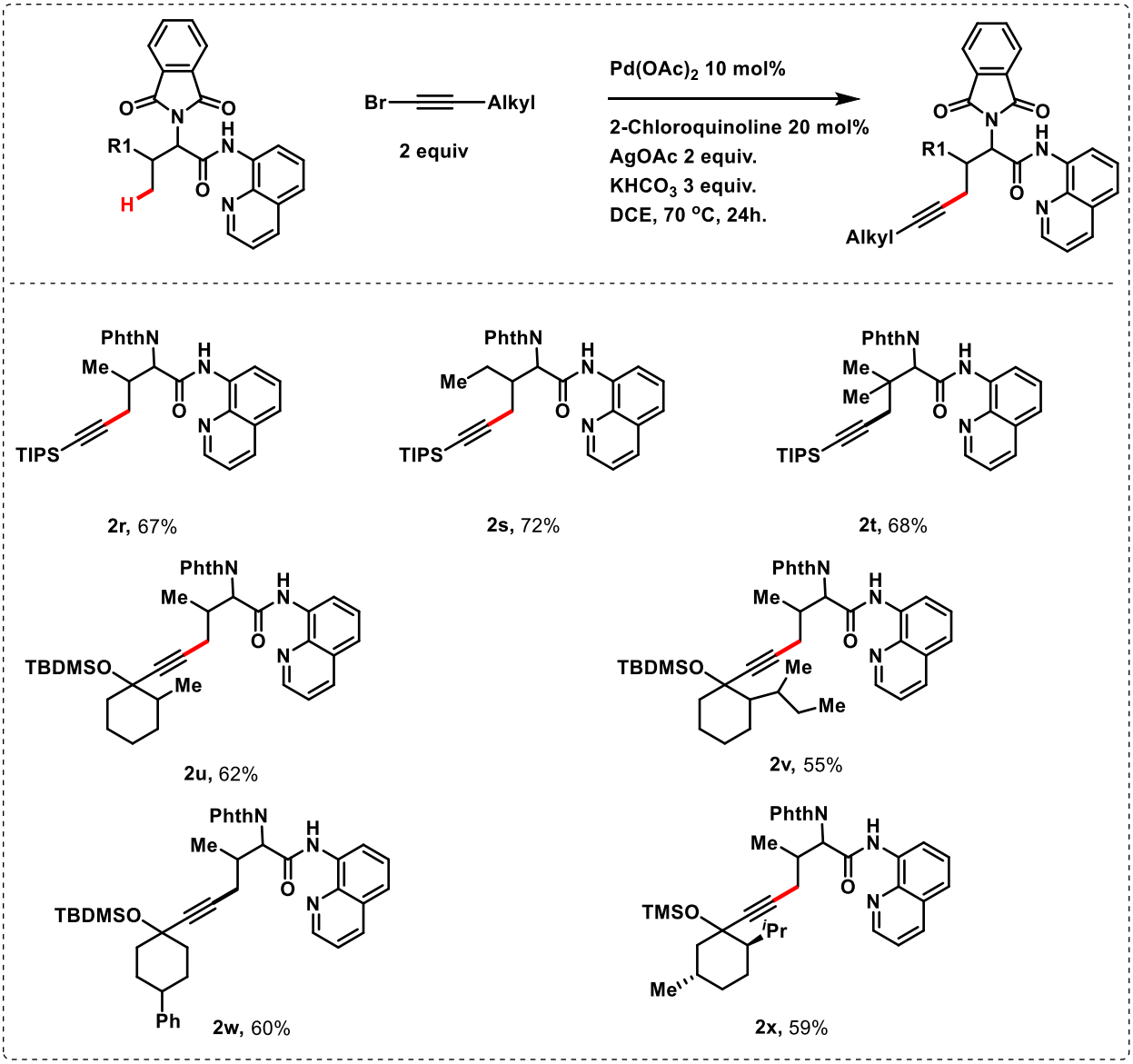
isovaryl carboxylic acid & 3 *tert*-butyl bunanoic acid reacted well with bromoethynyl triisopropylsilane giving 68% and 78 % mono alkynylated product. I also tested reaction with mono & di arylated aliphatic substrates and found that electron donating or

withdrawing groups on aryl do not render any effect on this reaction giving mono alkynylated product in moderate to good yields (Entries: **2i-2q**, **Scheme 5**). For this reaction amino acid protected with N-pthalamido group reacted well. When N-pthalamido protected aliphatic acid amide valine, isoleucine, L-*tert*-leucine were reacted with bromoethynyl triisopropylsilane mono alkynylated product was formed in 67%, 72% & 68% (**2r-2t**) yields respectively. Also, TBDMS protected substituted cyclohexylbromoalkyne reacted with phthalimide protected valine amide in 62% (**2u**), 55% (**2v**), 60% (**2w**) & 59% (**2x**) yield giving mono alkynylated product.

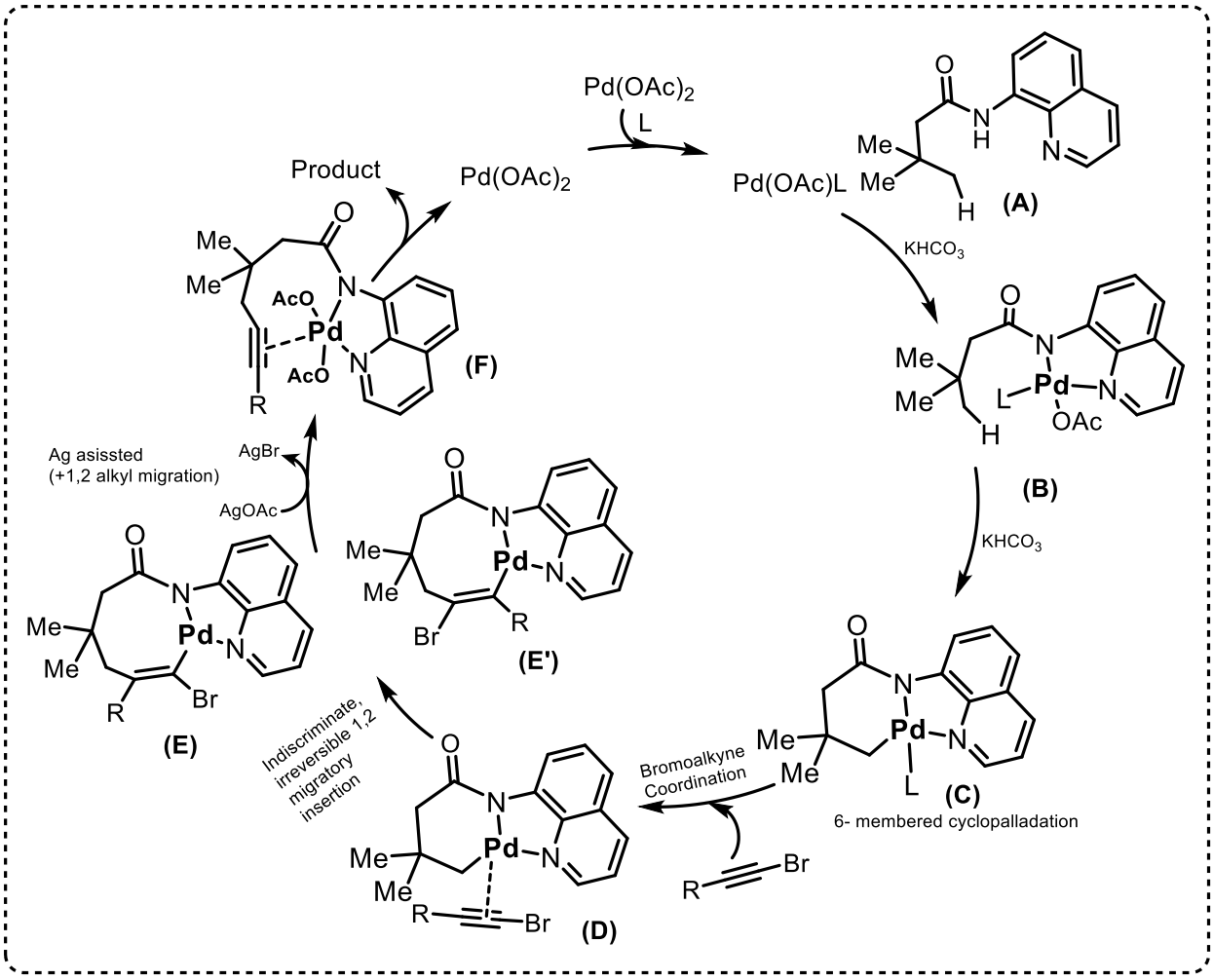


Scheme 5: Alkyne reactivity for alkynylation

Plausible reaction pathway can be depected in scheme 7. Reaction first proceeds by association of ligand with catalyst. Later base abstract the -NH proton from substrate gives complex **B** which upon base promoted C–H activation forms C–H activated 6 membered palladacycle adduct **C**. Alkyne coordination to palladium forms complex **D** and indiscriminatory irreversible addition of bromo alkyne takes place in such way to form intermediate **E** and **E'** forming 8 membered intermediate. It might be possible that Ag(OAc) assists in 1,2-alkyl migration and abstracting bromide to give out AgBr and releases regio-selective alkynyl product in subsequent reductive elimination step and catalyst is reused in further catalytic events.



Scheme 6: Substrate tolerance of amino acid derivatives with bromo substituted alkynes



Scheme 7: Possible reaction mechanism underlying alkynylation

3.3. Conclusion

In summary we have developed efficient protocol for γ-selective alkynylation of aliphatic carboxylic acid via 8-aminoquinoline as directing group. Overcoming the limitation of previous methods by utilizing various different substituted bulkier bromo alkyne makes this method more versatile and synthetically useful. Various amino acid substrate reacted

with exclusive mono alkynylated selectivity pointing towards regioselectivity and efficiency of reaction.

3.4. Experimental results

3.4.1 General Consideration

3.4.1.a. Reagent information:

Unless otherwise stated, all the reactions were carried out in screw cap reaction tube under air atmosphere with magnetic stirring. Palladium salts were purchased from Alfa Aesar and used directly. All oxidants were purchased from Alfa Aesar. All the solvents were bought from MERCK and used directly. All the other reagents were purchased from commercial source and used as received. For column chromatography silica gel (60-120 mesh and 100-200 mesh) was supplied from SRL Co. During elution hexane and ethyl acetate mixture was used. Thin layer chromatography was performed on EMD Chemicals Si 60 F_{254}. TLC plates (silica gel 60F_{254}) supplied from MERCK.

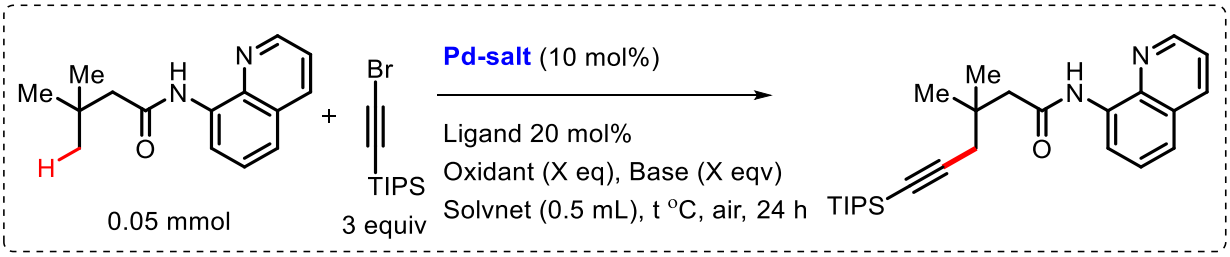
3.4.2.b. Analytical information:

All isolated compounds were characterized by ^{1}H, ^{13}C NMR spectroscopy, HR-MS, FT-IR. Unless otherwise stated, all Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 and 500 MHz instrument. The references used for NMR is tetramethylsilane (TMS) for ^{1}H and ^{13}C NMR. ^{1}H NMR data are reported in units, parts per million (ppm) and were recorded relative to the signals for residual chloroform (7.26 ppm). ^{13}C NMR data were obtained with ^{1}H decoupling and were recorded relative to the signals for residual chloroform (77.36 ppm). NMR yield was calculated using 1,3,5-trimethoxybenzene (TMB) as the internal standard. GC yield was calculated by using n-Decane as internal standard. High-resolution mass spectra (HRMS) were recorded on a micro-mass ESI TOF (time of flight) mass spectrometer.

3.4.3.c. Description of reaction tube:

Pictorial description of reaction tube used for γ–alkynylation of carboxyamides: Fisherbrand Disposable Borosilicate Glass Tubes (16*125mm) with Threaded End (Fisher Scientific Order No. 1495935A) [left hand side]; Kimble Black Phenolic Screw Thread Closures with Open Tops (Fisher Scientific Order No. 033407E) [right hand side, top]; Thermo Scientific National PTFE/Silicone Septa for Sample Screw Thread Caps (Fisher Scientific Order No. 03394A) [right hand side, bottom].

3.4.2. Optimization details:



Entry	Pd-salt	GC Yield *mono:di* (%)
1.	**$Pd(OAc)_2$**	**33:5**
2.	$Pd(OPiv)_2$	31:10
3.	$PdCl_2$	10:5
4.	*trans*-$Pd(PhCN)_2Cl_2$	20:10
5.	$Pd(CH_3CN)_2Cl_2$	25:9
6.	$Pd(TFA)_2$	33:10
7.	$Pd(acac)_3$	12:5

Table 1: Optimization of catalyst

Entry	Oxidant	GC Yield *mono:di* (%)
1.	AgI	30:5
2.	**AgOAc**	**45:9**
3.	Ag_2CO_3	35:10
4.	$AgNO_3$	33:9
5.	Ag_2SO_4	15:5
6.	AgOTf	29:20
7.	Benzoquinone	--
8.	CuO	-
9.	CuOAc	15:15

10.	CuCl	--
11.	CuF_2	22:8
12.	$Na_2S_2O_8$	13:2
13.	DDQ	--

Table 2: Optimization of oxidant

Entry	AgOAc (X eqv.)	GC Yield *mono:di* (%)
1.	1.0	45
2.	**2.0**	**45:9**
3.	2.5	45:8
3.	3.0	40:15
4.	3.5	33:20
5.	4.0	33:9
6.	4.5	28:5

Table 3: Optimization of amount of oxidant

Entry	Solvent	GC Yield *mono:di* (%)
1.	HFIP	10:1
2.	*iso*-amyl alcohol	16:6
3.	CF_3CH_2OH	15:3
4.	hexane-1-ol	-
5.	1,4 butanediol	Trace
6.	^{t}BuOH	20:10
7.	EtOH	19:15
8.	^{i}PrOH	-
9.	**DCE**	**50:10**
10.	MeOH	-
11.	*tert*-amyl alcohol	32:20
12.	Trifluorotoluene	--
13.	Cyclohexane	--
14.	Toluene	-
15.	2-methyl THF	--
16.	Benzene	--
17.	THF	40:5
18.	1,4-dioxane	39:20
19.	DMF	-

Table 4: Optimization of solvent

Entry	Base	GC Yield *mono:di* (%)
1.	K_2CO_3	8:1
2.	Na_2CO_3	45:15

3.	KO^tB	6:1
4.	$NaCO_2CF_3$	30:16
5.	NaOAc	48:20
6.	**$KHCO_3$**	**55:18**
7.	Cs2CO3	-
8.	NaOPiv	30:5
9.	CuCO3	35:9
10.	Na_2HPO_4	-
11.	$KHCO_3$ +AgOAc + $K_2S_2O_8$	40:18

Table 5: Optimization of base

Entry	Temperature	GC Yield *mono:di* (%)
1.	50	10:1
2.	60	28:10
3.	**70**	**60:10**
4.	90	45:10
5.	100	10:55
6.	110	10:49
7.	120	5:50

Table 6: Optimization of temperature

Entry	Ligand 20 mol%	GC Yield *mono:di* (%)
1.	Quinoline	30:10
2.	Isoquinoline	18:5
3.	2-Methoxy quinoline	35:15
4.	4-Methyl quinoline	48:15
5.	2-Chloro-4-methyl quinoline	40:18
6.	2-Methyl quinoline	28:15
7.	**2-Chloroquinoline**	**70:8**
8.	7-(tert-butyl)-2,5-dimethyl-3,4-dihydro-2H-pyrano[2,3-b]quinoline (Yu's Ligand)	20:5
9.	2-chloropyridine	18:5
10.	Pyridine	10:5
11.	4-Methyl pyridine	28:8
12.	5-bromo-2-Methoxypyridine	15:19
13.	2-Fluoropyridine	35:19
14.	1,10-Phenanthroline	10:10
15.	5-Nitro-1,10-Phenanthroline	28:9
16.	2-Trifluoromethyl-5-Fluoropyridine	28:22
17.	2-Fluoro-5-bromopyridine	30:10
18.	5-Bromo-2-Chloro-6-Methyl	18:15

pyridine

Table 7: Optimization of ligands

3.4.3. General procedures

3.4.3.a. General procedure for preparation of N-pthalimide protected amino acid:[1]

A solution of amino acid (10 mmol), phthalic anhydride (12 mmol), NEt_3 (12 mmol) and toluene (10 mL) was refluxed for 12-24 h in a round-bottomed flask. After completion of reaction solvent was removed under vacuum and ethyl acetate was added then the aqueous solution was slowly acidified with aqueous HCl (6 M) until pH = 1-2 at 0 °C. The mixture was extracted with EtOAc (30 mL × 3). The combined organic layers was washed with brine, dried with MgSO4, filtrated and concentrated affording the crude product which was purified by flash column chromatography (silica gel, hexane/EtOAc 3/1 to 1/1) to give pure product as a white solids which was further used to prepare corresponding acid chlorides by usual procedure and further to prepare amide as per procedure 3.4.3.b

3.4.3.b. General procedure for preparation aliphatic 8-aminoquinoline amide (1a):[2,3]

In a clean oven dried 100 mL round bottomed flask equipped with stir bar, 8-aminoquinoline (10 mmol) was taken and evacuated and purged with N_2. Later dry dichloromethane was added. Subsequently NEt_3 (10 mmol) was added via syringe and reaction mixture was cooled to 0 ^oC. Now, corresponding aliphatic acid chloride (10 mmol) in dichloromethane was added dropwise. Reaction mixture was allowed to stirred for 12 h and upon completion of reaction (monitored by TLC, complete consumption of 8-aminoquinoline), was quenched with saturated NH_4Cl and extracted in ethyl acetate thrice (3 X 50 mL). Organic layer was dried over Na_2SO_4 and solvent was removed under *vacuum* and purified with column chromatography by eluent as petroleum ether/ethyl

acetate (5:95 v/v).

[1] Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi. B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588-13592.
[2] Wasa, M.; Engle. K. M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2009**, *131*, 9886.
[3] For preparation of compound **12:** Frantz, D. E.; Weaver, D.G.; Carey, J. P.; Kress, M. H.; Dolling, U. H. *Org. Lett,* **2002**, *4*, 4717-4718.

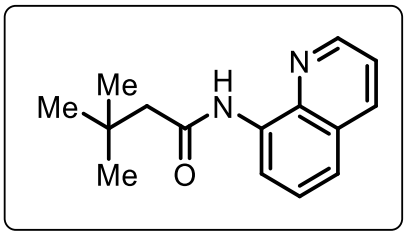
3.4.3.c. General procedure for palladium-catalyzed γ-alkynylation:

In a clean, oven–dried screw cap reaction tube containing magnetic stir-bar, 3,3-dimethyl-*N*-(quinolin-8-yl)butanamide (1 equiv), Bromo-triisopropylsilylacetylene (2 equiv), $Pd(OAc)_2$ (10 mol %, 0.01 mmol), AgOAc (2 equiv.), $KHCO_3$ (3 equiv.), 2-Chloroquinoline (20 mol%) were weighed. Solid reagents were weighed before the liquid reagents. Then 1,2-Dichloroehthane (DCE) (1 mL/0.1 mmol) was added in the reaction tube and the tube was tightly closed by screw cap. The reaction tube was placed in a preheated oil bath at 70 °C to stir vigorously (1000 rpm) for 24 h. After completion, the reaction mixture was cooled to room temperature and filtered through pad of Celite with aid of ethyl acetate (15 mL). This filtrate was concentrated under reduced pressure and purified by column chromatography through silica gel using petroleum ether/ethyl acetate as eluent.

3.5. Characterization Data:

3,3-Dimethyl-*N*-(quinolin-8-yl)butanamide (1a):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky slight brown liquid; isolated yield: **75%**



^{1}H NMR (500 MHz, Chloroform-*d*) δ: 9.74 (s, 1H), 8.80 (dd, *J* = 7.6, 1.1 Hz, 1H), 8.77 (dq, *J* = 4.0, 1.5 Hz, 1H), 8.10 (ddd, *J* = 8.2, 1.5 Hz, 1H), 7.50 (t, *J* = 7.9, 1H), 7.44 (d, *J* = 8.2, 1H), 7.40 (ddd, *J* = 8.2, 4.2, 1H), 2.41 (s, 2H), 1.15 (s, 9H).

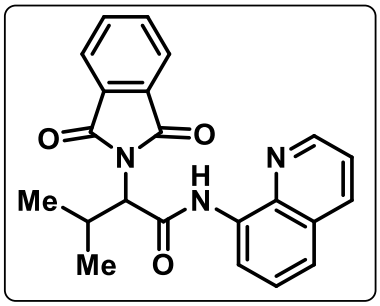
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.86, 148.37, 138.59, 136.54, 134.80, 128.14, 127.62, 121.78, 121.54, 116.52, 52.38, 31.52, 30.14.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{15}H_{18}N_2ONa$ *m/z* 265.1311 and found *m/z* 265.1328

IR (thin film, cm^{-1}): 3354, 2955, 2910, 2865, 1635, 1522, 1400, 1338, 1212, 825, 747, 665.

2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)butanamide or L-valine protected amino acid (1b):

Eluent: ethyl acetate/petroleum ether (10:90 v/v); pale yellow solid; isolated yield: 75%



^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.58 (s, 1H), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (m, 1H), 8.12 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.49 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.68 (t, *J* = 11.4 Hz, 1H), 3.22 (m, 1H), 1.22 (s, 3H), 0.98 (s, 3H).

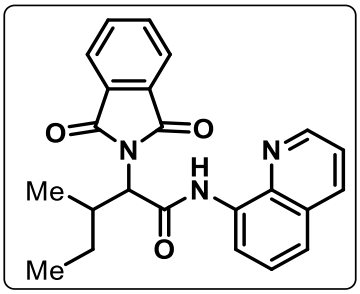
^{13}C NMR (126 MHz, $CDCl_3$) δ: ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.48, 167.19, 148.87, 139.03, 136.51, 134.60, 131.92, 128.23, 127.56, 123.99, 122.33, 121.95, 117.34, 63.56, 27.64, 20.77, 19.92.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{22}H_{19}N_3NaO_3$ *m/z* 396.1319 and found *m/z* 396.1316

IR (thin film, cm^{-1}): 3345, 2968, 2928, 2845, 1680, 1645, 1520, 1415, 1374, 1205, 875, 787, 669.

2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)pentanamide or Isoleucine protected amide (1c):

Eluent: ethyl acetate/petroleum ether (10:90 v/v); pale yellow solid; isolated yield: 80%



^{1}H NMR (500 MHz, Chloroform-*d*) δ: 10.60 (s, 1H), 8.85 (ddd, *J* = 15.4, 4.2, 1.7 Hz, 1H), 8.76 (m, 1H), 8.13 (m, 1H), 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.50 (m, 2H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 4.79 (dd, *J* = 10.8, 9.1 Hz, 1H), 3.07 (ddd, *J* = 4.2, 2.1, 0.9 Hz, 1H), 1.53 (ddd, *J* = 13.6, 7.5, 3.2 Hz, 1H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 1H), 0.95 (m, 3H).

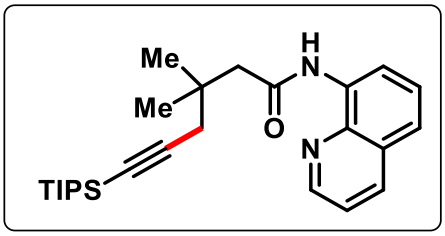
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.54, 167.38, 148.90, 139.07, 136.52, 134.60, 131.95, 128.24, 127.58, 124.00, 122.34, 121.96, 117.39, 62.41, 33.10, 25.99, 16.70, 10.67.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{23}H_{21}N_3NaO_3$ *m/z* 410.1475 and found *m/z* 410.1473

IR (thin film, cm^{-1}): 3346, 2967, 2924, 2844, 1684, 1647, 1525, 1411, 1365, 1254, 865, 784, 670.

3,3-dimethyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2a):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 70%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (s, 1H), 8.80 – 8.77 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.59 (s, 2H), 2.43 (s, 2H), 1.24 (s, 6H), 1.11 – 1.07 (m, 21H).

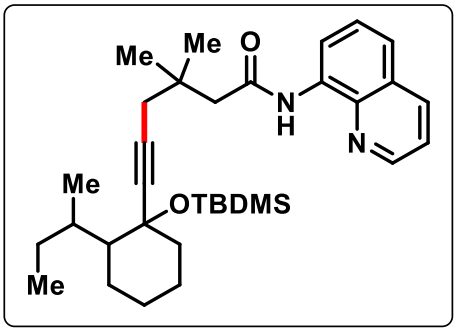
^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.40, 148.33, 138.67, 136.48, 134.75, 128.13, 127.58, 121.76, 121.62, 116.67, 106.51, 83.08, 49.17, 34.51, 33.83, 27.34, 18.91, 11.58.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for C26H38N2OSiNa *m/z* 445.2646 and found *m/z* 445.2650

IR (thin film, cm^{-1}): 3356, 3053, 3017, 2957, 2856, 1685, 1524, 1485, 1324, 1213, 1050, 909, 827, 750, 670.

6-(2-(sec-butyl)-1-((tert-butyldimethylsilyl)oxy)cyclohexyl)-3,3-dimethyl-N-(quinolin-8-yl)hex-5-ynamide (2b):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 59%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.80 – 8.77 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.52 (dt, *J* = 8.2, 7.4 Hz, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.57 (s, 2H), 2.44 (s, 2H), 2.01 (dt, *J* = 9.1, 5.8 Hz, 2H), 1.67 (s, 2H), 1.62 (ddd, *J* = 14.0, 10.2, 6.7 Hz, 2H), 1.55 – 1.43 (m, 2H), 1.39 – 1.29 (m, 2H), 1.24 (d, *J* = 1.4 Hz, 6H), 1.21 – 1.10 (m, 2H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.88 – 0.85 (m, 12H), 0.18 (s, 3H), 0.15 (s, 3H).

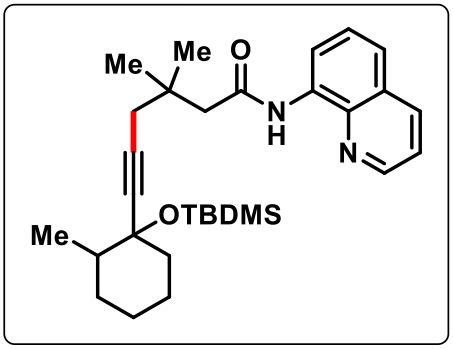
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.30, 148.30, 138.67, 136.51, 134.74, 128.16, 127.61, 121.77, 121.62, 116.67, 85.63, 85.14, 73.44, 55.63, 52.91, 49.50, 44.57, 34.53, 33.12, 32.57, 30.70, 27.41, 26.50, 26.03, 24.64, 24.49, 19.96, 18.33, 15.47, 12.44, -2.30, -2.77.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{33}H_{50}N_2O_2SiNa$ *m/z* 557.3534 and found *m/z* 557.3539

IR (thin film, cm^{-1}): 3350, 3058, 3023, 2945, 2865, 1615, 1542, 1475, 1335, 1200, 1045, 901, 815, 745, 677.

6-(1-((tert-butyldimethylsilyl)oxy)-2-methylcyclohexyl)-3,3-dimethyl-N-(quinolin-8-yl)hex-5-ynamide (2c):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 63%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.80 – 8.77 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.57 (s, 2H), 2.44 (s, 2H), 2.05 – 1.95 (m, 2H), 1.65 – 1.60 (m, 2H), 1.56 – 1.42 (m, 2H), 1.37 – 1.33 (m, 1H), 1.24 (d, *J* = 1.4 Hz, 6H), 1.23 – 1.12 (m, 2H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.86 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H).

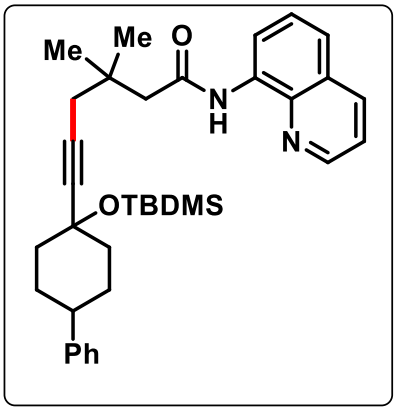
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.31, 148.31, 138.66, 136.50, 134.74, 128.15, 127.60, 121.76, 121.62, 116.67, 84.77, 84.18, 74.79, 49.42, 44.37, 42.33, 34.50, 32.91, 32.35, 29.62, 27.40, 26.25, 25.99, 24.55, 21.45, 18.30, 16.94, -2.39, -2.81.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{33}H_{50}N_2O_2SiNa$ *m/z* 515.3064 and found *m/z* 515.3070

IR (thin film, cm^{-1}): 3350, 3046, 3028, 2947, 2868, 1680, 1520, 1487, 1300, 1235, 913, 814, 715, 659.

6-(1-((tert-butyldimethylsilyl)oxy)-4-phenylcyclohexyl)-3,3-dimethyl-N-(quinolin-8-yl)hex-5-ynamide (2d):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 68%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 8.81 (dd, *J* = 7.4, 1.3 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 – 7.20 (m, 4H), 7.14 – 7.10 (m, 1H), 2.62 (s, 2H), 2.49 (s, 2H), 2.12 (d, *J* = 12.3 Hz, 2H), 1.94 – 1.82 (m, 4H), 1.71 – 1.65 (m, 3H), 1.29 (s, 6H), 0.88 (s, 9H), 0.18 (s, 6H).

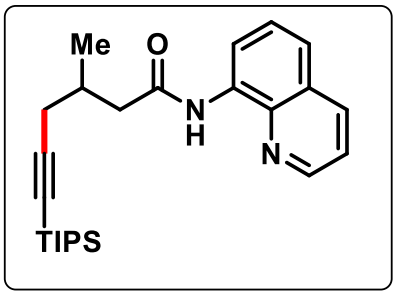
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.12, 166.38, 148.66, 147.03, 138.84, 136.30, 134.53, 131.86, 128.42, 127.41, 127.14, 126.00, 123.95, 122.24, 121.80, 117.21, 87.07, 82.69, 70.56, 59.64, 43.94, 42.06, 31.94, 31.22, 25.97, 24.27, 18.16, 16.80, -2.48, -2.55.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{35}H_{46}N_2O_2SiNa$ *m/z* 577.3221 and found *m/z* 577.3225

IR (thin film, cm^{-1}): 3351, 3053, 3027, 2947, 2866, 1675, 1545, 1480, 1300, 1235, 1015, 9935, 845, 730, 670.

3-methyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2e):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 68%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 8.80 – 8.77 (m, 2H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.75 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.49 – 2.39 (m, 4H), 1.18 (d, *J* = 5.9 Hz, 3H), 1.09 (d, *J* = 3.6 Hz, 21H).

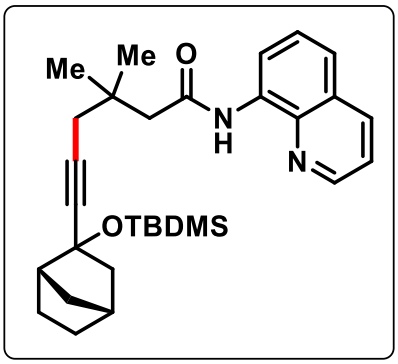
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.99, 148.33, 138.56, 136.52, 134.69, 128.13, 127.60, 121.79, 121.67, 116.64, 106.58, 82.57, 44.38, 30.56, 27.09, 19.64, 18.89, 11.54.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{25}H_{36}N_2OSiNa$ *m/z* 431.2489 and found *m/z* 431.2491

IR (thin film, cm^{-1}): 3356, 3054, 3013, 2985, 2845, 1685, 1527, 1489, 1325, 1200, 910, 825, 737, 660.

6-((1S,4R)-2-((tert-butyldimethylsilyl)oxy)bicyclo[2.2.1]heptan-2-yl)-3,3-dimethyl-N-(quinolin-8-yl)hex-5-ynamide (2f):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 59%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 8.82 – 8.76 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.55 (s, 2H), 2.43 (d, *J* = 3.5 Hz, 1H), 2.36 (s, 2H), 2.19 (d, *J* = 4.1 Hz, 1H), 2.12 (ddd, *J* = 12.5, 4.7, 3.0 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.82 (d, *J* = 9.9 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.33 – 1.24 (m, 4H), 1.21 (s, 6H), 0.87 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H).

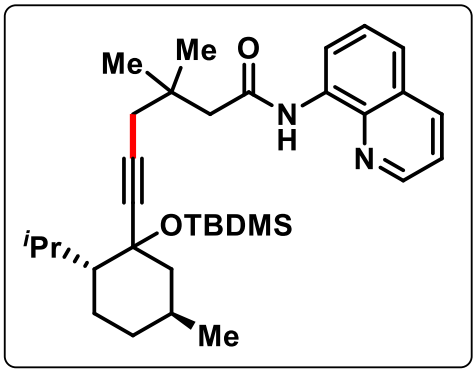
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.38, 148.38, 138.65, 136.50, 134.76, 128.13, 127.59, 121.78, 121.63, 116.89, 116.64, 89.59, 81.43, 74.65, 51.30, 50.21, 49.32, 38.26, 37.10, 34.64, 32.58, 29.07, 27.56, 27.53, 26.10, 21.54, 18.35, -2.96.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{30}H_{42}N_2O_2SiNa$ *m/z* 513.2908 and found *m/z* 513.2910

IR (thin film, cm^{-1}): 3349, 3032, 3000, 2945, 2865, 1694, 1565, 1490, 1326, 1209, 835, 745, 670.

6-((2R,5S)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexyl)-3,3-dimethyl-N-(quinolin-8-yl)hex-5-ynamide (2g):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 55%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 8.79 (ddd, *J* = 7.2, 4.0, 1.8 Hz, 2H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.55 (d, *J* = 2.0 Hz, 2H), 2.44 – 2.38 (m, 2H), 2.19 (dddd, *J* = 20.4, 18.6, 9.4, 4.5 Hz, 1H), 2.04 – 1.86 (m,

1H), 1.73 – 1.66 (m, 1H), 1.63 (s, 2H), 1.57 (dt, *J* = 9.0, 4.1 Hz, 1H), 1.34 (ddd, *J* = 26.1, 13.0, 3.6 Hz, 1H), 1.22 (d, *J* = 1.7 Hz, 6H), 1.20 – 1.15 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 1H), 0.93 (ddd, *J* = 16.5, 6.3, 4.2 Hz, 6H), 0.86 (t, *J* = 4.7 Hz, 12H), 0.17 (s, 3H), 0.15 (s, 3H).

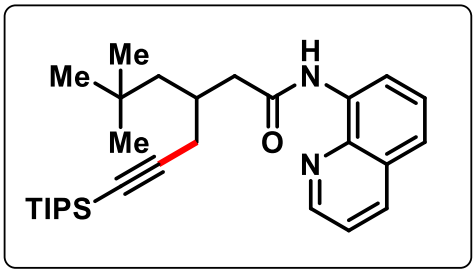
^{13}C NMR (101 MHz, $CDCl_3$) δ: 170.32, 148.34, 138.63, 136.54, 134.70, 128.14, 127.60, 121.79, 121.65, 116.65, 85.63, 85.06, 77.23, 74.27, 73.53, 54.49, 52.84, 51.73, 49.48, 46.19, 35.20, 34.50, 33.04, 30.83, 27.40, 26.52, 26.02, 24.42, 23.81, 22.27, 20.89, 18.11, 1.24.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{33}H_{50}N_2O_2SiNa$ *m/z* 557.3534 and found *m/z* 557.3540

IR (thin film, cm^{-1}): 3356, 3054, 3013, 2985, 2845, 1685, 1527, 1489, 1325, 1200, 905, 815, 757, 672.

3-neopentyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2h):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 78%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.85 (s, 1H), 8.80 – 8.76 (m, 2H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.75 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.62 (dd, *J* = 14.6, 5.5 Hz, 1H), 2.48 (dd, *J* = 5.0, 1.9 Hz, 2H), 2.43 – 2.35 (m, 1H), 1.60 (dd, *J* = 14.3, 5.9 Hz, 1H), 1.33 (dd, *J* = 14.3, 4.6 Hz, 1H), 1.09 (d, *J* = 2.4 Hz, 21H), 0.96 (s, 9H).

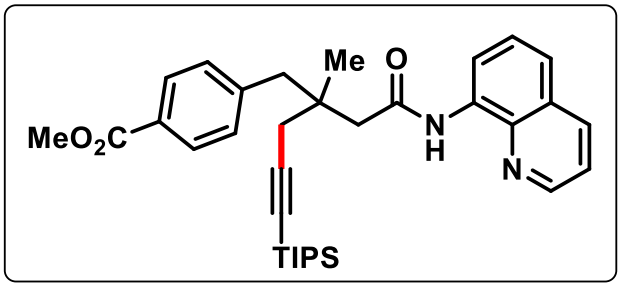
^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.08, 148.30, 138.59, 136.47, 134.75, 128.12, 127.59, 121.77, 121.62, 116.63, 106.79, 82.57, 47.00, 44.44, 31.44, 31.23, 30.17, 26.48, 18.91, 11.57.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{29}H_{44}N_2OSiNa$ *m/z* 487.3115 and found *m/z* 487.3116

IR (thin film, cm^{-1}): 3347, 3030, 3018, 2988, 2958, 2869, 1690, 1564, 1475, 1329, 1200, 837, 740, 666.

methyl 4-(2-methyl-2-(2-oxo-2-(quinolin-8-ylamino)ethyl)-5-(triisopropylsilyl)pent-4-yn-1-yl)benzoate (2i):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 60%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 8.81 – 8.77 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.50 (m, 2H), 7.47 – 7.43 (m, 3H), 3.91 (s, 3H), 3.08 (d, *J* = 13.0 Hz, 1H), 3.00 (d, *J* = 13.0 Hz, 1H), 2.58 (s, 2H), 2.36 (s, 2H), 1.21 (s, 3H), 1.11 (d, *J* = 2.3 Hz, 21H).

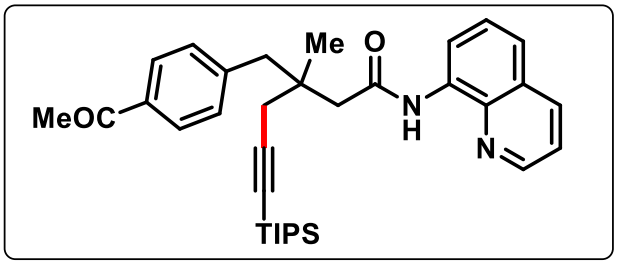
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.07, 167.40, 148.37, 143.87, 138.64, 136.53, 134.62, 131.07, 129.48, 128.47, 128.15, 127.56, 121.82, 116.76, 106.13, 84.48, 52.23, 46.67, 44.48, 38.32, 30.89, 24.70, 18.93, 11.60.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{34}H_{44}N_2O_3SiNa$ *m/z* 579.3013 and found *m/z* 579.3015

IR (thin film, cm^{-1}): 3349, 3029, 3052, 2925, 2865, 1615, 1564, 1475, 1319, 1209, 837, 757, 666.

3-(4-acetylbenzyl)-3-methyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2j):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 58%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.84 (s, 1H), 8.82 – 8.77 (m, 2H), 8.17 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.50 (m, 2H), 7.49 – 7.44 (m, 3H), 3.09 (d, *J* = 12.9 Hz, 1H), 3.01 (d, *J* = 12.9 Hz, 1H), 2.59 (s, 5H), 2.37 (s, 2H), 1.22 (s, 3H), 1.11 (s, 21H).

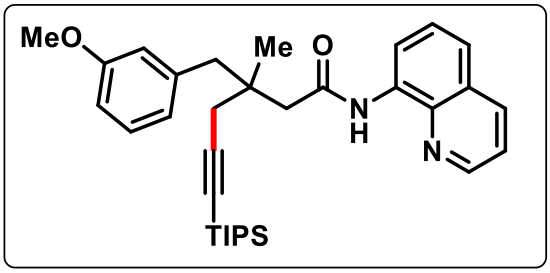
^{13}C NMR (126 MHz, $CDCl_3$) δ: 198.26, 170.05, 148.37, 144.20, 138.63, 136.54, 135.60, 134.60, 131.25, 128.54, 128.29, 128.15, 127.55, 121.84, 116.76, 106.07, 84.52, 46.65, 44.43, 38.35, 30.92, 26.80, 24.73, 18.93, 11.59.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{34}H_{44}N_2O_2SiNa$ *m/z* 563.3064 and found *m/z* 563.3070

IR (thin film, cm^{-1}): 3354, 3019, 3062, 2912, 2866, 1618, 1550, 1475, 1365, 1215, 875, 750, 669.

3-(3-methoxybenzyl)-3-methyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2k):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 48%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.83 (s, 1H), 8.82 – 8.77 (m, 2H), 8.16 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.95 – 6.91 (m, 2H), 6.78 (dd, *J* = 8.1, 2.3 Hz, 1H), 3.77 (s, 3H), 2.98 (d, *J* = 13.1 Hz, 1H), 2.91 (d, *J* = 13.1 Hz, 1H), 2.64 – 2.57 (m, 2H), 2.45 – 2.36 (m, 2H), 1.22 (s, 3H), 1.11 (d, *J* = 2.8 Hz, 21H).

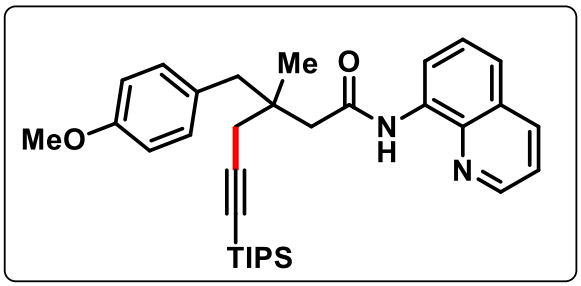
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.34, 159.53, 148.33, 139.77, 138.65, 136.50, 134.72, 129.08, 128.14, 127.58, 123.55, 121.79, 121.71, 116.73, 116.46, 112.17, 106.56, 84.07, 55.36, 46.84, 44.86, 38.19, 30.87, 24.73, 18.94, 11.62.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{33}H_{44}N_2O_2SiNa$ *m/z* 551.3064 and found *m/z* 551.3068

IR (thin film, cm^{-1}): 3355, 3018, 3062, 2915, 2975, 2875, 1615, 1564, 1475, 1319, 1209, 837, 757, 666.

3-(4-methoxybenzyl)-3-methyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2l):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 66%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (s, 1H), 8.81 – 8.75 (m, 2H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.27 – 7.23 (m, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 2.93 (d, *J* = 13.4 Hz, 1H), 2.84 (d, *J* = 13.4 Hz, 1H), 2.59 (d, *J* = 13.9 Hz, 1H), 2.54 (d, *J* = 13.9 Hz, 1H), 2.35 (d, *J* = 2.2 Hz, 2H), 1.18 (s, 3H), 1.10 (d, *J* = 2.2 Hz, 21H).

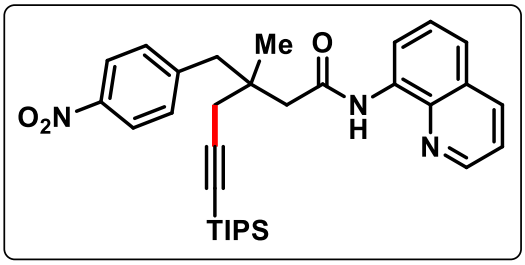
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.44, 158.35, 148.32, 138.65, 136.50, 134.72, 131.97, 130.20, 128.14, 127.57, 121.78, 121.70, 116.74, 113.59, 106.63, 83.98, 55.43, 46.75, 43.91, 38.24, 30.69, 24.56, 18.94, 11.61.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{33}H_{44}N_2O_2SiNa$ *m/z* 551.3064 and found *m/z* 551.3066

IR (thin film, cm^{-1}): 3354, 3025, 3057, 2912, 2875, 1645, 1549, 1415, 1315, 1246, 849, 782, 652.

3-methyl-3-(4-nitrobenzyl)-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2m):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 65%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.86 (s, 1H), 8.81 – 8.77 (m, 2H), 8.19 – 8.13 (m, 3H), 7.59 – 7.53 (m, 4H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.15 (d, *J* = 12.9 Hz, 1H), 3.08 (d, *J* = 12.9 Hz, 1H), 2.61 – 2.52 (m, 2H), 2.35 (s, 2H), 1.23 (s, 3H), 1.11 (s, 21H).

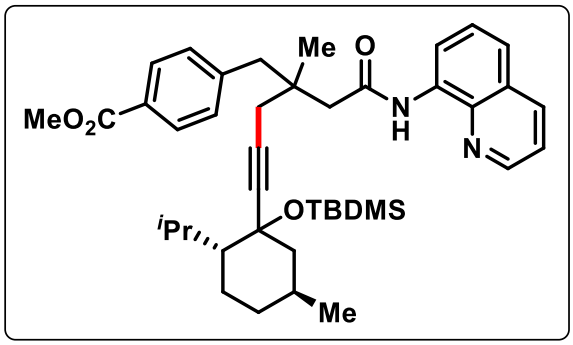
^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.82, 148.42, 146.94, 146.39, 138.61, 136.59, 134.50, 131.83, 128.17, 127.55, 123.41, 121.98, 121.90, 116.79, 105.64, 84.94, 46.39, 43.91, 38.45, 31.07, 24.81, 18.93, 11.57.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{32}H_{41}N_3O_3SiNa$ *m/z* 566.2809 and found *m/z* 566.2813

IR (thin film, cm^{-1}): 3355, 3023, 3052, 2923, 2895, 1639, 1515, 1439, 1378, 1298, 815, 735, 655.

methyl 4-(5-((2R,5S)-1-((tert-butyldimethylsilyl)oxy)-2-isopropyl-5-methylcyclohexyl)-2-methyl-2-(2-oxo-2-(quinolin-8-ylamino)ethyl)pent-4-yn-1-yl)benzoate (2n):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 67%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (s, 1H), 8.82 – 8.78 (m, 2H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.96 (dd, *J* = 8.3, 2.1 Hz, 2H), 7.57 – 7.51 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 3.91 (s, 3H), 3.05 – 2.98 (m, 2H), 2.54 (dt, *J* = 10.0, 4.3 Hz, 2H), 2.39 (ddd, *J* = 12.4, 6.2, 4.0 Hz, 2H), 2.34 – 2.24 (m, 1H), 2.02 (t, *J* = 12.1 Hz, 1H), 1.88 – 1.70 (m, 2H), 1.69 – 1.64 (m, 1H), 1.34 (dd, *J* = 28.2, 14.9 Hz, 1H), 1.20 (d, *J* = 4.1 Hz, 2H), 1.02 (dt, *J* = 6.7, 3.5 Hz, 1H), 0.99 – 0.95 (m, 3H), 0.92 (dd, *J* = 7.0, 2.8 Hz, 3H), 0.89 – 0.84 (m, 12H), 0.20 – 0.18 (m, 3H), 0.18 – 0.15 (m, 3H).

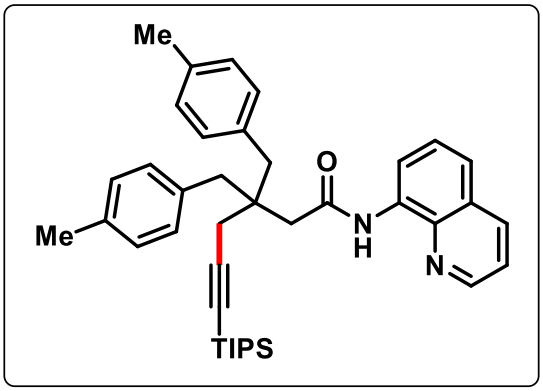
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.02, 167.40, 148.41, 148.38, 143.94, 138.61, 136.59, 134.59, 131.09, 129.50, 128.51, 128.18, 127.58, 121.86, 116.76, 86.71, 84.68, 74.35, 73.68, 54.54, 52.87, 52.25, 46.43, 44.60, 38.24, 35.15, 31.03, 26.50, 26.00, 24.99, 24.41, 23.98, 22.23, 18.33, -2.18, -2.66.

HRMS (ESI-QTOF): [M + Na]$^+$ calculated for $C_{41}H_{56}N_2O_4SiNa$ *m/z* 691.3902 and found *m/z* 691.3905

IR (thin film, cm^{-1}): 3354, 3023, 3050, 2910, 2835, 1632, 1565, 1475, 1329, 1246, 848, 791, 668.

3,3-bis(4-methylbenzyl)-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2o):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 80%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.72 (s, 1H), 8.89 (dd, *J* = 10.0, 3.4 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 – 8.16 (m, 1H), 7.59 (t, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 4H), 7.06 (d, *J* = 7.9 Hz, 4H), 3.32 (d, *J* = 13.3 Hz, 2H), 2.97 (d, *J* = 13.3 Hz, 2H), 2.34 (s, 2H), 2.30 (d, *J* = 4.5 Hz, 6H), 2.16 (s, 2H), 1.18 (d, *J* = 3.1 Hz, 21H).

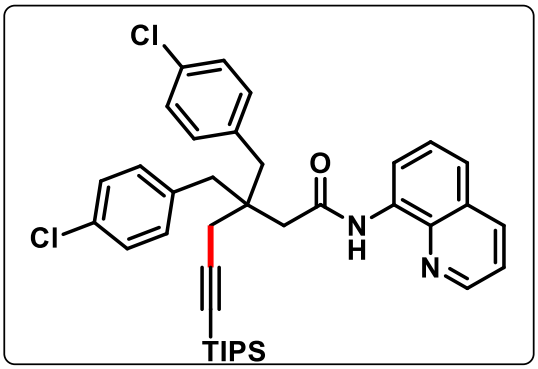
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.56, 148.25, 138.62, 136.52, 135.89, 135.18, 134.79, 131.17, 131.10, 128.96, 128.21, 127.64, 121.82, 121.65, 116.67, 106.97, 85.18, 42.02, 41.53, 41.11, 28.10, 21.22, 19.00, 18.86, 11.71.

HRMS (ESI-QTOF): [M + Na]$^+$ calculated for $C_{40}H_{50}N_2OSiNa$ *m/z* 625.3585 and found *m/z* 625.3590

IR (thin film, cm^{-1}): 3355, 3019, 3049, 2974, 2865, 1685, 1515, 1485, 1335, 1245, 865, 791, 650.

3,3-bis(4-chlorobenzyl)-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2p):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 78%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.73 (s, 1H), 8.85 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 4H), 7.23 – 7.20 (m, 4H), 3.34 (d, *J* = 13.3 Hz, 2H), 2.97 (d, *J* = 13.3 Hz, 2H), 2.27 (s, 2H), 2.10 (s, 2H), 1.18 (d, *J* = 2.0 Hz, 21H).

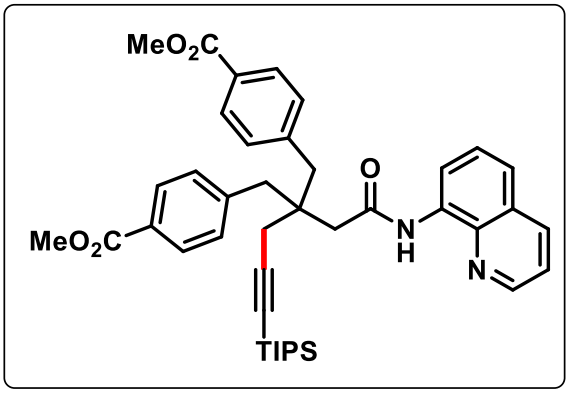
^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.08, 148.42, 138.56, 136.59, 136.49, 134.51, 132.53, 132.43, 128.48, 128.23, 127.58, 121.96, 116.73, 106.10, 86.00, 41.99, 41.22, 40.82, 27.99, 18.99, 18.83, 11.66.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{38}H_{44}Cl_2N_2OSiNa$ *m/z* 665.2492 and found *m/z* 665.2498

IR (thin film, cm^{-1}): 3359, 3039, 3052, 2914, 2875, 1675, 1541, 1423, 1300, 1213, 847, 732, 655.

dimethyl 4,4'-(2-(2-oxo-2-(quinolin-8-ylamino)ethyl)-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)propane-1,3-diyl)dibenzoate (2q):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 73%



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.72 (s, 1H), 8.86 (dd, *J* = 7.4, 1.2 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 4H), 7.62 – 7.55 (m, 2H), 7.51 (d, *J* = 8.3 Hz, 4H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.89 (s, 6H), 3.45 (d, *J* = 13.1 Hz, 2H), 3.08 (d, *J* = 13.1 Hz, 2H), 2.28 (s, 2H), 2.11 (s, 2H), 1.19 (d, *J* = 1.8 Hz, 21H).

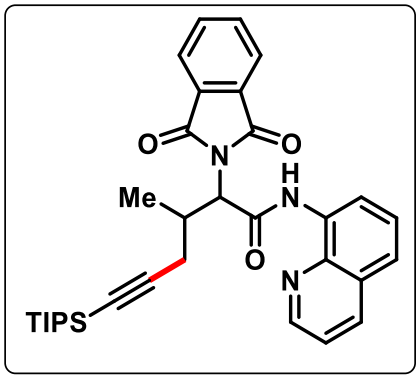
^{13}C NMR (126 MHz, $CDCl_3$) δ: 169.95, 167.34, 148.43, 143.64, 138.56, 136.58, 134.47, 131.15, 129.63, 128.60, 128.23, 127.56, 122.00, 121.95, 116.76, 105.91, 86.21, 52.23, 42.22, 41.57, 41.26, 28.18, 18.99, 11.66.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{42}H_{50}N_2O_5SiNa$ *m/z* 713.3381 and found *m/z* 713.3382

IR (thin film, cm^{-1}): 3355, 3020, 3049, 2900, 2873, 1668, 1514, 1477, 1395, 1223, 865, 778, 628.

2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2r):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 67%



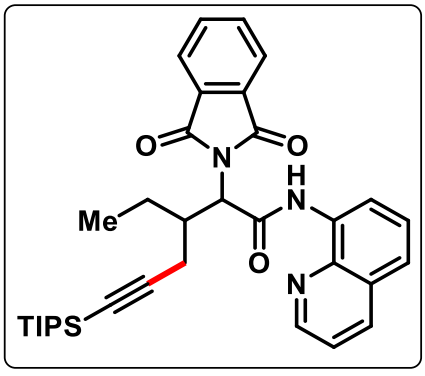
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.38 (s, 1H), 8.76 – 8.73 (m, 2H), 8.11 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.89 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.50 – 7.48 (m, 2H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.11 (d, *J* = 10.8 Hz, 1H), 3.41 – 3.32 (m, 1H), 2.66 (d, *J* = 4.6 Hz, 2H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 2.8 Hz, 21H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.14, 166.49, 148.61, 138.82, 136.30, 134.46, 134.33, 131.83, 128.03, 127.38, 123.89, 122.23, 121.80, 117.20, 104.88, 84.10, 59.56, 30.91, 25.15, 18.88, 16.49, 11.51.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{33}H_{39}N_3O_3SiNa$ *m/z* 576.2653 and found *m/z* 576.2632

IR (thin film, cm^{-1}): 3353, 3020, 3052, 2913, 2878, 1647, 1545, 1411, 1317, 1246, 849, 780, 650.

2-(1,3-dioxoisoindolin-2-yl)-3-ethyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2s):



Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 72%

^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.39 (s, 1H), 8.77 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.75 (t, *J* = 4.5 Hz, 1H), 8.12 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.72 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.49 (d, *J* = 4.5 Hz, 2H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.21 (d, *J* = 11.1 Hz, 1H), 3.23 – 3.16 (m, 1H), 2.71 (d, *J* = 4.5 Hz, 2H), 1.54 – 1.49 (m, 2H), 1.09 – 1.06 (m, 21H), 0.97 (t, *J* = 7.4 Hz, 3H).

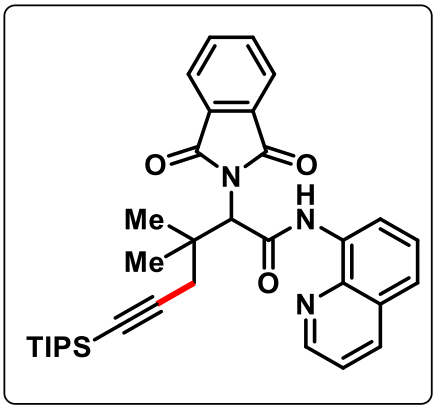
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.19, 166.65, 148.63, 138.84, 136.29, 134.42, 134.40, 131.89, 128.04, 127.38, 123.88, 122.23, 121.80, 117.22, 104.35, 84.10, 58.77, 36.09, 21.92, 20.57, 18.87, 11.53, 10.67.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{34}H_{41}N_3O_3SiNa$ *m/z* 590.2809 and found *m/z* 590.2815

IR (thin film, cm^{-1}): 3354, 3022, 3051, 2965, 2824, 1663, 1541, 1447, 1398, 1232, 874, 722, 680.

2-(1,3-dioxoisoindolin-2-yl)-3,3-dimethyl-N-(quinolin-8-yl)-6-(triisopropylsilyl)hex-5-ynamide (2t):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 68%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.15 (s, 1H), 8.69 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.53 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.90 (dt, *J* = 6.9, 3.5 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.53 – 7.46 (m, 2H), 7.35 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.26 (s, 1H), 3.02 (d, *J* = 16.9 Hz, 1H), 2.59 (d, *J* = 16.9 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.04 (d, *J* = 3.9 Hz, 21H).

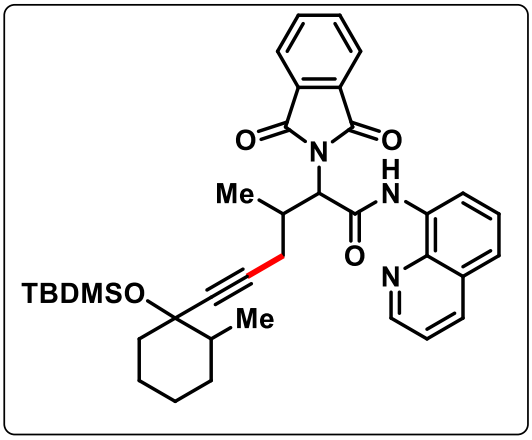
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.47, 165.82, 148.39, 138.79, 136.35, 134.52, 134.26, 131.88, 128.03, 127.50, 123.95, 121.96, 121.70, 117.11, 105.87, 83.53, 61.39, 39.13, 32.00, 25.93, 25.45, 18.84, 11.53.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{34}H_{41}N_3O_3SiNa$ *m/z* 590.2809 and found *m/z* 590.2813

IR (thin film, cm^{-1}): 3352, 3053, 2915, 2854, 1619, 1528, 1415, 1371, 1267, 833, 783, 659.

6-(1-((tert-butyldimethylsilyl)oxy)-2-methylcyclohexyl)-2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)hex-5-ynamide (2u):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 63%



^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.40 (s, 1H), 8.76 – 8.73 (m, 2H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.89 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.50 (d, *J* = 4.9 Hz, 2H), 7.43 – 7.39 (m, 1H), 5.06 (dd, *J* = 12.3, 8.4 Hz, 1H), 3.39 – 3.30 (m, 1H), 2.63 (dt, *J* = 15.3, 3.6 Hz, 2H), 2.01 (t, *J* = 11.6 Hz, 1H), 1.58 – 1.28 (m, 6H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.02

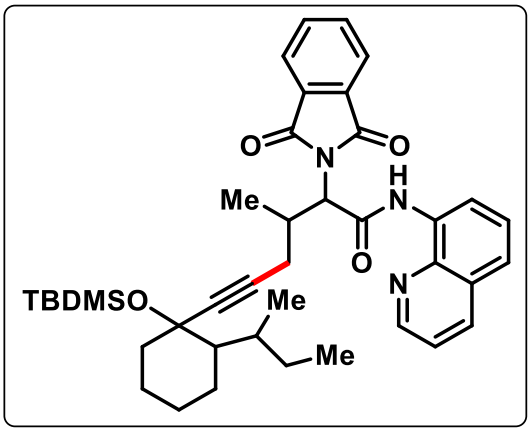
(d, *J* = 6.3 Hz, 3H), 0.87 (d, *J* = 1.3 Hz, 2H), 0.82 (d, *J* = 3.9 Hz, 9H), 0.10 (dd, *J* = 11.7, 4.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.14, 166.40, 148.62, 138.83, 136.33, 134.51, 134.32, 131.82, 128.05, 127.40, 123.93, 122.25, 121.82, 117.21, 83.50, 74.78, 59.68, 44.29, 42.23, 32.29, 31.13, 26.21, 25.95, 24.55, 24.14, 18.27, 16.89, 16.69, -2.45, -2.87.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{40}H_{51}N_3O_4SiNa$ *m/z* 665.3649 and found *m/z* 665.3655

IR (thin film, cm^{-1}): 3355, 3009, 2917, 2865, 1649, 1523, 1467, 1315, 1227, 845, 788, 670.

6-(2-(sec-butyl)-1-((tert-butyldimethylsilyl)oxy)cyclohexyl)-2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)hex-5-ynamide (2v)



Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 59%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.39 (s, 1H), 8.74 (dd, *J* = 5.9, 4.1 Hz, 2H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.90 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.50 (d, *J* = 4.0 Hz, 2H), 7.41 (dd, *J* = 8.2, 4.2 Hz, 1H), 5.05 – 4.99 (m, 1H), 3.37 – 3.28 (m, 1H), 2.61 (dt, *J* = 16.8, 6.3 Hz, 2H), 2.05 – 1.96 (m, 2H), 1.75 – 1.67 (m, 2H), 1.35 (m, 9H), 1.12 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 1H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.5 Hz, 9H), 0.15 – 0.06 (m, 6H).

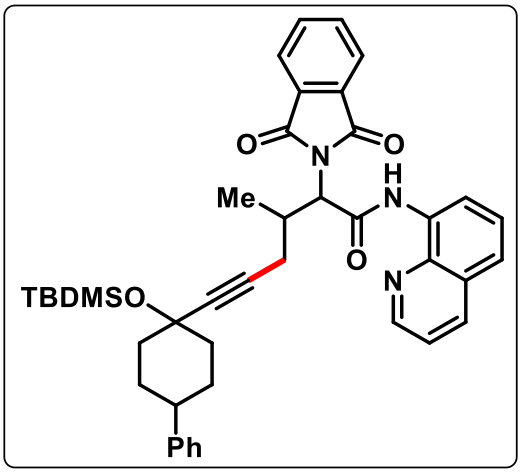
^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.13, 166.36, 166.29, 148.61, 138.86, 136.34, 134.52, 134.34, 131.85, 128.07, 127.42, 123.94, 122.23, 121.81, 117.22, 86.28, 83.88, 73.40, 59.79, 55.59, 52.88, 44.45, 33.38, 32.54, 31.17, 30.66, 26.48, 26.00, 24.30, 19.92, 18.32, 16.69, 15.48, 12.44, -2.25, -2.83.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{40}H_{51}N_3O_4SiNa$ *m/z* 665.3649 and found *m/z* 665.3655

IR (thin film, cm^{-1}): 3359, 3044, 2913, 2849, 1687, 1544, 1469, 1337, 1279, 883, 755, 668.

6-(1-((tert-butyldimethylsilyl)oxy)-4-phenylcyclohexyl)-2-(1,3-dioxoisoindolin-2-yl)-3-methyl-N-(quinolin-8-yl)hex-5-ynamide (2w):

Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 68%



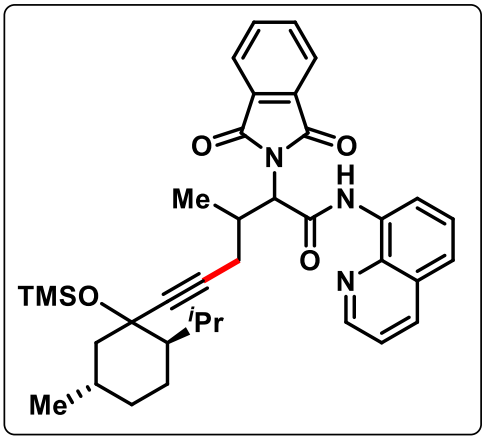
^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.43 (s, 1H), 8.75 (dd, *J* = 6.2, 2.7 Hz, 1H), 8.65 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.10 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.90 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.52 – 7.50 (m, 2H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.20 – 7.14 (m, 5H), 7.10 – 7.07 (m, 1H), 5.10 (d, *J* = 10.6 Hz, 1H), 3.41 – 3.34 (m, 1H), 2.69 (d, *J* = 5.2 Hz, 2H), 2.48 (ddd, *J* = 14.9, 7.5, 3.4 Hz, 1H), 2.16 – 2.09 (m, 2H), 1.93 – 1.81 (m, 4H), 1.69 – 1.62 (m, 2H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.84 (s, 9H), 0.15 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 168.12, 166.38, 148.66, 147.03, 138.84, 136.30, 134.53, 134.32, 131.86, 128.42, 128.07, 127.41, 127.14, 126.00, 123.95, 122.24, 121.80, 117.21, 87.07, 82.69, 70.56, 59.64, 43.94, 42.06, 31.94, 31.87, 31.22, 25.97, 24.27, 18.16, 16.80, -2.48, -2.55.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{42}H_{47}N_3O_4SiNa$ *m/z* 708.3228 and found *m/z* 708.3232

IR (thin film, cm^{-1}): 3359, 3017, 2975, 2823, 1611, 1555, 1469, 1383, 1265, 869, 791, 668.

2-(1,3-dioxoisoindolin-2-yl)-6-((2R,5S)-2-isopropyl-5-methyl-1-((trimethylsilyl)oxy)cyclohexyl)-3-methyl-N-(quinolin-8-yl)hex-5-ynamide (2x)



Eluent: ethyl acetate/petroleum ether (5:95 v/v); appearance: sticky pale yellow liquid; isolated yield: 59%

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.38 (s, 1H), 8.77 – 8.72 (m, 2H), 8.12 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.90 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.75 – 7.72 (m, 2H), 7.50 (d, *J* = 5.1 Hz, 2H), 7.43 – 7.39 (m, 1H), 5.01 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.38 – 3.27 (m, 1H), 2.62 (td, *J* = 9.6, 6.0 Hz, 2H), 2.46 – 2.23 (m, 1H), 2.04 – 1.89 (m, 1H), 1.46 – 1.15 (m, 5H), 1.11 (d, *J* = 6.7 Hz, 3H), 0.99 (t, *J* = 6.6 Hz, 1H), 0.95 – 0.81 (m, 10H), 0.12 (d, *J* = 3.8 Hz, 9H).

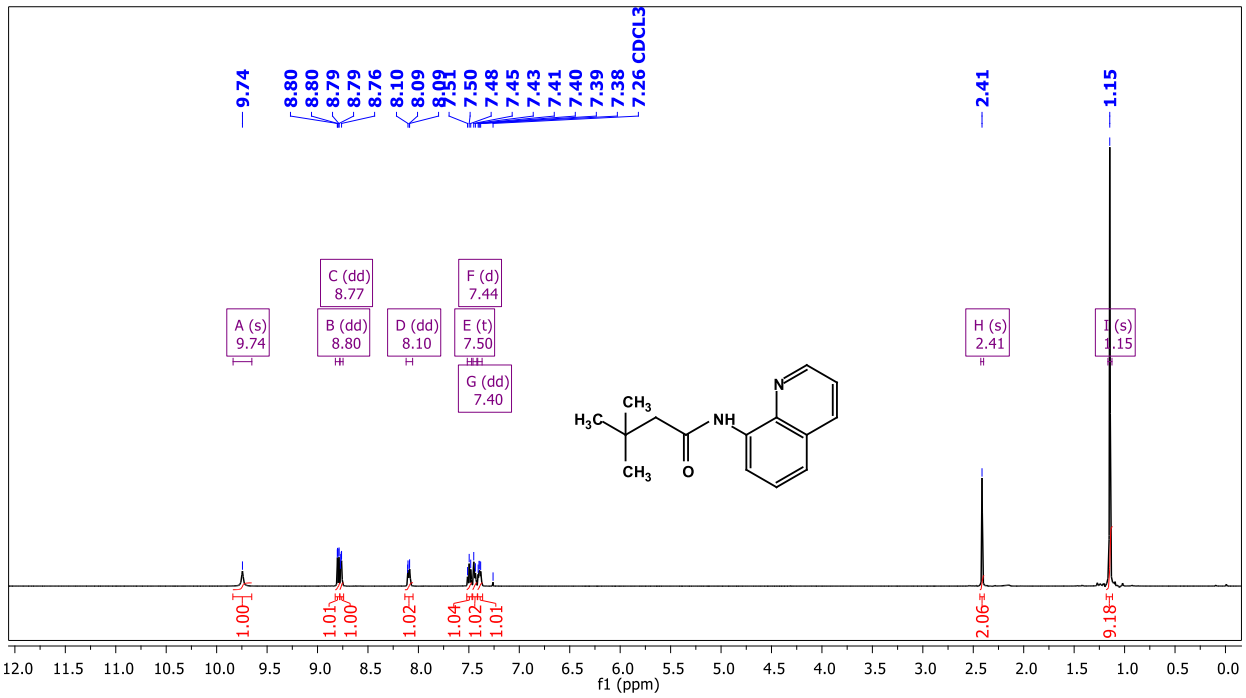
^{13}C NMR (101 MHz, $CDCl_3$) δ: 168.13, 166.42, 166.32, 148.66, 138.83, 136.36, 134.51, 134.32, 131.85, 128.07, 127.42, 123.93, 122.23, 121.81, 117.20, 88.56, 80.75, 73.53, 59.72, 52.20, 50.95, 35.22, 31.32, 28.65, 27.44, 24.22, 24.13, 22.19, 20.72, 18.50, 16.65, 2.30, 1.99.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{37}H_{45}N_3O_4SiNa$ *m/z* 646.3072 and found *m/z* 646.3082

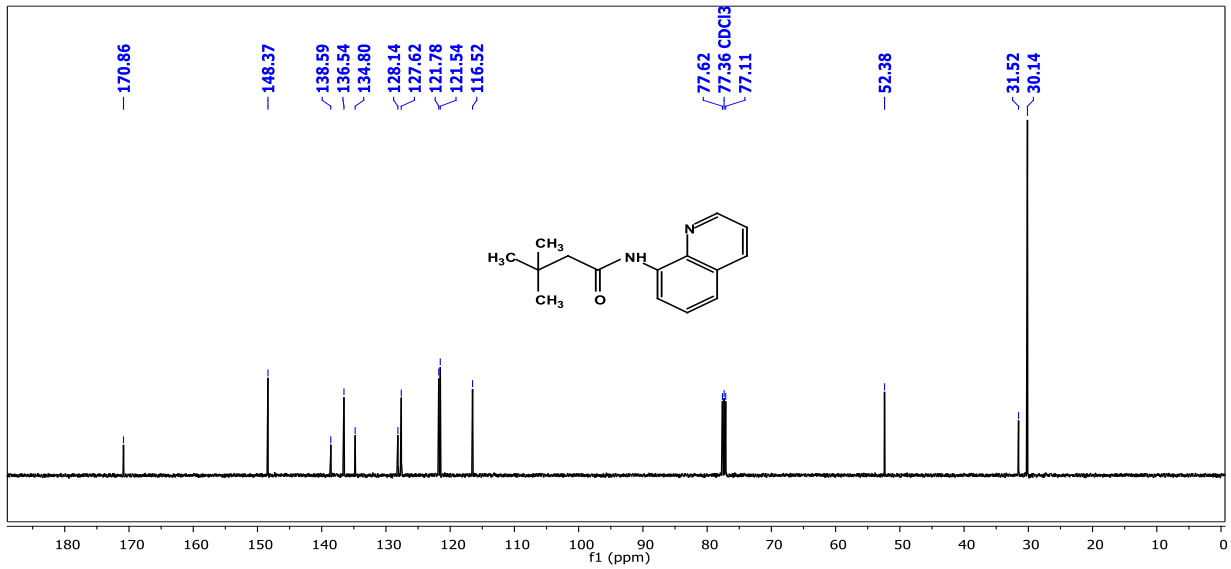
IR (thin film, cm^{-1}): 3352, 3059, 2973, 2859, 1655, 1563, 1459, 1370, 1259, 849, 752, 667.

3.6. Spectra of representative compounds

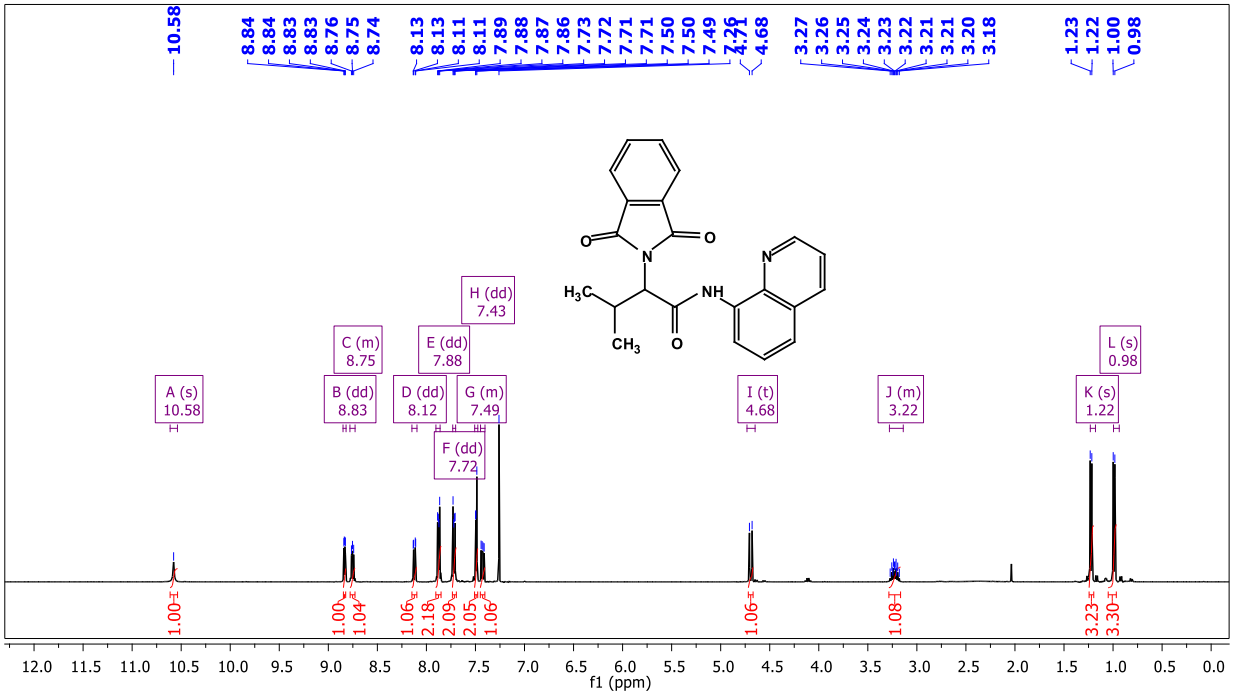
^{1}H Spectra of 1a:



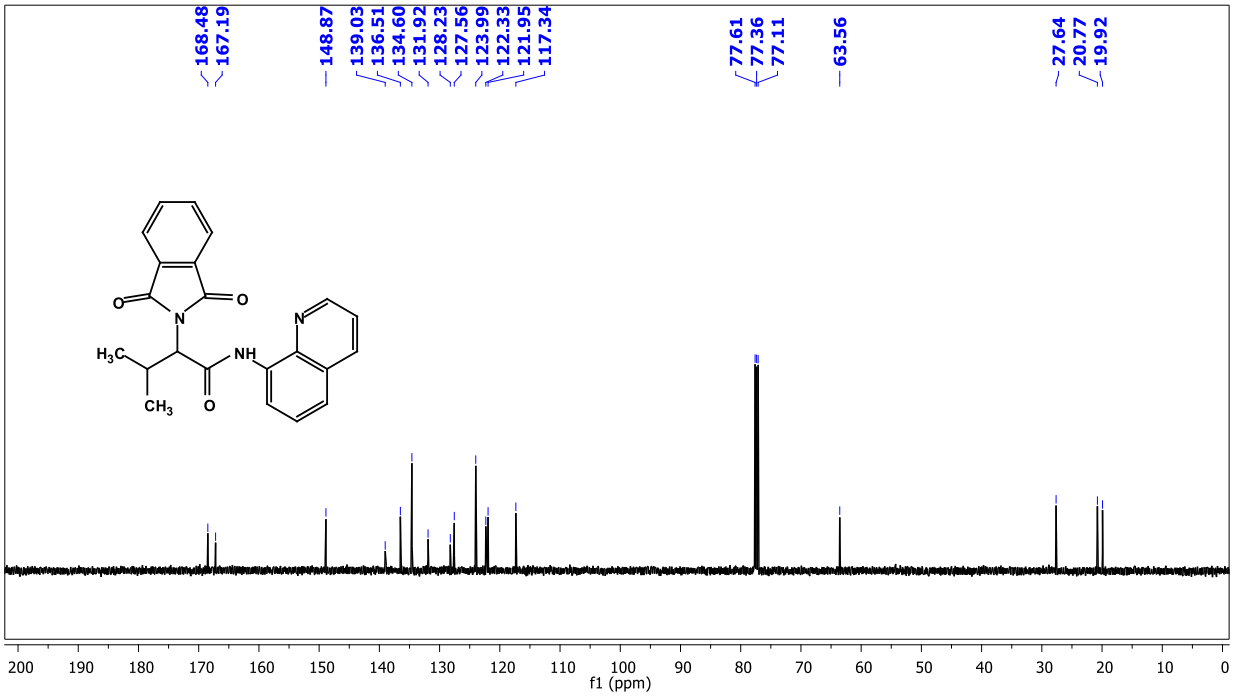
^{13}C Spectra of 1a:



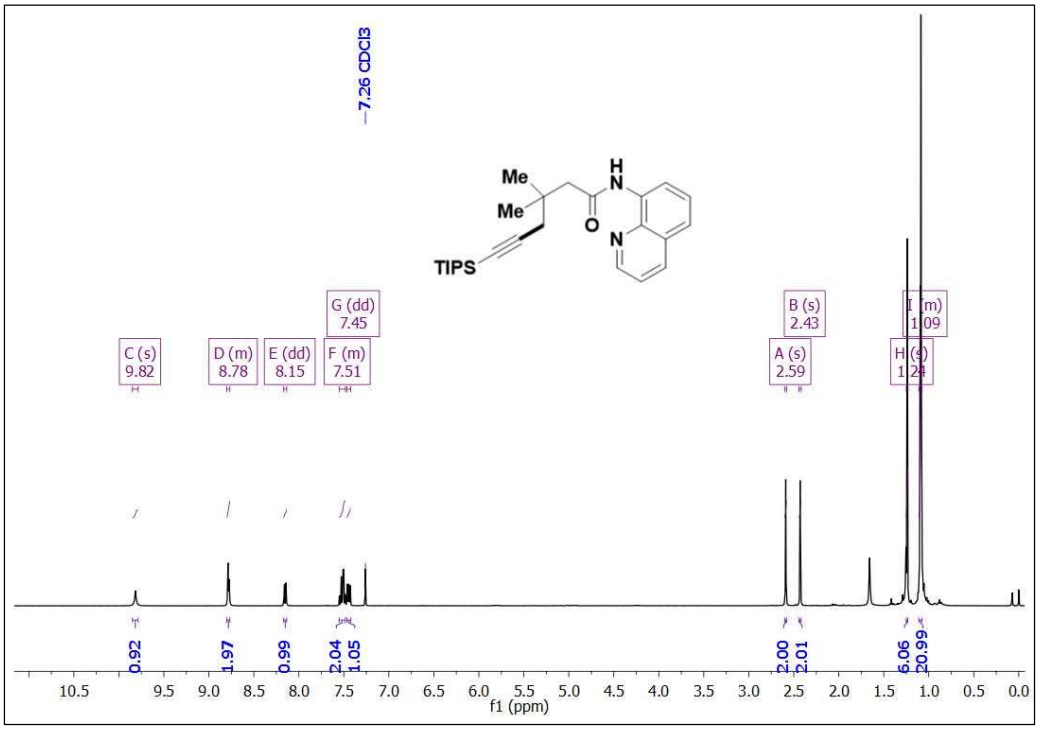
^{1}H Spectra of 1b:



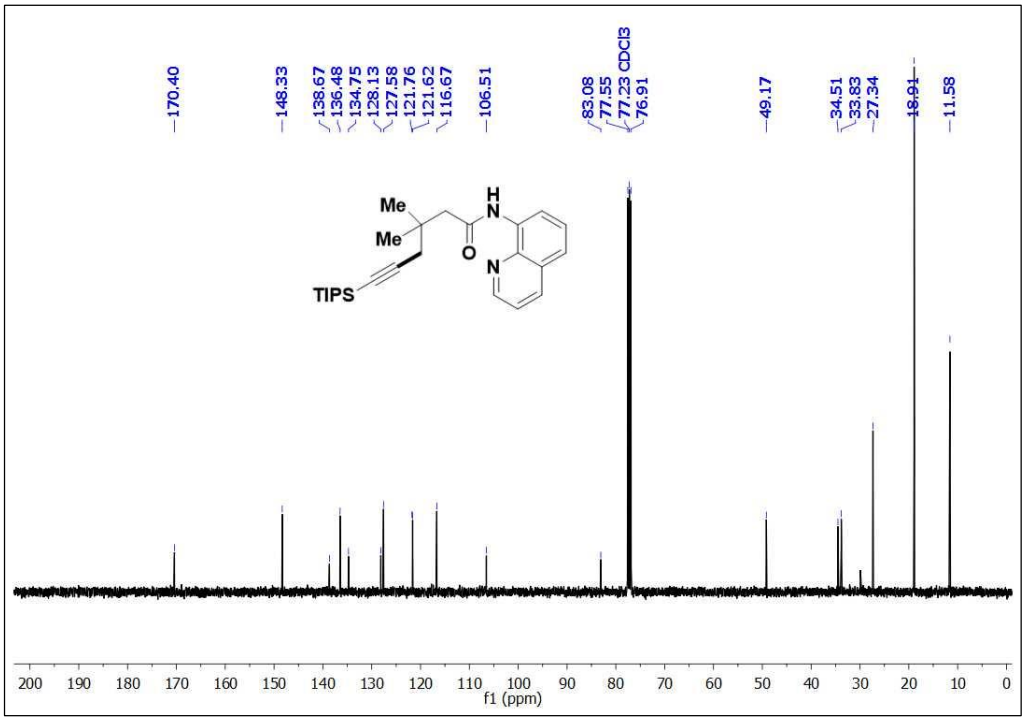
^{13}C Spectra of 1b:



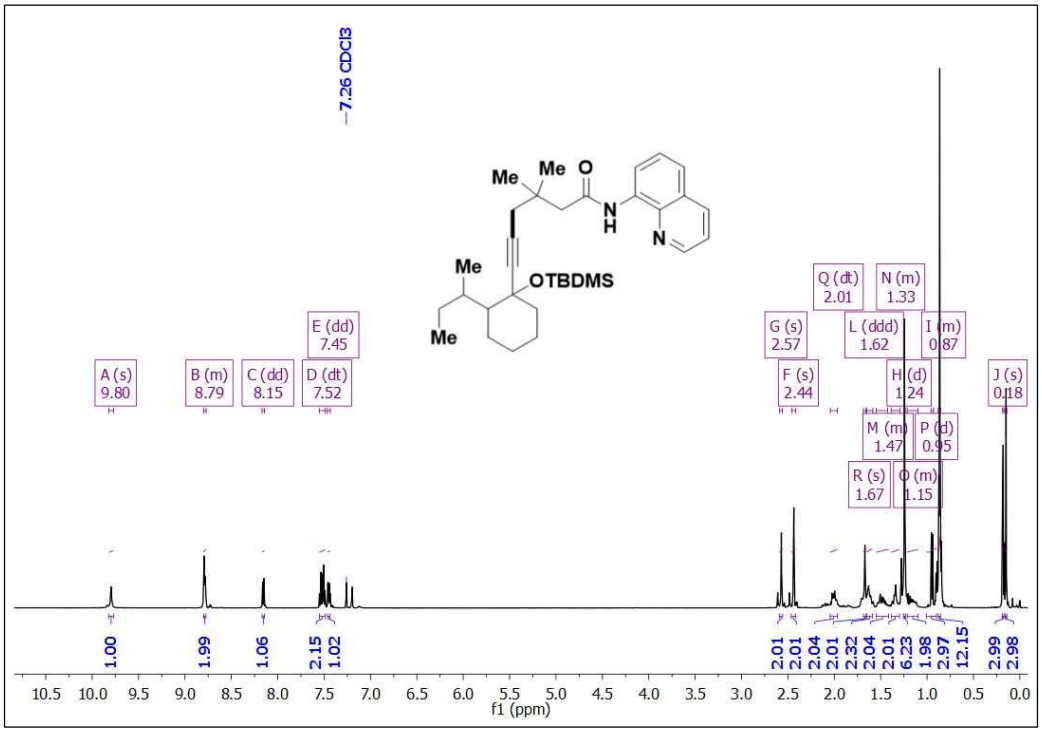
^{1}H NMR of 2a:



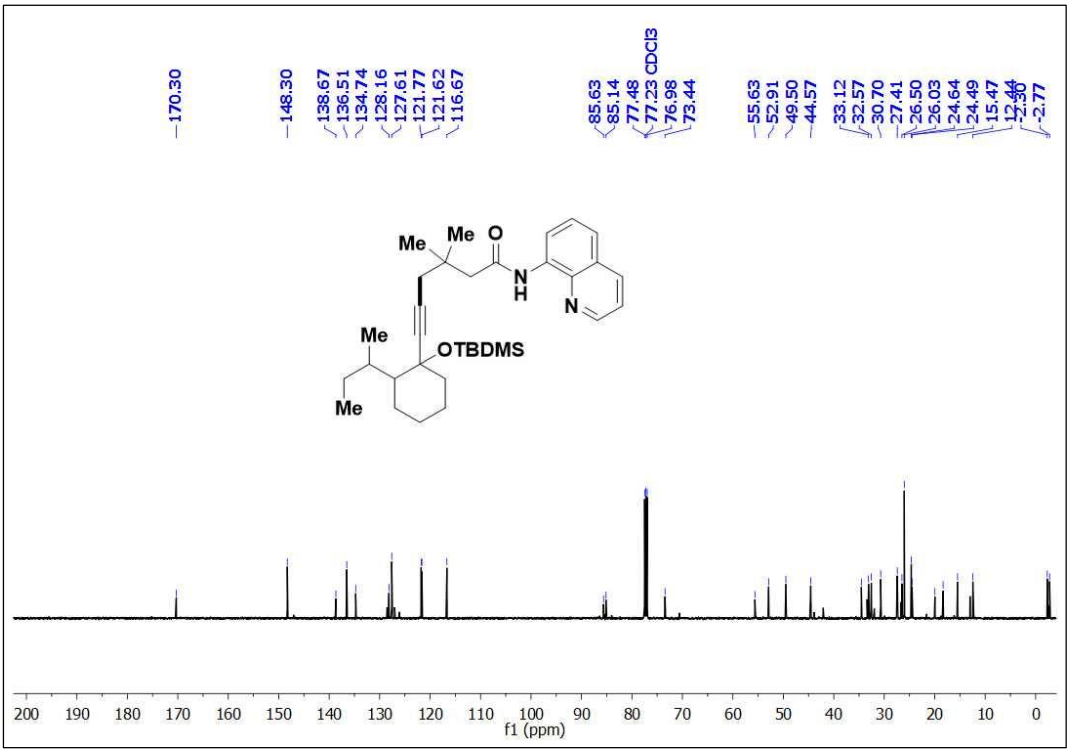
^{13}C NMR of 2a:



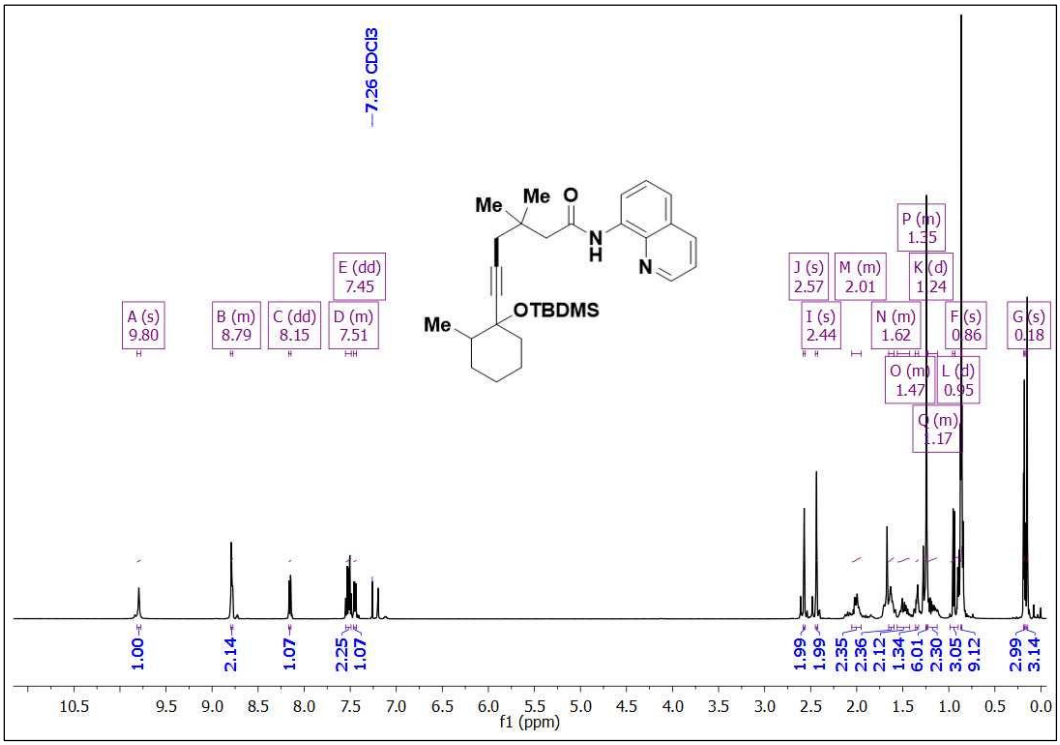
^{1}H NMR of 2b:



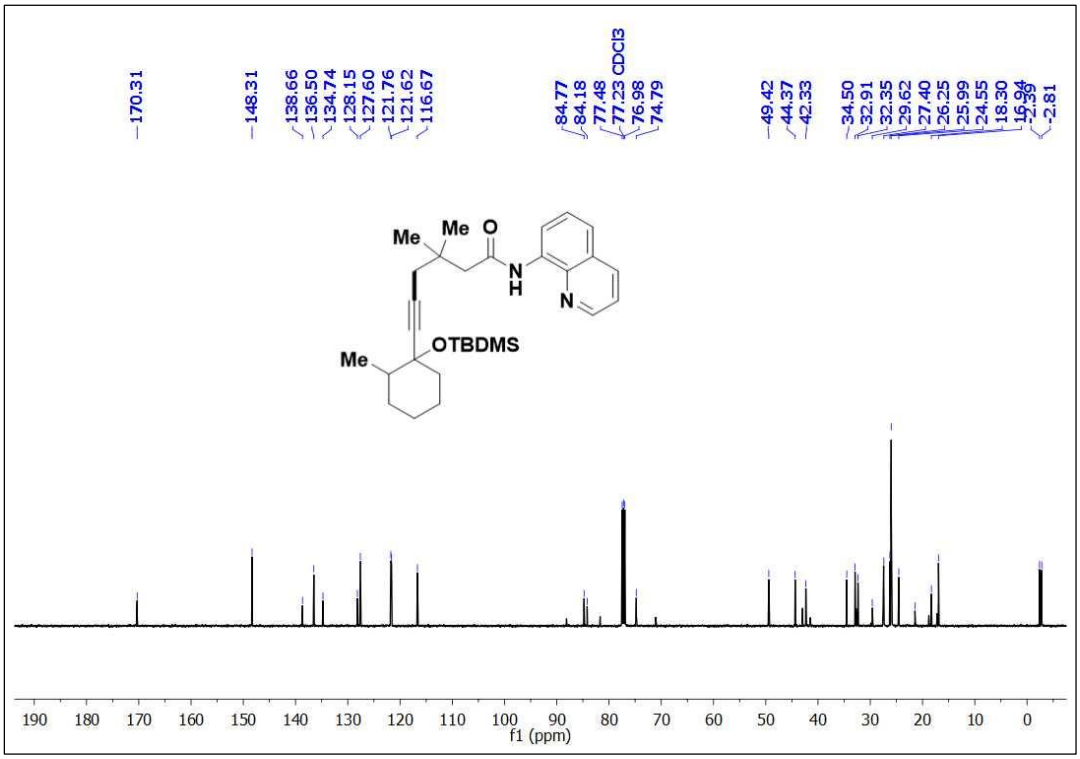
^{13}C NMR of 2b:



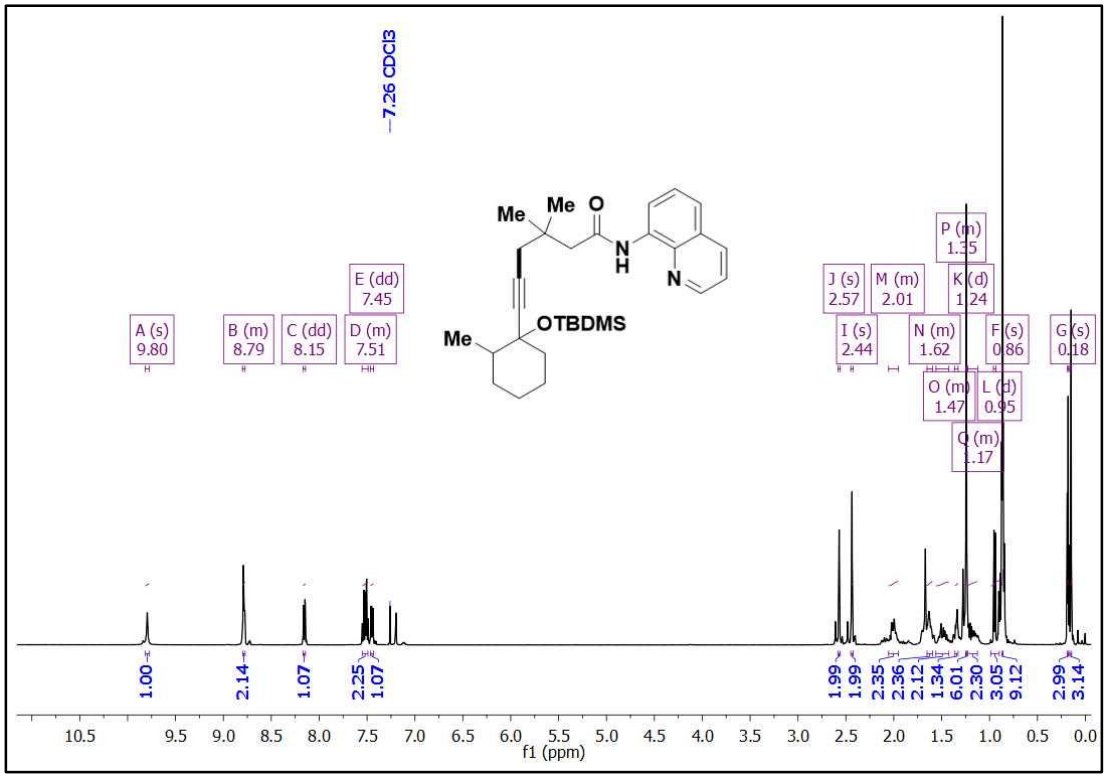
^{1}H NMR of 2c:



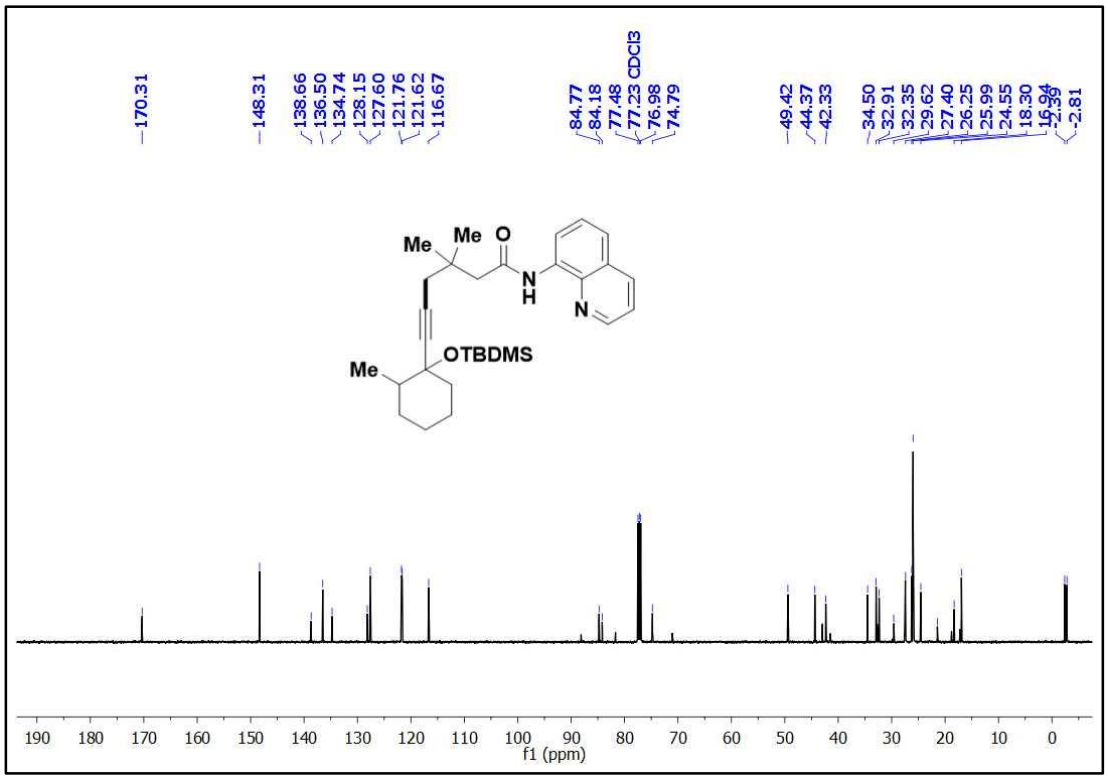
^{13}C NMR of 2c:



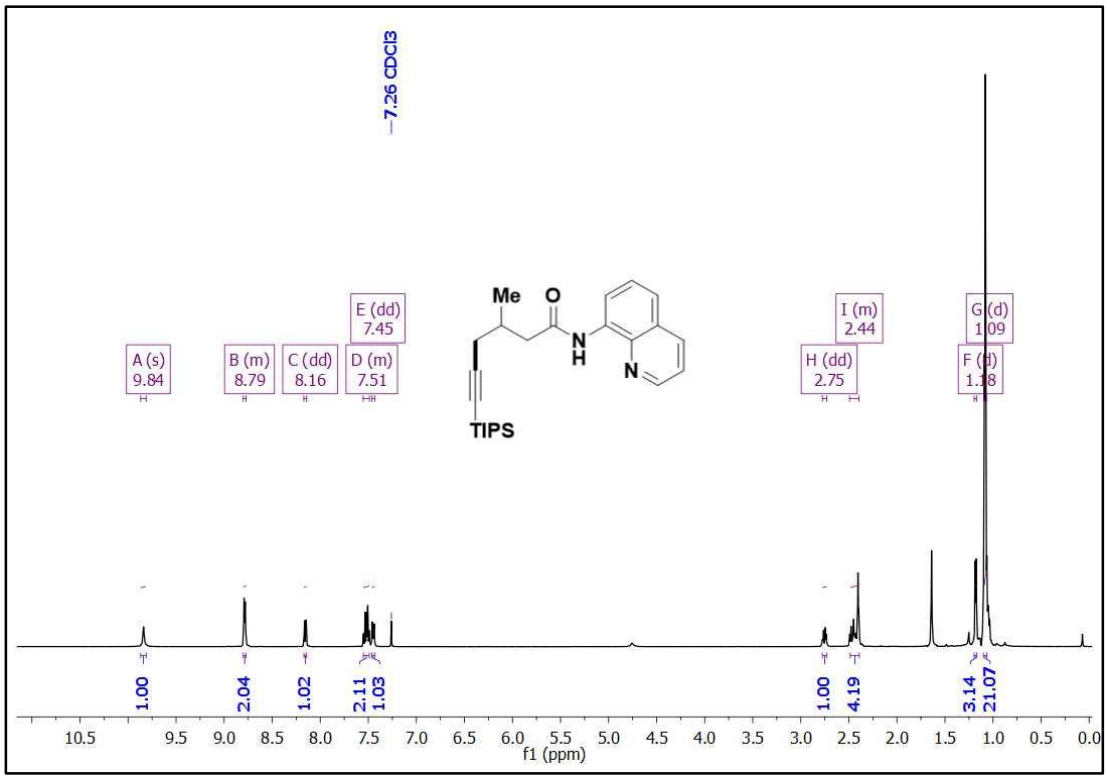
1H spectra of 2d:



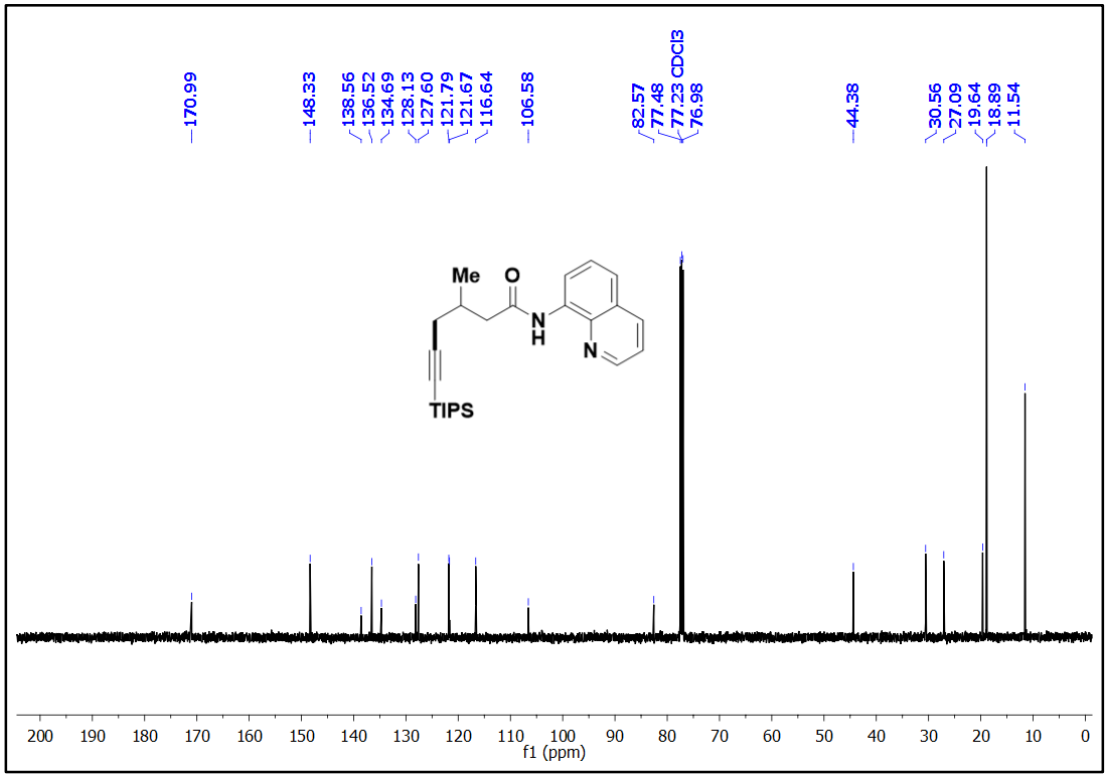
13C spectra of 2d:



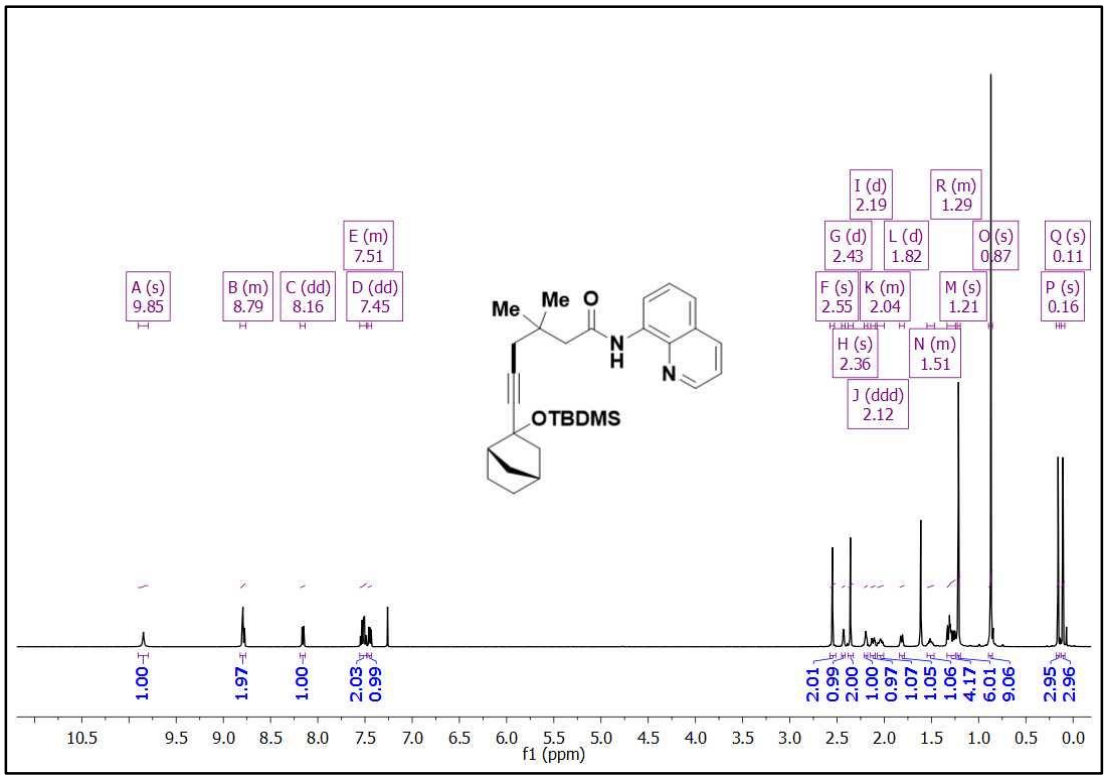
1H spectra of 2e:



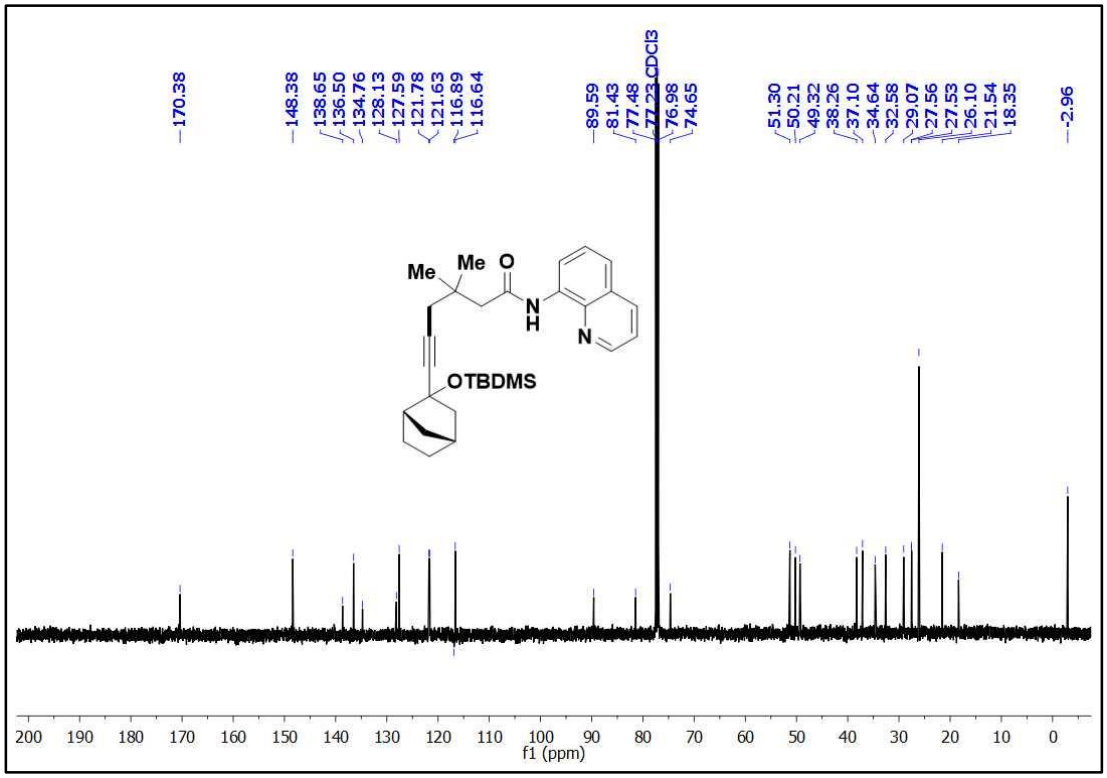
13C spectra of 2e:



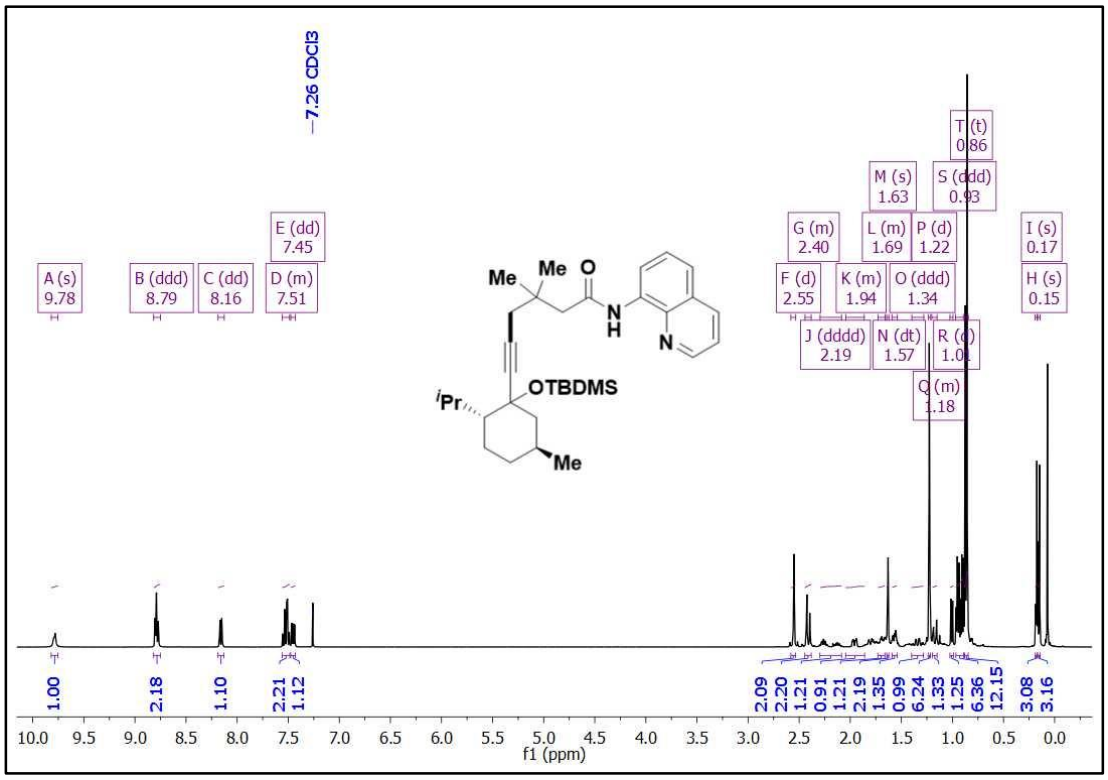
1H spectra of 2f:



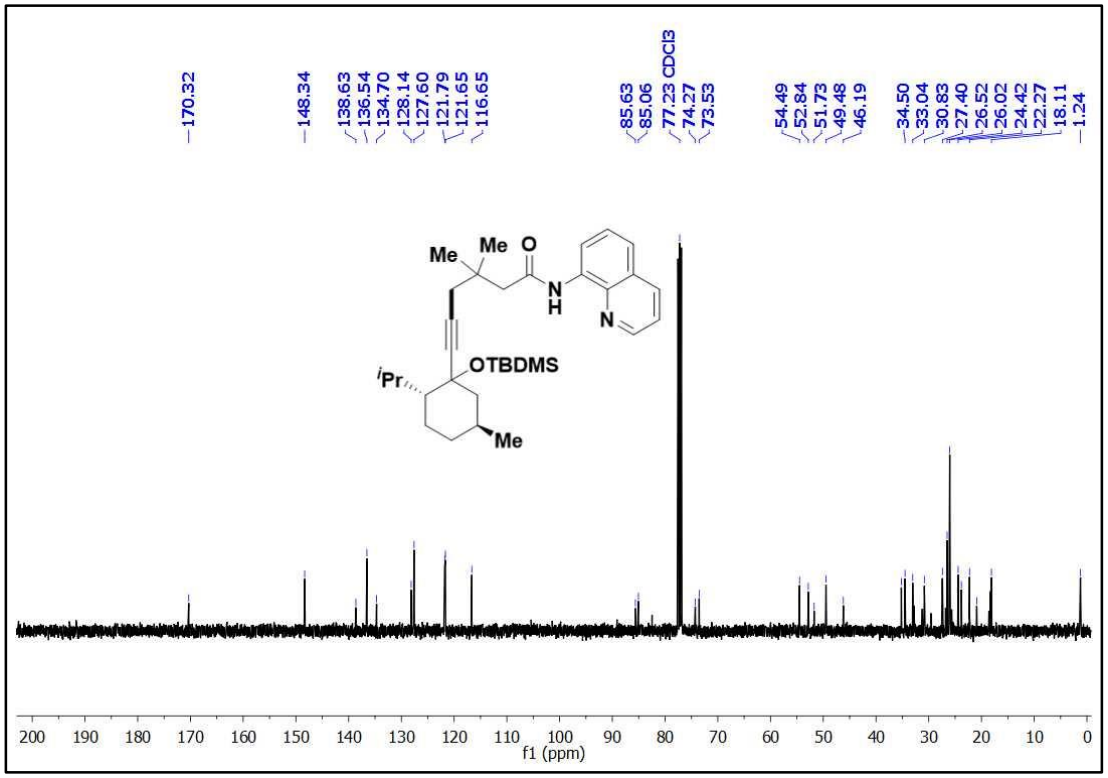
13C spectra of 2f:



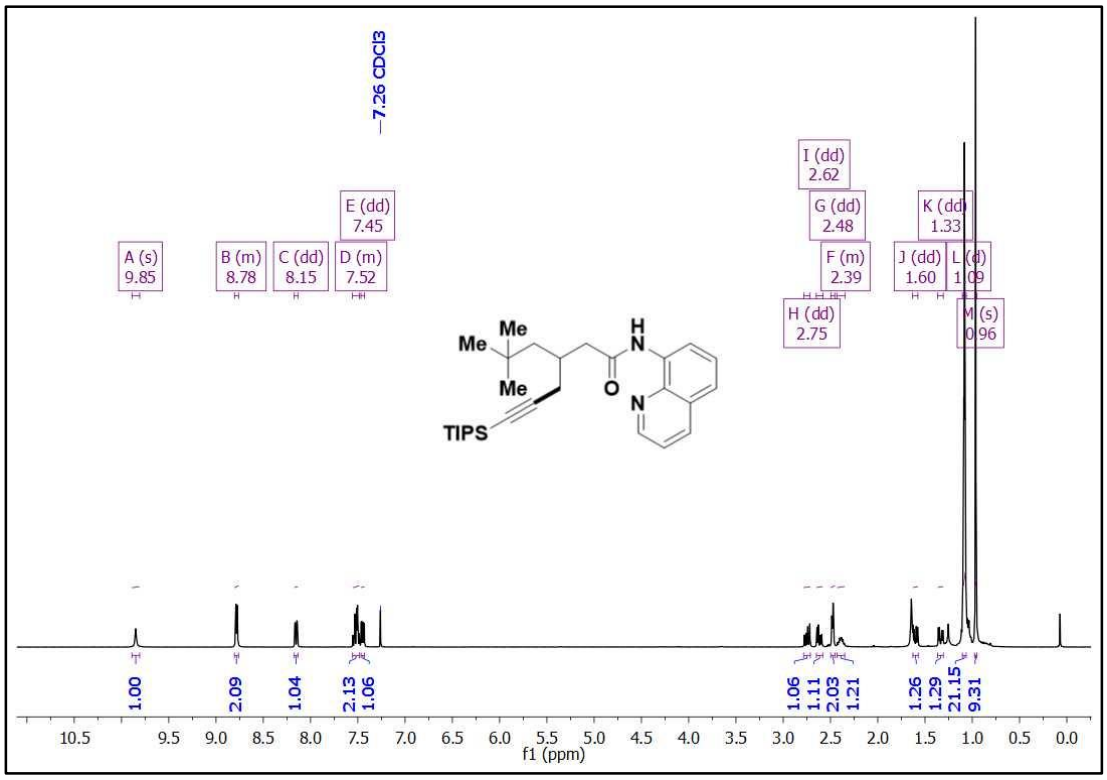
1H spectra of 2g:



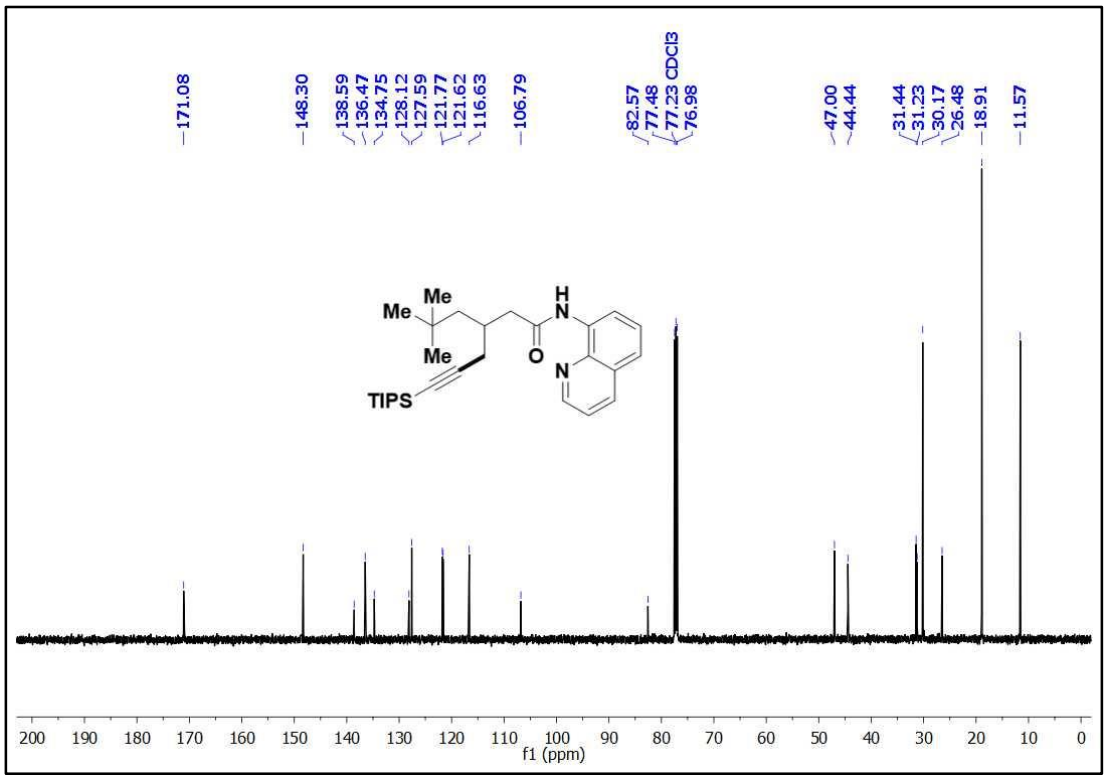
13C spectra of 2g:



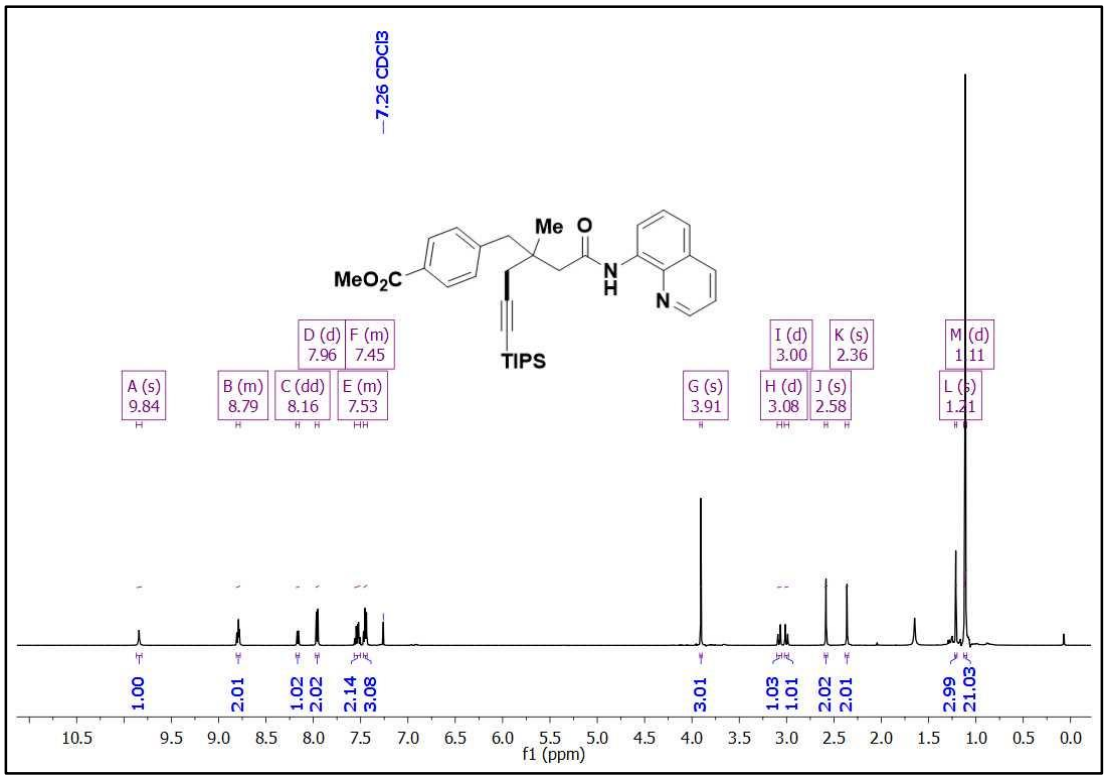
1H spectra of 2h:



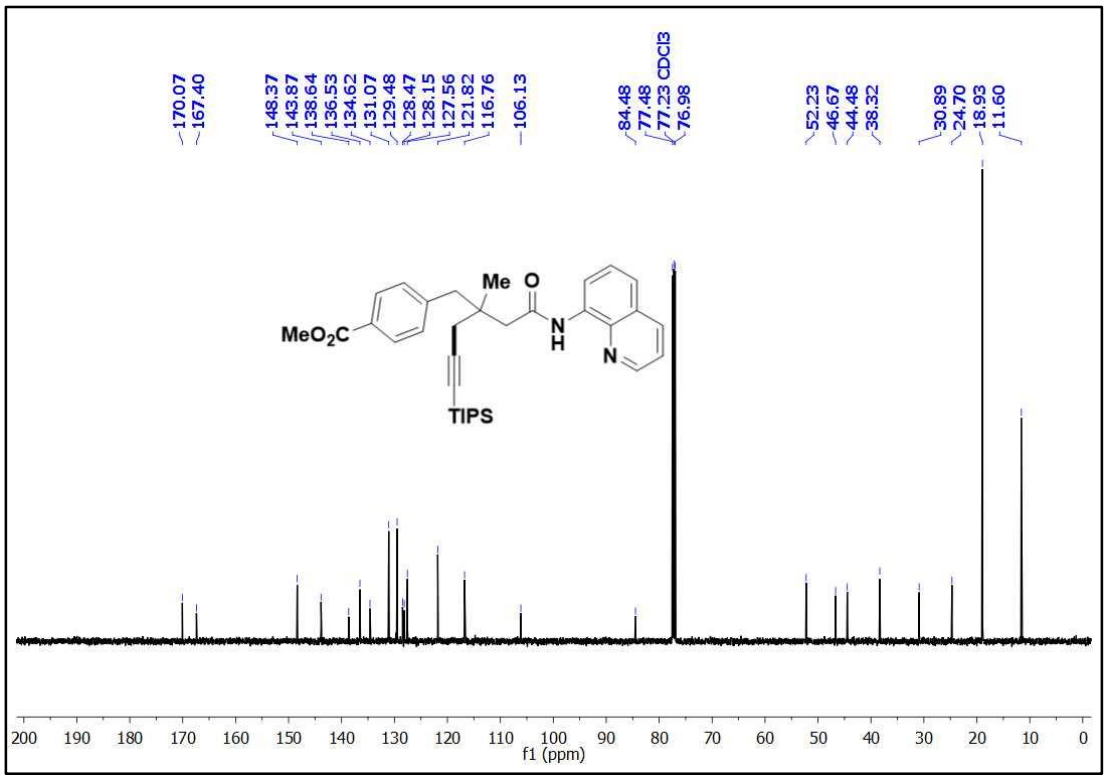
13C spectra of 2h:



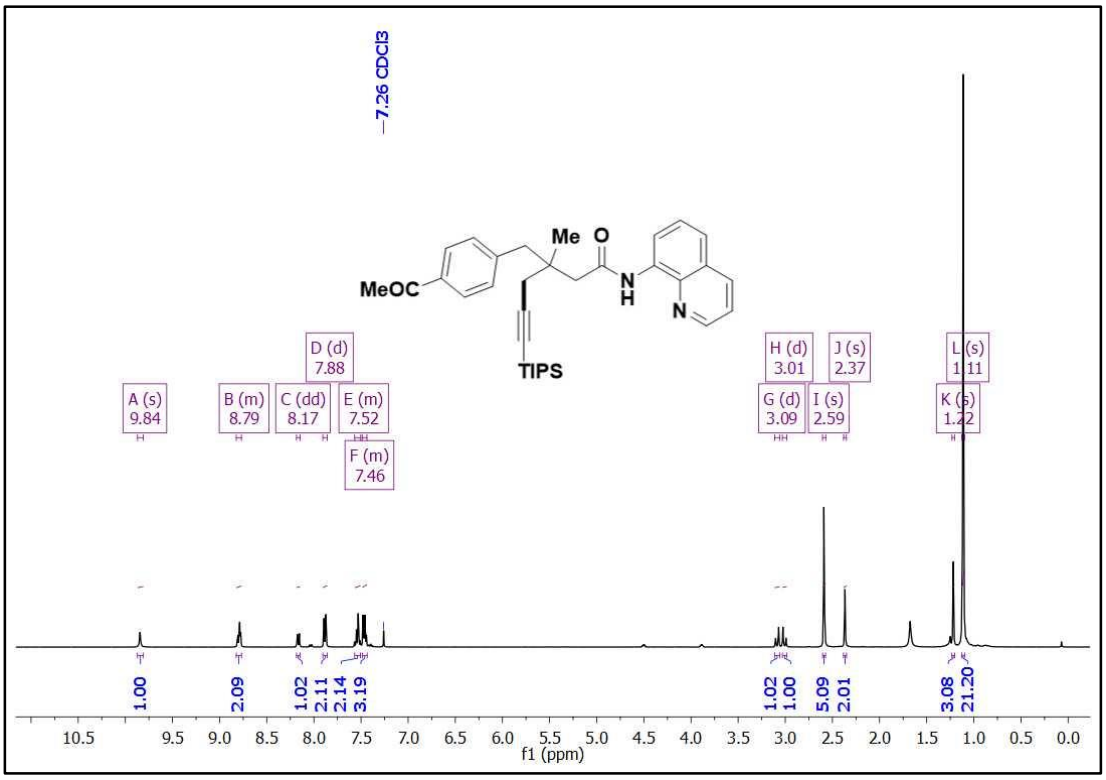
1H spectra of 2i:



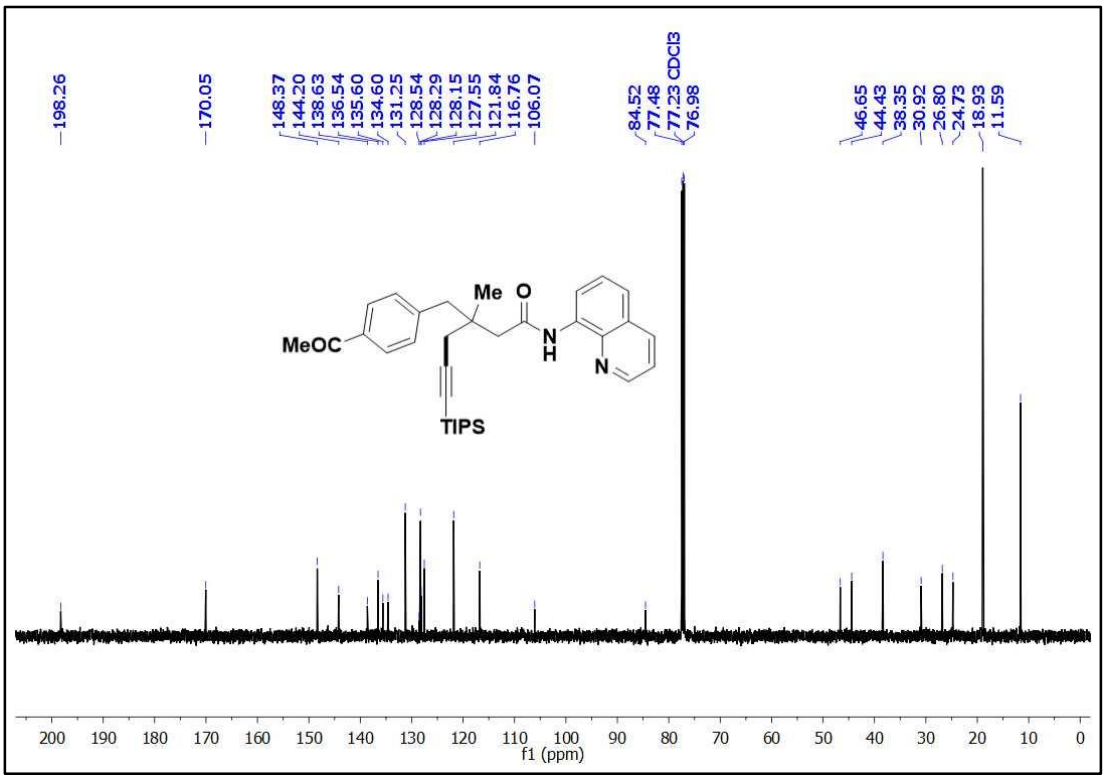
13C spectra of 2i:



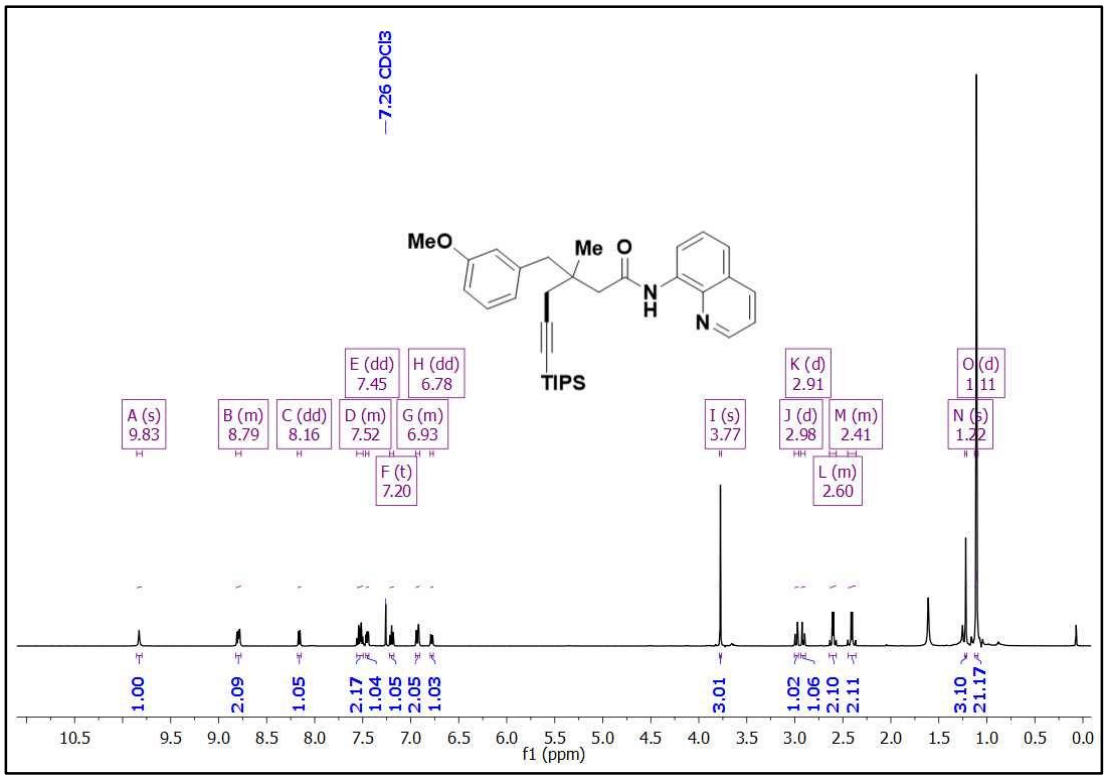
1H Spectra of 2j:



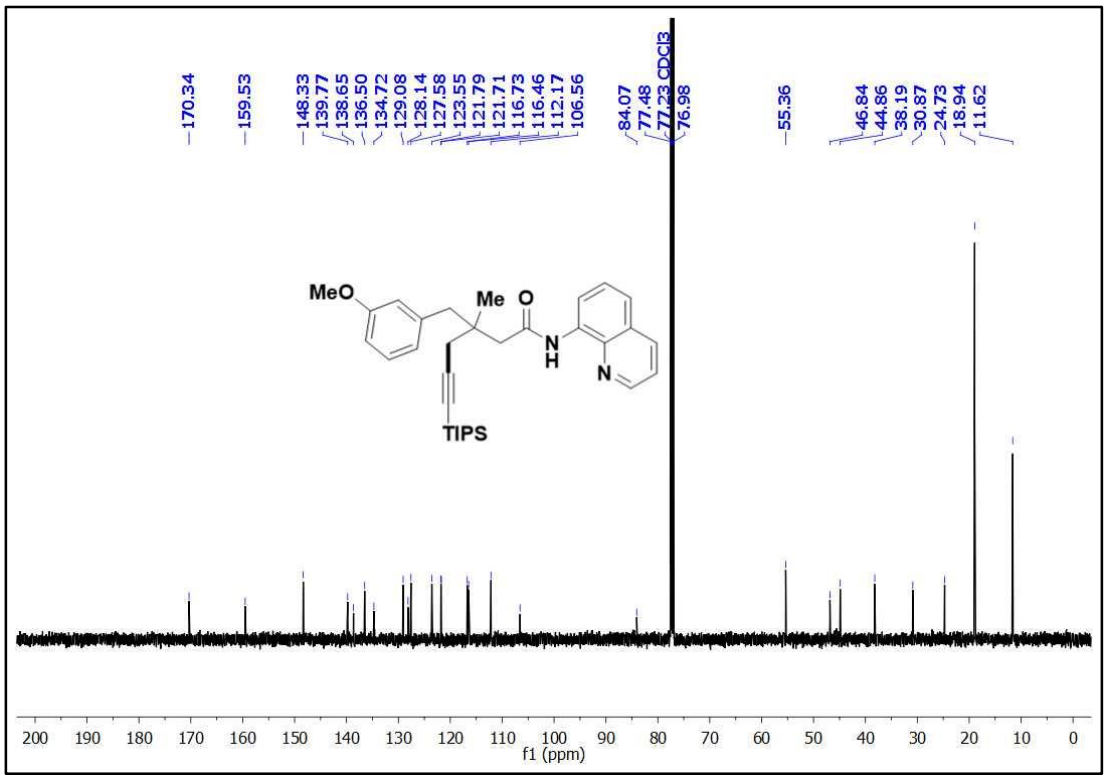
13C spectra of 2j:



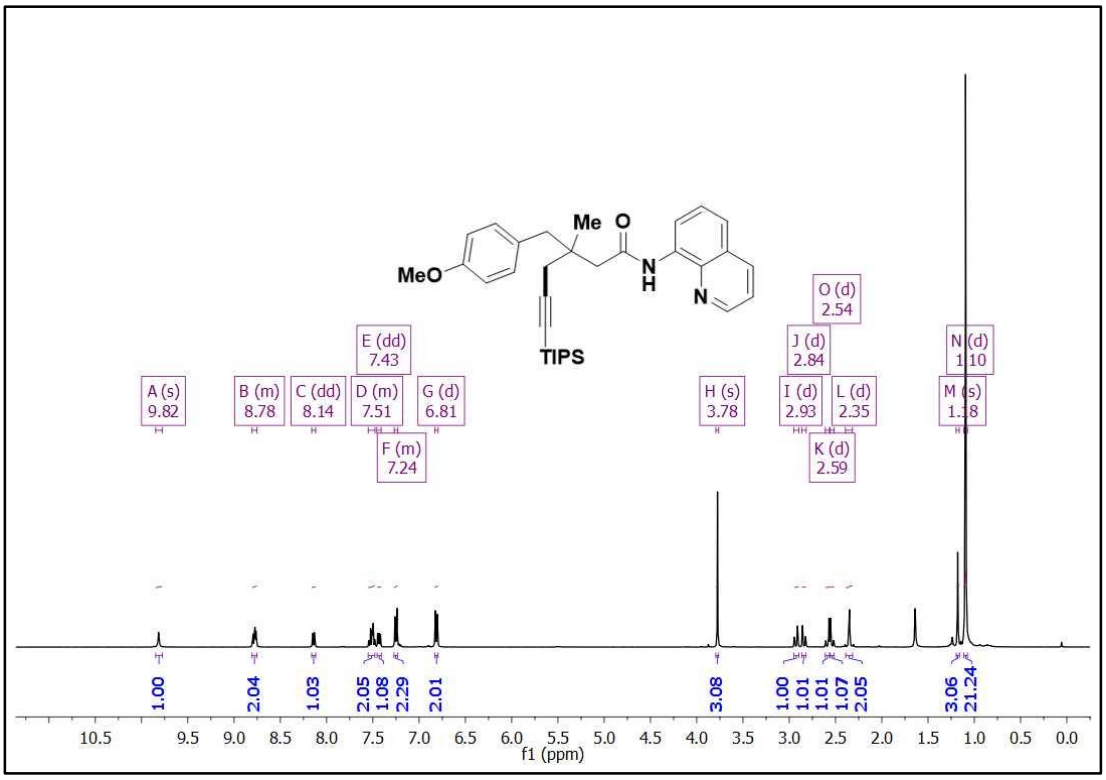
1H spectra of 2k:



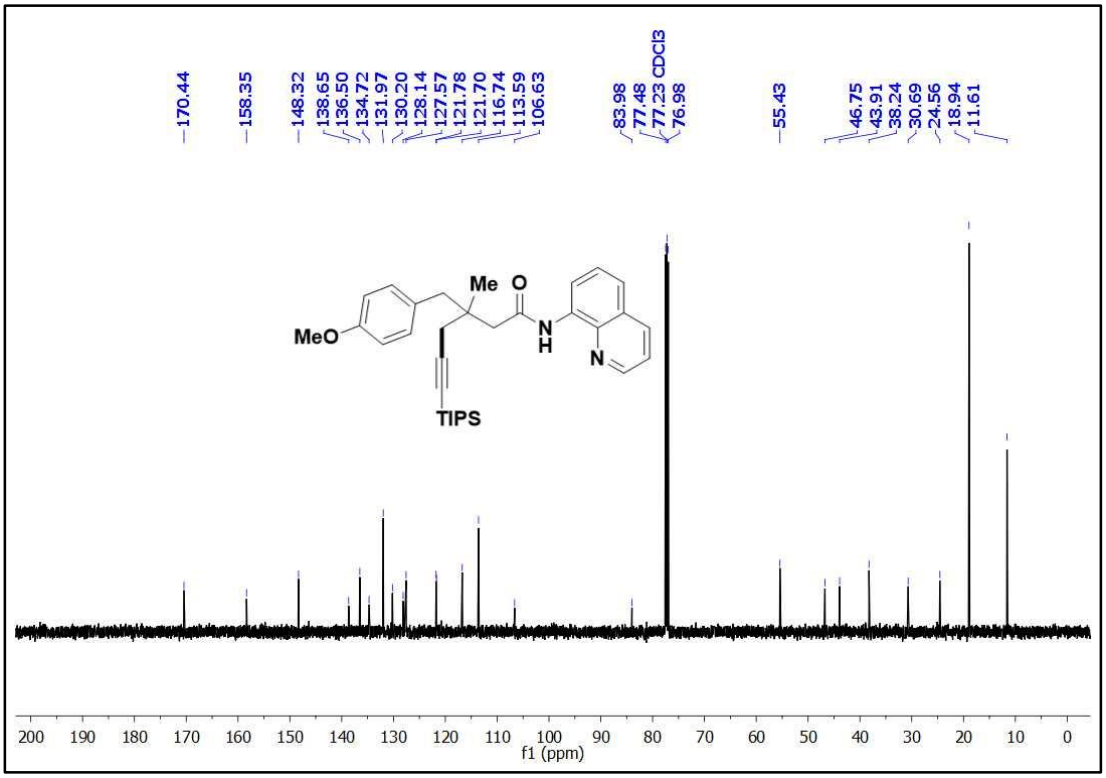
13C spectra of 2k:



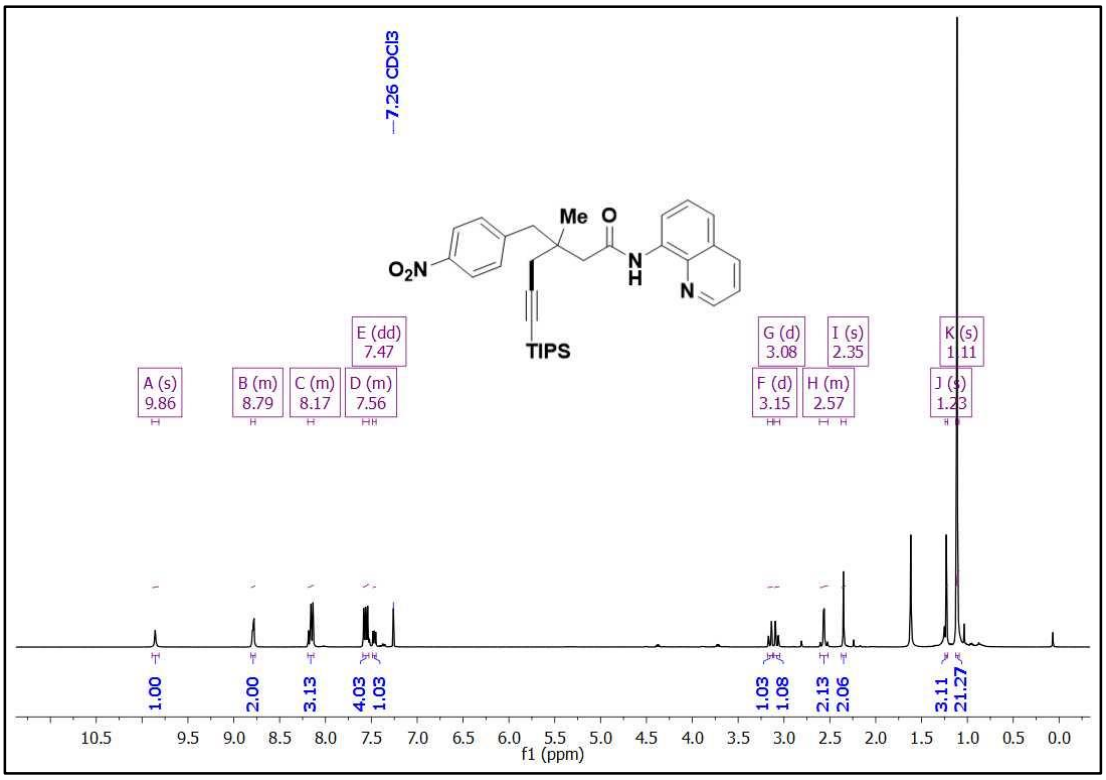
1H spectra of 2l:



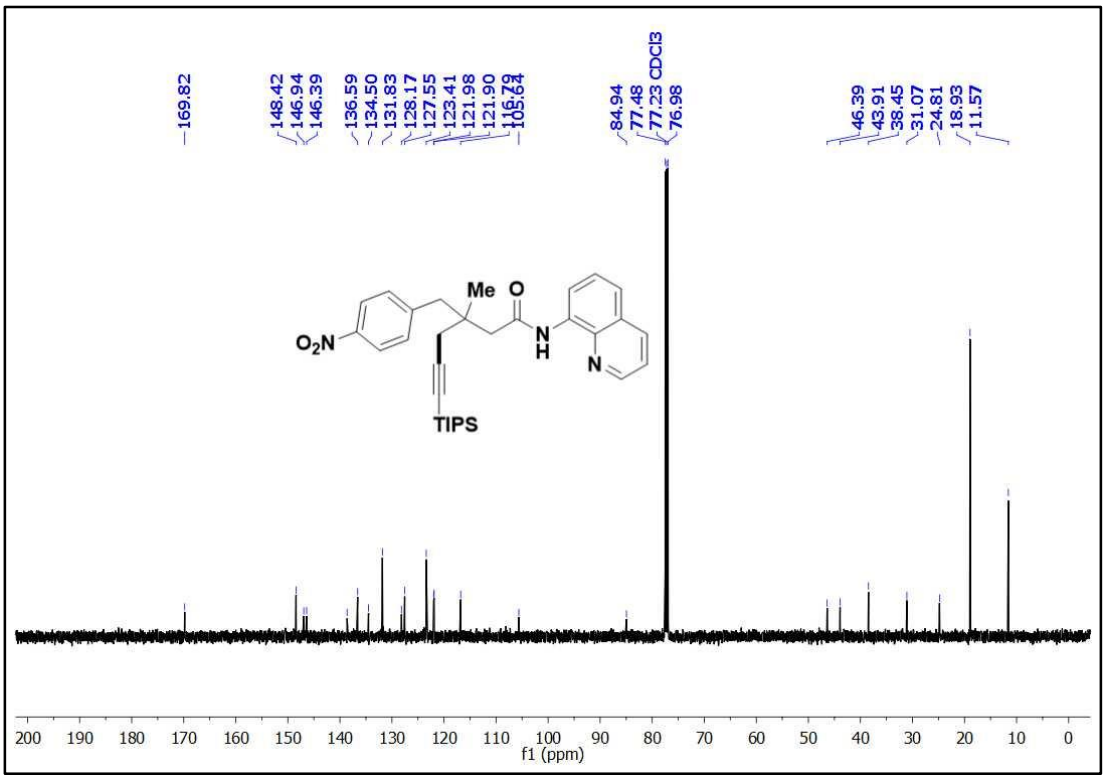
13C spectra of 2l:



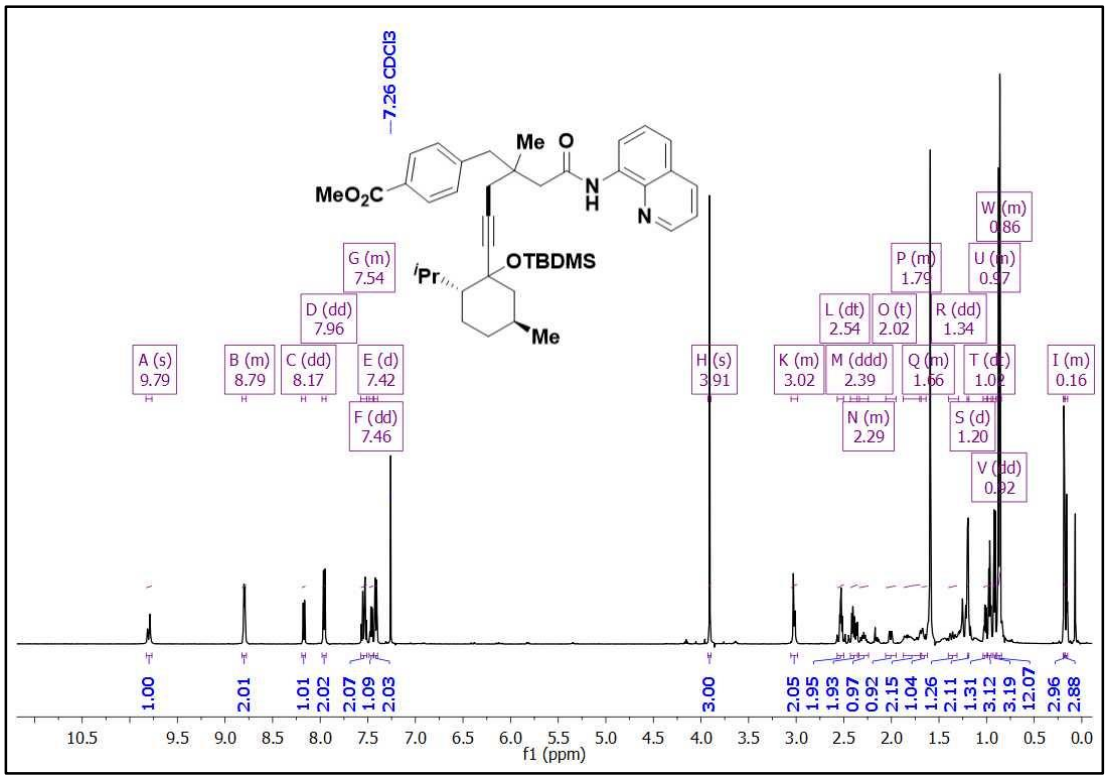
1H spectra of 2m:



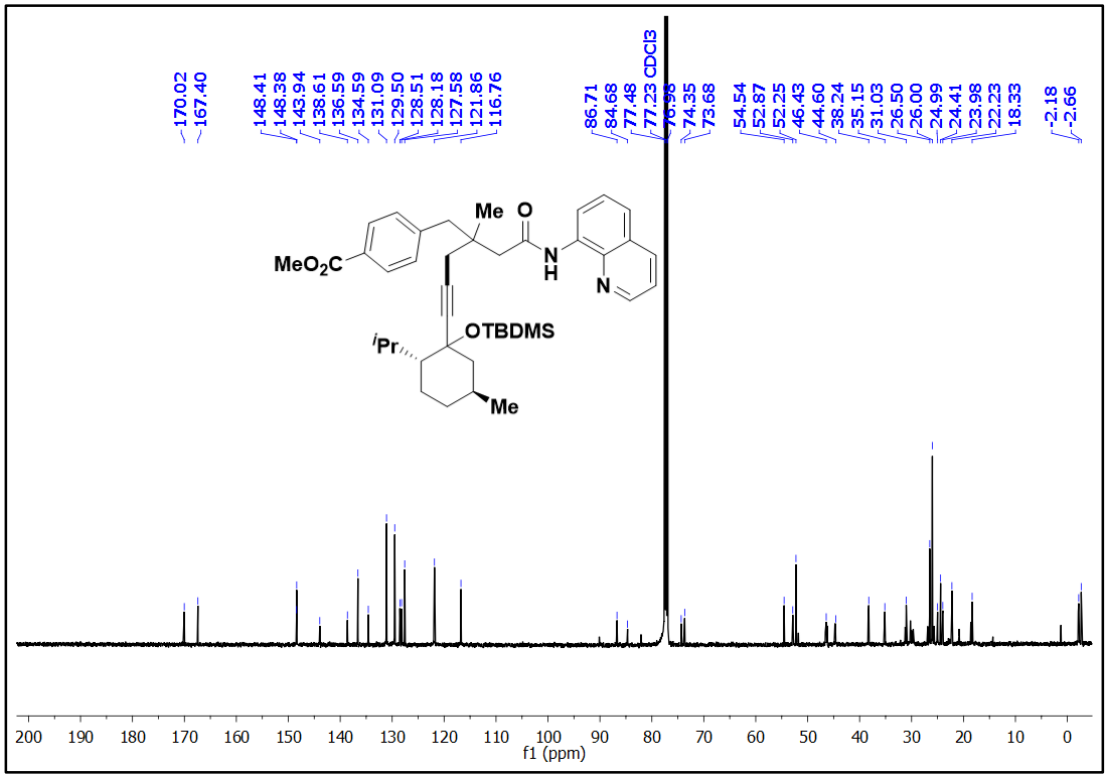
13C spectra of 2m:



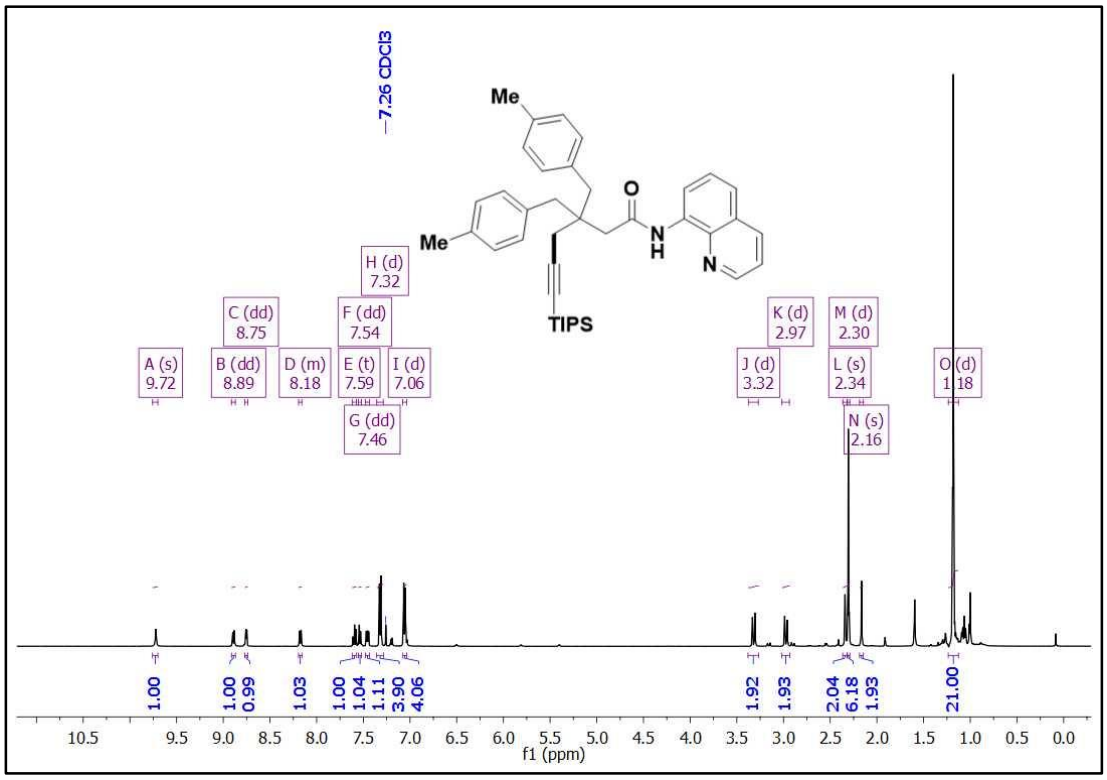
1H spectra of 2n:



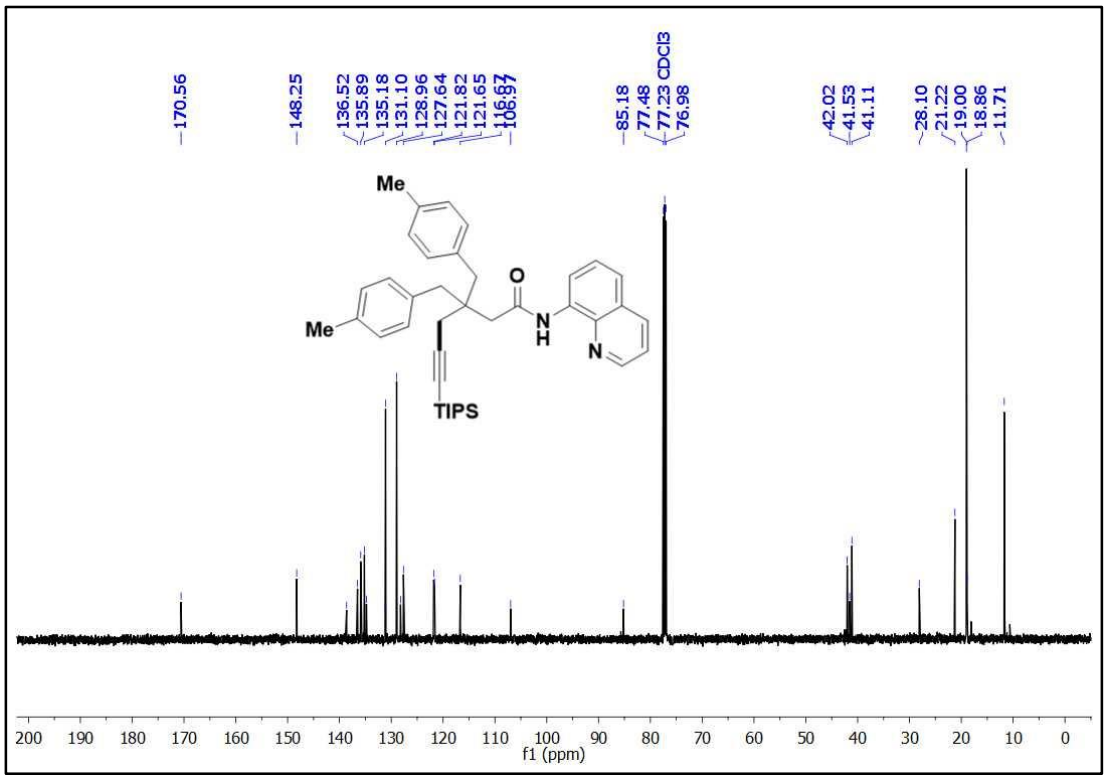
13C spectra of 2n:



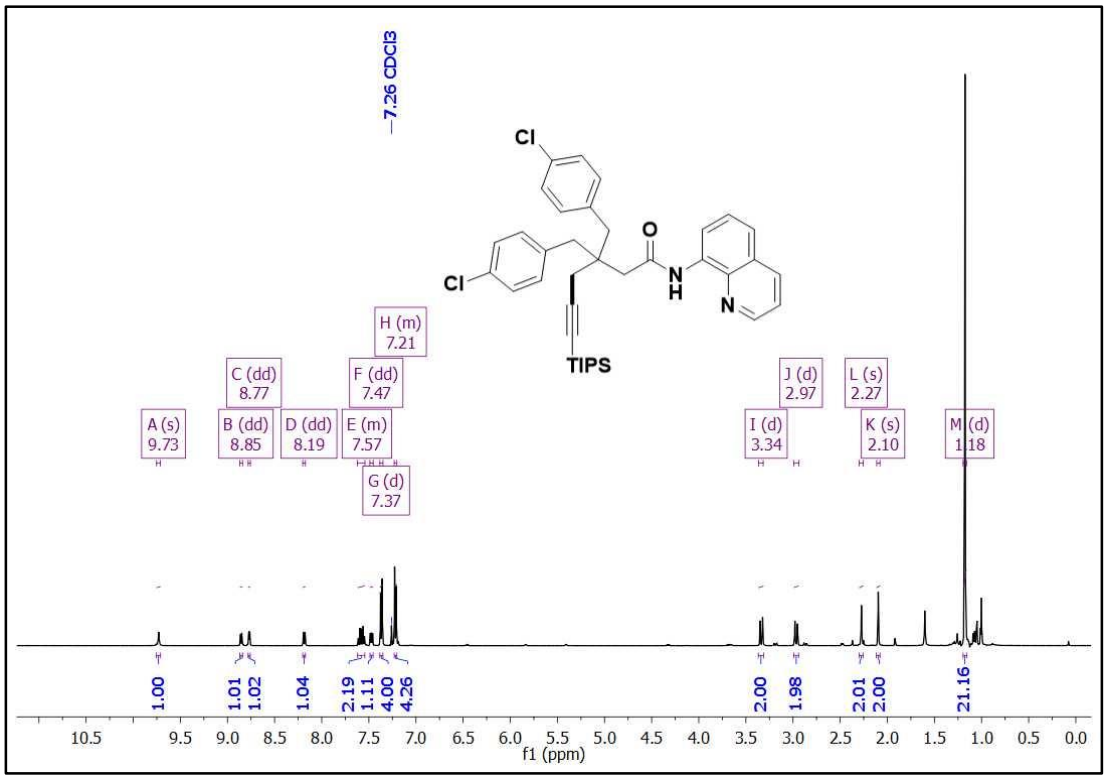
1H spectra of 2o:



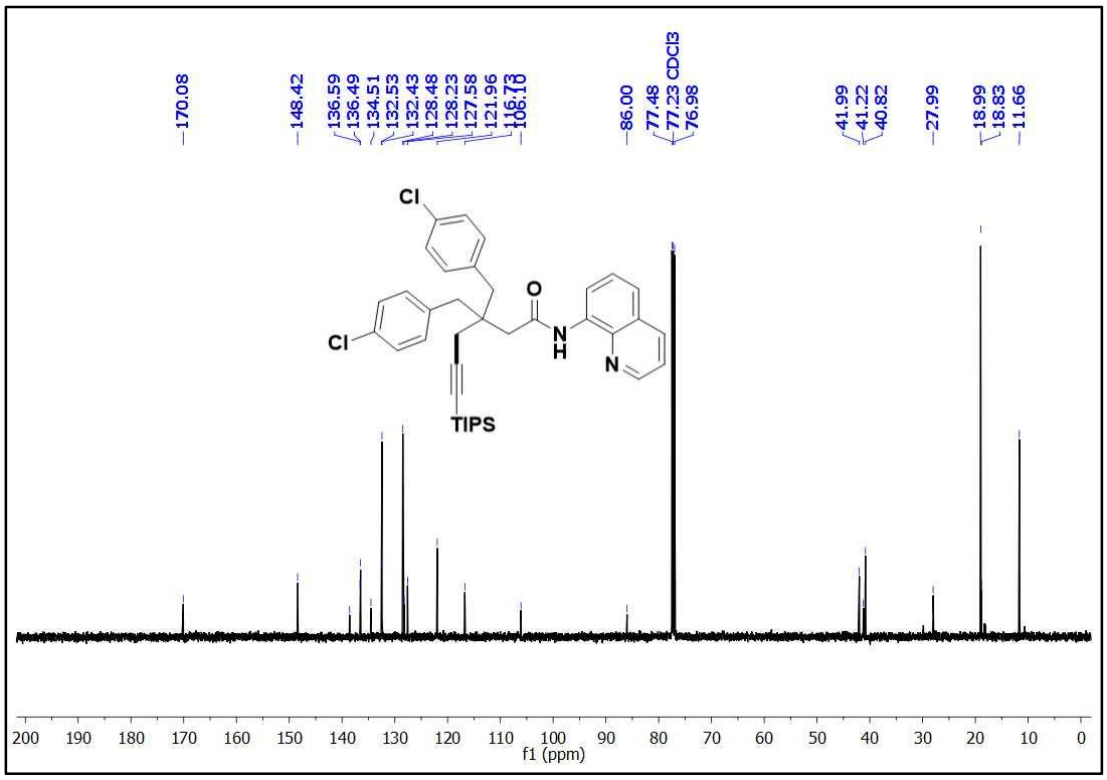
13C spectra of 2o:



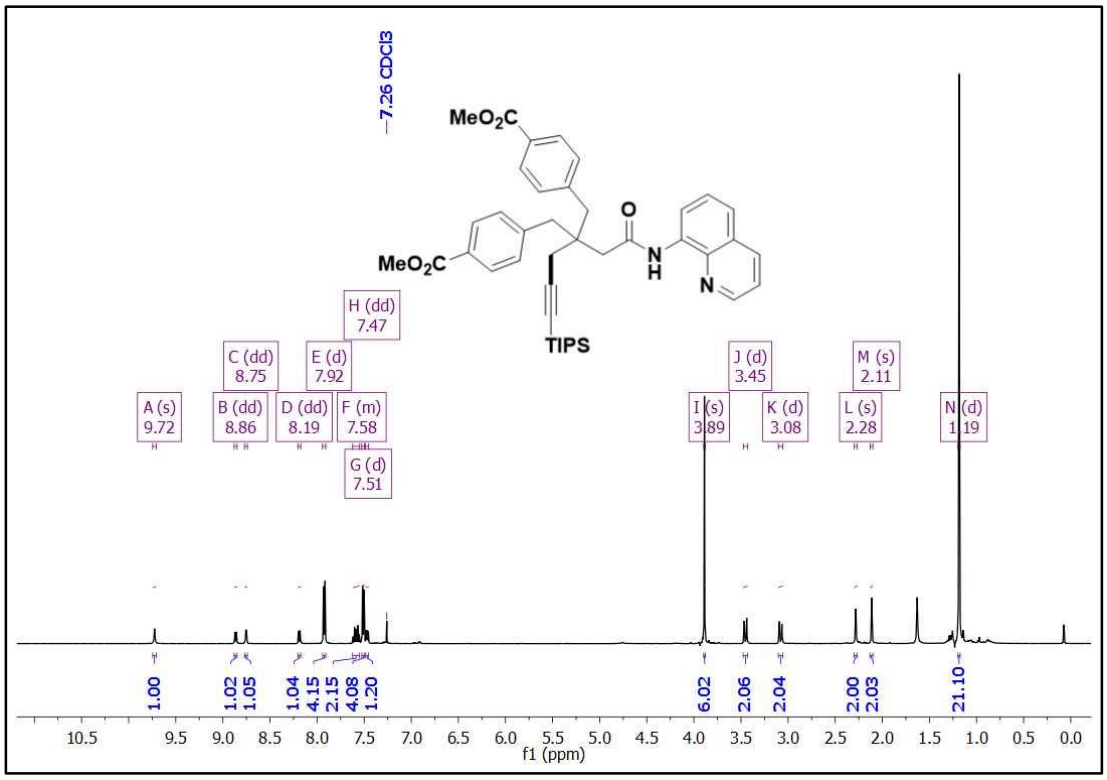
1H spectra of 2p:



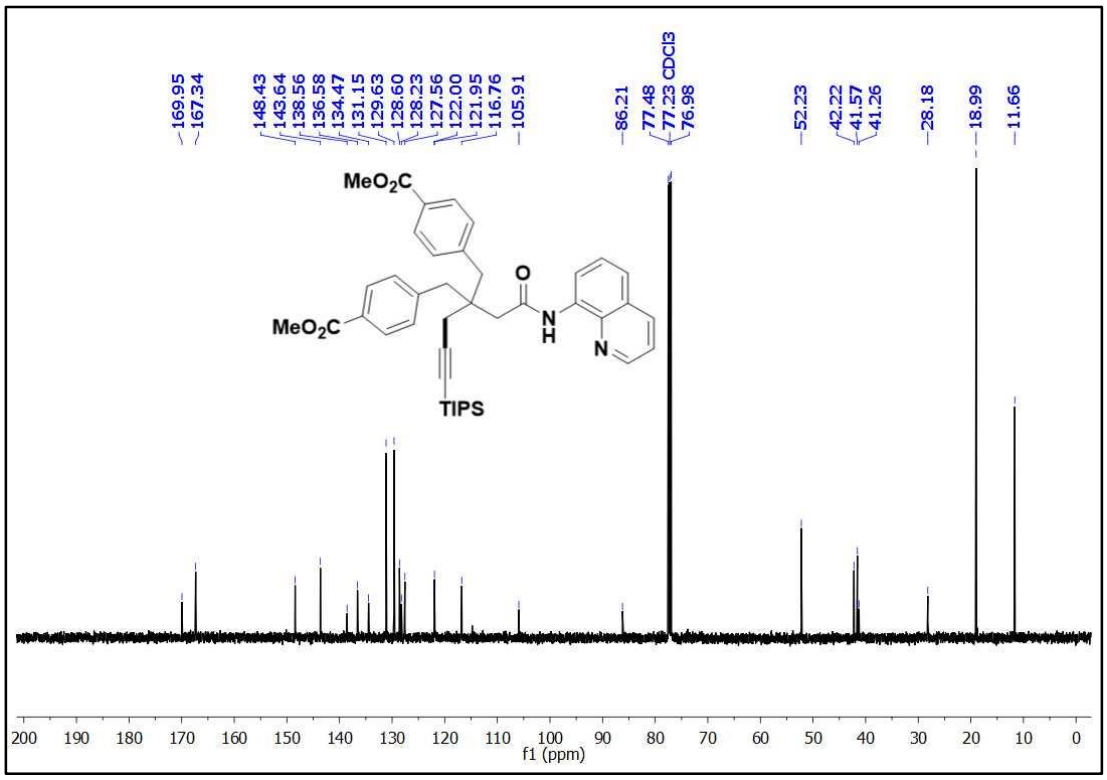
13C spectra of 2p:



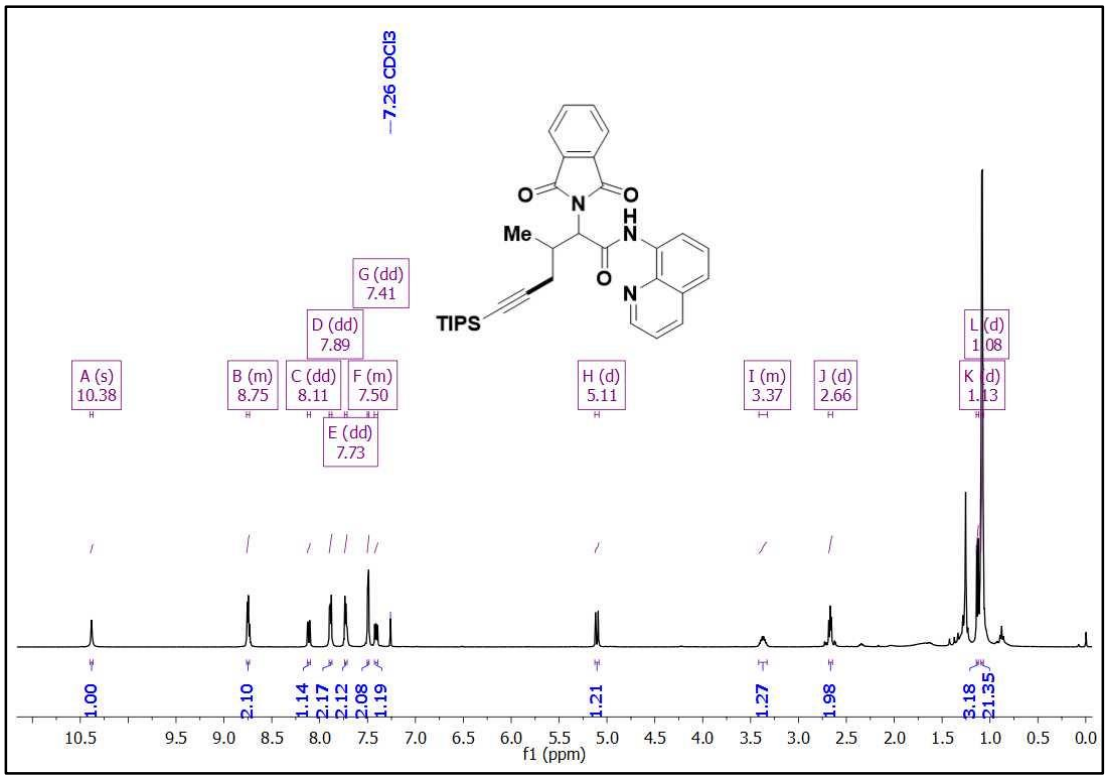
1H spectra of 2q:



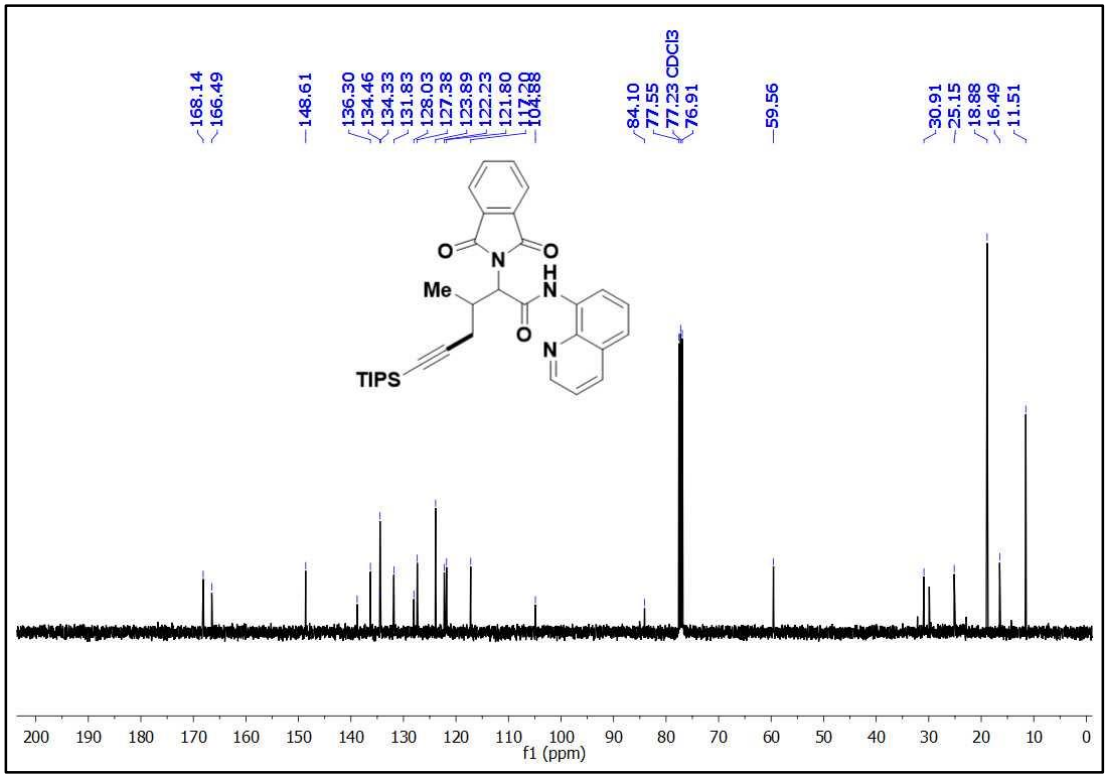
13C spectra of 2q:



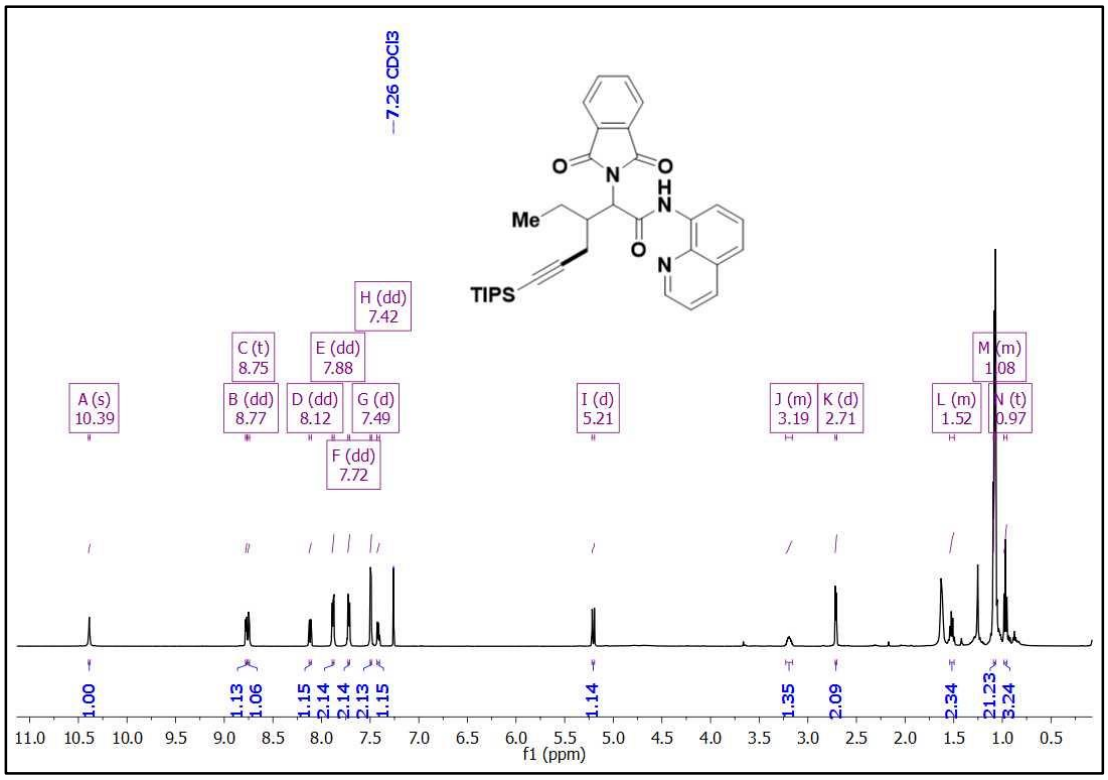
1H spectra of 2r:



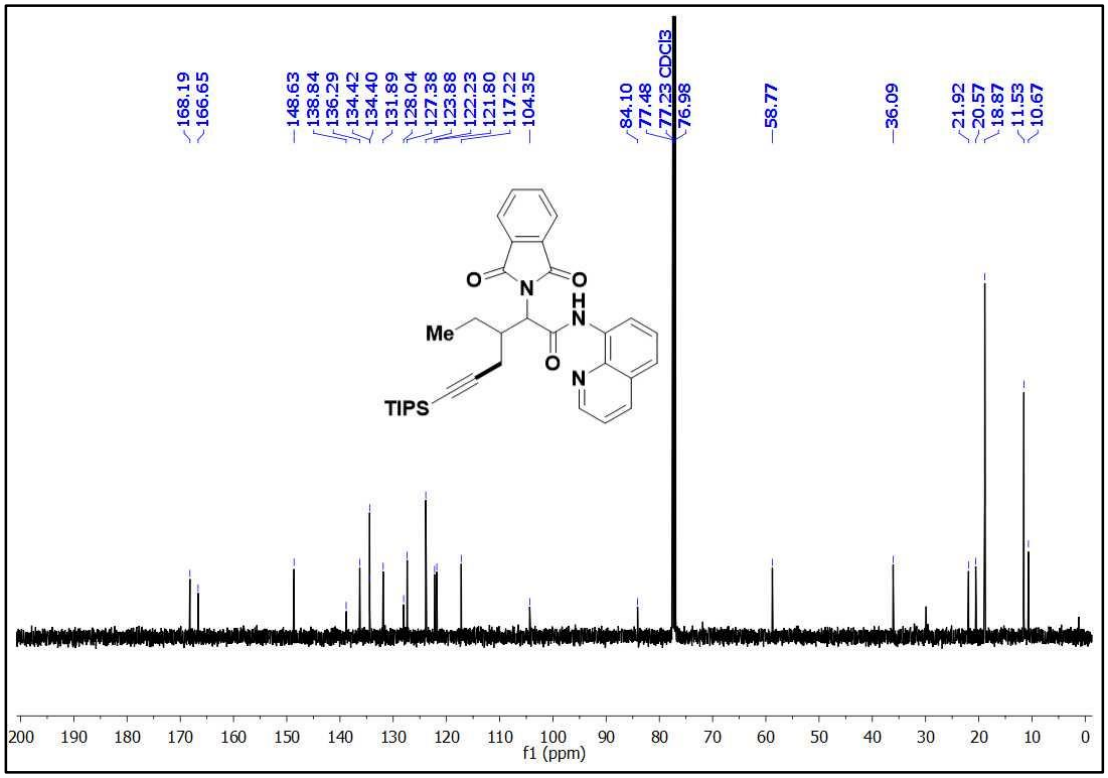
13C spectra of 2r:



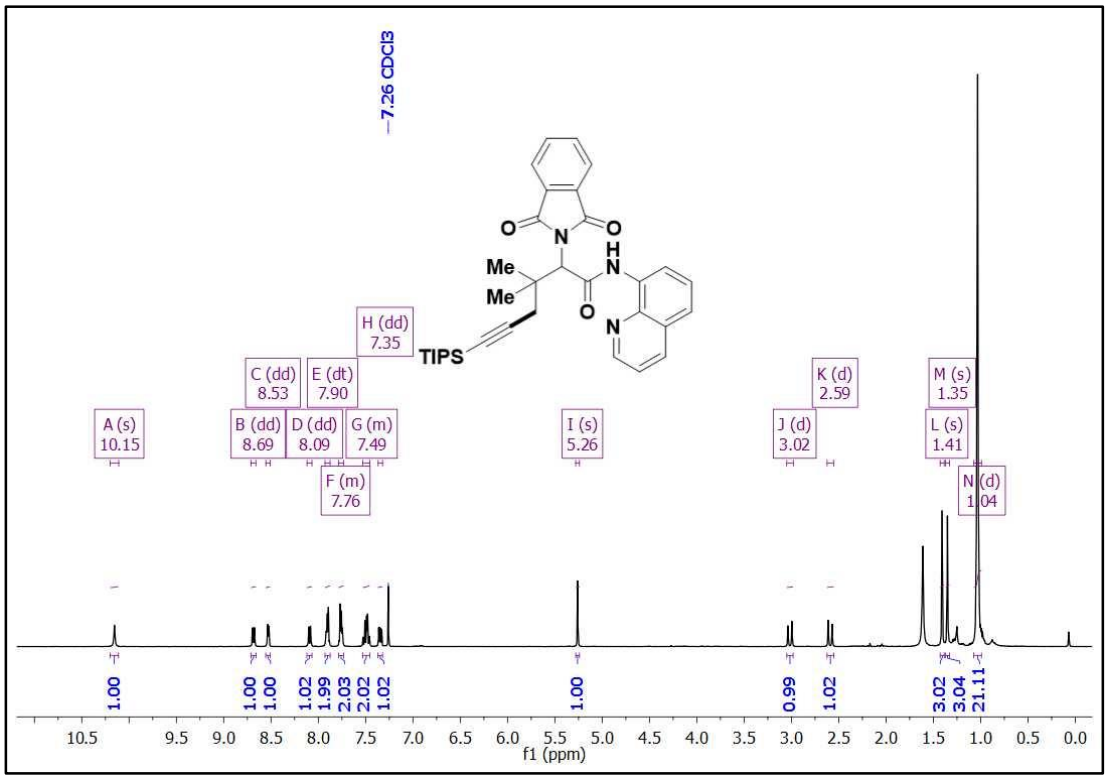
1H spectra of 2s:



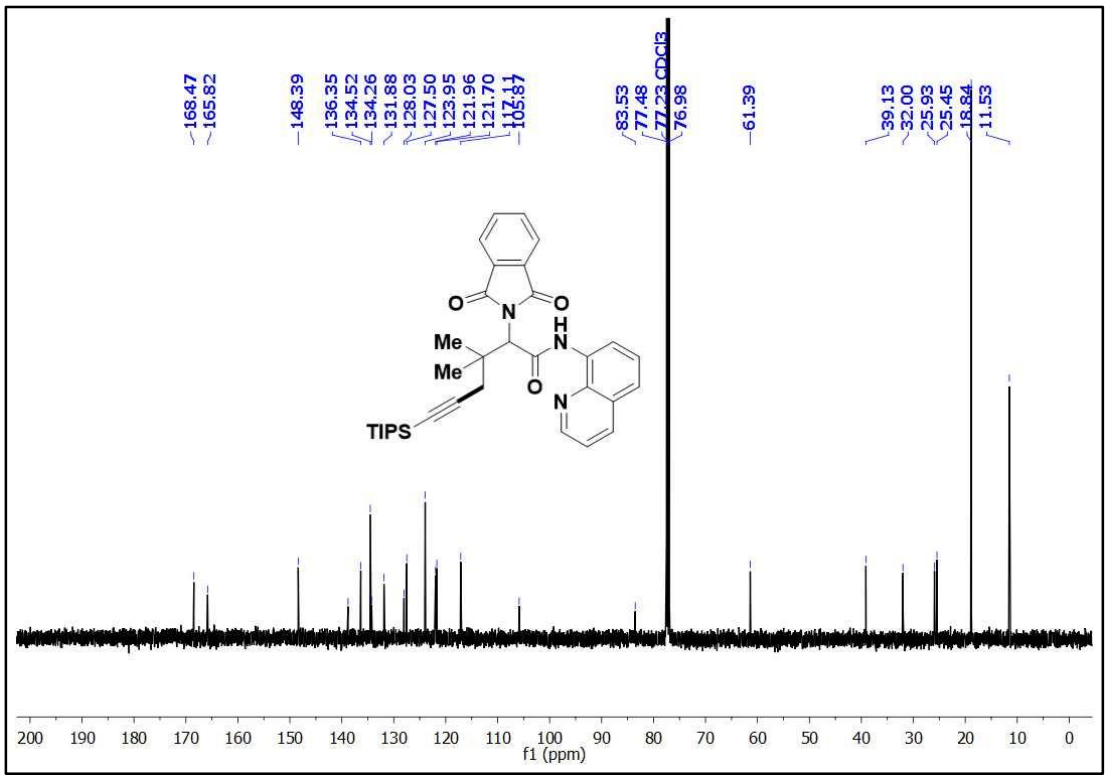
13C spectra of 2s:



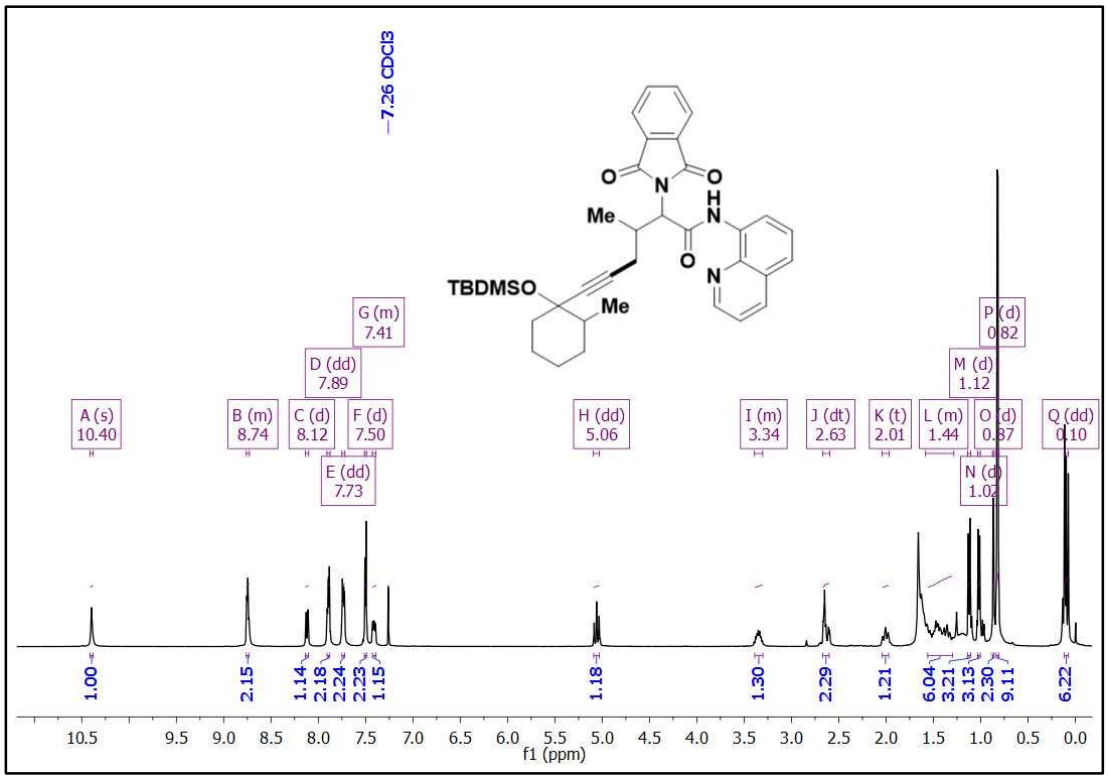
1H spectra of 2t:



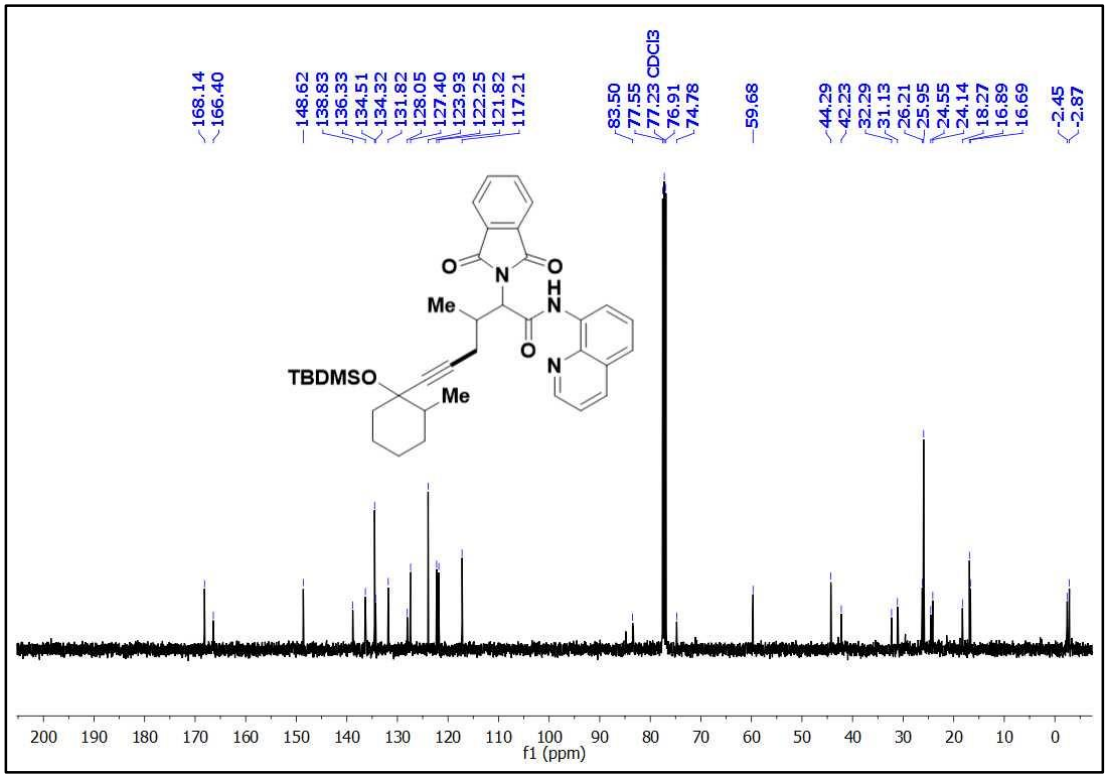
13C spectra of 2t:



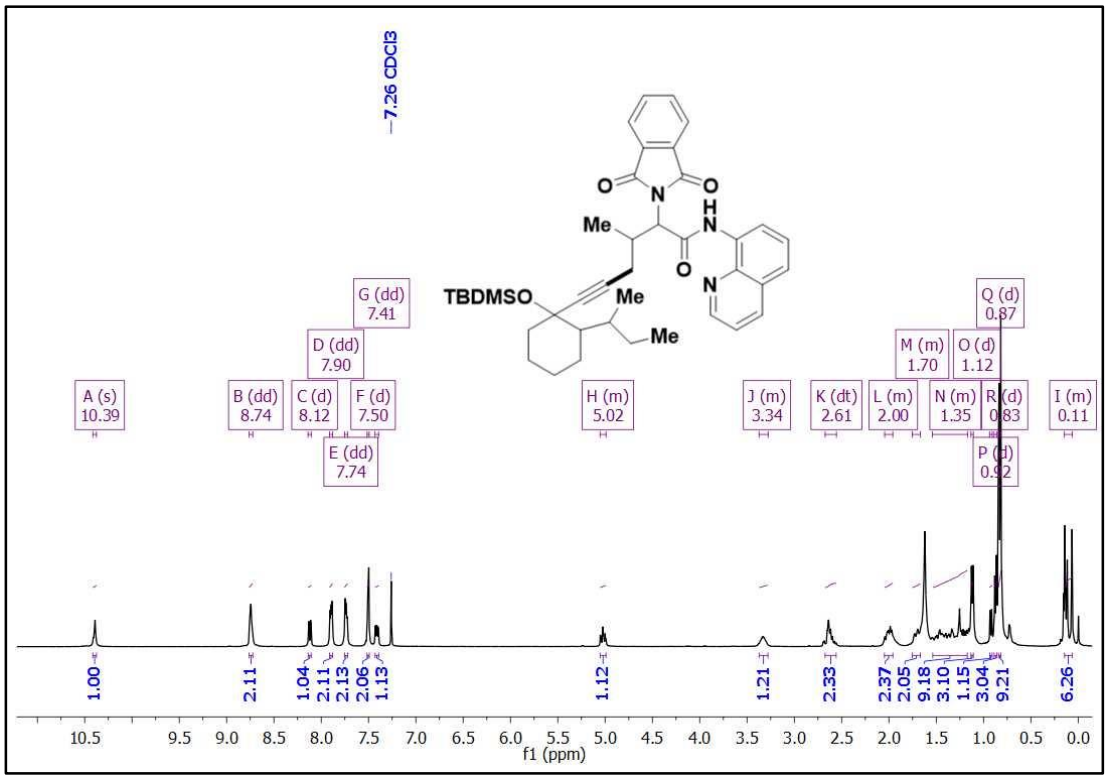
1H spectra of 2u:



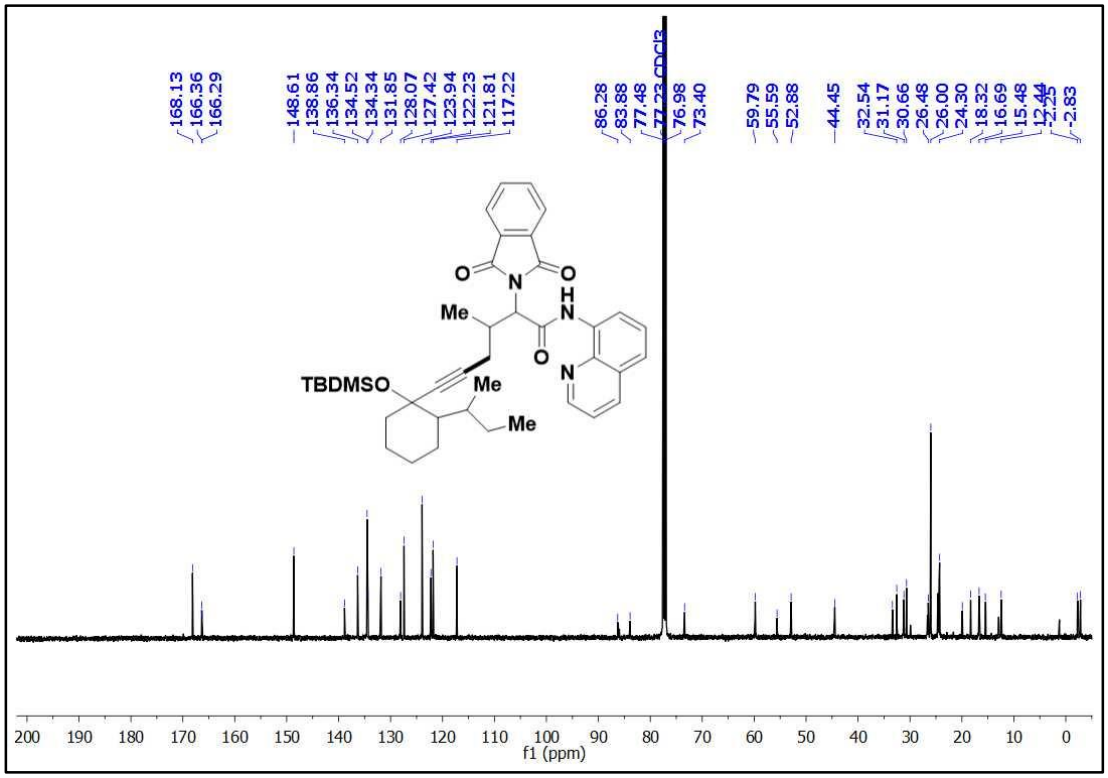
13C spectra of 2u:



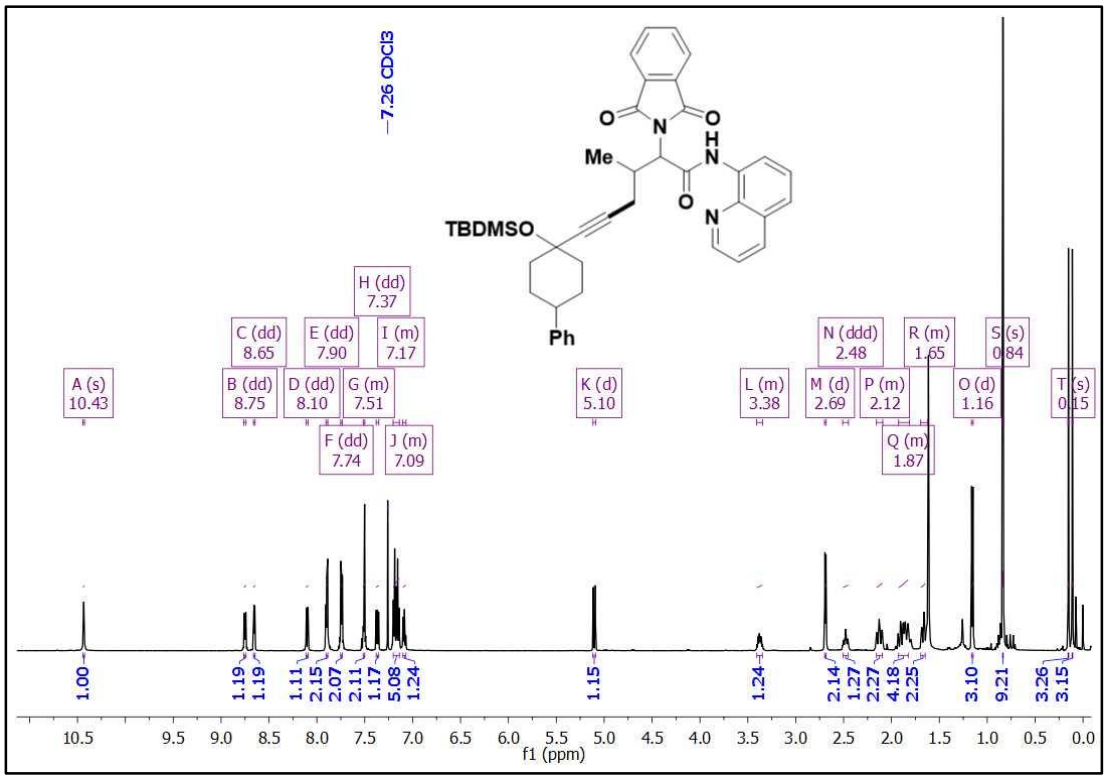
1H spectra of 2v:



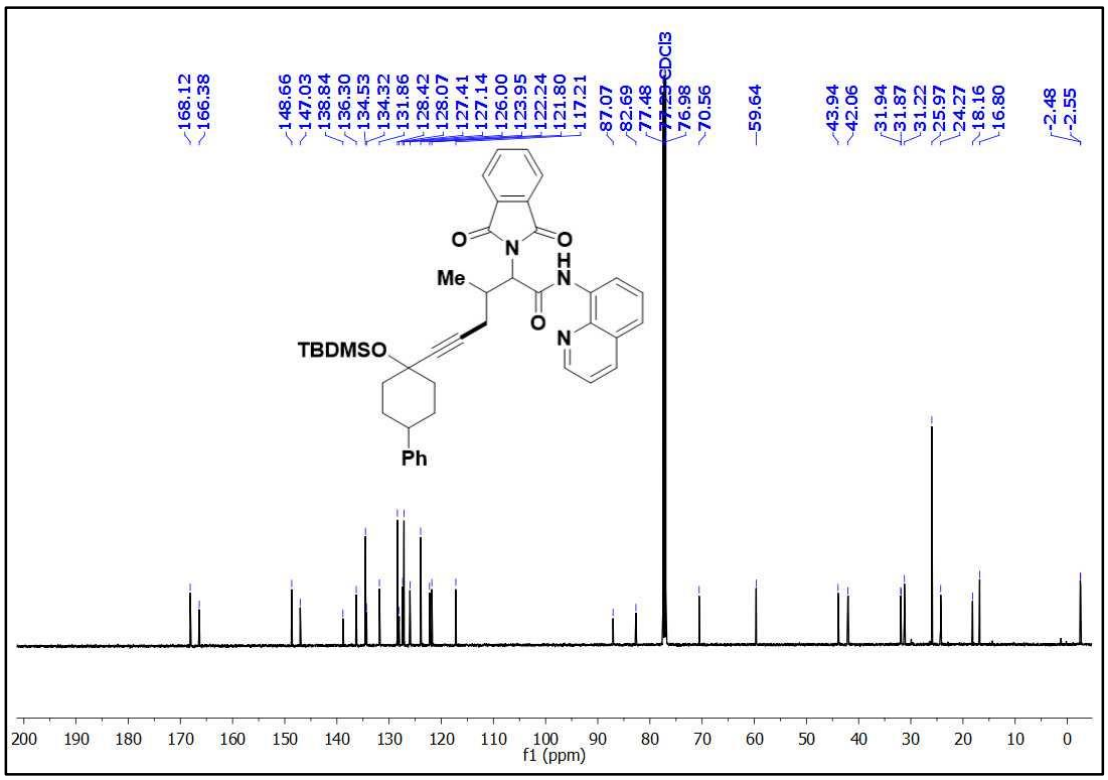
13C spectra of 2v:



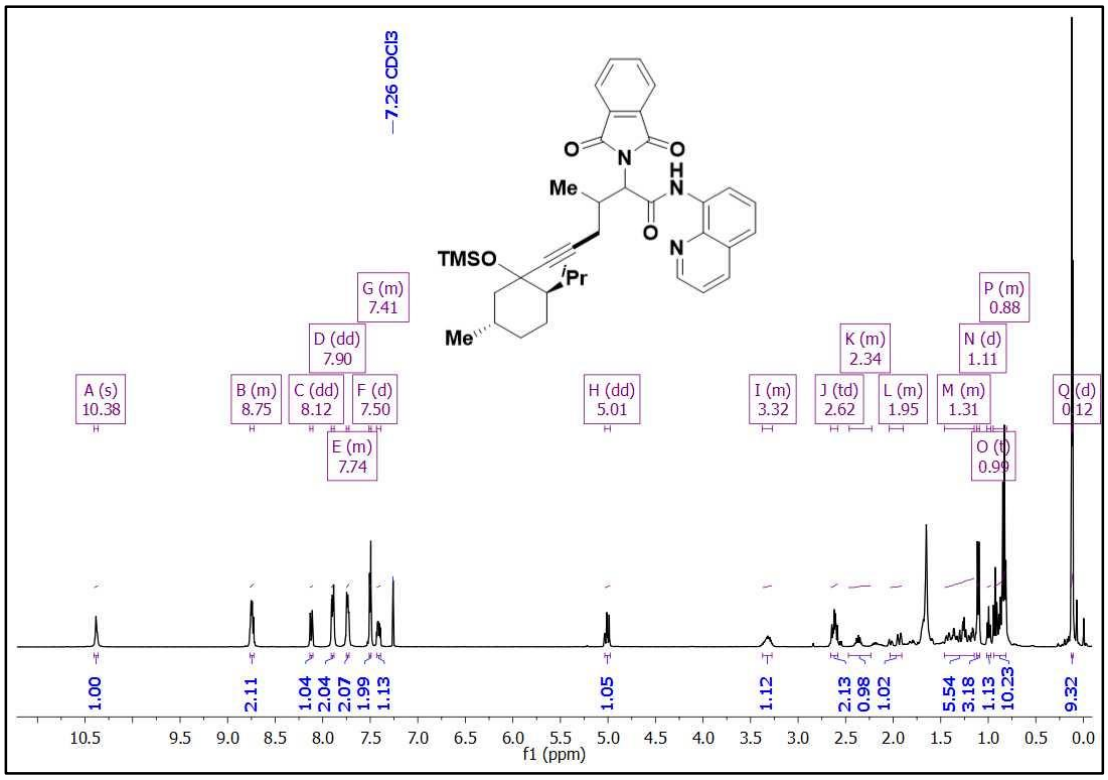
1H spectra of 2w:



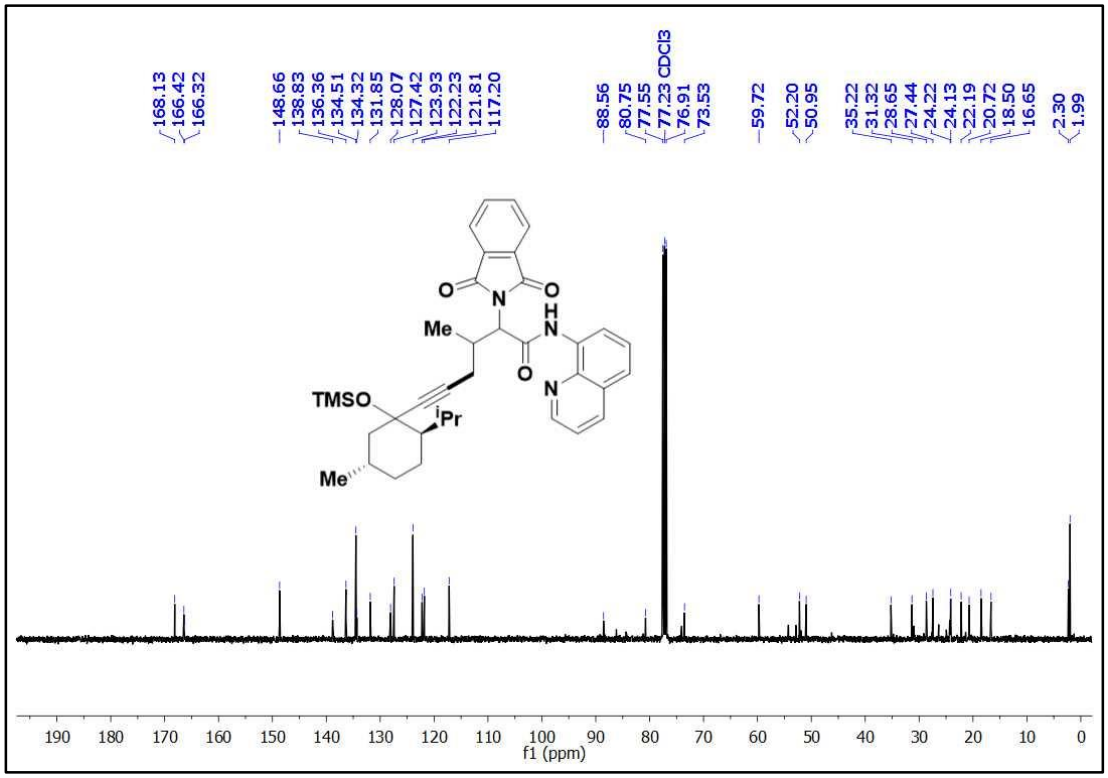
13C spectra of 2w:



1H spectra of 2x:



13C spectra of 2x:



3.7. References

1) For selective examples on sp^2/sp^3 C-H functionalization see: a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593(b) Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958(c) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 463(d) Xie, Y.; Yang, Y.; Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2012**, *14*, 1238(e) Ren, Z.; Mo, F.; Dong, G. *J. Am. Chem. Soc.* **2012**, *134*, 16991(f) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135(g) Hussain, N.; Frensch, G.; Zhang, J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3693(h) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602(i) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 3868(j) Maity, S.; Agasti, S.; Earsad, A. M.; Hazra, A.; Maiti, D. *Chem. Eur. J.* **2015**, *21*, 11320(k) Xu, Y.; Yan, G.; Ren, Z.; Dong, G. *Nat Chem* **2015**, *7*, 829(l) Gao, F.; Kim, B.-S.; Walsh, P. J. *Chem. Sci.* **2016**, *7*, 976(m) Li, M.; González-Esguevillas, M.; Berritt, S.; Yang, X.; Bellomo, A.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 2825(n) Ménard, G.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 4409(o) Gigant, N.; Bäckvall, J.-E. *Chem. Eur. J.* **2013**, *19*, 10799(p) Liu, Y.; Yang, K.; Ge, H. *Chem. Sci.* **2016**, *7*, 2804.

2) For selected examples on C(sp^2) & C(sp^3) alkynylation see a) Liu, Y-H.; Liu, Y.-J.; Yan, S.-Y.; Shi, B.-F. *Chem. Commun.,* **2015**, *51*, 11650. b) Diederich, F.; Stang P. J.; Tykwinski, R. R. *Acetylene Chemistry: Chemistry, Biology and Material Science*, Wiley-VCH, Weinheim, **2005.** c) Anastasia L.; Negishi, E. *Chem. Rev.,* **2003**, *103*, 1979. d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev*., **2004**, *104*, 3079. e) Liu, C.; Zhang, H.; Shi W.; Lei, A.-W. *Chem. Rev*. **2011**, *111*, 1780 f) Brand, J. P.; Waser, J. *Chem. Soc. Rev.*, **2012**, *41*, 4165. g) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.,* **2011**, *111*, 2937. h) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci*., **2013**, *4*, 4187. i) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.-J.; Chen, F.-J. Shi, B.-F. *Angew. Chem., Int. Ed.,* **2013**, *52*, 13588. j) *Acetylene Chemistry*, Ed. Diederich, F.; Stang, P. J; Tykwinski, R. R Wiley-VCH, Weinheim, Germany, 2005

3) a) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.,* **2011**, *133*, 12984–12986. b) Al-Amin, M.; Arisawa, M.; Shuto, S.; Ano, Y.; Tobisu, M.; Chatani, N. *Adv. Synth. Catal.,* **2014**, *356*, 1631–1637. c) Wang, B.; Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.*, **2014**, *16*, 6260–6263. d) Wang, B.; He, G.; Chen, G. *Sci. China: Chem.*, **2015**, *58*, 1345–1348. e) Liu, T.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Angew. Chem., Int. Ed.,* **2017**, *56*, 10924–10927. f) He, J.; Wasa, M.; Chan, L. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.,* **2013**, *135*, 3387–3390. g) Ye, X.; Xu, C.; Wojtas, L.; Akhmedov, N. G.; Chem, H.; Shi, X. *Org. Lett*., **2016**, *18*, 2970–2973. h) Fu, H.; Shen, P.-X.; He, J.; Zhang, F.; Li, S.; Wang, P.; Liu, T.; Yu, J.-Q. *Angew. Chem., Int. Ed.*, **2017**, *56*, 1873–1876. i) Landge, V. G.; Parveen, A.; Nandakumar, A.; Balaraman, E. *Chem, Commun.*, **2018**, *54*, 7438.

4) For selective examples on directed γ-C-H functionalization see: (a) Fan, M.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12152(b) Li, Q.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Adv. Synth. Catal.* **2014**, *356*, 1544(c) Pasunooti, K. K.; Banerjee, B.; Yap, T.; Jiang, Y.; Liu, C.-F. *Org. Lett.* **2015**, *17*, 6094(d) Ling, P.; Xiang; Fang, S.; Long; Yin, X.; Song; Chen, K.; Sun, B.; Zheng; Shi, B.; Feng *Chem. Eur. J.* **2015**, *21*, 17503(e) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. *Org. Lett.* **2015**, *17*, 2546(f) Wang, P.-L.; Li, Y.; Wu, Y.; Li, C.; Lan, Q.; Wang, X.-S. *Org. Lett.* **2015**, *17*, 3698(g) Han, J.; Zheng, Y.; Wang, C.; Zhu, Y.; Shi, D.-Q.; Zeng, R.; Huang, Z.-B.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 9297(h) Wang, C.; Zhang, L.; Chen, C.; Han, J.; Yao, Y.; Zhao, Y. *Chem. Sci.* **2015**, *6*, 4610 (j) Huang, D. S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 5757(k) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3(l) Franzoni, I.; Guenee, L.; Mazet, C. *Chem. Sci.* **2013**, *4*, 2619(m) Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830(n) Zhou, X.-L.; Wang, P.-S.; Zhang, D.-W.; Liu, P.; Wang, C.-M.; Gong, L.-Z. *Org. Lett.* **2015**, *17*, 5120(o) Jiang, H.; He, J.; Liu, T.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2055.

Chapter 4

Palladium Catalyzed Distal *para* C(sp^2)-H Cyanation of Arene by U-shaped template

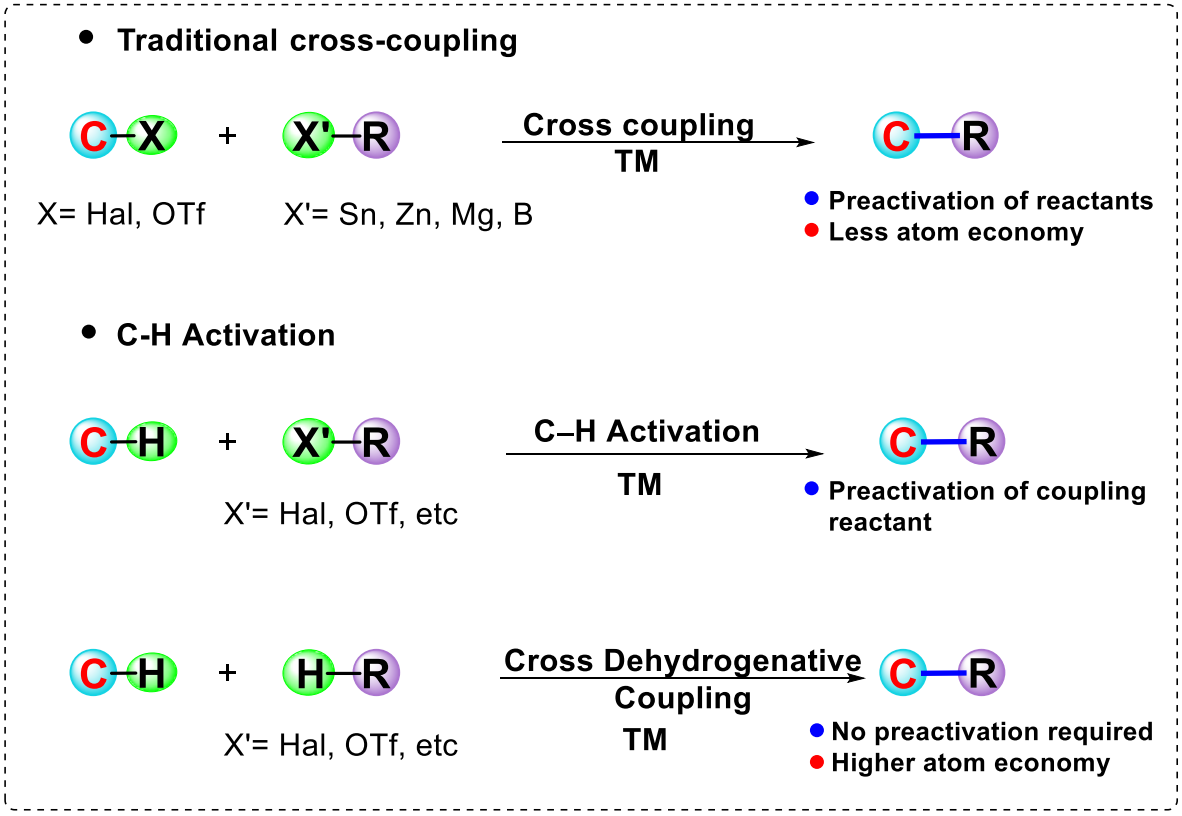
Abstract:

A Detachable hydrogen bonding enabled template developed for *para* selective cyanation of arenes via Pd(II) catalysis. The scope of transformation was examined for number of electronically rich and deficient toluenes with minimum intrinsic bias. The synthetic utility of methodology highlighted with removal of template and ulitilising post-synthetic product for further functionalization.

4.1. Introduction

Selectivity in the ring substitution reaction of aromatics is always been a challenge to synthetic chemist. Functionalization of substituted aromatic ring via nucleophilic/electrophilic substitution reaction, there poses at least three active sites. Also, substitution is totally dependent on the functionality present on aromatic ring because it imparts its electronic characters to the ring (*-ortho/para selective* or *-meta selective*) so it always remains unselective. Since more than three decade this selectivity issues has been addressed by installing a directing group on the ring which assist the metal to form stable intermediate by activating the aromatic *ortho*-C–H bond but to activate *distal* or *remote* C–H bond on aromatic ring is always a challenging task due to availability of multiple sites of activation in target ring.

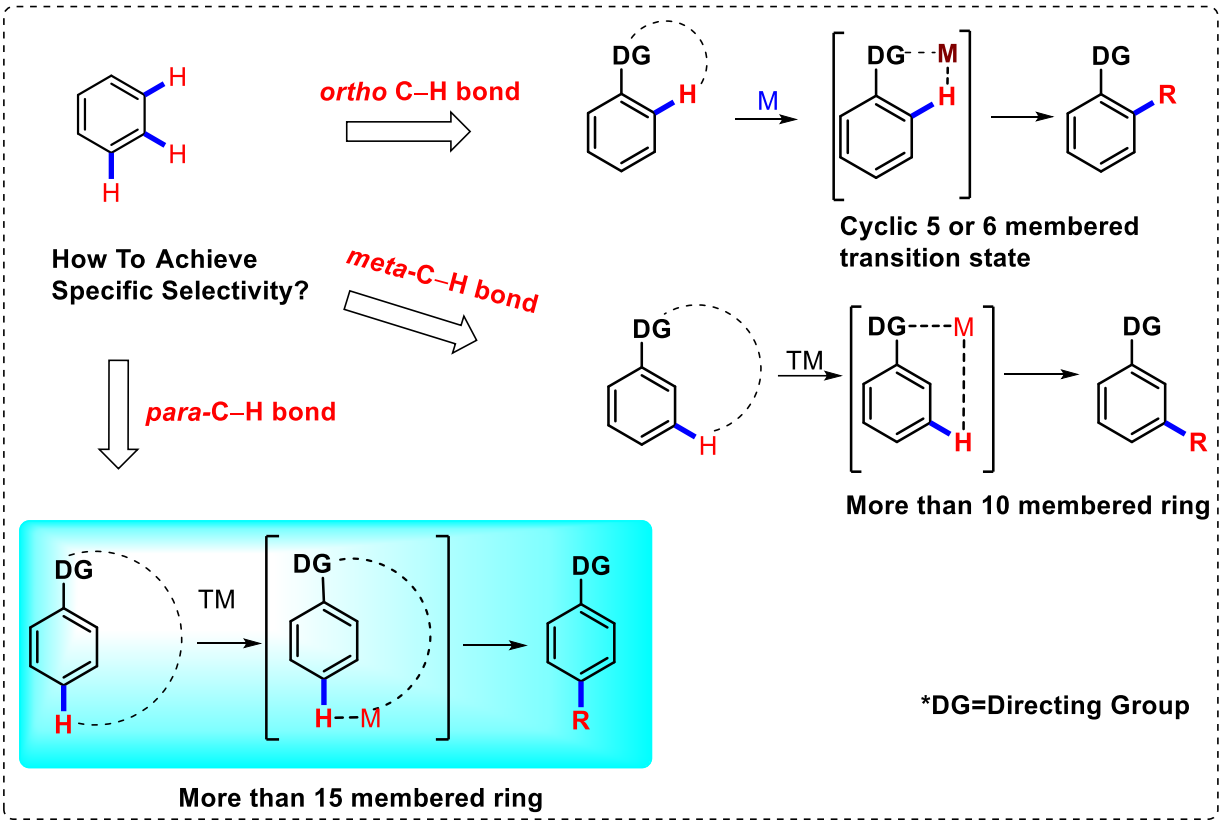
Total abundance of C–H bonds in any aromatic molecules urged synthetic community to look carefully at those and possibly utilize them. Prior to C–H activation, pre-activation of coupling partner is one of major criteria for coupling reaction but newer C–H activation strategies enabled catalysis which gave complete control over reaction in terms of atom economy and such process are referred now widely as environmentally benign reaction as they reduces amount of waste produced as byproduct (Scheme **1**). Due to common interest of various research groups across the globe now we sit on wide pool of knowledge based on catalytic activity of various transition metals such as Rh, Ru, Pd, Fe, Co, Mn, Cu, Ir, Mg. etc.[1] This has now made many chemical transformation possible which were previously inaccessible by kinetically and thermodynamically, by fine tuning suitable catalytic/ligand combinations.[1] In the complexity and nature of aliphatic or aromatic molecule having multiple C–H bonds usually less energetically favored (i.e. more reactive) C–H bond in structure is favored (Scheme **1**). However, due to presence of multiple C–H bonds controlling selectivity is cumbersome challenge. Due to this a donor group or directing group was introduced and it is widely applicable in catalysis. The DG is commonly referred as Lewis base so it coordinates with metal and brings metal to close proximity to active C–H bond (Scheme **2**)



Scheme 1: Overview of C–H functionalization, history, recent developement.

***Ortho*-C–H Activation:**

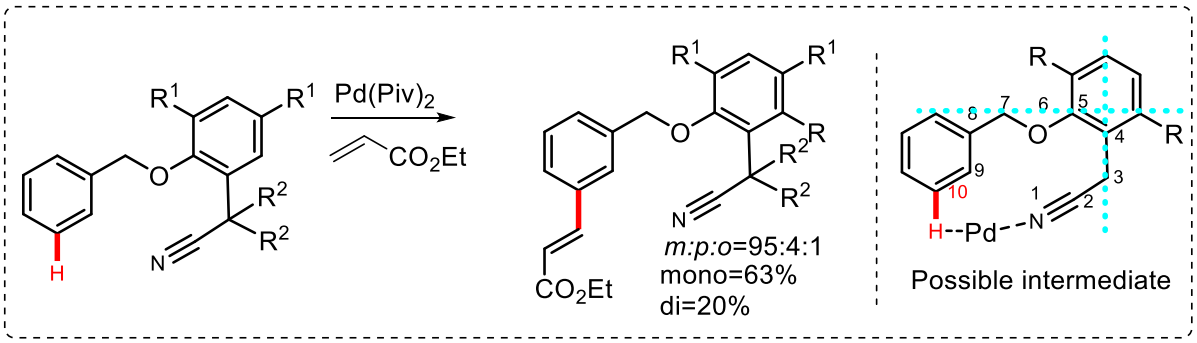
Since the two decades and more, various groups around the globe have solved this problem by introducing directing group on the arenes to facilitate the chelation of transition metal and subsequent activating the specifically *ortho* C–H bond which is present in *close* proximity. This strategy is now well diversified with various directing groups that include amides, anilides, aldehydes, ketones, carboxylates to give olefinated, arylated, hydroxylated, alkenylated arenes and heteroarenes.[1] Even this methodology has been studied for different transition metals that includes Rh, Ru, Co, Ni, Ir, Mn, Cu, & Pd. It was always a difficult task to approach the '*distal*' C–H bond due to instability of macrocyclic transition states or limitation of 5 or 6 membered transition states.



Scheme 2: Site selectivity for *ortho*-, *meta*- & *para*-C–H activation by Directing Group (DG)

meta-C-H activation:

Yu et al in 2012 overruled this limitation by employing a strategy of template assisted distal C–H activation by taking advantage of nitrile template to chelate Pd catalyst with weakly coordinating Nitrile reach the distal *meta* C–H bond and subsequently further functionalization. (Scheme **3**).[2a, 2] This delivered the palladium to the vicinity of tethered arene to promote olefination of *meta* C–H bond of arene with good selectivity. To overcome the limitation of traditional directed C–H activation, linear 'end-on' co-ordinating directing group had been proposed to accommodate a macrocyclic cyclophane like pre-transition state.

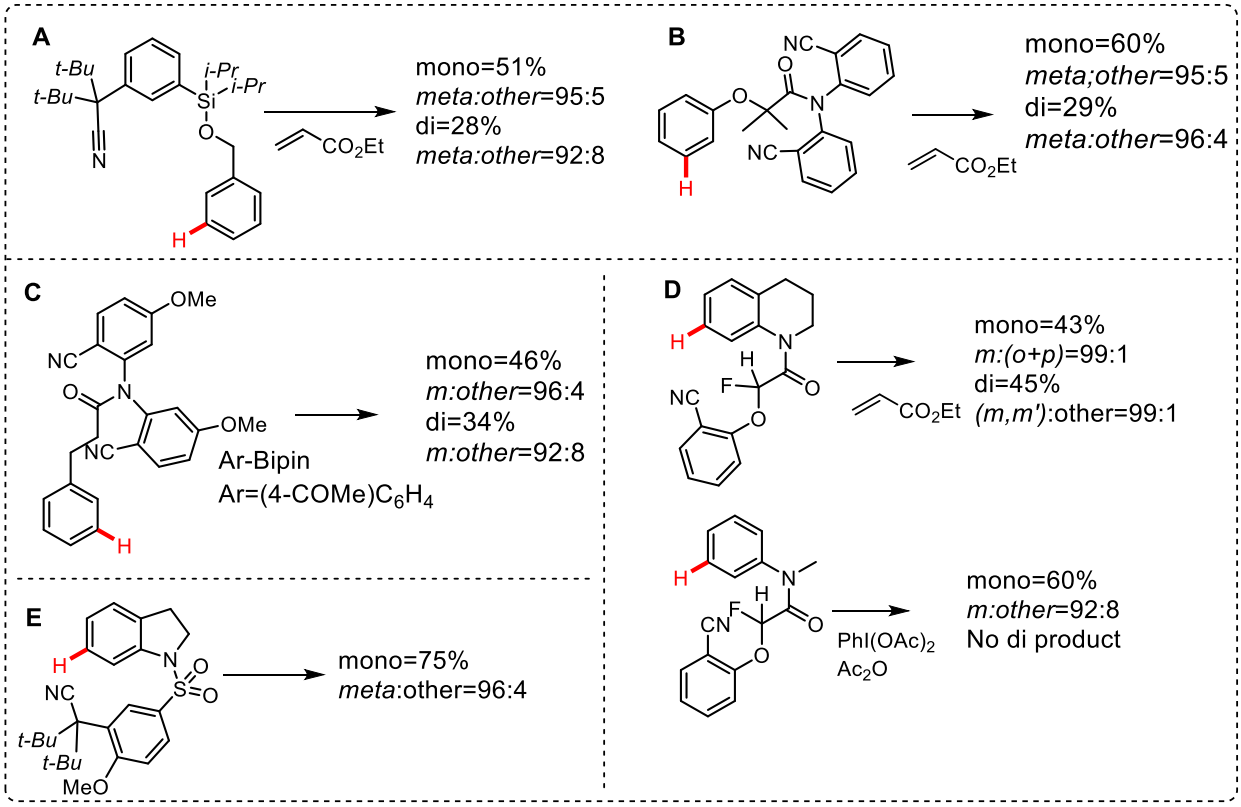


Scheme 3: First 'end-on" Template for *meta* C-H activation

This methodology was then applied to hydrocinnamic acid amide which also gave good selectivity and moderate to good yields. Diversification was shown on functionalization of tetrasubstituted arenes, biphenyl, amino acid modification and baclofen diversification. Later same group has reported mechanistic investigation report which proved that reaction proceeded through four major steps: C–H activation (concerted metalation deprotonation pathway)-a rate as well as regioselectivity determining step, alkene insertion, *β*-hydride elimination and reductive elimination. A combined experimental/computational study on the amino acid ligand on this template revealed that amino acid acts as both a dianionic bidentate ligand and an internal base to abstract the proton. Also this explained the effects of amino acids on reactivity and selectivity and unveils the dual role of amino acids (1) stabilizing monomeric Pd(MPAA) [Monoprotected amino acid] complexes and (2) serving as the internal base for proton abstraction which is crucial step during C–H activation.[3]

Later, having all proof in hand that nitrile can act as a weakly coordination site, various templates were reported based on nitrile directing templates. Inspired from this, *meta* C–H activation was achieved by using new silyl based nitrile directing template by Tan and coworker. This template tolerated variety of activated alkenes and it proved that Silyl-linker can be cleaved easily and hence increases the practicability of methodology[4] (Scheme **4 A**). Later, Yu group developed a template for *meta* olefination of phenols[5] (Scheme **4 B**). This gave *meta*:*other* selectivity as 95:1 with moderate to excellent yield as mono-olefinated product. Similar strategy was used to develop U-shaped template for cross coupling reaction for arylation of hydrocinnamic acid derivatives giving *mono* & *di*

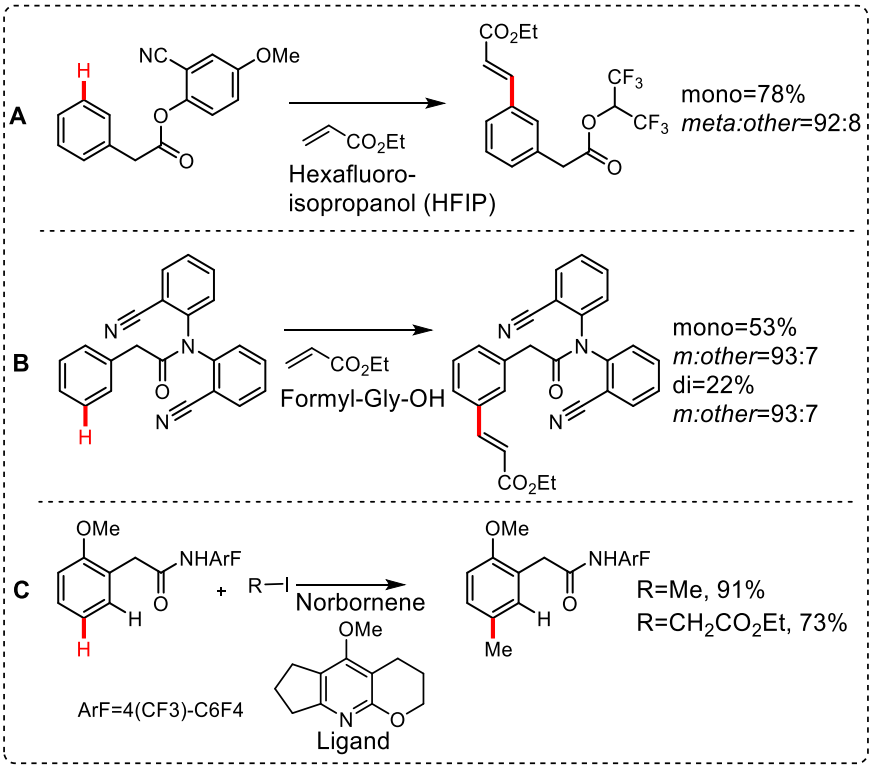
olefinated products in 46 and 34% yield with *m:other* 96:4 and 92:8 selectivity respectivily. Ar-Bpin was used as aryl source for this reaction.[6] In 2014, Yu and co-workers reported *meta* olefination and acetoxylation of aniline and benzylic amines.[7] X-ray crystallography and NMR studies revealed that the conformational biases induced by a single fluorine substitution in the template can be enhanced by using a ligand to switch from *ortho*- to *meta*-selectivity (scheme 4 **D**). Also later indonline based U shaped template was developed for selective Pd (II) catalyzed *meta* C–H activation using Ac-Gly-OH as effective ligand.[7] This reaction was well tolerated different activated alkenes giving 60-81% yield with *meta:other* selectivity as 96:4. Also this scaffold worked very well with



Scheme 4: A-Silyl Thether, **B-**Phenol derivative, **C-H**ydrocinnamic acid **D-**anilines/benzyllic amines and **E**-Indolines derivative

$PhI(OAc)_2$ as oxidant to give acetoxylated product in 25-75% yield with average 83:17 *meta:other* selectivity (Scheme **3 E**). Later, Yu et al reported *meta*- C–H activation of phenylacetic acid by U shaped Nitrile based template.[8] For this conversion formyl-Gly-OH ligand and KH_2PO_4 as additive served well in reaction conditions. This methodology

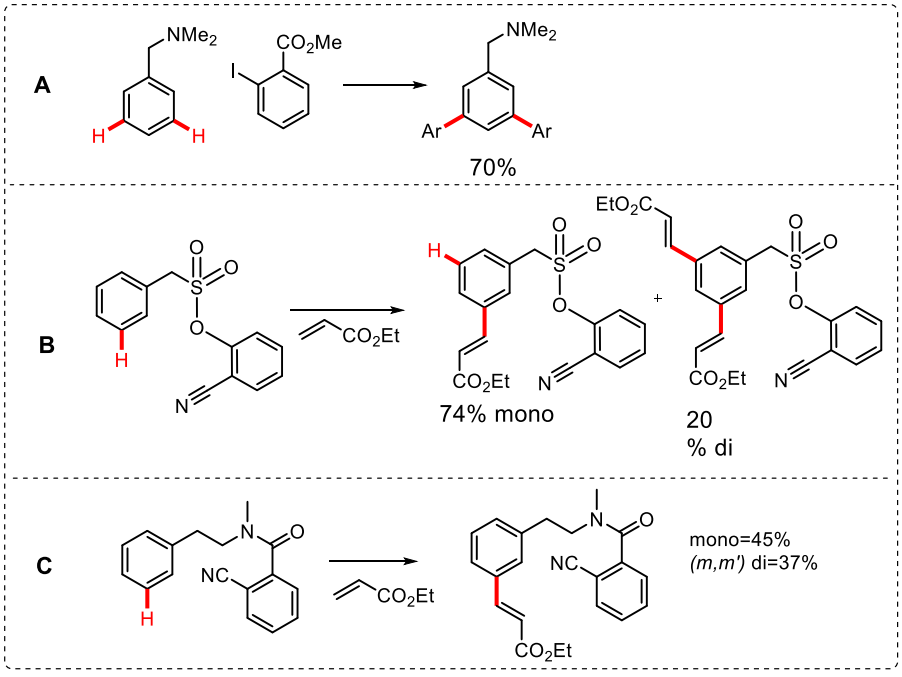
delivered various olefinated products as well as it tolerated various substituted phenylacetic acid amides(Scheme **5 A**). In 2014, Maiti and coworkers reported *meta* selective Arene C–H bond olefination of phenylacetic acid derivative using nitrile based template.[9] This protocol was applicable to wide variety of phenylacetic acid derivative and was shown useful by drug diversification of Ibuprofen, Naproxen, Ketoprofen. Advantage of this template was exclusive mono olefinatated *meta* selective product and directing group was easily removable. Different substituents were well tolerated at all positions on the phenylacetic acid framework. This strategy for directing remote C–H activation provided a novel route for the preparation of *meta*-olefinated phenylacetic acid derivatives and drug molecules that were difficult to access using conventional methods (Scheme **5 A**). Along with this, an alternative approach by Yu and coworkers was disclosed, employing norbornene as transient mediator to achieve *meta* selectivity of common *ortho* directing groups. The use of pyridine based ligand was crucial for relaying the palladium to *meta* position by norbornene after initial *ortho* C–H activation. This gave a tool to switch the selectivity from *ortho* to *meta* by catalyst control (Scheme **5 C**).



Scheme 5: **A**-Phenyl acetic acid ester. **B** & **C**-Phenyl acetic acid amide

This gave alkylation product with moderate to high yield. A similar catalytic system Pd/norbornene was used for the *meta* selective arylation by Dong *et al* recently with tertiary amines (Scheme **6 A**).[10] In this case, aryl iodides as coupling partner with an *ortho* electron-withdrawing group were employed. Different ranges of functional groups, including some heteroarenes were tolerated under this reaction conditions. In addition, the amine directing group was easily uninstalled and transformed to other functional groups.

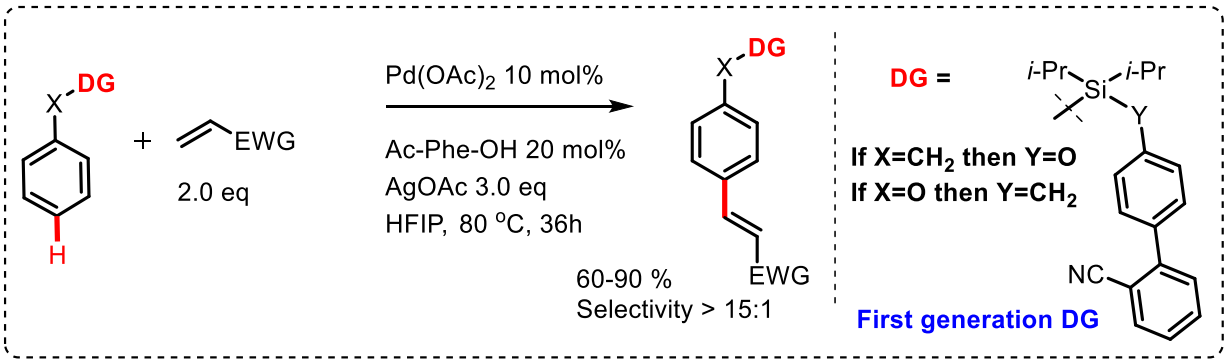
Recently Maiti and coworker disclosed new sulfone-based arene nitrile template which proved useful for *meta* selective homo-diolefination and hetero-diolefination using Pd(II) catalyst.[11] This methodology gave access to successful sequential olefinations in a position-selective manner providing a novel route for the synthesis of hetero-dialkenylated products which are difficult to access using conventional methods. In addition to that 1,3,5- trialkenylated compounds were synthesized upon successful removal of the directing group (Scheme **6 B**). Recently Li et al has also developed nitrile based template for *meta* selective functionalization of phenylethylamines by using 2-cyanobenzoyl group as the directing functionality. The potential of the method was exemplified by sequential functionalization of both *ortho* and *meta* C–H bonds of a phenylethylamine derivative in a sequential manner (Scheme **6 C**).[12]



Scheme 6: A-Norbornene as transient mediator**, B-**Sulfone-based arene **& C-**phenylethylamine derivative

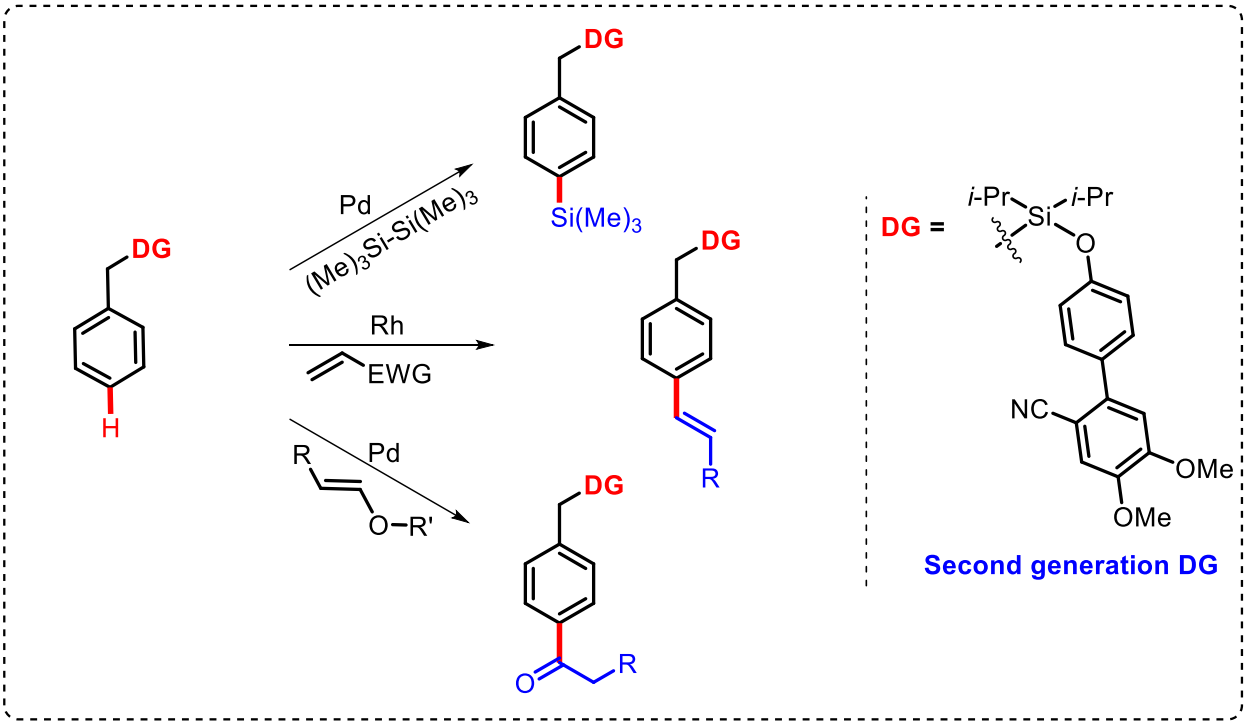
***para*-C-H Activation:**

Use of various templates has proven the efficient and promising strategy to recognize *specific* C–H bond for further functionalization. Since few years various studies has been disclosed to reach *meta*-C–H bond but *para*-C–H bond activation is merely studied. This present chapter includes study on development of novel methodology for *para* selective cyanation of toluene by using a silyl based nitrile template. Couple of years before Maiti et al for the first time has reported a strategy based on nitrile template which can deliver metal at *para*-position of aromatic with the help of D-shaped template and which resulted in *para*-C–H activation of toluene and phenol derivatives.[13] The template designed utilized Thorpe-Ingold effect to make the system strain but flexible in such way so that co-ordination site can undermine *ortho*- and *meta*- position and selectively reaches *para*-position to deliver the metal. When toluene template (Scheme **7**) was subjected to react with activated olefins in presence of $Pd(OAc)_2$ catalyst, protected amino acid ligand N-Acetyl-L-Phenylalanine, AgOAc as oxidant in hexafluoroisopropanol as solvent at 60 °C gave *para*- selective product in more than 15:1 selectivity where other product were *ortho*- & *meta*- products. When template was used for *para*- functionalization of phenols similar optimized condition gave *para*-selective olefination of phenol in good to excellent yields in good selectivity. Both templates tolerated wide range of aromatic systems and serve well for synthesis of *para*-selective natural products.[13]



Scheme 7: *para*-selective olefination of toluene & phenol derivatives

Later same group developed 2nd generation superior para directing template for Pd & Rh catalyzed for Silylation, carboalkylation by Pd catalysis and Rh catalyzed olefination of toluene derivatives. Newer directing group developed was more electronically rich due to the presence of dimethoxy group which justifies the better metal binding and yield whereas H-bonding interaction with the solvent is likely to provide optimal structural rigidity for superior *para* selectivity (Scheme **8**).[14]

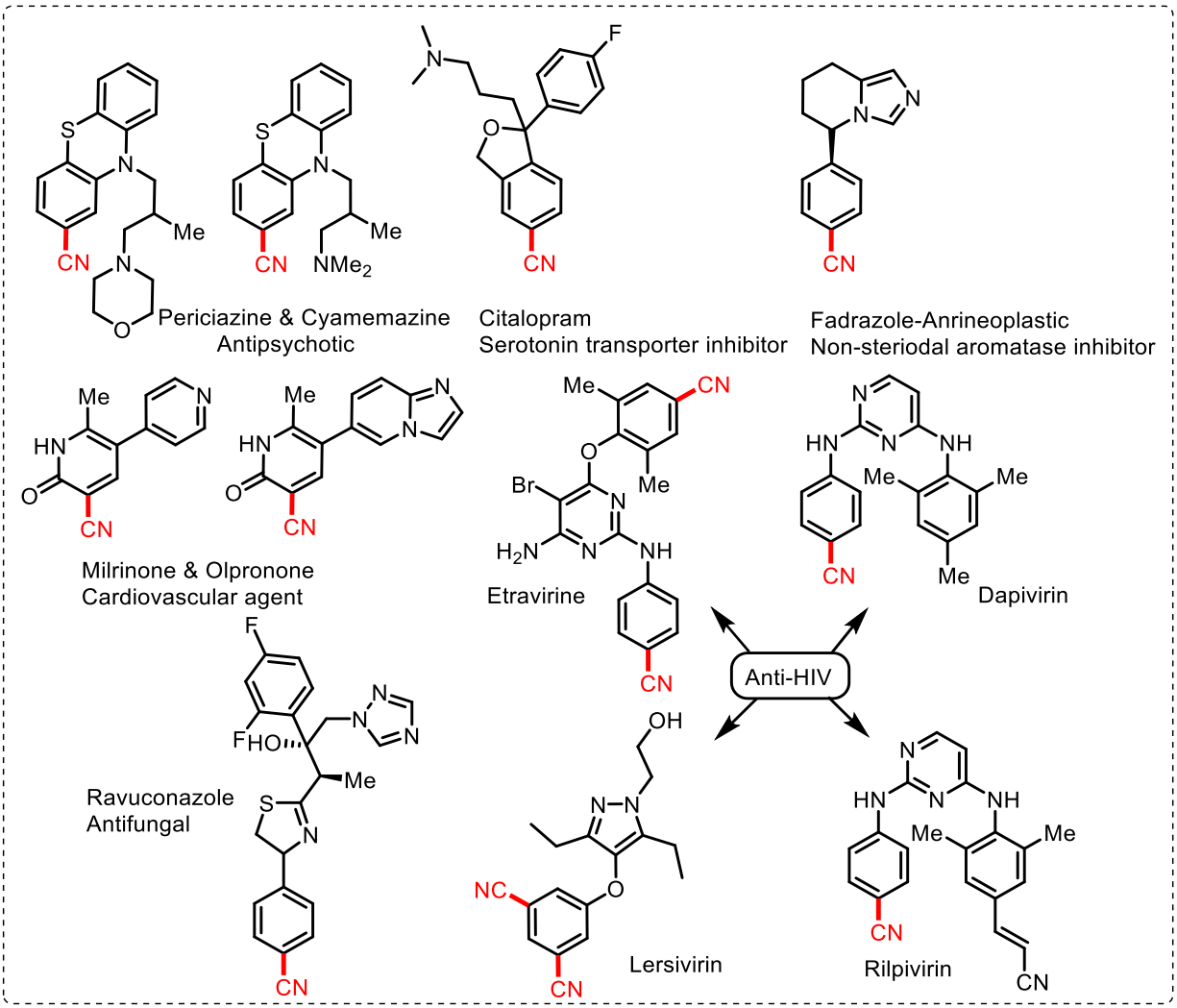


Scheme 8: Design of 2nd generation DG for *para* functionalization.

***Current work: para*-selective cyanation of aromatics:**

Cyanoarenes found in todays' advanced synthetic intermediates, various natural products and drug motifs. Presence of cyano functional group can lead to various functionalities like carbonyl, carboxyl, amino or heterocyclic groups by synthetic modifications. So installing cyano group is beneficial and of high interests. However other methods available in literature to introduce cyano group relies on conventional Sandmayer reaction by diazotization and Rosenmund-Von Broun reaction by transition metal catalysed cross couokibg reaction.[15] So directed C–H cyanation will be offering more reliable solution to earlier methods which involves highly reactive diazonium intermediate. Past decade had

witnessed development on direct C–H cyanation by directing group approach via Pd, Ru, Rh and Co catalysts. Along with these methods for direct C–H cyanation by radical approach has also been achieved. Also pyridine based ligand catalysed by Pd approach also gave non directed cyanoarenes method.[16] Cyano or nitrile group are used for wide variety of functional group inter conversion in synthetic chemistry. It can be converted to corresponding acid, benzyl alcohols, ester by using synthetic routes and which can lead to different functionality in motifs.



Scheme 9: Cyano functional group containing drugs and medicinal important motifs

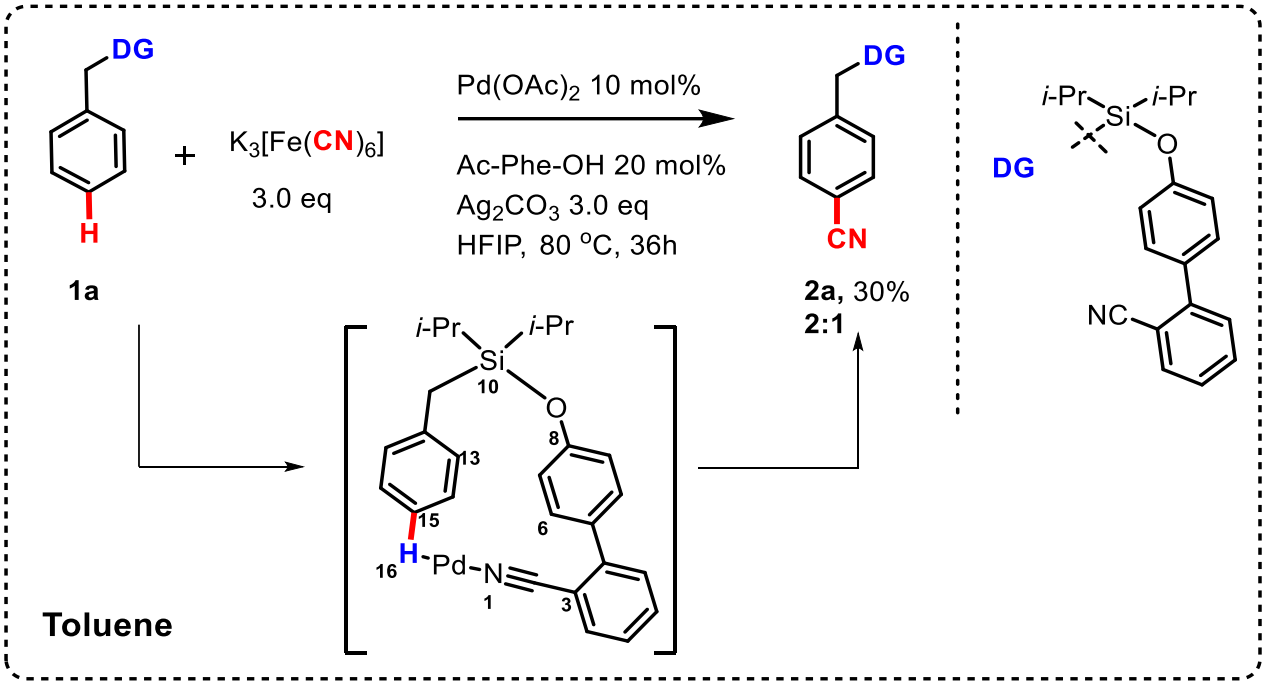
Currently over 30 nitrile-containing pharmaceuticals are prescribed for a diverse variety of medicinal conditions with 20 in queue for clinical development. Also few drugs

molecules like Etravirine (Anti HIV agent), Periciazine (Antipsychotic and neuroleptic), Vildagliptin (Antidiabetic drug), Fadrozole monohydrochloride (One of the first nonsteroidal aromatase inhibitors for treatment of breast cancer), Tanaproget (Nonsteroidal contraceptives), Etravirin, Dapivirin, Rilpivirin, Lersivirin (New class of anti-HIV drugs) and Citalopram (Selective serotonin transport inhibitor) has cyano group. Introducing in cyano group in aromatic ring either requires substitution reaction (Sandmeyer reaction) or pre-activated halides (Rosenmund-von Braun reaction). Since there are adequate methods reported about *ortho*-selective cyanation of aromatics by various directing groups like amides, oximes, indoles, 2-phenyl pyridines, aromatic phosphonate esters, vinylic amides, tert-amines[14] but there is no study or report for distal C–H activation for cyanation. My study for this chapter includes details about the template assisted *para*- selective cyanation of toluene derivatives, optimization studies and exploring tolerance of methodology with respect to substituent on ring.

4.2 Results and discussion:

My study began with tolyl-derived biphenyl template to accommodate the transition metal by Nitrile co-ordination at *para*-C–H bond. Design of directing group was specifically important for *para*-selectivity. So silyl tethering with biphenyl system was necessary for this purpose. So toluene was first tethered to 4'-hydroxy-[1,1'-biphenyl]-2-carbonitrile via diisopropyl silyl linker due to which ring strain will allow it form stable 15-16 membered ring and will help to deliver metal selectively at *para*-position and which will lead to *para*-functionalization. Search for nitrile functionalization under catalytic conditions in presence of nitrile as directing groups posed difficult challenges. Apart from the competitive coordination with the directing group, nitrile group (a) can saturate the catalytic site of the transition metal and eventually deactivate it and further limiting the reaction (b) can trigger undesired nucleophilic reaction and (c) remains sensitive towards the redox and acid-base conditions. Under such circumstance's judicial choice of cyano source with appropriate concentration minimize deactivation routes. The selection of the metal catalyst was also crucial to trigger successful bond connectivity between nucleophilic -

CN and nucleophilic metallacycle. Consequently, development of synthetic methodology for directed cyanation is important for both scientific impetus and synthetic advantages.



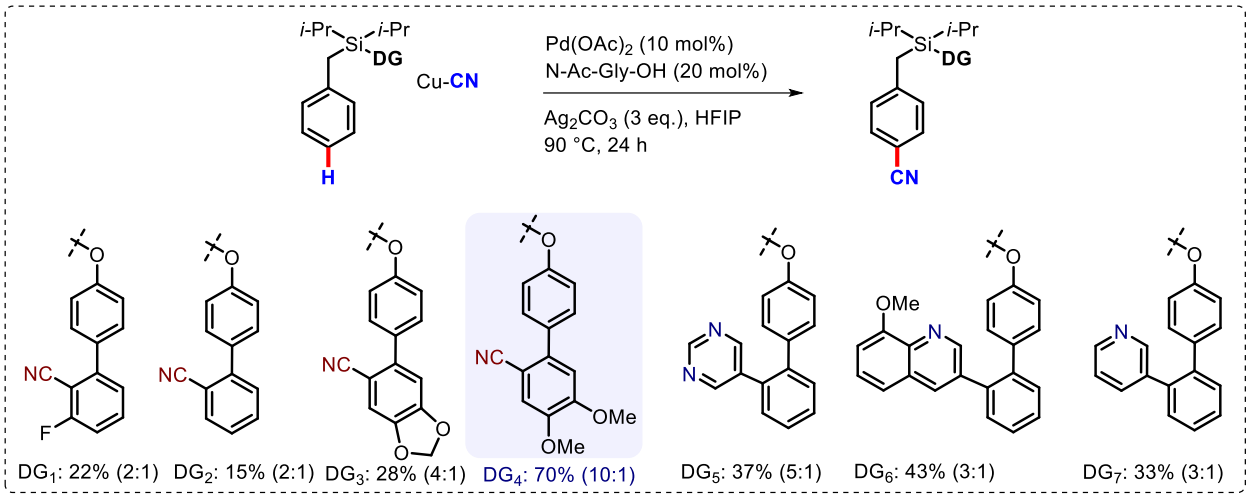
Scheme 10: *para*-selective cyanation of toluene

Initially I started investigating with 1st generation template DG_2 (Scheme **10)**. Optimization of the reaction parameters offered a yield of 30% with 2:1 *para* selectivity. (Table **1**) During the screening of directing templates from strong coordinating pyridine or quinoline (Scheme **11** DG_5-DG_7) improved the yield yet compromised the selectivity. Modification of the electronic environment around the nitrile group showed further improvements ($DG_{1/3/4}$). Maximum output was obtained with dimethoxy substituted template (DG_4). Enhanced electron density due to the presence of dimethoxy group justified the better metal binding and whereas H-bonding interaction with the solvent is likely to provide optimal structural rigidity for superior *para* selectivity. Cuprous cyanide was found to be most effective cyanation agent and N-aceyl-glycine was found best mono-protected amino acid ligand to enhance the catalytic activity. Among various silver oxidants, Ag_2CO_3 was better suitable with combination of HFIP as solvent to increase the H-bonding interaction. I also optimize the amount of CuCN required and found to be 1 eq as optimum and an overall yield of 70% of cyanation product with 10:1 *para* selectivity was obtained

in presence of 10 mol% $Pd(OAc)_2$, 20 mol% *N*-Ac-Gly-OH, 1 equiv. of CuCN and 2 equiv. of Ag_2CO_3 in hexafluoroisopropanol (HFIP) solvent was obtained (Table **2**)

Sr. No	Cyanation source	Yield % (^{1}H NMR)	Selectivity (*para*:other)
1	AgCN	12	1:1
2	$K_4Fe(CN)_6$	30	2:1
3	Zn(CN)2	15	2:1
4	**CuCN**	**33**	**4:1**

Table 1: Screening of initial Cyanation source.

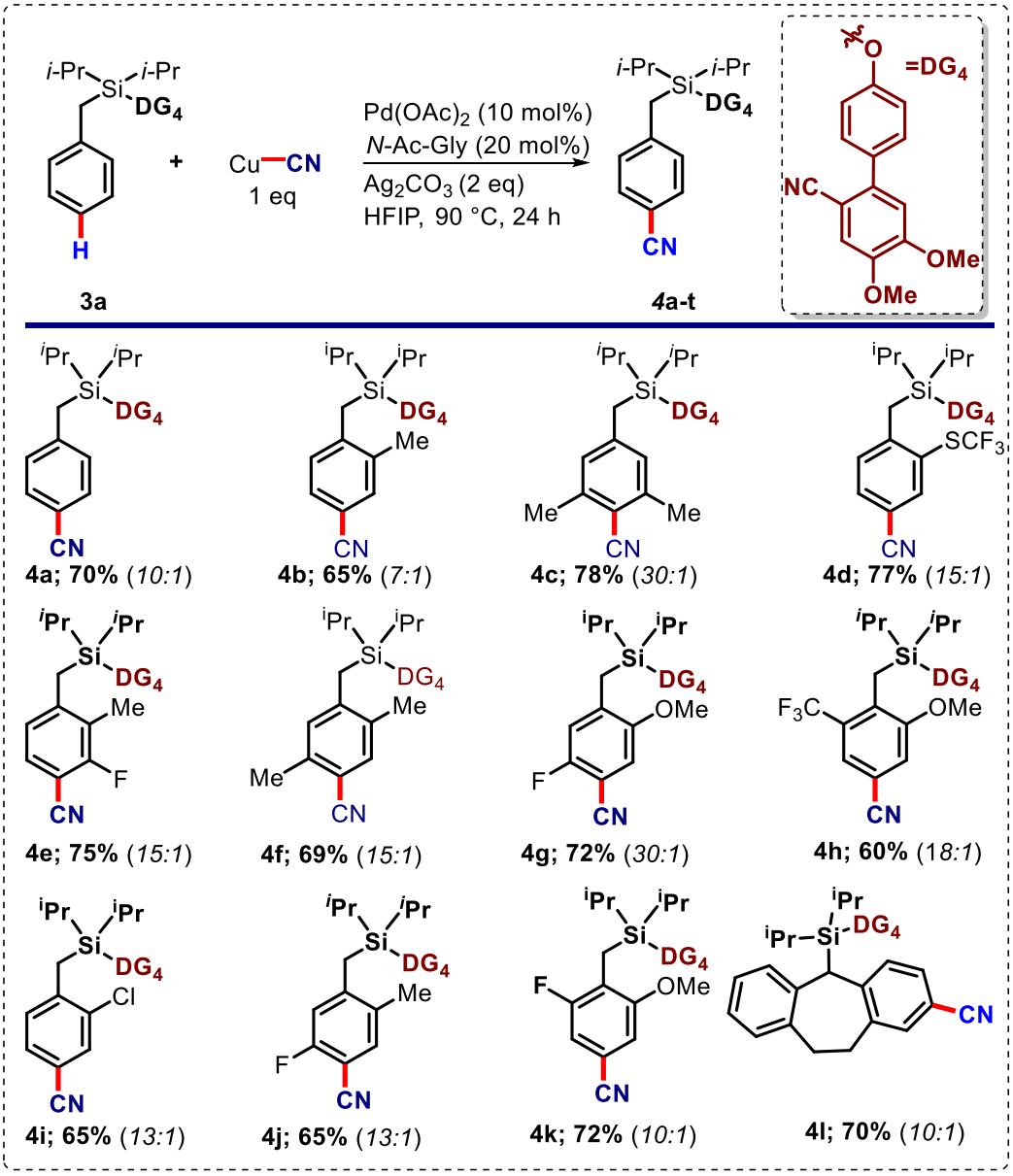


Scheme 11: Screening of various directing groups

Sr No	**Pd cat (10 mol%)**	**Oxidant (X equiv.) + CuCN (X equiv)**	**Ligand (Monoprotected amino acid) 20 mol%**	**Solvent**	**Yield % (1HNMR)**	***p:others***
1	Pd(II)pivalate	Ag_2CO_3 3 + CuCN 3	N-Ac-Gly-OH	HFIP	5	1:1
2	$Pd(PhCN)_2Cl_2$	Ag_2CO_3 3 +CuCN 3	N-Ac-Gly-OH	HFIP	11	1.5:1
3	$Pd(OAc)_2$	Ag_2CO_3 3 +CuCN 3	Cbz-Gly-OH	HFIP	22	1:1
4	$Pd(OAc)_2$	Ag_2CO_3 3 +CuCN 3	F-Moc-Gly-OH	HFIP	11	1:1
5	$Pd(OAc)_2$	Ag_2CO_3 3 +CuCN 3	N-Formyl-Gly-OH	HFIP	12	1.2:1
6	$Pd(OAc)_2$	Ag_2CO_3 3 +CuCN 3	N-Ac-Gly-OH	HFIP	45	5:1
7	$Pd(OAc)_2$	$Cu(OAc)_2$ +CuCN 3	Boc-Leu-OH	HFIP	NP	-
8	$Pd(OAc)_2$	$Ag(CO_2CF_3)$ +CuCN 3	N-Ac-Gly-OH	HFIP	33	4:1
9	$Pd(OAc)_2$	*P*-Benzoquinone 3+CuCN 3	N-Ac-Gly-OH	HFIP	NP	-
10	$Pd(OAc)_2$	Ag_2CO_3 4 +CuCN 3	N-Ac-Gly-OH	HFIP	41	6:1
11	$Pd(OAc)_2$	Ag_2CO_3 2 + CuCN 1	N-Ac-Gly-OH	HFIP	70	10:1

Table 2: Screening of optimization parameters.

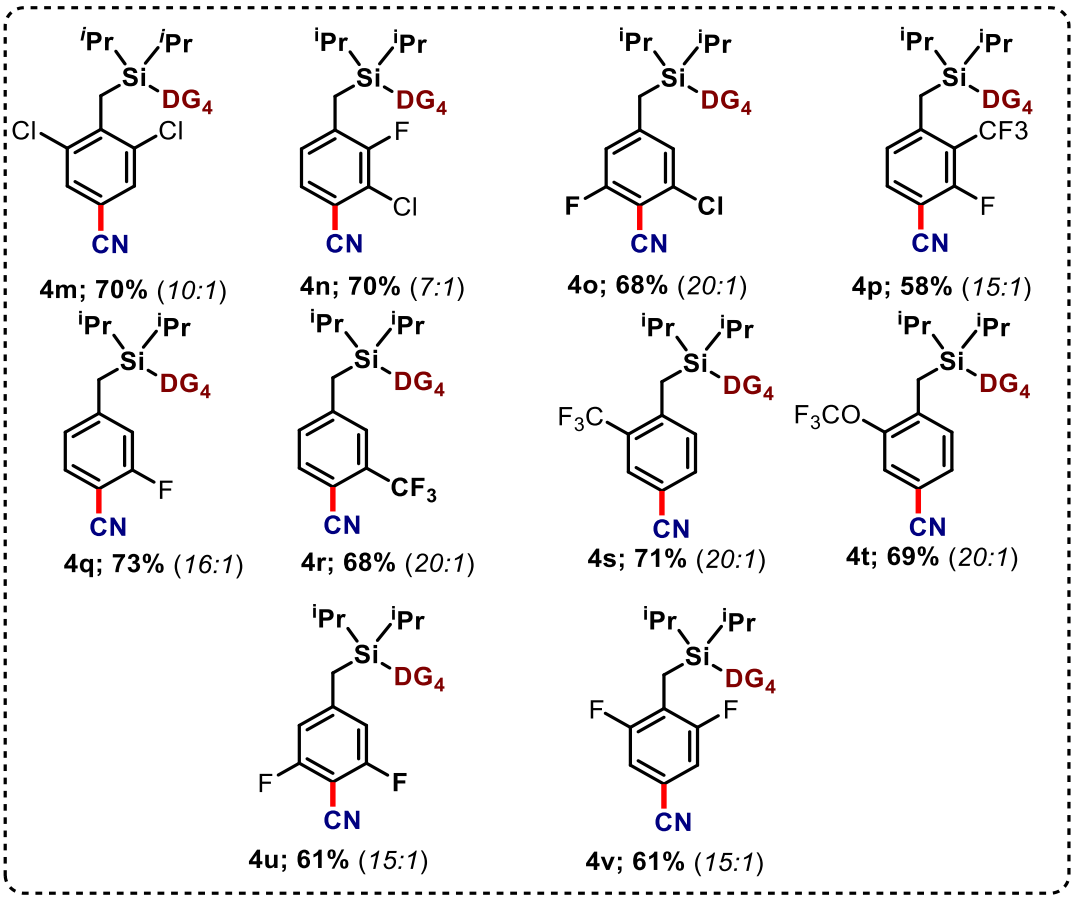
Upon optimization with unbiased model substrate **4a** a variety of toluene substrates were investigated. Reaction tolerated a different class of substituent which did not affected the positional selectivity due to presence of template. Notably the transformation was found to be indifferent towards electronic and steric inclination of the arene systems.



Scheme 12: Scope of *para*-cyanation on different tolyl substrates

Both electron rich and electron deficient substitutions were tolerated well under the reaction condition. Substituent like 2-methyl, 3,5-dimethyl, 2,5-dimethyl (**4b**, **4c & 4f**) gave yield 65%, 78% & 69% respectively at moderate to good *p:other* selectivity (Scheme **12**).

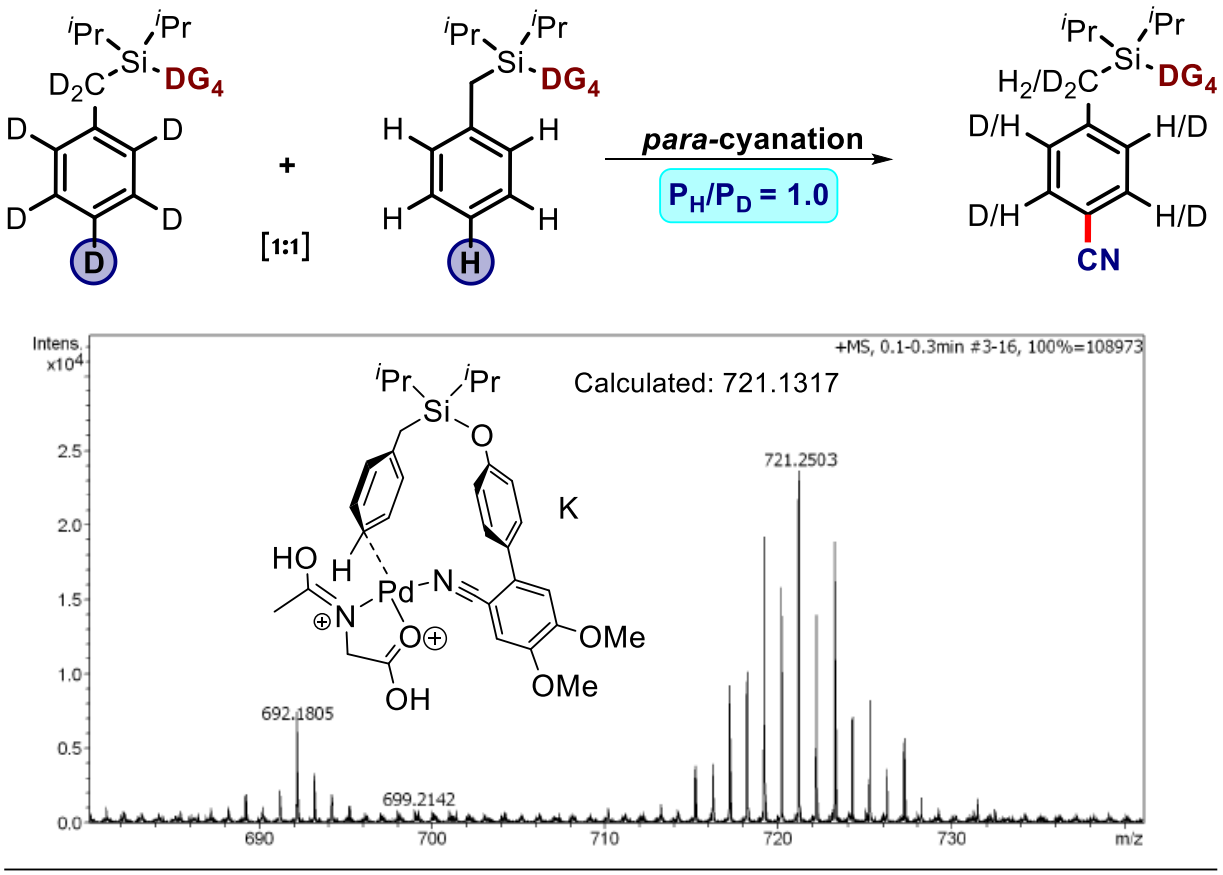
2-((trifluoromethyl)thio) (**4d**) as substituent worked very well giving 77% yield with 15:1 *p:other* selectivity. For this reaction we tried to employ arenes which has mixed functionality of both electron withdrawing and donating on same ring. All such substrate did not impose their electronic character for reaction but rather gave good yield. We assume that directing group has better control on arenes irrespective of electronic biasness on arens, which itself proves reason for better selectivity in most of cases. 2-methyl-3-fluoro (**4e**), 2-methoxy-5-fluoro (**4g**), 2-methoxy-6-trifluoromethyl (**4h**), 2-methyl-5-fluoro (**4j**) & 2-methoxy-6-fluoro (**4k**) having mixed functionality reacted well with good selectivity. In fact, electron withdrawing groups like 2-chloro (**4i**) gave 65 % yield.



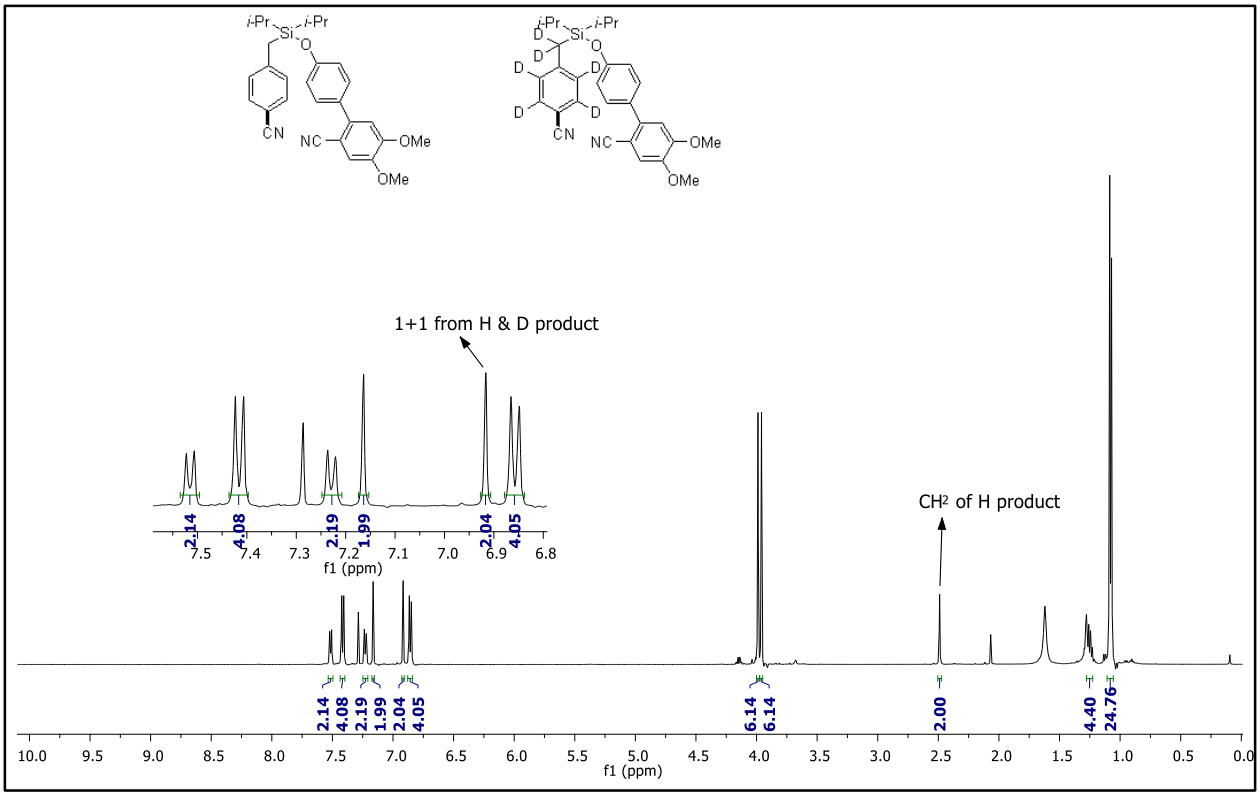
Scheme 13: Scope of *para*-cyanation on different tolyl substrates

Under optimized reaction conditions bisarenes fused with cycloheptane ring substrate (**4l**) possessing two equivalent *para* C-H bond selectively give mono cyanated product in 70% yield with 10:1 *p:other* selectivity proving stability of template to choose particular C–H

bond over another. Along with these substrate with electron withdrawing group reacted well, like 2,6-dichloro (**4m**), 2-fluoro-3-chloro (**4n**), 3-chloro-5-fluoro (**4o**) gave modetate to good cyanated product. Substituents like 2-trifluromethyl-3-fluoro (**4p**), 3-fluoro (**4q**), 3-trifluoromethyl (**4r**), 2-trifluoromethyl (**4s**), 2-trifluromethoxy (**4t**) also reacted with good selectivity. Even the ring containing multiple fluoro containing substituent like 2-fluoro-5-fluoro (**4u**), 3- fluoro-5- fluoro (**4v**) & 2- fluoro-6- fluoro (**4w**) gave good yield with para selective products (Scheme **13**).



Scheme 14: Product distribution study and mechanistic probing

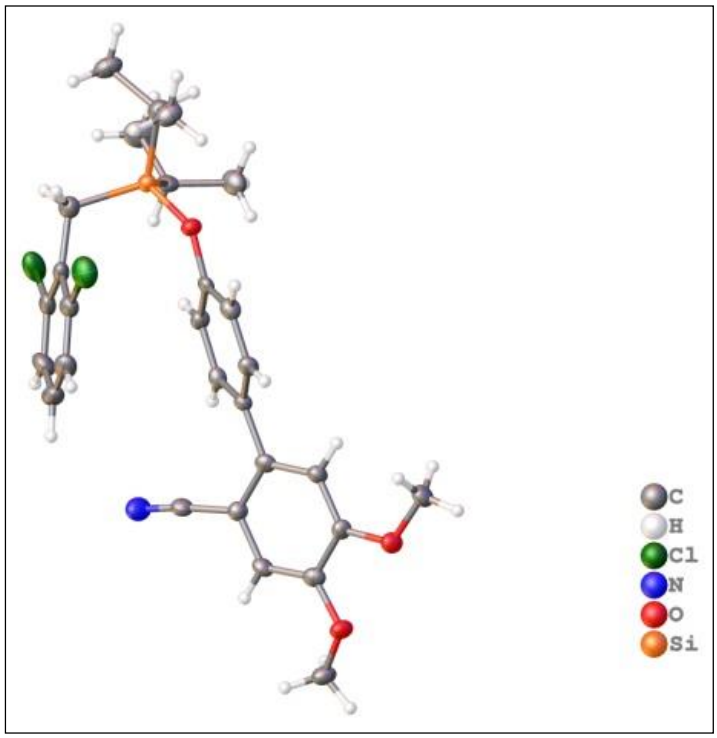


Scheme 15: P_H/P_D study*

*(Reaction was carried out in standard conditions with equimolar mixture of H-Substrate and D-Substrate, reaction was filtered through pad of celite and NMR was recorded as crude mixure NMR).

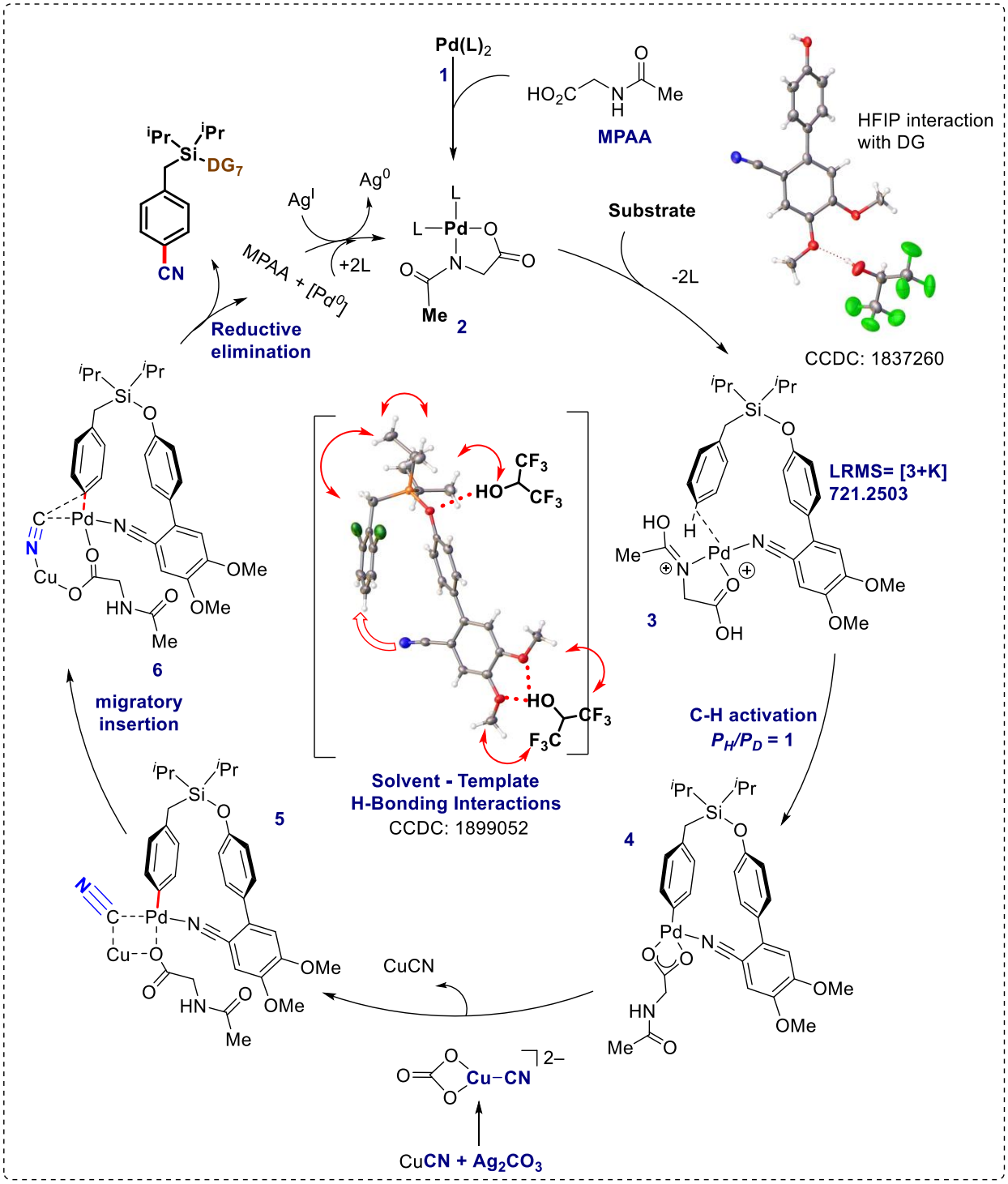
Following the scope of the reaction we intended to gain better insight of the mechanistic pathway. Interestingly, product distribution study (Ph/Pd=~1) suggested that C–H activation step is not associated in the rate limiting step of the transformation (Scheme **15**). Such an observation is indicative of the fact that C–H activation step is no more the most energy demanding step. A plausible reaction mechanism is depicted in scheme **17**. At first mono protected amino acid (MPAA) ligates to catalyst (2) and which subsequently add to substrate forming 3. However, our attempt to trap the complex by reacting stoichiometric amount of catalyst, ligand and substrate in HFIP at 60 °C for 48 h gave us clue by LRMS that Pd is forming *pre*-C–H activation complex with substrate and ligand (scheme **14**). In the medium Cu-CN and Ag_2CO_3 forms $CuCN(CO_3)$ adds to the 4 which on migratory insertion inserts CN substrate selectively at *para*-position thereby completing catalytic cycle after releasing product and reduced catalyst. Oxidant reactivate the catalyst for next catalytic event. Our attempts to show how HFIP interacts with

substrate in reaction medium, we started to grow directing group single crystal in HFIP. It was seen after diffraction in XRD that indeed HFIP exhibits H-bonding between two methoxy group which possibly might help in better selectivity among various directing group under study (DG_1-DG_7).



Scheme 16: π-stacking of substrate & directing group ring results in favorable orientation

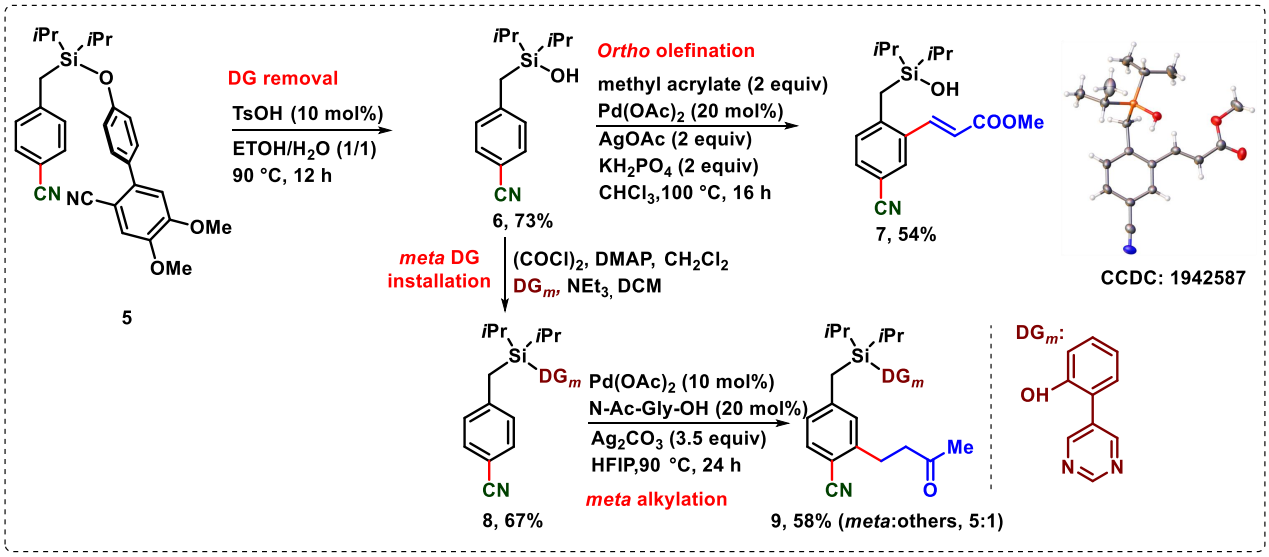
When crystal of 2,6-dichloro scaffold was diffracted in single XRD we observed that two biphenyl ring of directing group are in perpendicular orientation because of π interaction between upper ring and substrate ring, now which results in specific orientation of Nitrile towards to *para*-C–H bond, this conformation is quite important to understand the reactivity and high *para* selectivity of reaction (Scheme **16**). Although we are trying to get intermediate metallacycle for *para*-C–H activation but none of attempts were successful till now. Also computational studies were concluded after performing DFT study in collaboration with Prof. Gang Lu from University of Pittusberg (Currently at Shandong University, 250100, Jinan, China.) and we found that Cu-CN can bind with the carbonate anion (from Ag_2CO_3) to form a stable $CuCN(CO_3)$ species. The transmetallation between the Pd(II) intermediate (Scheme **17**, **4**) after C-H activation with $CuCN(CO_3)$ has a high barrier (29 kcal/mol), representing the rate-determining step. While the C-H activation



Scheme 17: Plausible catalytic cycle

step (24.7 kcal/mol) is reversible.

To illustrate the synthetic utility of directing group, cyanated product was cleaved under ambient conditions to recover the directing template by hydrolytic pathway & formed silanol, a prominent substrate for directed *ortho* functionalization to various functional groups interconversion for late stage modifications (Scheme **18**). Para cyanated Silanol product obtained was ortho functionalized with reported method with methyl acrylate in 54%. Also cyanated silanol was used as substrate to install meta selective DG and meta alkylation was carried out in 58% (*m:other* 5:1) yield (Scheme **18**).



Scheme 18: Post-synthetic applications

4.3. Conclusion:

Present report described the effort towards the development of a novel strategy to reach distal *para*-C–H bond of aromatic. The detailed optimization carried out to improve the reaction conditions are pointing towards the increasing yield and selectivity. Also present conditions are well tolerated for various electron donating and withdrawing group present in aromatic ring.

4.4. Experimental results

4.4.1 General Consideration

4.4.1.a. Reagent information:

Unless otherwise stated, all the reactions were carried out in screw cap reaction tube under air atmosphere with magnetic stirring. Palladium salts were purchased from Alfa Aesar and used directly. All oxidants were purchased from Alfa Aesar. All the solvents were bought from MERCK and used directly. All the other reagents were purchased from commercial source and used as received. For column chromatography silica gel (60-120 mesh and 100-200 mesh) was supplied from SRL Co. During elution hexane and ethyl acetate mixture was used. Thin layer chromatography was performed on EMD Chemicals Si 60 F_{254}. TLC plates (silica gel 60F_{254}) supplied from MERCK.

4.4.2.b. Analytical information:

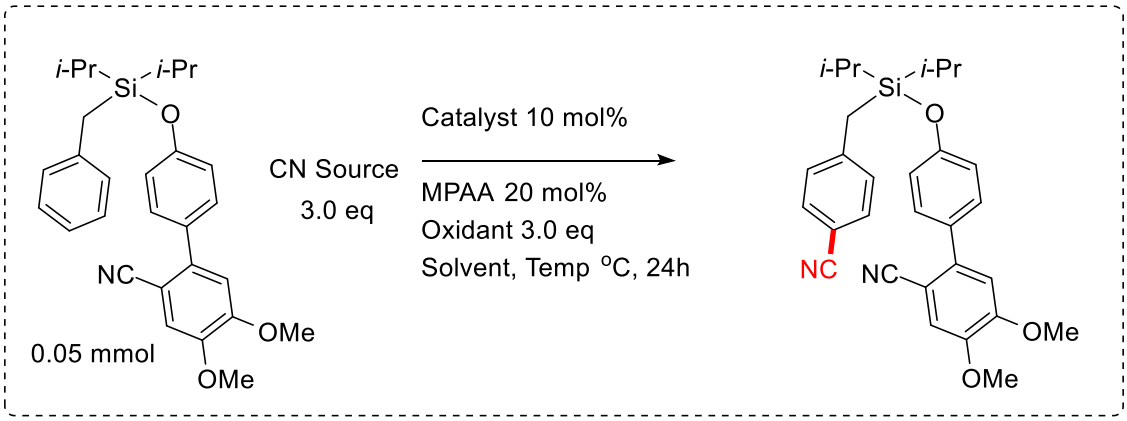
All isolated compounds were characterized by ^{1}H, ^{13}C NMR spectroscopy, IR spectroscopy, HR-MS. Copies of NMR files can be found in the supporting information. Unless otherwise stated, all Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 and 500 MHz instrument. The references used for NMR is tetramethylsilane (TMS) for ^{1}H and ^{13}C NMR. ^{1}H NMR data are reported in units, parts per million (ppm) and were recorded relative to the signals for residual chloroform (7.26 ppm). ^{13}C NMR data were obtained with ^{1}H decoupling and were recorded relative to the signals for residual chloroform (77.36 ppm). NMR yield was calculated using 1,3,5-trimethoxybenzene (TMB) as the internal standard. GC yield was calculated by using n-Decane as internal standard. High-resolution mass spectra (HRMS) were recorded on a micro-mass ESI TOF (time of flight) mass spectrometer.

4.4.3.c. Description of reaction tube:

Pictorial description of reaction tube for nitro aminoxylation of alkyne: Fisherbrand Disposable Borosilicate Glass Tubes (16*125mm) with Threaded End (Fisher Scientific Order No. 1495935A) [left hand side]; Kimble Black Phenolic Screw Thread Closures with Open Tops (Fisher Scientific Order No. 033407E) [right hand side, top]; Thermo Scientific National PTFE/Silicone Septa for Sample Screw Thread Caps (Fisher Scientific Order No. 03394A) [right hand side, bottom].

4.4.2. Optimization details

Optimization conditions:



Sr. No	Cyanation source + $Pd(OAc)_2$ 10 mol%	Yield % (^{1}H NMR)	Selectivity (*para*:other)
1	AgCN	12	1:1
2	$K_4Fe(CN)_6$	30	2:1
3	Zn(CN)2	15	2:1
4	**CuCN**	**33**	**4:1**

Table 3: Optimization for cyanation source

Sr. No	Catalyst	Yield % (^{1}H NMR)	Selectivity (*para*:other)
1	$Pd(Pivalate)_2$	5	1:1

2	$PdCl_2$ + 20 mol% NaOAc	-	-
3	$Pd(PPh_3)_4$	-	-
4	$Pd(PhCN)_2Cl_2$	11	1.5:1
5	**$Pd(CH_3CN)_2Cl_2$**	**9**	**1.5:1**
6	$Pd(dba)_2$	-	
7	**$Pd(OAc)_2$**	**33**	**4:1**
8	$Pd(TFA)_2$	18	1:1

Table 4: Optimization for catalysts

Sr. No	MPAA 20 mol%	Yield % (^{1}H NMR)	Selectivity (*para*:other)
1	Boc-Ala-OH	9	1.5:1
2	Boc-Gly-OH	21	3:1
3	Boc-Leu-OH (DL)	9	1:1
4	Ac-Glu-OH	-	-
5	Boc-Leu-OH	-	-
6	Boc-*tert*-Lue-OH	-	-
7	Cbz-Gly-OH	19	1:1
8	F-Moc-Gly-OH	10	1:1
9	N-Formyl-Gly-OH	9	1.2:1
10	N-Acetyl glycine ethyl ester	-	-
11	Glycine	29	3:1
12	N-Acetyl Glycine	36	5:1
13	Boc-L-Phenyl glycine	7	1.5:1

MPAA: N-Monoprotected amino acid

Table 5: Optimization for Monoprotected amino acid ligands

Sr. No	**Temerature**	**Yield % (^{1}H NMR)**	**Selectivity (*para*:other)**
1	50	7	3:1
2	60	20	3.1:1
3	70	33	5:1
4	80	37	3:1
5	**90**	**49**	**6:1**
6	100	33	5:1
7	110	27	4:1
8	120	22	4:1

Table 6: Optimization for temperature

Sr. No	Oxidant (3.0 equiv)	Yield % (^{1}H NMR)	Selectivity (*para*:other)
1	*P*-Benzoquinone	-	-

2	AgOAc	22	5:1
3	$Ag(CO_2CF_3)$	33	4:1
4	Ag_2O	12	5:1
5	$Cu(OAc)_2$	-	-
6	$Cu(OAc)_2.H_2O$	-	-
7	**Ag_2CO_3**	**60**	**8:1**
8	$Cu(TFA)_2$	22	3:1

Table 7: Optimization for oxidant

Sr. No	Oxidant Amount	Yield % (^{1}H NMR)	Selectivity (*para*:other)
1	1	22	5:1
2	**2**	**60**	**8:1**
3	3	55	6:1
8	4	41	4:1

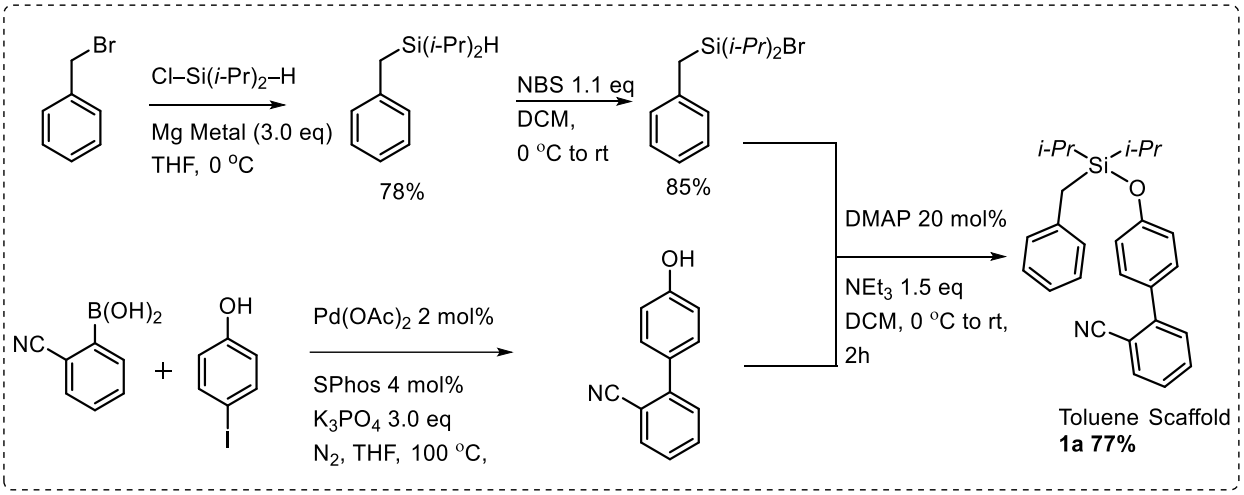
Table 8: Optimization for oxidant amount

Sr. No	Solvent	Yield % (^{1}H NMR)	Selectivity (*para*:other)
1	DCE	60	8:1
2	THF	36	5:1
3	t-BuOH	12	4:1
4	t-Butyl methyl ether	-	-
5	**HFIP**	**70**	**10:1**
6	DCE:HFIP (1:1)	55	7:1
7	**TFE**	**45**	**3:1**
8	Chlorobenzene	5	1:1

Table 9: Optimization for solvent

4.4.3. General procedures

Synthesis of scaffold 1a:



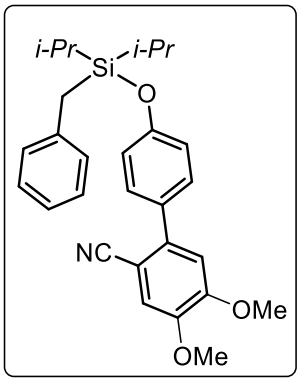
Preparation of 4'-hydroxybiphenyl-2-carbonitrile: Suzuki coupling was done by adding 2-cyanophenyl boronic acid (2 mmol) and 4-bromophenol (2 mmol), SPhos (4mol% and K_3PO_4 (3 equiv.) in a clean reaction tube equipped with stirred bar. The reaction tube was closed with screw cap followed by evacuation in vacuum and purged with N_2 several times. To this dry THF was added and was purged N_2 again. Tube was placed in preheated oil bath at 100 ˚C for 24 h and stirred. After cooling to room temperature reaction mixture was filtered through pad of silica and pure product was isolated by column chromatography using neutral alumina and petroleum-ether/ethyl acetate (85/15, v/v) as the eluent. White solid, 73%; Spectroscopic data was matched with previously reported compound.

Step 1: In a clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar, activated magnesium turnings/powder (15 mmol, 3 equiv) and I_2 (one bid) were taken. Then the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. Then dry THF (3x mL, 15 mL) followed by diisopropylchlorosilane (6 mmol, 1.2 equiv) was added to the tube. Now in another oven dried screw cap reaction tube, benzyl chloride/bromide (5 mmol) was taken in dry THF (2xmL, 10 mL). The solution of benzyl chloride was added drop by drop during 30 minutes to the aforementioned reaction mixture in an ice cold condition. The mixture was

vigorously stirred for 4 hours. After the reaction was completed, the reaction mixture was quenched with saturated sodium chloride solution and extracted thrice with ethyl acetate (3X20 mL) and brine solution (3X10 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude mixture was purified by flash column chromatography using silica gel (60-120/100-200 mesh size) and petroleum-ether as the eluent. Benzyldiisopropylsilane was collected and used for next step.

Step 2: To a nice-cold suspension of N-bromosuccinamide (6 mmol, 1.2 equiv) in 15 mL (3x mL) dry DCM, benzyldiisopropylsilane was added drop by drop under N2 atmosphere. The reaction was kept for stirring at room temperature for 2 hours. Now in another clean, oven dried round bottomed flask with previously placed magnetic stir–bar was charged with 4-hydroxybiphenyl-2-carbonitrile (5.5 mmol, 1.1 equiv), 4-dimethylaminopyridine (10 mol%). Then the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. 10 mL (2x mL) dry DCM was added to it, followed by trimethylamine (7.5 mmol, 1.5 equiv) was added dropwise. The entire solution was kept for stirring at 0 °C until 4-hydroxybiphenyl-2-carbonitrile gets dissolved. To this ice-cold reaction mixture, the aforementioned solution of benzylbromodiisopropylsilane was added drop by drop under the positive flow of nitrogen. The reaction mixture was then stirred in room temperature for 2 hours. After completion of reaction, solvent was evaporated and extracted thrice with ethyl acetate (3X30 mL) and water (3X10 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography using silica gel (60-120/100-200 mesh size) and petroleum-ether/ethyl acetate (99/1, v/v) as the eluent. Product was isolated as colorless oil and yielded 77%.

Synthesis of scaffold 3a:



Synthesis of corresponding Nitrile for Suzuki coupling from aldehyde: To a mixture of 6-bromo-3,4-dimethoxy benzaldehyde (5 mmol) was added sodium azide (7.5 mmol) and triflic acid (15 mmol) in acetonitrile. Reaction mixture was allowed to stir at 12 hour and extracted in ethyl acetate and water. Organic layer was separated and dried over $NaSO_4$. Organic solvent was removed and product was purified by column chromatography to give corresponding nitrile in 80% yield which was for Suzuki coupling as per procedure for preparation of 4'-hydroxybiphenyl-2-carbonitrile. Further synthesis was carried out similar to **1a.**

General procedure for cyanation of 1a or 3a:

To a clean reaction tube equipped with magnetic stirred bar was added **1a/3a** (0.05 mmol), N-Acetyl glycine (20 mol%), CuCN (1.0 eq), Ag_2CO_3 (3.0 eq) and 1 mL of hexafluoroisopropanol. Reaction mixture was allowed to stir at 90 °C for 24 hour. Later cooling to rt reaction mixture was filtered through pad of celite and purified on column chromatography by (95:5) petroleum ether /ethyl acetate to give pure **2a/4a** as sticky solid.

General procedure for DG Removal: A screw cap reaction tube containing stirring bar was charged with compound **4a** (0.4 mmol) and *p*-toluenesulfonic acid (0.04 mmol). Then 3 mL of aqueous ethanol (EtOH: H2O; 3:1) was added at room temperature and the reaction mixture was heated at 100 °C for 16 h. After work up with ethyl acetate combined organic layer was concentrated and purified by column chromatography using silica gel. Eluent: ether/ ethyl acetate (90/10 v/v).

***Ortho* olefination**: A screw cap reaction tube containing stirring bar was charged with Pd(OAc)2 (20 mol%), compound **6** (0.1 mmol), AgOAc (2 equiv), KH_2PO_4 (2 equiv), methyl acrylate (2 equiv) and $CHCl_3$ (1 mL). The reaction tube was sealed and heated at 100 °C for 16 h with vigorous stirring. The reaction mixture was cooled and filtered through celite. The filtrate was concentrated and purified by column chromatography using silica gel.

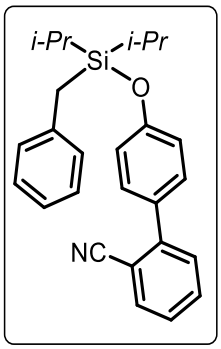
***Meta* DG Installation:** To a stirred solution of **6** (0.5 mmol) and DMAP (0.75 mmol) in dry DCM (4 mL), oxalyl chloride (2 mmol) was added dropwise under inert atmosphere at 0 °C slowly to maintain a gentle exotherm. After addition, the reaction mixture was stirred overnight at room temperature. DCM was removed by evaporation; diethyl ether (10 mL) was added and filtered through celite. Then diethyl etherwas removed to get crude chlorosilane. DCM solution of this crude chlorosilane was added dropwise to a stirred solution of 2-(pyrimidin-5-yl)phenol(0.5 mmol) and trimethylamine (2 equiv) in dry DCM at 0 °C under inert atmosphere. After stirring for 5 h at room temperature, DCM was removed and hexane (10 mL x 3) was added and filtered through celite. Concentration under reduced pressure followed by purification by column chromatography afforded 4-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)benzonitrile (**8**) as yellowish oil.

***Meta*-alkylation of arene:**

A Clean oven-dried screw cap reaction tube was charged with a magnetic stir-bar, $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), Ag_2CO_3 (3.5 equiv), 4-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)benzonitrile **8** (0.2 mmol). Then 2 mL of 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) was added and followed by 3-buten-2-ol (0.6 mmol) into the reaction tube by syringe. The reaction tube was screwed by a cap fitted with a rubber septum. The reaction mixture was stirred vigorously on a preheated oil bath at 90 ˚C along. The reaction was carried out for 24 h and the reaction mixture was diluted with EtOAc and filtered through a celite pad. After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography using neutral alumina and petroleum ether/ethyl acetate as the eluent.

4.5. Characterization Data

4'-((benzyldiisopropylsilyl)oxy)-[1,1'-biphenyl]-2-carbonitrile (1a):,



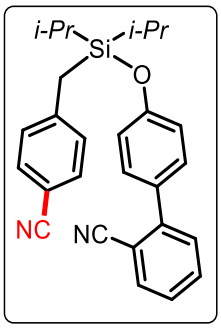
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.61 (td, *J* = 7.7, 1.3 Hz, 1H), 7.49 (m, 1H), 7.41 (m, 3H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 7.3 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 2.41 (s, 2H), 1.24 (dt, *J* = 14.8, 7.4 Hz, 2H), 1.06 (dd, *J* = 7.4, 4.9 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.61, 145.57, 138.78, 134.12, 133.05, 131.41, 130.30, 130.23, 129.20, 128.78, 128.65, 127.36, 124.81, 120.42, 119.25, 111.35, 50.96, 21.29, 17.76, 17.72, 13.19.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{26}H_{29}NNaOSi$ m/z 422.1913 and found m/z 422.1911.

IR: (thin film, cm^{-1}): 2925, 2867, 2223, 1732, 1603, 1501, 1462, 1215, 1106, 881, 840, 771.

4'-(((4-cyanobenzyl)diisopropylsilyl)oxy)-[1,1'-biphenyl]-2-carbonitrile (2a):



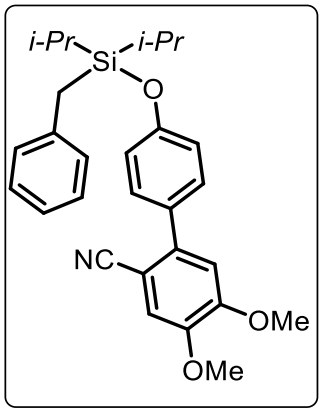
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.62 (td, *J* = 7.8, 1.2 Hz, 1H), 7.49 (dd, *J* = 8.2, 2.0 Hz, 3H), 7.42 (dd, *J* = 8.2, 1.9 Hz, 3H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 2.47 (s, 2H), 1.21 (m, 2H), 1.03 (dd, *J* = 20.5, 6.3 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.15, 145.57, 145.38, 134.11, 133.13, 132.40, 131.86, 130.46, 130.20, 129.80, 127.53, 120.21, 119.63, 119.20, 113.93, 111.41, 108.48, 92.07, 90.23, 30.03, 22.43, 17.73, 17.65, 13.32.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{27}H_{28}N_2NaOSi$ m/z 447.1863 and found m/z 447.1866

IR: (thin film, cm^{-1}): 2926, 2867, 2223, 1732, 1603, 1501, 1462, 1215, 1106, 881, 840, 771.

4'-((benzyldiisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (3a):



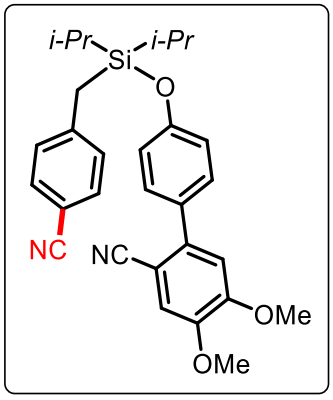
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.91 (s, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 2.41 (s, 2H), 1.24 (dt, *J* = 14.8, 7.5 Hz, 2H), 1.06 (dd, *J* = 7.4, 4.5 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 156.29, 152.75, 148.21, 140.27, 138.71, 131.44, 130.10, 129.11, 128.58, 124.74, 120.29, 119.58, 115.25, 112.58, 102.36, 56.51, 56.39, 21.20, 17.69, 17.66, 13.11.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{28}H_{33}NNaO3Si$ m/z 482.2123 and found m/z 482.2122

IR: (thin film, cm^{-1}): 2923, 2867, 2223, 1732, 1603, 1501, 1462, 1215, 1106, 881, 840, 771.

4'-(((4-cyanobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4a): Yield: 70%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



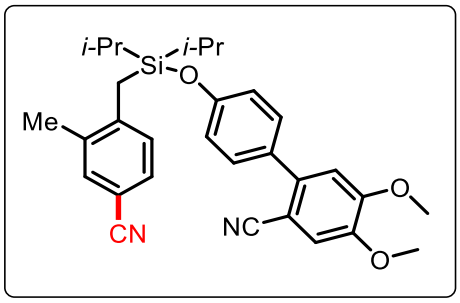
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.14 (s, 1H), 6.89 (s, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 3.96 (s, 2H), 3.94 (s, 2H), 2.46 (s, 1H), 1.24 – 1.19 (m, 1H), 1.05 (d, *J* = 7.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 155.93, 152.91, 133.67, 132.43, 132.40, 131.95, 130.36, 130.33, 129.81, 129.36, 128.66, 120.15, 119.65, 115.33, 112.75, 112.61, 112.51, 56.63, 56.53, 22.43, 21.20, 17.75, 17.67, 13.33.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{29}H_{32}N_2NaO_3Si$ m/z 507.2074 and found m/z 507.2078

IR: (thin film, cm^{-1}): 2926, 2867, 2223, 1732, 1603, 1501, 1462, 1215, 1106, 881, 840, 771.

4'-(((4-cyano-2-methylbenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4b): Yield: 65%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



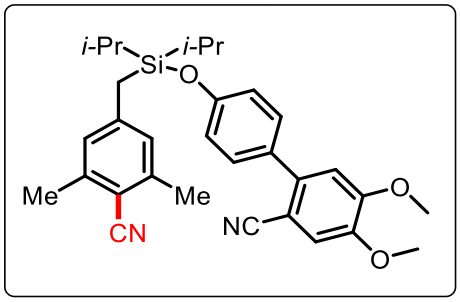
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (s, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.13 (s, 1H), 6.87 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.43 (s, 2H), 2.31 (s, 3H), 1.29 (d, *J* = 7.1 Hz, 2H), 1.09 (d, *J* = 7.5 Hz, 6H), 1.03 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.61, 152.80, 148.30, 144.45, 140.08, 137.10, 133.83, 131.71, 130.10, 130.01, 129.71, 119.77, 115.23, 112.51, 102.41, 56.53, 56.44, 20.51, 19.41, 17.75, 17.52, 13.55.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{30}H_{34}N_2O_3SiK$ *m/z 537.1970* and found *m/z 537.1973*

IR (thin film, cm^{-1}): 2924, 2857, 2223, 1500, 1266, 1216, 1140, 917, 840, 761.

4'-(((4-cyano-3,5-dimethylbenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4c): Yield: 78%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



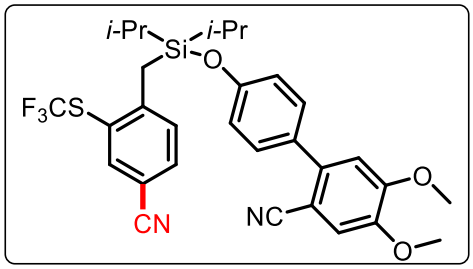
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 8.7 Hz, 2H), 7.14 (s, 1H), 6.89 (s, 1H), 6.83 (d, *J* = 8.7 Hz, 4H), 3.97 (s, 3H), 3.93 (s, 3H), 2.43 (s, 6H), 2.36 (s, 2H), 1.23 – 1.18 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 12H).

^{13}C NMR (101 MHz, CDCl3) δ: 155.72, 152.60, 148.09, 144.21, 141.88, 139.83, 131.48, 129.91, 127.92, 119.85, 119.28, 115.06, 112.29, 109.23, 102.17, 56.30, 56.18, 20.70, 17.43, 17.36, 13.03.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{31}H_{36}N_2O_3SiK$ *m/z 551.2127* and found *m/z 551.2120*

IR (thin film, cm^{-1}): 2930, 2859, 2220, 1516, 1260, 1215, 1141, 920, 840, 762.

4'-(((4-cyano-2-((trifluoromethyl)thio)benzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4d): Yield: 77%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



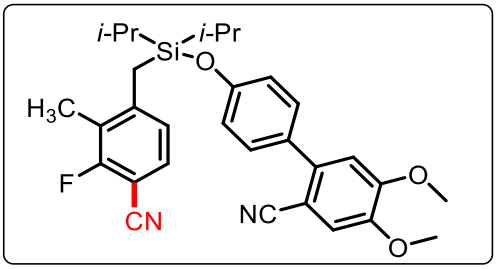
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (s, 1H), 7.61 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 7.13 (s, 1H), 6.87 (s, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.84 (s, 2H), 1.29 (d, *J* = 9.2, 5.8 Hz, 2H), 1.10 (s, 3H), 1.08 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.37, 154.32, 152.81, 151.93, 148.34, 141.48, 139.90, 134.12, 131.97, 131.34, 130.22, 119.64, 115.22, 112.48, 109.94, 77.55, 77.23, 76.91, 56.51, 56.40, 21.37, 17.72, 17.49, 13.66.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{30}H_{31}F_3N_2SO_3SiNa$ *m/z* 607.1669 and found *m/z* 607.1665

IR (thin film, cm^{-1}): 2929, 2866, 2225, 1732, 1602, 1500, 1254, 1110, 1031, 916, 842.

4'-(((4-cyano-3-fluoro-2-methylbenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4e): Yield: 75%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



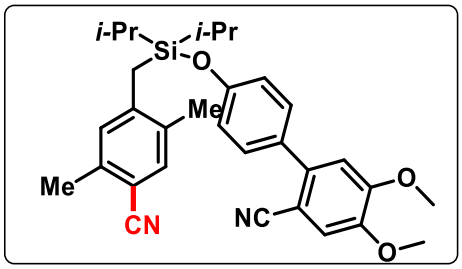
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 7.0 Hz, 1H), 7.13 (s, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 6.88 (s, 1H), 6.70 (d, *J* = 8.7 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 2.46 (s, 2H), 2.22 (d, *J* = 2.3 Hz, 3H), 1.28 – 1.26 (m, *J* = 3.1 Hz, 2H), 1.10 (d, *J* = 7.4 Hz, 6H), 1.07 – 1.03 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 161.91 (d, *J* = 254.9 Hz, C-F coupling), 155.40, 152.79, 148.28, 147.84 (d, *J* = 5.2 Hz, C-F coupling), 147.80, 139.96, 131.84, 130.10, 129.77, 125.49, 125.47 (d, *J* = 3.3 Hz, C-F coupling), 124.37, 124.26 (d, *J* = 14.6 Hz, C-F coupling), 119.63, 115.16, 112.49, 102.33, 56.49, 56.42, 19.84, 17.67, 17.46, 13.55, 11.61, 11.57 (d, *J* = 5.7 Hz, C-F coupling).

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{30}H_{30}N_2F_4O_3SiNa$ *m/z 593.1854* and found *m/z 593.1855*

IR (thin film, cm^{-1}): 2925, 2860, 2225, 1733, 1605, 1500, 1462, 1266, 1218, 1035, 920, 840.

4'-(((4-cyano-2,5-dimethylbenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4f): Yield: 69%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



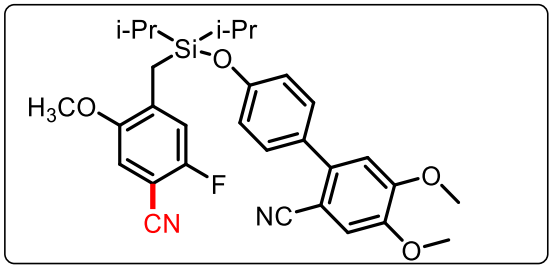
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 8.5 Hz, 1H), 7.29 (s, 1H), 7.13 (s, 1H), 7.03 (s, 1H), 6.87 (s, 1H), 6.69 (t, *J* = 7.2 Hz, 1H), 3.96 (s, 2H), 3.93 (s, 2H), 2.42 (s, 2H), 2.37 (d, *J* = 8.4 Hz, 1H), 2.26 (s, 2H), 1.29 – 1.26 (m, 1H), 1.09 (d, *J* = 7.4 Hz, 3H), 1.04 (t, *J* = 5.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.79, 152.90, 148.38, 144.23, 140.17, 139.20, 134.16, 134.13, 131.75, 131.30, 130.18, 119.90, 119.61, 119.12, 115.33, 112.60, 108.81, 102.47, 56.62, 56.53, 20.27, 20.06, 19.30, 17.84, 17.63, 13.69.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{31}H_{36}N_2O_3SiK$ *m/z 535.2387* and found *m/z 535.2395*

IR (thin film, cm^{-1}): 2925, 2837, 2230, 1512, 1264, 1211, 1050, 839, 767.

4'-(((4-cyano-5-fluoro-2-methoxybenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4g): Yield: 72%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



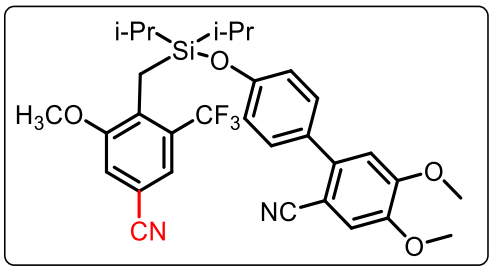
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.5 Hz, 2H), 7.13 (s, 1H), 6.88 (d, *J* = 7.5 Hz, 2H), 6.82 (d, *J* = 5.1 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.73 (s, 3H), 2.44 (s, 2H), 1.24 – 1.21 (m, 2H), 1.07 (d, *J* = 7.3 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.96, 156.96, 155.90, 153.12, 152.92, 148.39, 140.20, 138.10, 138.04, 131.78, 130.17, 119.98, 119.67, 117.88, 117.71, 115.31, 114.95, 112.64, 112.54, 102.46, 96.72, 96.59, 56.62, 56.52, 56.04, 17.62, 17.54, 16.63, 13.81.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{30}H_{33}FN_2O_4SiK$ *m/z 571.1825* and found *m/z 571.1823*

IR (thin film, cm^{-1}): 2923, 2856, 2222, 1607, 1458, 1498, 1352, 1267, 1217, 1068, 917, 843.

4'-(((4-cyano-2-methoxy-6-(trifluoromethyl)benzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4h): Yield: 60%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



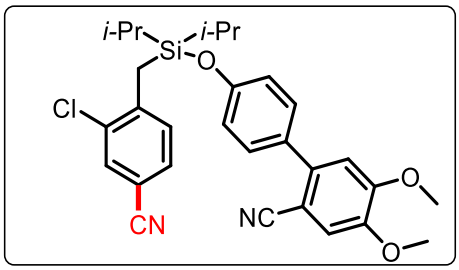
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 – 7.26 (m, 3H), 7.05 (s, 1H), 6.96 (s, 1H), 6.80 (s, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.76 (s, 3H), 2.56 (s, 2H), 1.31 – 1.26 (m, 2H), 1.09 (d, *J* = 7.4 Hz, 6H), 1.05 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.07, 156.36, 152.82, 152.69, 148.20, 140.33, 137.91, 131.23, 130.96, 129.82, 129.24, 128.93, 127.43 (d, *J* = 1.5 Hz,C-F coupling), 127.12, 120.06, 122.20 (q, J = 270.2 Hz CF3), 119.80, 116.62, 116.58 (d, *J* = 6.0 Hz, C-F coupling), 116.46, 115.19, 112.37, 111.36, 102.23, 56.57, 56.39, 55.62, 17.78, 14.34, 12.61.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{31}H_{33}F_3N_2O_4SiNa$ *m/z 605.2054* and found *m/z 605.2057*

IR (thin film, cm^{-1}): 2927, 2871, 2222, 1732, 1603, 1563, 1503, 1464, 1264, 1035, 881, 809.

4'-(((2-chloro-4-cyanobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4i) : Yield: 65%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



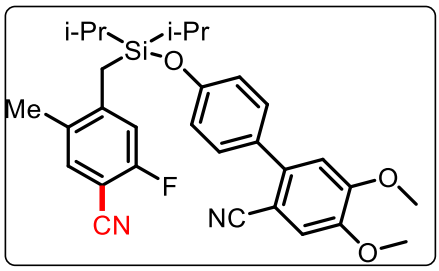
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 3H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.13 (s, 1H), 6.88 (s, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.62 (s, 2H), 1.33 – 1.28 (m, 2H), 1.06 (t, *J* = 7.7 Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.64, 152.78, 148.29, 144.29, 140.04, 133.99, 132.98, 131.81, 131.39, 130.20, 130.19, 119.89, 119.52, 118.13, 115.18, 112.48, 109.79, 102.41, 56.52, 56.42, 19.92, 17.61, 17.45, 13.73.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{29}H_{31}N_2ClO_3SiNa$ *m/z 541.1685* and found *m/z 541.1681*

IR (thin film, cm^{-1}): 2947, 2869, 2229, 1735, 1603, 1563, 1503, 1463, 1389, 1249, 1216, 1027, 839, 809.

4'-(((4-cyano-5-fluoro-2-methylbenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4j): Yield: 65%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



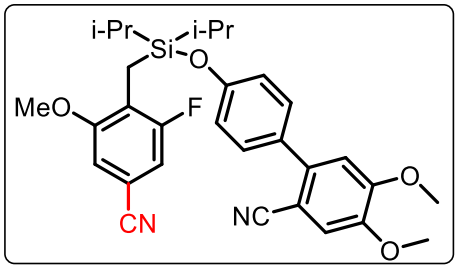
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 6.7 Hz, 1H), 7.13 (s, 1H), 6.96 (d, *J* = 10.2 Hz, 1H), 6.87 (s, 1H), 6.71 (d, *J* = 8.7 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.41 (s, 2H), 2.27 (s, 3H), 1.32 – 1.29 (m, 2H), 1.10 (d, *J* = 7.4 Hz, 6H), 1.05 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.28, 155.44, 152.84, 148.35, 147.59, 140.00, 134.28, 131.93, 130.18, 119.71, 116.72, 116.53, 115.25, 112.54, 102.44, 56.54, 56.45, 22.95, 20.03, 19.78, 17.73, 17.50, 13.62.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{30}H_{33}FN_2O_3SiNa$ *m/z 539.2137* and found *m/z 539.2132*

IR (thin film, cm^{-1}): 2926, 2857, 2225, 1732, 1605, 1500, 1462, 1266, 1217, 1032, 842.

4'-(((4-cyano-2-fluoro-6-methoxybenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4k): Yield: 72%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



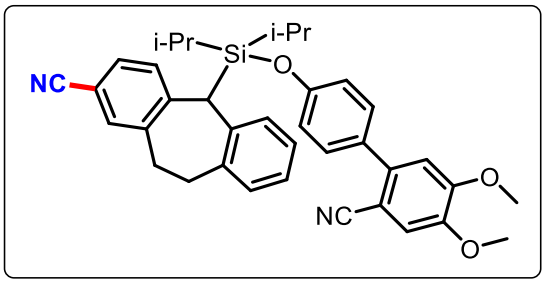
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34 – 7.27 (m, 3H), 7.12 (s, 1H), 6.89 (s, 1H), 6.71 (d, *J* = 8.3 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 3.75 (s, 3H), 2.35 (d, *J* = 1.9 Hz, 2H), 1.30 – 1.27 (m, 2H), 1.10 (t, *J* = 6.9 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 161.99 (d, *J* = 223.9 Hz, C-F coupling), 156.03, 152.95, 148.35, 140.40, 131.35, 130.54, 130.00, 119.73, 117.36 (d, *J* = 17.8 Hz, C-F coupling), 115.43 (d, *J* = 13.6 Hz, C-F coupling), 112.75, 106.74, 102.34, 93.42, 56.64, 56.55, 56.32, 23.04, 17.58, 17.53, 14.11, 7.79 (d, *J* = 2.8 Hz, C-F coupling).

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{30}H_{33}FN_2O_4SiK$ *m/z 571.1825* and found *m/z 571.1823*

IR (thin film, cm^{-1}): 2927, 2857, 2227, 1609, 1460, 1501, 1357, 1270, 1220, 1068, 917, 844.

5-(((2'-cyano-4',5'-dimethoxy-[1,1'-biphenyl]-4-yl)oxy)diisopropylsilyl)-10,11-dihydro-5H-dibenzo[a,d][7]annulene-1-carbonitrile (4l): Yield: 70%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.32 (d, *J* = 1.4 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 2H), 7.14 – 7.10 (m, 4H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.84 (s, 1H), 6.30 (d, *J* = 8.6 Hz, 2H), 4.07 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.53 – 3.43 (m, 2H), 2.86 (td, *J* = 9.2, 2.6 Hz, 2H), 1.30 – 1.28 (m, 2H), 1.09 (d, *J* = 7.5 Hz, 3H), 1.06 (d, *J* = 7.5 Hz, 3H), 0.99 (d, *J* = 7.4 Hz, 3H), 0.94 (d, *J* = 7.4 Hz, 3H).

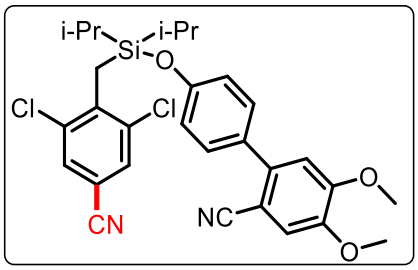
^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.25, 152.88, 148.37, 145.94, 141.84, 140.22, 139.80, 138.21, 134.18, 131.62, 131.07, 130.98, 130.41, 129.96, 129.72, 126.63, 119.58, 115.32,

112.60, 109.53, 102.51, 56.61, 56.54, 46.71, 33.16, 32.78, 18.21, 18.17, 17.88, 17.83, 14.31, 14.13.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{37}H_{38}N_2O_3SiNa$ *m/z 609.2544* and found *m/z 609.2543*

IR (thin film, cm^{-1}): 2927, 2866, 2223, 1731, 1602, 1498, 1264, 1134, 1030,913, 839.

4'-(((2,6-dichloro-4-cyanobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4m): Yield: 70%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



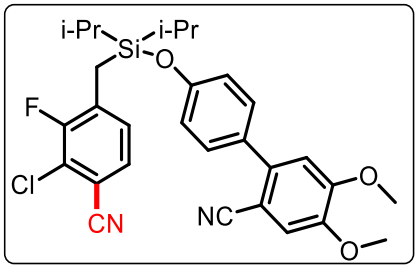
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (dt, *J* = 6.6, 5.2 Hz, 4H), 7.12 (s, 1H), 6.89 (s, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H), 2.80 (s, 2H), 1.42 – 1.36 (m, 2H), 1.16 (d, *J* = 7.4 Hz, 6H), 1.10 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.47, 152.84, 148.27, 140.11, 139.43, 139.30, 136.51, 131.40, 130.44, 129.91, 128.72, 119.38, 116.28, 115.28, 112.62, 112.59, 102.26, 56.54, 56.46, 22.94, 17.64, 17.52, 14.75.

HRMS (ESI-QTOF): $[M + Na]^+$ calculated for $C_{29}H_{30}Cl_2N_2O_3SiNa$ *m/z 575.1295* and found *m/z 575.1291*

IR (thin film, cm^{-1}): 2925, 2868, 2219, 1732, 1603, 1503, 1445, 1385, 1352, 1242, 1216, 1138, 1027, 900, 807.

4'-(((2-chloro-4-cyano-6-fluorobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4n): Yield: 70%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).

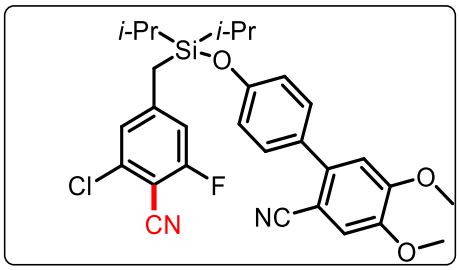


^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (dd, *J* = 8.6, 5.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.12 (s, 1H), 7.01 (t, *J* = 8.7 Hz, 1H), 6.89 (s, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.56 (d, *J* = 3.1 Hz, 2H), 1.37 – 1.33 (m, 2H), 1.12 (dd, *J* = 13.0, 7.4 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 162 (d, *J* = 254.9 Hz, C-F coupling), 155.49, 152.83, 148.26, 140.12, 131.54, 131.45, 129.99, 129.1 (d, *J* = 20.3 Hz, C-F coupling), 119.52, 116.32, 115.24, 114.70 (d, *J* = 24.6 Hz, C-F coupling), 112.61, 110.12 (d, *J* = 3.6 Hz, C-F coupling), 102.27, 56.53, 56.46, 22.94, 17.53, 17.41, 14.21, 12.8.
HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{29}H_{30}ClFN_2O_3SiK$ *m/z 575.1330* and found *m/z 575.1327*

IR (thin film, cm^{-1}): 2928, 2870, 2223, 1735, 1604, 1450, 1265, 1243, 1220, 1138, 920, 838.

4'-(((3-chloro-4-cyano-5-fluorobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4o): Yield: 68%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



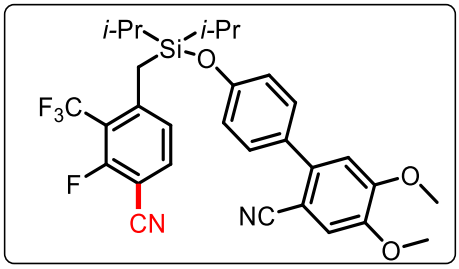
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.6 Hz, 2H), 7.14 (s, 1H), 7.04 (s, 1H), 6.90 (s, 1H), 6.85 (d, *J* = 9.6 Hz, 3H), 3.97 (s, 3H), 3.93 (s, 3H), 2.43 (s, 2H), 1.24 – 1.18 (m, 2H), 1.08 (dd, *J* = 7.4, 3.6 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 158.21 (d, *J* = 210.3 Hz, C-F coupling), 155.59, 152.93, 148.36, 140.21, 137.35, 137.29, 131.64 (d, *J* = 11.7 Hz, C-F coupling), 130.09, 129.20 (d, *J* = 20.1 Hz, C-F coupling), 119.62, 115.33, 114.8 (d, *J* = 24.7Hz, C-F coupling), 112.71, 110.22, 102.37, 56.63, 56.56, 23.04, 17.63, 17.51, 14.31, 12.8 (d, *J* = 2.3 Hz, C-F coupling)

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{29}H_{30}ClFN_2O_3SiK$ *m/z 575.1330* and found *m/z 575.1327*

IR (thin film, cm^{-1}): 2930, 2856, 2228, 1732, 1601, 1443, 1264, 1240, 1150, 919, 841.

4'-(((4-cyano-3-fluoro-2-(trifluoromethyl)benzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4p): Yield: 61%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



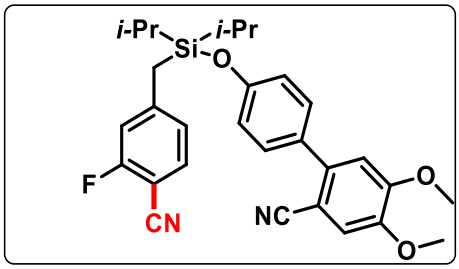
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 – 7.57 (m, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.13 (s, 1H), 6.89 (s, 1H), 6.81 (d, *J* = 8.3 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 2.72 (s, 2H), 1.31 (d, *J* = 7.5 Hz, 2H), 1.08 (d, *J* = 7.5 Hz, 6H), 1.01 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.43, 152.84, 148.5 (d, *J* = 15.4 Hz, C-F coupling), 139.94, 135.08, 132.09, 130.30, 128.3 (d, *J* = 4.0 Hz, C-F coupling), 119.82, 119.49, 115.21, 113.32, 112.51, 102.46, 99.4 (d, *J* = 17.1 Hz, C-F coupling), 56.54, 56.44, 20.98, 17.59, 17.36, 13.61.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{30}H_{30}F_4N_2O_3SiK$ *m/z 609.1593* and found *m/z 609.1600*

IR (thin film, cm^{-1}): 2927, 2870, 2222, 1732, 1604, 1562, 1503, 1464, 1309, 1268, 1038, 881, 809.

4'-(((4-cyano-3-fluorobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4q): Yield: 73%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



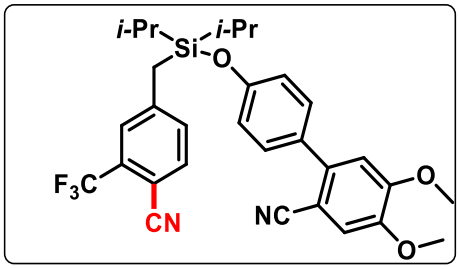
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (dd, *J* = 17.5, 8.2 Hz, 1H), 7.14 (s, 1H), 6.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.93 (d, *J* = 10.3 Hz, 1H), 6.90 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 3.96 (s, 1H), 3.93 (s, 1H), 2.46 (s, 1H), 1.24 – 1.18 (m, 1H), 1.06 (dd, *J* = 7.4, 2.1 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.8 (d, *J* = 258 Hz, C-F coupling), 161.99, 155.62, 152.83, 149.06 (d, *J* = 8.3 Hz, C-F coupling), 148.98, 148.34, 139.98, 133.19, 132.04, 130.28, 125.6 (d, *J* = 3 Hz, C-F coupling), 119.97, 119.47, 116.6 (d, *J* = 19.5 Hz, C-F coupling), 115.22, 114.63, 112.53, 102.41, 97.4 (d, *J* = 15.5 Hz, C-F coupling), 56.52, 56.41, 22.61, 17.61, 17.52, 13.26.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{29}H_{31}FN_2O_3SiK$ *m/z 541.1725* and found *m/z 541. 1732*

IR (thin film, cm^{-1}): 2947, 2867, 2223, 1734, 1603, 1460, 1263, 1242, 1137, 918, 838.

4'-(((4-cyano-3-fluorobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4r): Yield: 68%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



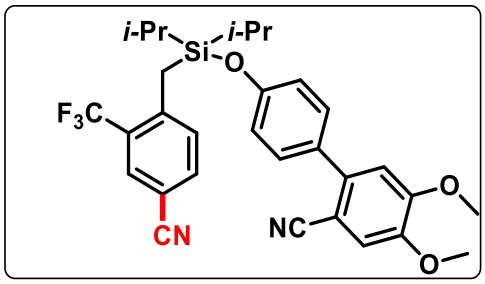
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 14.1 Hz, 1H), 7.49 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.13 (s, 1H), 6.93 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 3.96 (s, 1H), 3.93 (s, 1H), 2.48 (s, 1H), 1.25 – 1.20 (m, 1H), 1.07 (dd, *J* = 8.5, 7.6 Hz, 7H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.48, 152.80, 148.29, 142.55, 139.93, 135.42, 132.09, 130.37, 130 130 (q, *J* = 3.5 Hz, C-CF_3 coupling), 129.97, 125.2 (q, *J* = 3.8 Hz, C-CF_3 coupling), 125.19, 123.7 (q, *J* = 273.6 Hz, C-CF_3 coupling), 119.81, 119.48, 117.87, 115.18, 113.28, 112.59, 102.34, 56.49, 56.42, 21.20, 17.62, 17.51, 13.28.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{30}H_{31}F3N_2O_3SiK$ *m/z 591.1693* and found *m/z 591.1700*

IR (thin film, cm^{-1}): 2929, 2868, 2230, 1732, 1602, 1532, 1503, 1470, 1350, 1267, 1053, 840, 708.

4'-(((4-cyano-2-(trifluoromethyl)benzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4s): Yield: 71%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



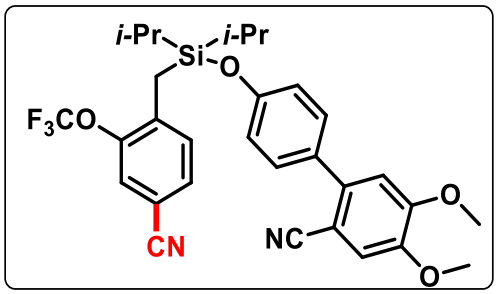
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.87 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.14 (s, 1H), 6.89 (s, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 4H), 3.93 (s, 3H), 2.65 (s, 2H), 1.29 (dd, *J* = 14.9, 7.5 Hz, 2H), 1.06 (d, *J* = 7.5 Hz, 6H), 0.97 (d, *J* = 7.4 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.58, 152.82, 148.35, 148.09, 145.22, 139.97, 134.62, 132.70, 131.98, 130.4 (q, *J* = 5.8 Hz, C-F coupling), 130.41, 130.29, 119.90, 119.49, 118.12, 115.22, 112.50, 109.02, 102.46, 56.54, 56.43, 19.37, 17.58, 17.32, 13.54.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{30}H_{31}F3N_2O_3SiK$ *m/z 591.1693* and found *m/z 591.1698*

IR (thin film, cm^{-1}): 2930, 2869, 2224, 1735, 1606, 1550, 1501, 1467, 1302, 1263, 1050, 838, 731.

4'-(((4-cyano-2-(trifluoromethoxy)benzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4t): Yield: 69%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



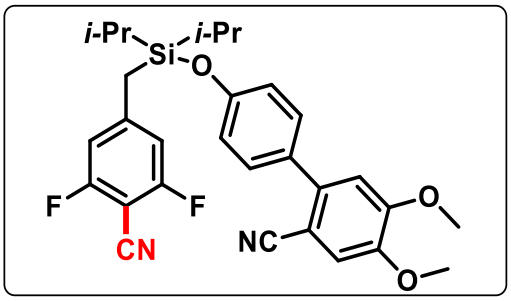
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.46 (s, 1H), 7.42 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 1H), 6.88 (s, 1H), 6.79 (d, *J* = 8.6 Hz, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 2.49 (s, 3H), 1.27 (dd, *J* = 13.5, 5.9 Hz, 2H), 1.06 (dd, *J* = 7.4, 3.0 Hz, 13H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.61, 152.83, 148.35, 146.89, 140.02, 138.91, 132.39, 131.91, 130.23, 130.20, 123.64, 120.4 (q, *J* = 261.2, Hz, C-CF_3), 119.85, 119.49, 118.06, 115.25, 112.52, 109.74, 102.46, 56.54, 56.42, 17.47, 17.35, 16.09, 13.55.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{30}H_{31}F3N_2O_4SiK$ *m/z 607.1337* and found *m/z 607.1345*

IR (thin film, cm^{-1}): 2948, 2869, 2224, 1732, 1604, 1500, 1213, 1170, 1142, 1031, 840, 713.

4'-(((4-cyano-3,5-difluorobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4u): Yield: 61%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



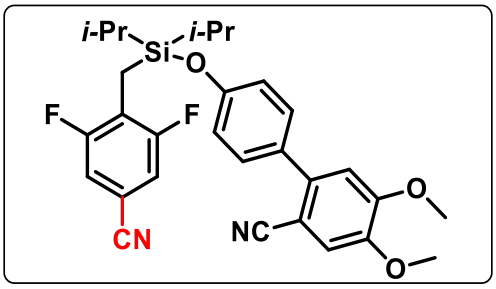
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.13 (s, 1H), 6.89 (s, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 2.69 (s, 2H), 1.32 (dt, *J* = 14.8, 7.5 Hz, 2H), 1.08 (dd, *J* = 11.4, 7.5 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 155.44, 152.83, 148.33, 146.44, 140.00, 136.02, 133.15, 131.92, 131.03, 130.16, 128.93, 128.57, 127.14, 126.9 (d, *J* = 36.9 Hz, C-F coupling), 119.75, 119.52, 116.17, 115.18, 112.51, 111.19, 102.40, 56.53, 56.47, 21.46, 17.63, 17.46, 13.85, 13.27.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{29}H_{30}F2N_2O_3SiK$ *m/z 559.1625* and found *m/z 559.1634*

IR (thin film, cm-^{1}): 2948, 2869, 2220, 1735, 1603, 1464, 1389, 1263, 1242, 1138, 839·

4'-(((4-cyano-2,6-difluorobenzyl)diisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile (4v): Yield: 61%. Yellow semisolid, Eluent: petrolium ether/ ethyl acetate (95:5 v/v).



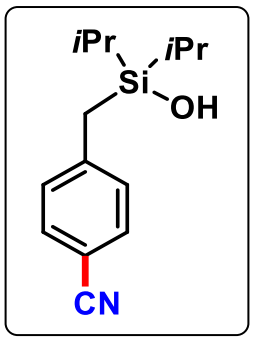
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 5.7 Hz, 1H), 6.87 (s, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 3.95 (s, 1H), 3.93 (s, 1H), 2.41 (t, *J* = 1.8 Hz, 1H), 1.31 (dd, *J* = 15.1, 7.6 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 160.6 (dd, *J* = 248.6, 9.7 Hz, C-F coupling), 159.71, 159.64, 155.53, 152.78, 148.27, 140.06, 131.74, 130.09, 124.4 (d, *J* = 50.8 Hz, C-F coupling), 123.20, 119.73, 119.53, 115.31, 115.24 (d, *J* = 21.6 Hz, C-F coupling), 115.1 (d, *J* = 17.4 Hz, C-F coupling), 112.50, 109.16, 102.38, 56.51, 56.41, 17.37, 17.30, 13.82, 13.53, 8.30.

HRMS (ESI-QTOF): $[M + K]^+$ calculated for $C_{29}H_{30}F2N_2O_3SiK$ *m/z 559.1625* and found *m/z 559.1633*

IR (thin film, cm^{-1}): 2950, 2867, 2225, 1738, 1602, 1467, 1390, 1264, 1250, 1140, 841.

4-((hydroxydiisopropylsilyl)methyl)benzonitrile (6): Yellowish solid, yield: 73%;

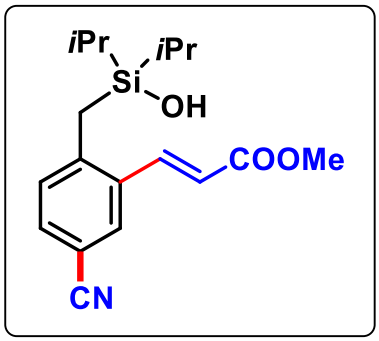


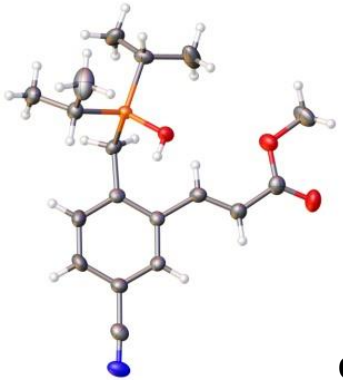
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 2.28 (s, 2H), 0.99 (d, *J* = 3.2 Hz, 14H).

^{13}C NMR (126 MHz, $CDCl_3$) δ; 146.30, 132.22, 129.27, 119.46, 107.91, 22.96, 17.32, 17.28, 12.84.

HRMS (*m/z*): $[M+Na^+]$ calcd for $C_{14}H_{22}NOSi$, 248.1471; found, 248.1437.

methyl (E)-3-(5-cyano-2-((hydroxydiisopropylsilyl)methyl)phenyl)acrylate (7): 54% Yellowish oil. Eluent: ether/ethyl acetate (88/12 v/v).





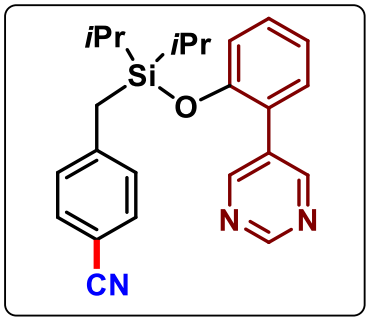
CCDC: 1942587

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 15.9 Hz, 1H), 7.78 (d, *J* = 1.6 Hz, 1H), 7.49 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.28 (s, 2H), 6.36 (d, *J* = 15.9 Hz, 1H), 3.82 (s, 3H), 2.42 (s, 2H), 1.03 – 0.97 (m, 14H).

^{13}C NMR (126 MHz, CDCl3) δ: 167.17, 146.22, 145.31, 141.45, 135.57, 133.59, 132.55, 131.12, 130.56, 120.86, 114.21, 109.01, 52.12, 29.84, 21.05, 17.32, 17.23, 13.09.

HRMS (*m/z*): [M+H$^+$] calcd for $C_{18}H_{25}NNaO_3Si$, 334.1501; found, 344.1501.

4-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)benzonitrile (8): Yield: 67%. Eluent: petrolium ether/ ethyl acetate (88:12 v/v).

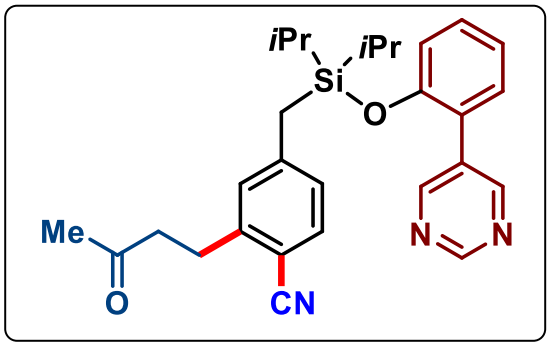


^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.79 (s, 2H), 7.42 – 7.39 (m, 2H), 7.28 (ddd, *J* = 8.0, 4.6, 1.9 Hz, 2H), 7.25 (s, 1H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.78 (dd, *J* = 8.1, 0.7 Hz, 1H), 2.38 (s, 2H), 1.12 (dt, *J* = 14.7, 7.5 Hz, 2H), 0.92 – 0.88 (m, 14H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 157.16, 156.93, 152.60, 144.78, 132.72, 132.20, 130.84, 130.46, 129.30, 125.76, 122.42, 119.23, 119.17, 108.45, 22.42, 17.32, 17.26, 13.02.

HRMS (*m/z*): [M+H$^+$] calcd for $C_{24}H_{28}N_3OSi$, 402.2002; found, 402.1994.

4-((diisopropyl(2-(pyrimidin-5-yl)phenoxy)silyl)methyl)-2-(3-oxobutyl)benzonitrile (9): Eluent: petroleum ether/ethyl acetate (88/12, v/v); Yellowish oil. yield: 58% (*meta*:others=5:1)



^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.16 (s, 1H), 8.79 (s, 2H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.27 (m, 2H), 7.10 (td, *J* = 7.5, 0.9 Hz, 1H), 6.92 (s, 1H), 6.84 – 6.82 (m, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.35 (s, 2H), 2.11 (s, 3H), 1.11 (dt, *J* = 14.8, 7.5 Hz, 2H), 0.90 (dd, *J* = 11.5, 7.5 Hz, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.69, 157.17, 156.94, 152.65, 145.15, 144.97, 132.97, 130.84, 130.47, 130.31, 127.13, 125.76, 122.43, 119.27, 118.31, 108.33, 43.92, 30.00, 28.39, 22.43, 17.36, 17.30, 13.03.

HRMS (*m/z*): [M+Na^+] calcd for $C_{28}H_{34}N_3O_2Si$, 472.2420; found, 472.2419.

4.6. Crystal Data:

DM-AJ-87B_Mo: CCDC 1899052

This crystal was developed to see the molecular orientation & to show π stacking of two biphenyl rings and direction of CN directing group to para C-H bond.

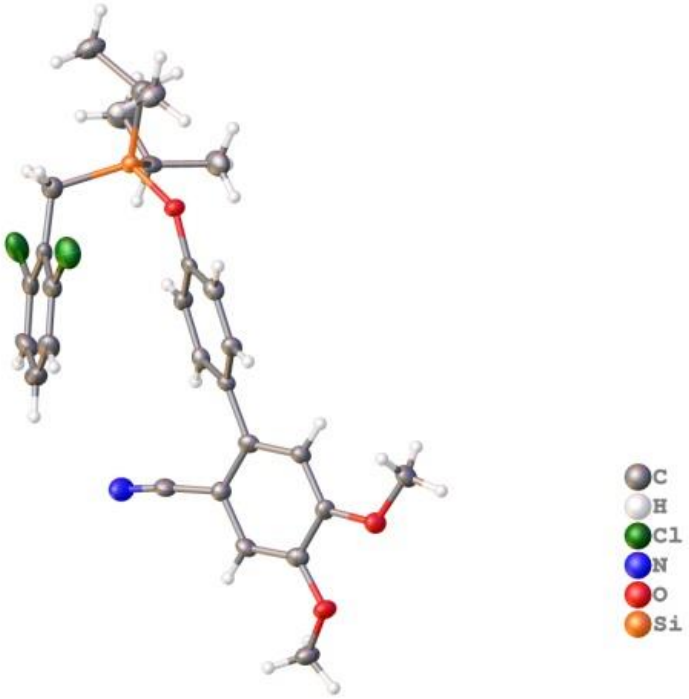
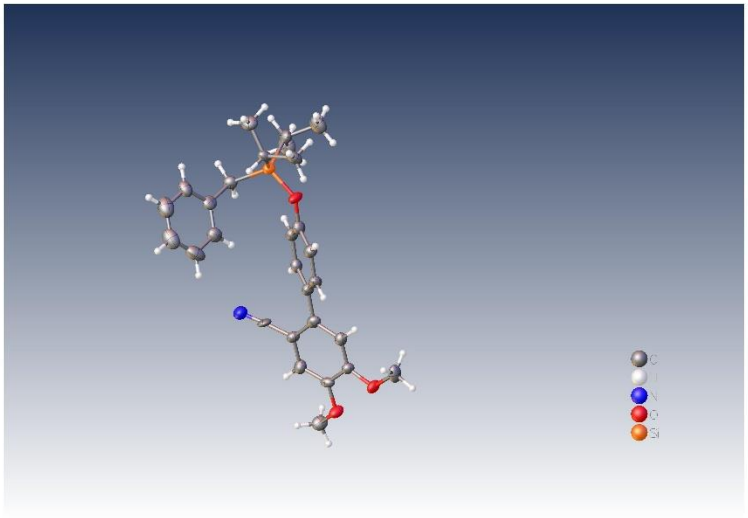


Table 1 Crystal data and structure refinement for DM-AJ-87B_Mo.	
Identification code	DM-AJ-87B_Mo
Empirical formula	$C_{9.33}H_{10.33}Cl_{0.67}N_{0.33}OSi_{0.33}$
Formula weight	176.18
Temperature/K	150
Crystal system	monoclinic
Space group	C2/c
a/Å	44.3092(19)
b/Å	8.4076(3)
c/Å	14.5077(6)
α/°	90
β/°	96.108(4)
γ/°	90
Volume/$Å^3$	5373.9(4)
Z	24
$\rho_{calc}g/cm^3$	1.307

μ/mm^{-1}	0.316
F(000)	2224.0
Crystal size/mm^3	0.158 × 0.131 × 0.032
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.548 to 49.984
Index ranges	-52 ≤ h ≤ 52, -8 ≤ k ≤ 9, -17 ≤ l ≤ 10
Reflections collected	9046
Independent reflections	4711 [R_{int} = 0.0695, R_{sigma} = 0.1074]
Data/restraints/parameters	4711/0/322
Goodness-of-fit on F^2	1.085
Final R indexes [I>=2σ (I)]	R_1 = 0.0650, wR_2 = 0.1355
Final R indexes [all data]	R_1 = 0.0998, wR_2 = 0.1594
Largest diff. peak/hole / e Å^{-3}	0.45/-0.46

Crystal structure for 3a:



$C_{56}H_{66}N_2O_6Si_2$

(*M* =919.28 g/mol):

triclinic,

space group P-1 (no. 2),

a = 10.8456(10) Å,

b = 12.2141(11) Å,

c = 19.7814(19) Å,

α = 100.983(8)°,

β = 93.599(8)°,

γ = 94.169(7)°,

V = 2557.8(4) $Å^3$,

Z = 2,

T = 150 K,

μ(MoKα) = 0.120 mm^{-1},

Dcalc = 1.194 g/cm^3,

25718 reflections measured (3.638° ≤ 2Θ ≤ 50°),

8998 unique (R_{int} = 0.1565, R_{sigma} = 0.2320)

The final R_1 was 0.0983 (I > 2σ(I)) and

wR_2 was 0.2981 (all data).

Crystal data of compound 7 (Scheme 18):

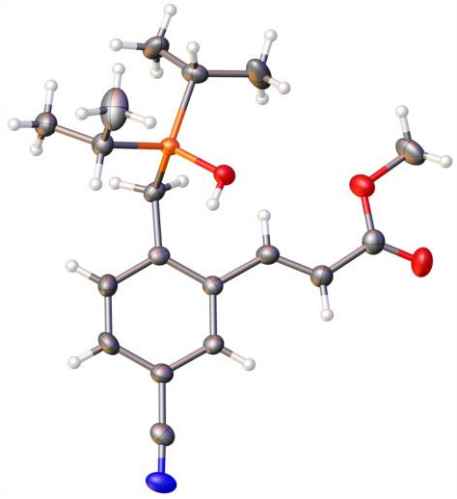
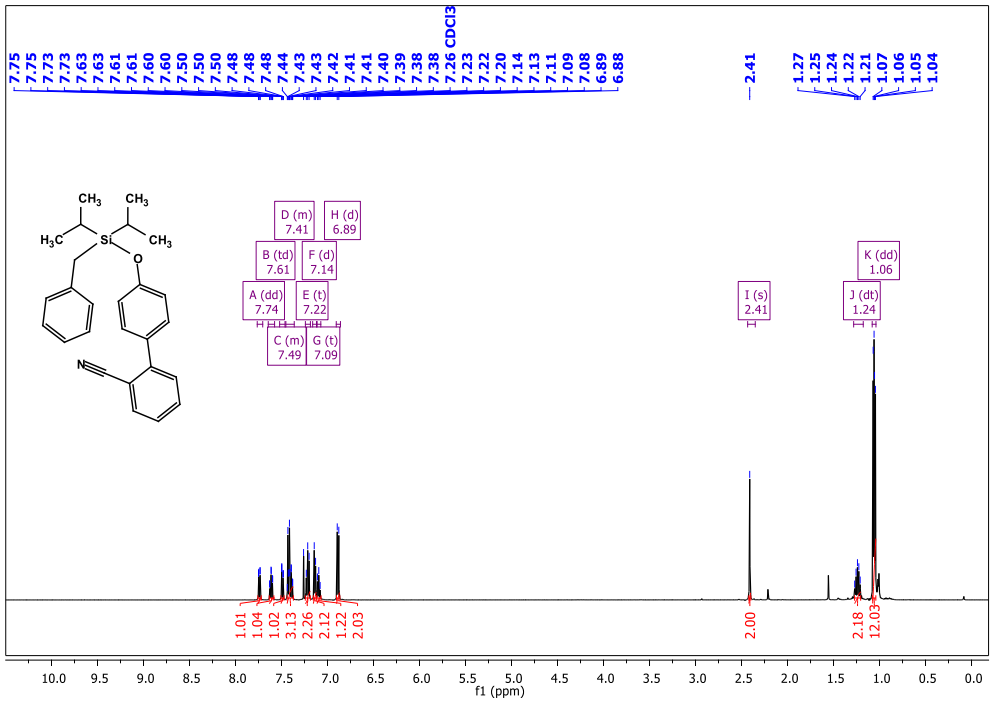


Table 1 Crystal data and structure refinement for	
Identification code	
Empirical formula	$C_{11}H_{10}NOClS_{0.25}Si_{0.25}$
Formula weight	165.74
Temperature/K	150 K
Crystal system	triclinic
Space group	P-1
a/Å	6.4396(3)
b/Å	8.3556(4)
c/Å	17.2449(7)
α/°	91.400(4)
β/°	98.203(4)
γ/°	93.406(4)
Volume/Å^3	916.26(8)

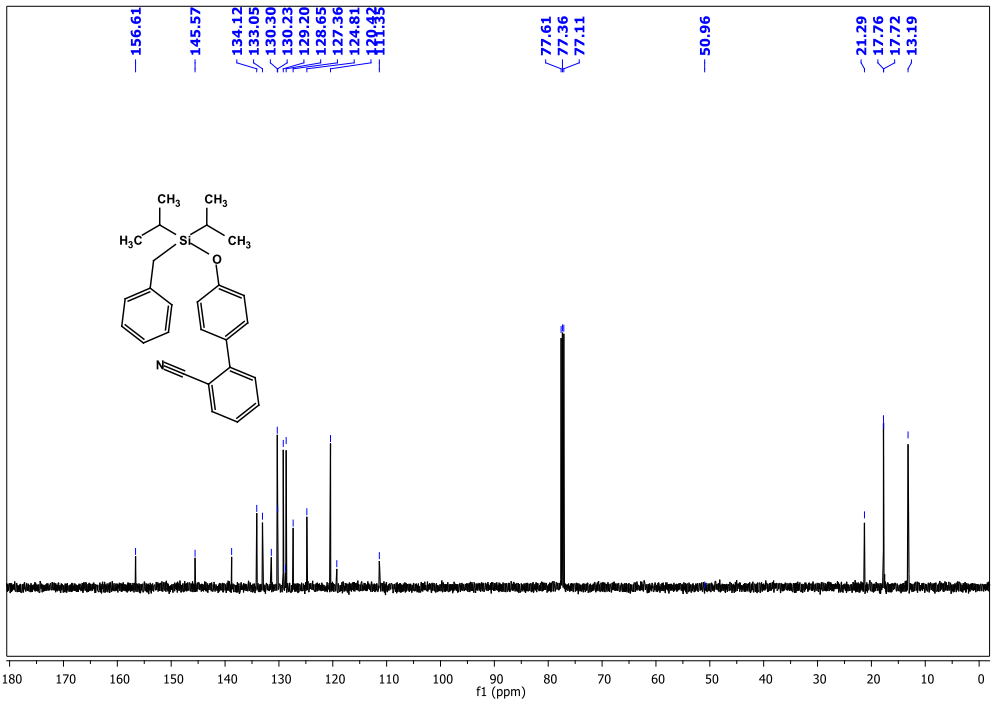
Z	4
ρ_{calc}mg/mm^3	1.2014
m/mm^{-1}	0.142
F(000)	356.3
Crystal size/mm^3	0.226 × 0.098 × 0.082
2Θ range for data collection	4.78 to 50°
Index ranges	-8 ≤ h ≤ 8, -11 ≤ k ≤ 12, -19 ≤ l ≤ 24
Reflections collected	8253
Independent reflections	3152[R(int) = 0.0434]
Data/restraints/parameters	3152/0/213
Goodness-of-fit on F^2	1.028
Final R indexes [I>=2σ (I)]	R_1 = 0.0508, wR_2 = 0.1867
Final R indexes [all data]	R_1 = 0.0678, wR_2 = 0.1867
Largest diff. peak/hole / e Å^{-3}	0.50/-0.58

4.7. Spectra of Representative Compounds:

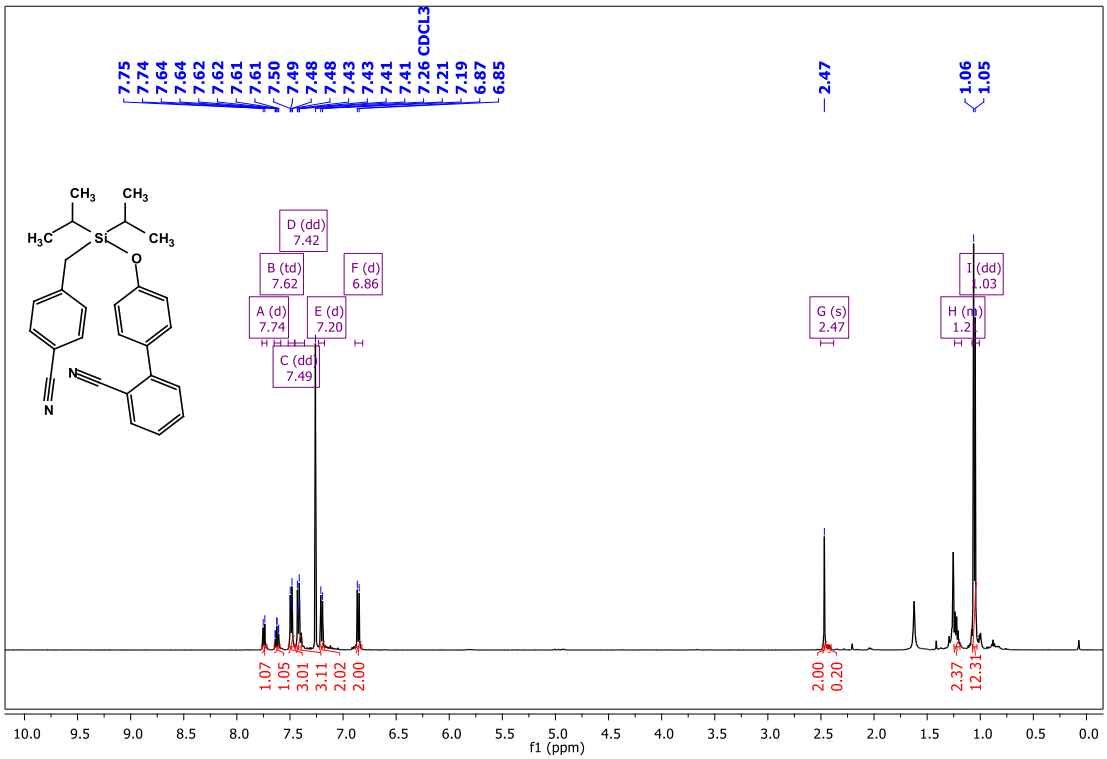
^{1}H Spectra of 1a:



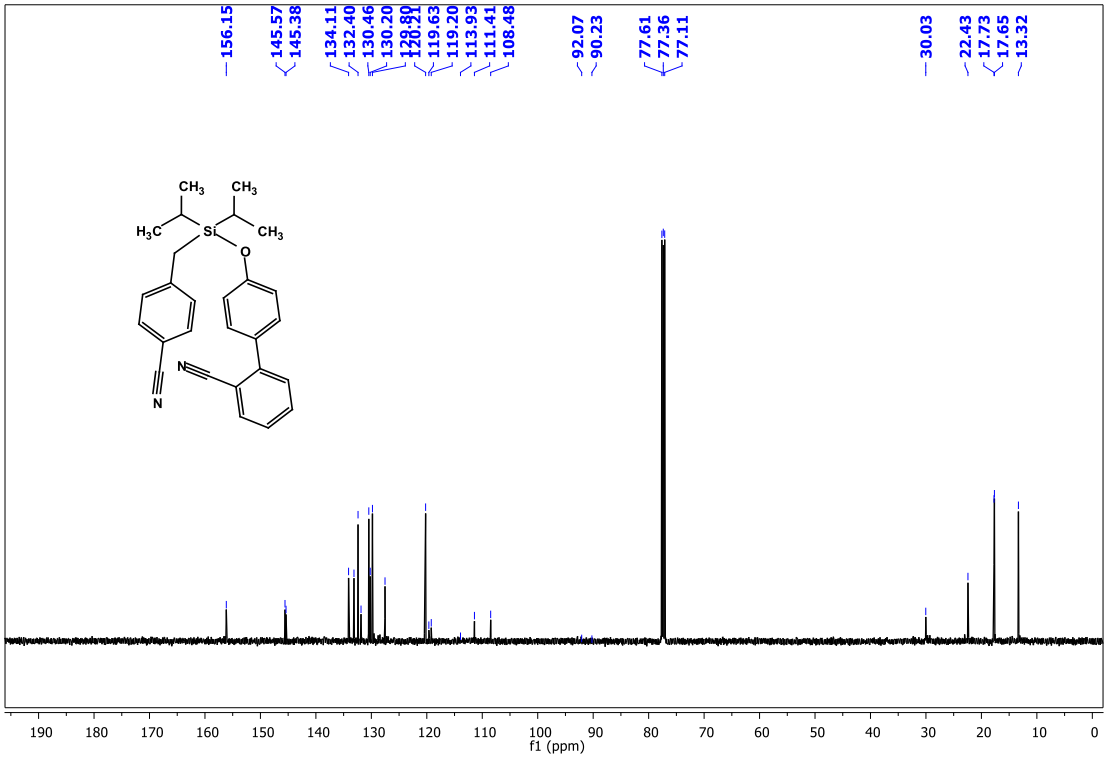
^{13}C NMR of 1a:



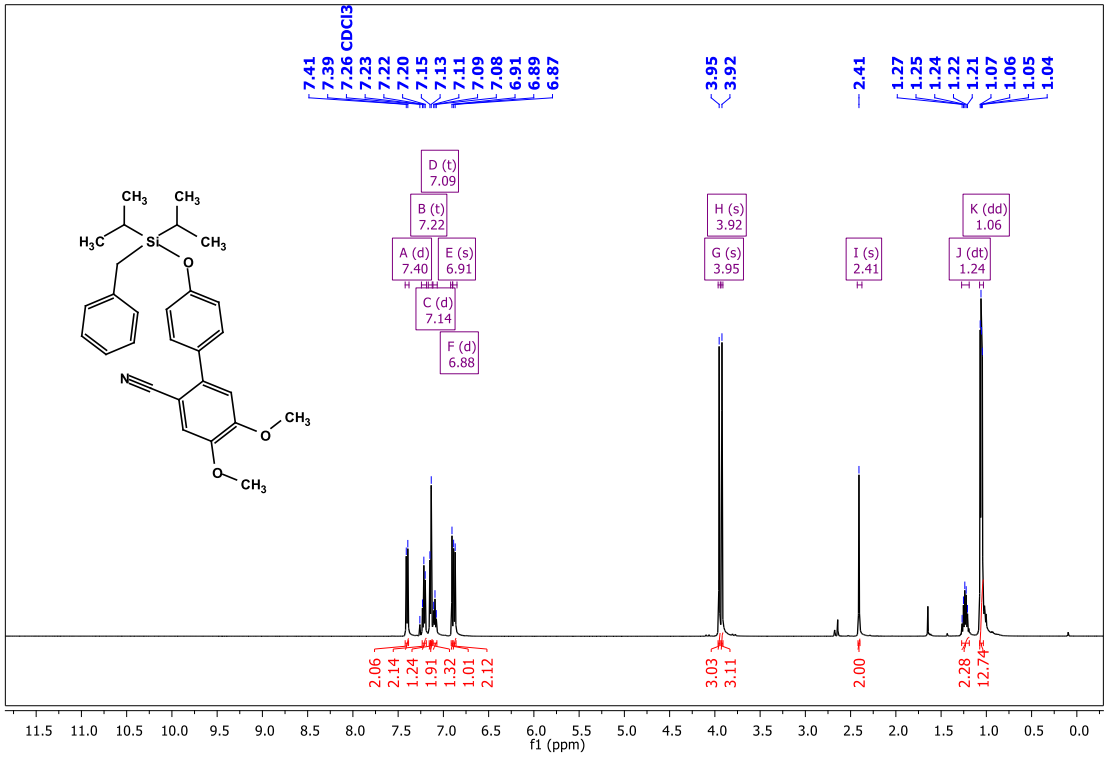
^{1}H NMR of 2a:



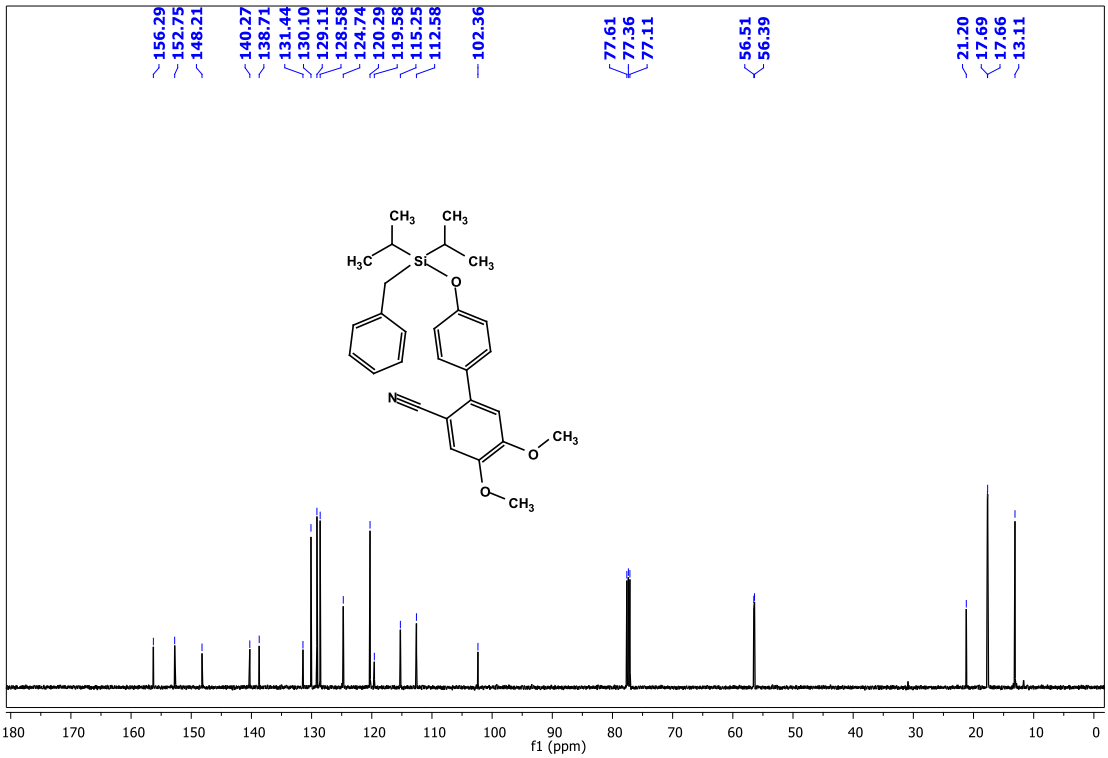
^{13}C NMR of 2a:



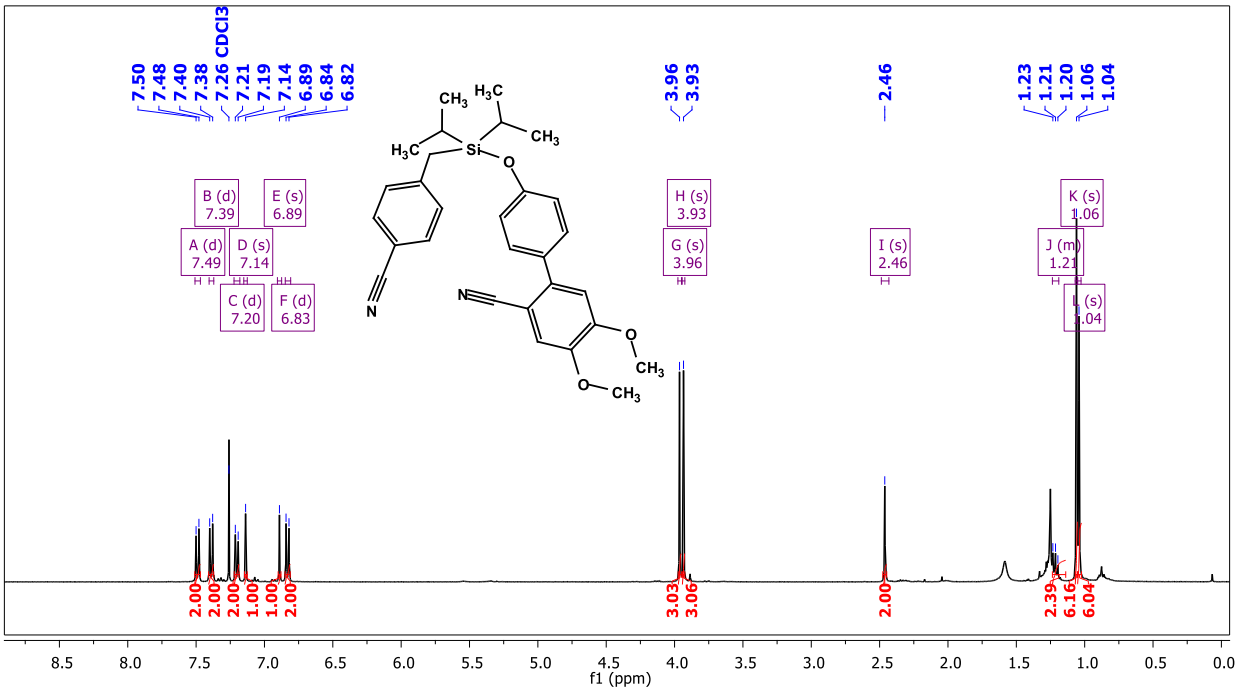
^{1}H NMR of 3a:



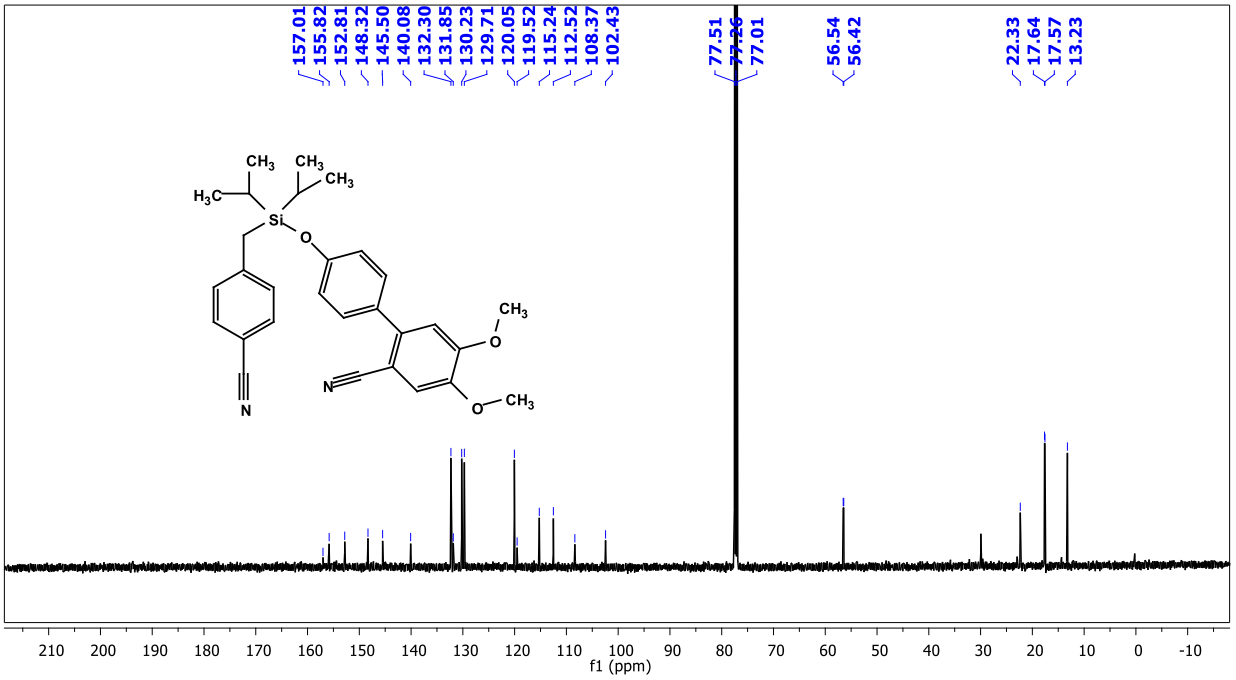
^{13}C NMR of 3a:



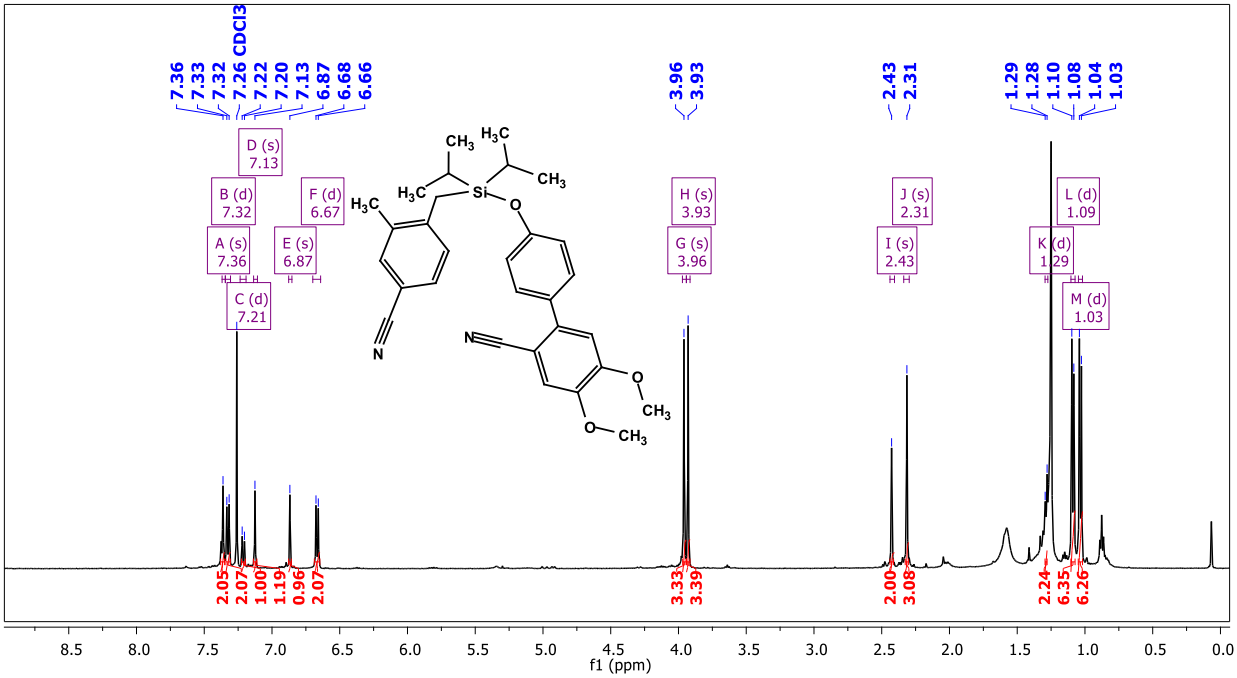
^{1}H NMR of 4a:



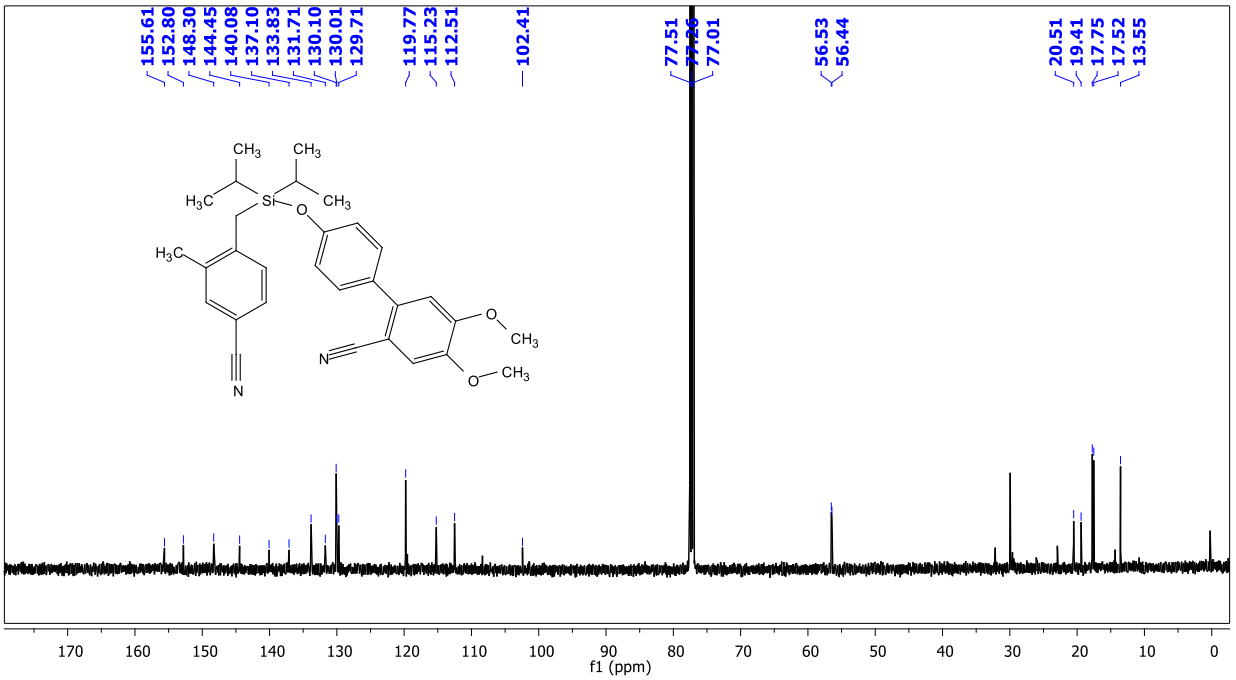
^{13}C NMR of 4a:



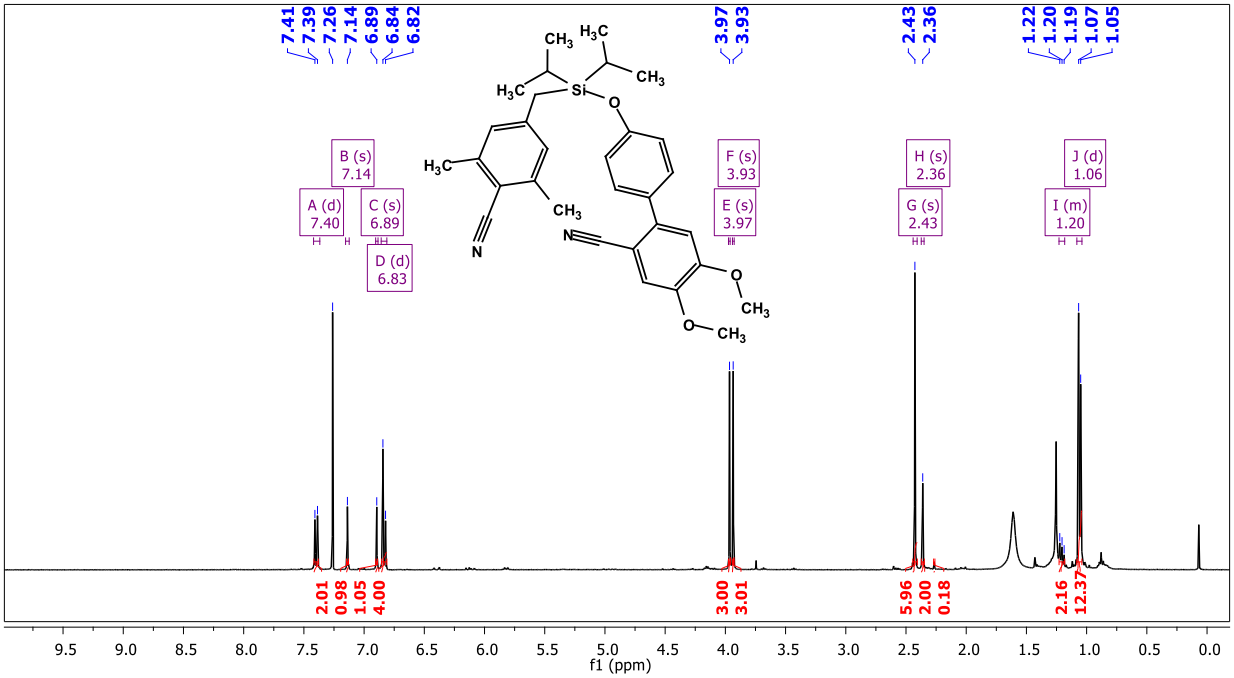
^{1}H NMR of 4b:



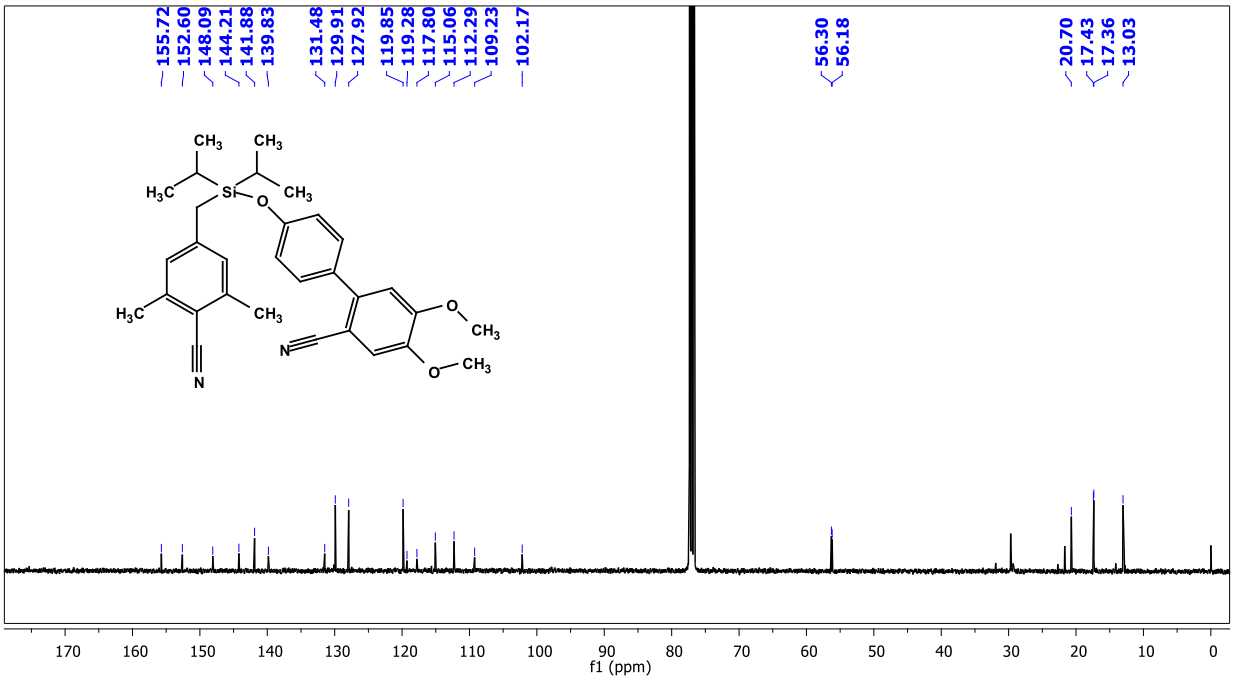
^{13}C NMR of 4b:



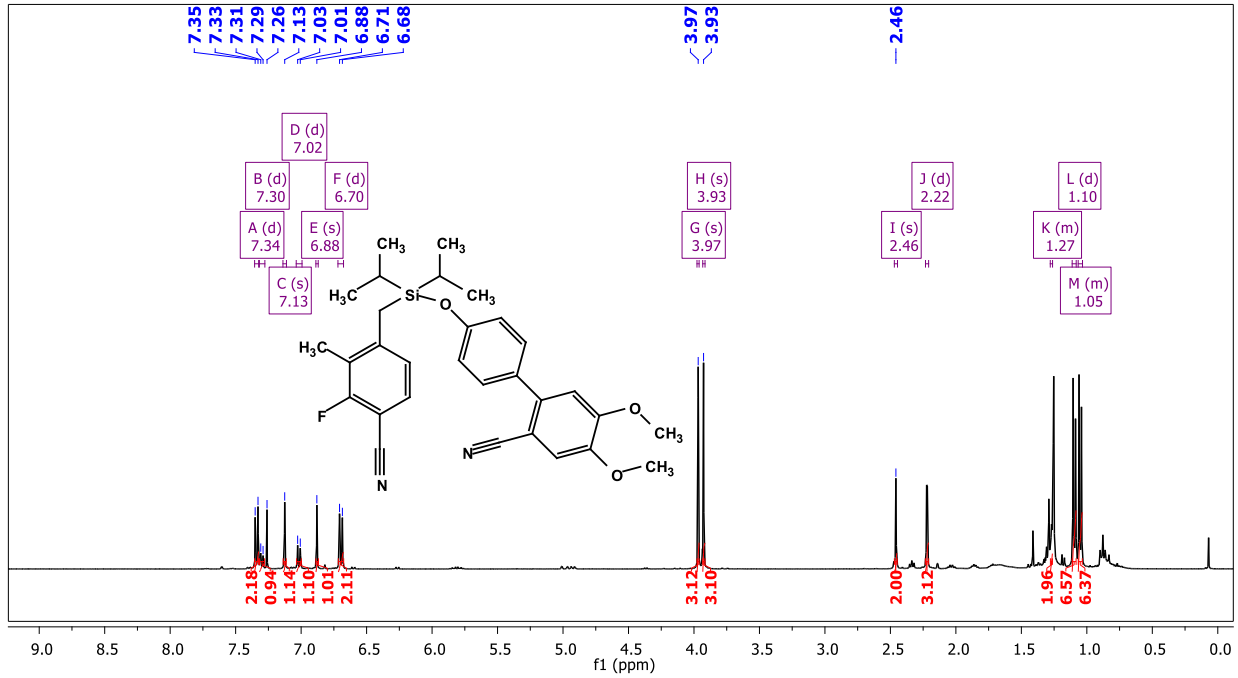
^{1}H NMR of 4c:



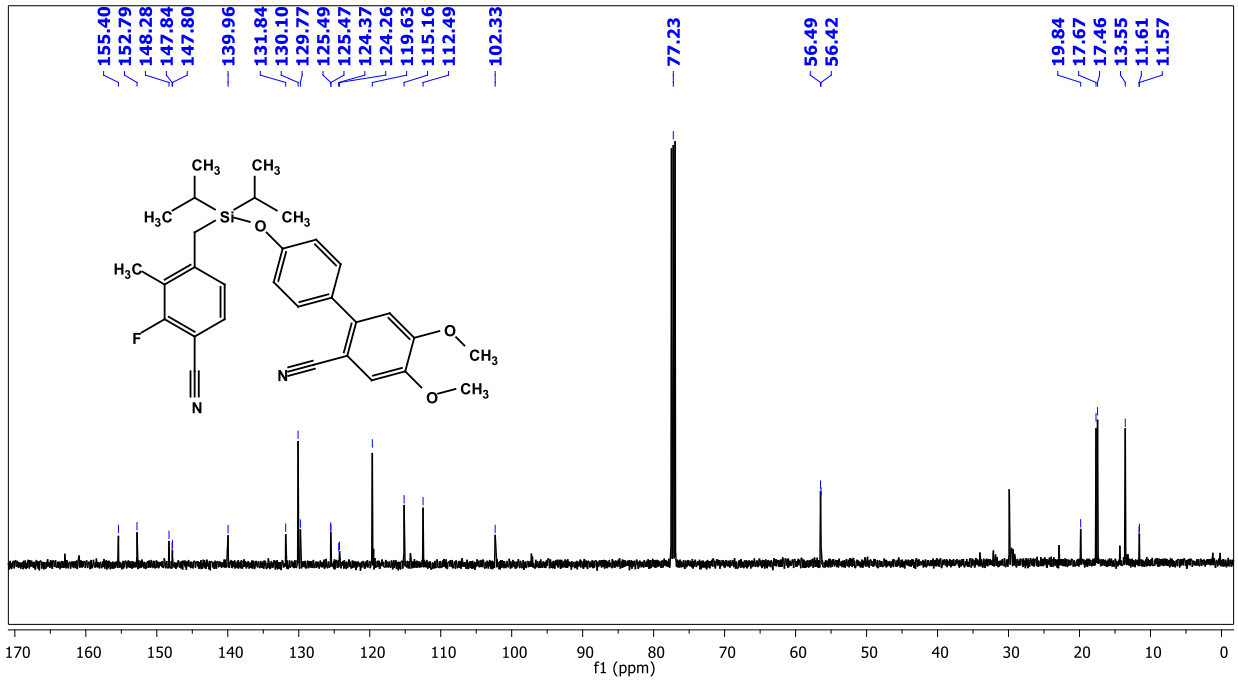
^{13}C NMR of 4c:



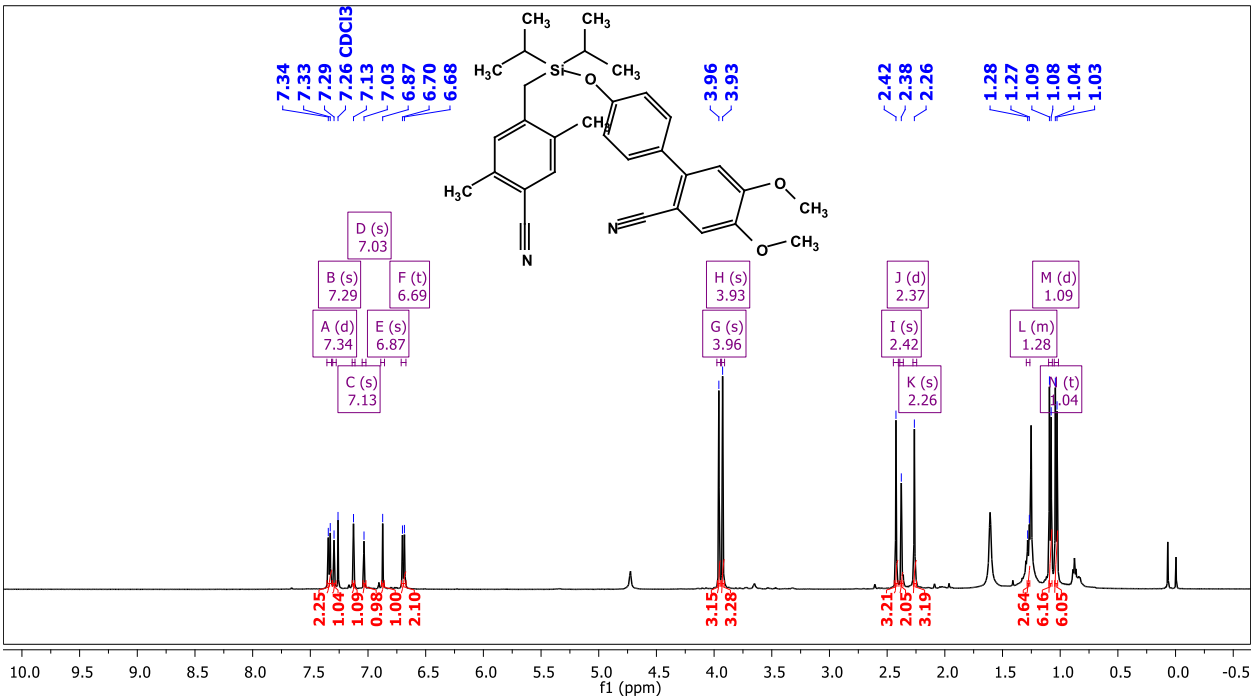
^{1}H spectra of 4e:



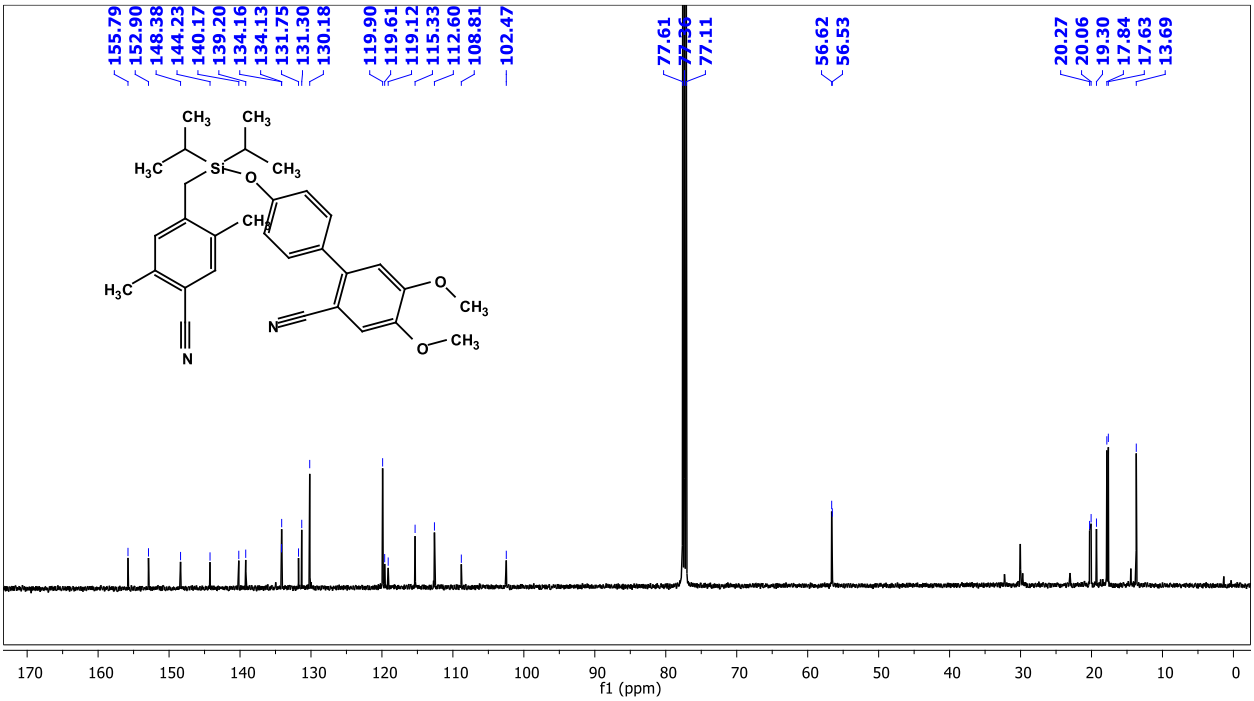
^{13}C NMR of 4e:



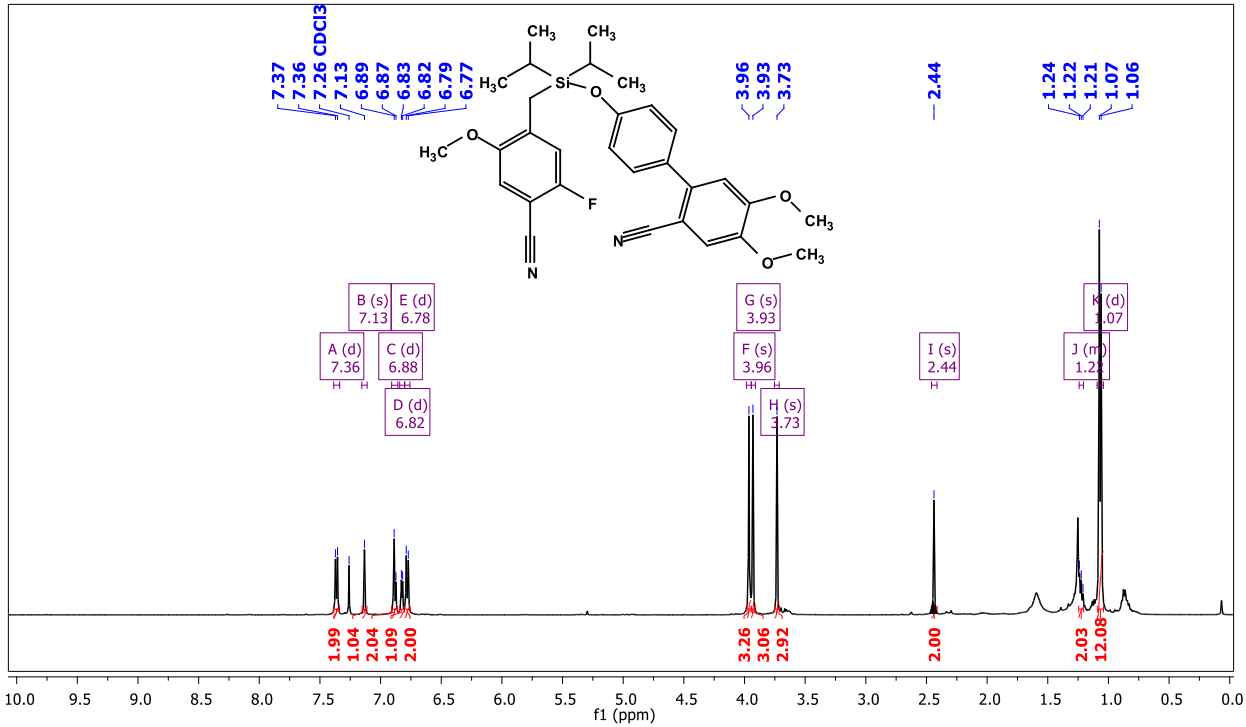
^{1}H NMR of 4f:



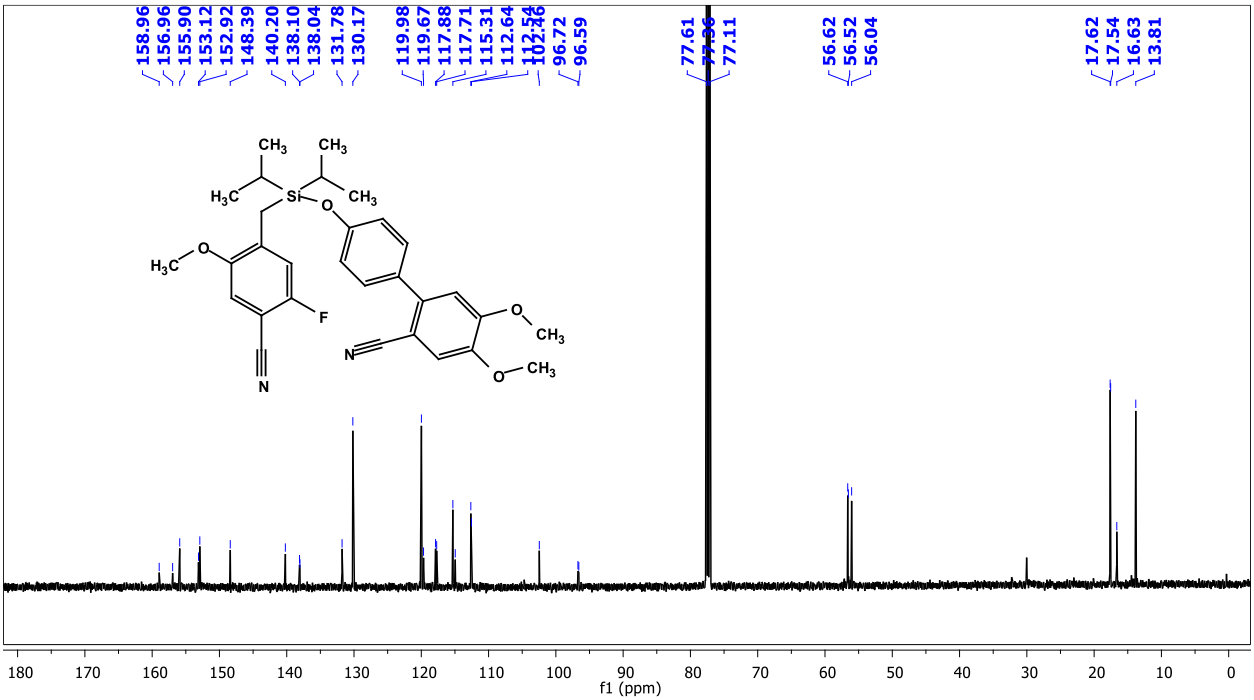
^{13}C NMR of 4f:



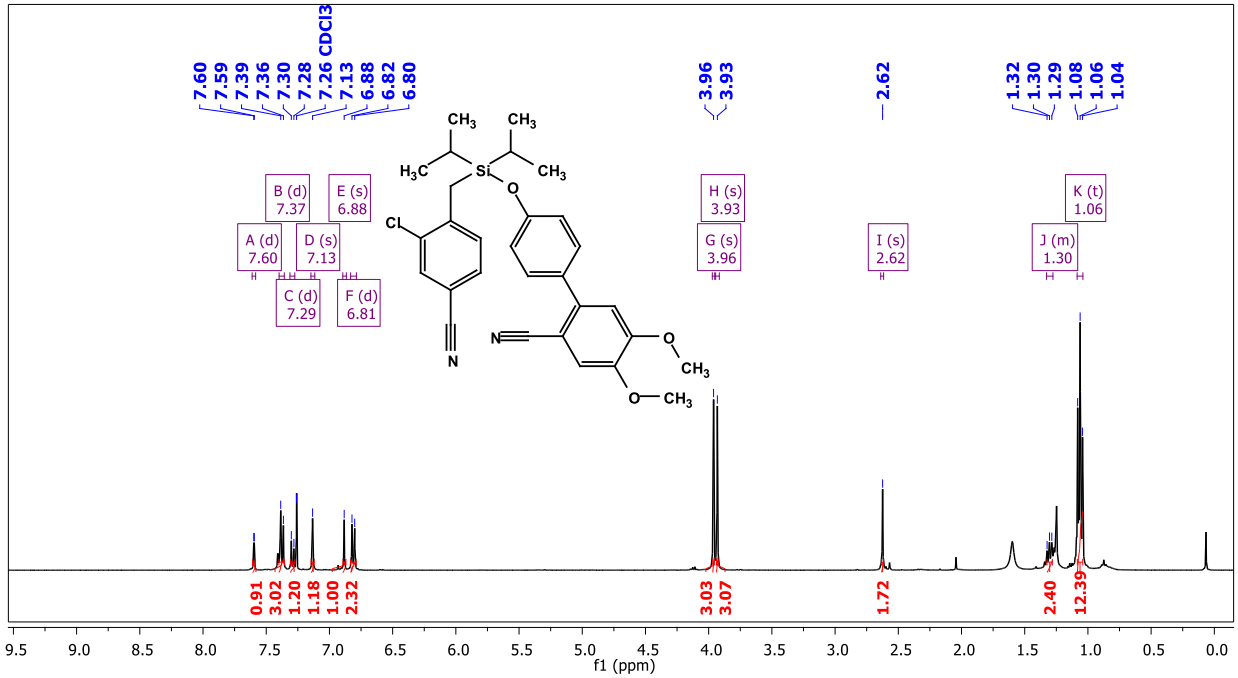
^{1}H spectra of 4g:



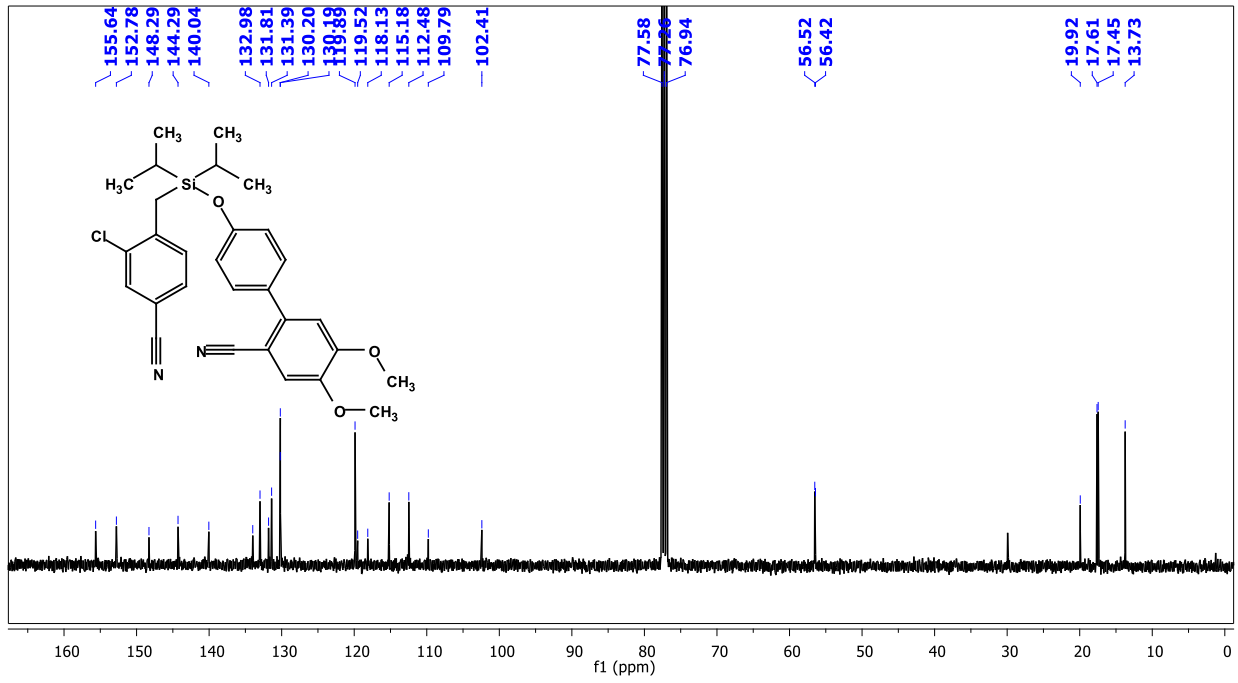
^{13}C NMR of 4g:



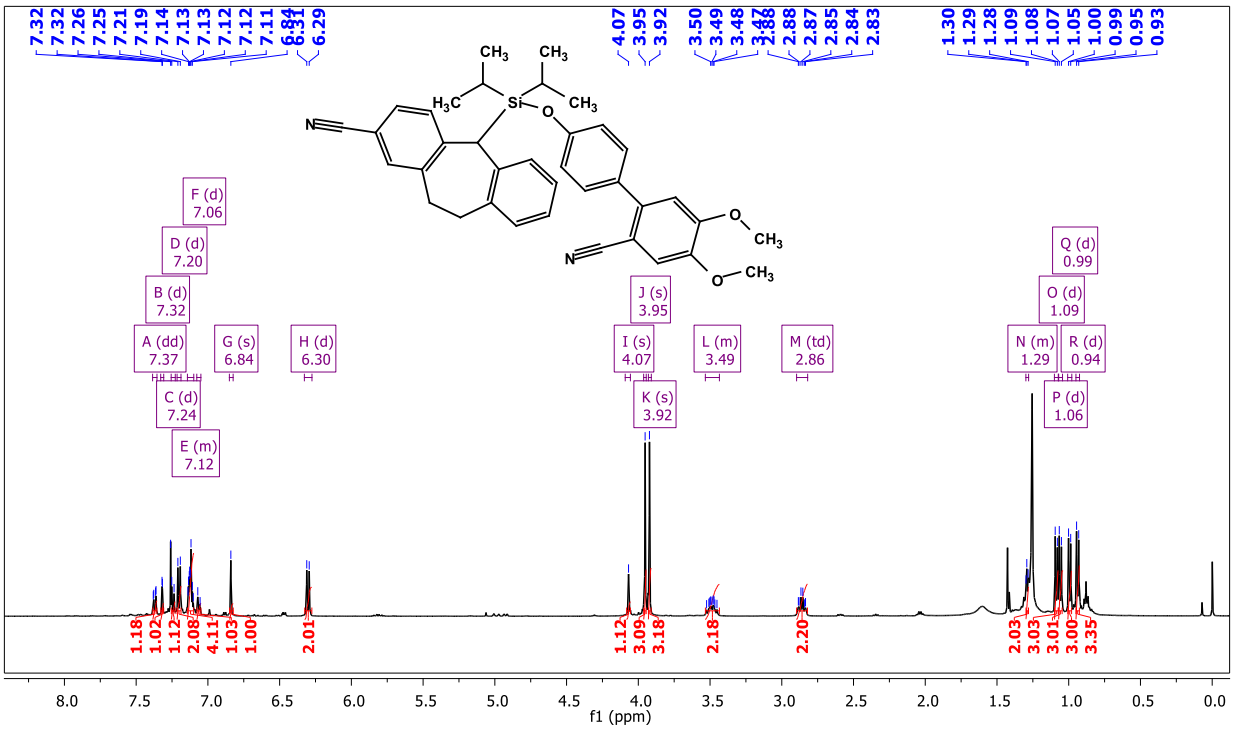
^{1}H spectra of 4i:



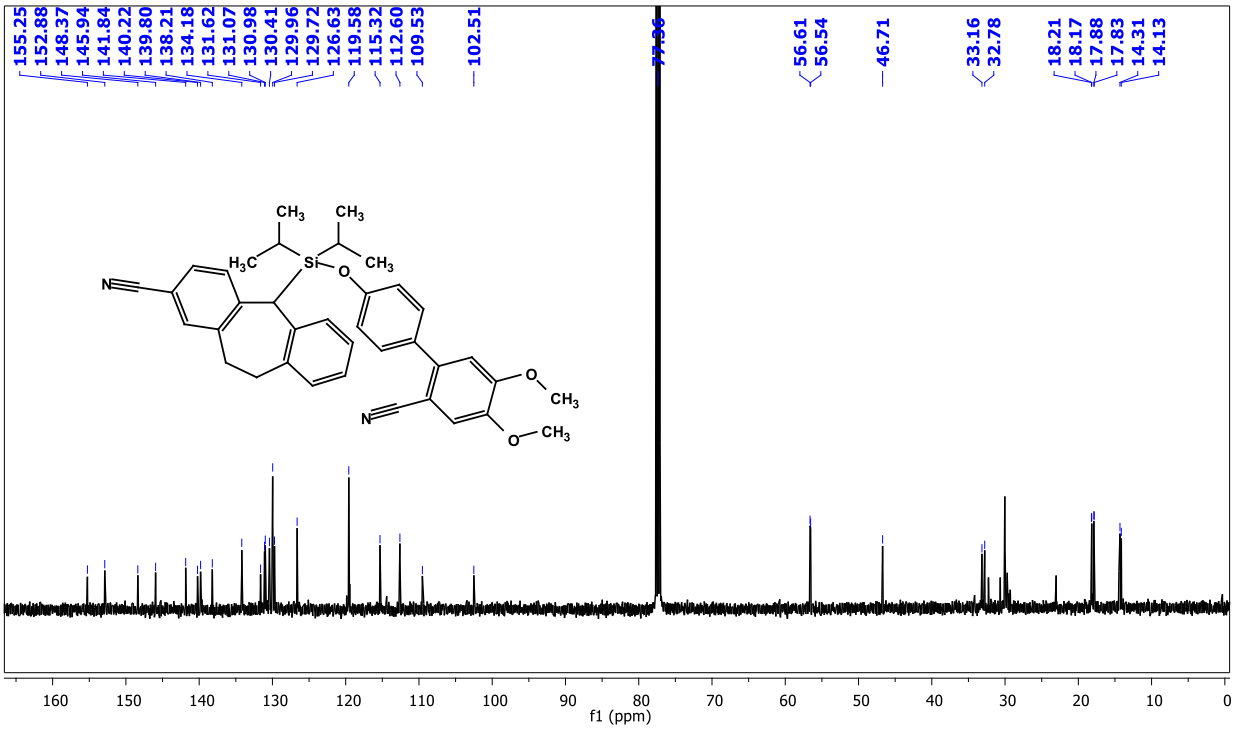
^{13}C NMR of 4i:



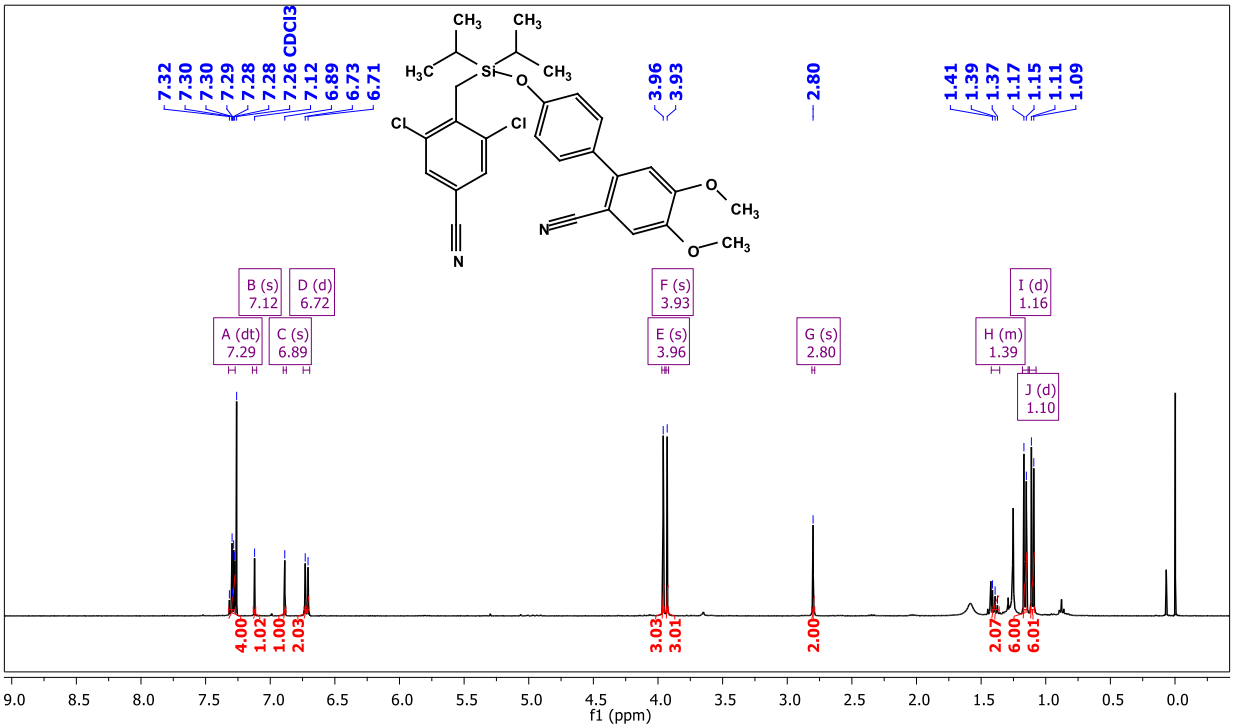
^{1}H spectra of 4l:



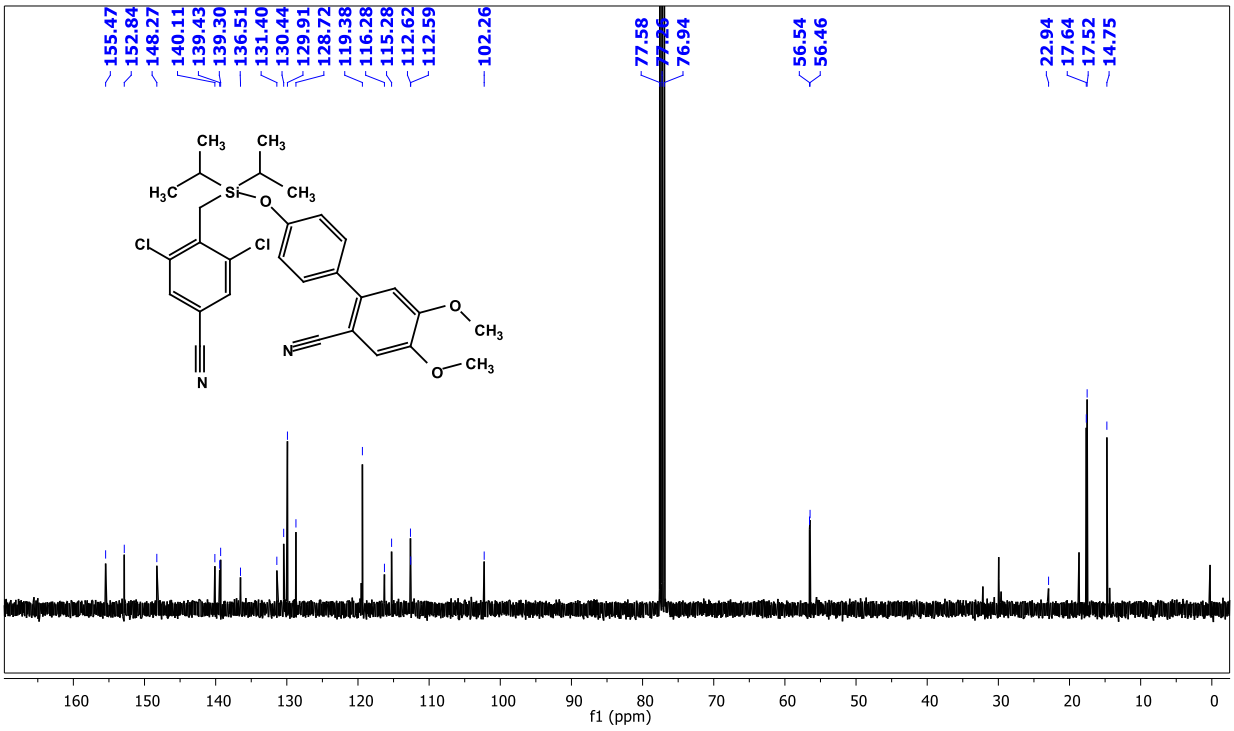
^{13}C NMR of 4l:



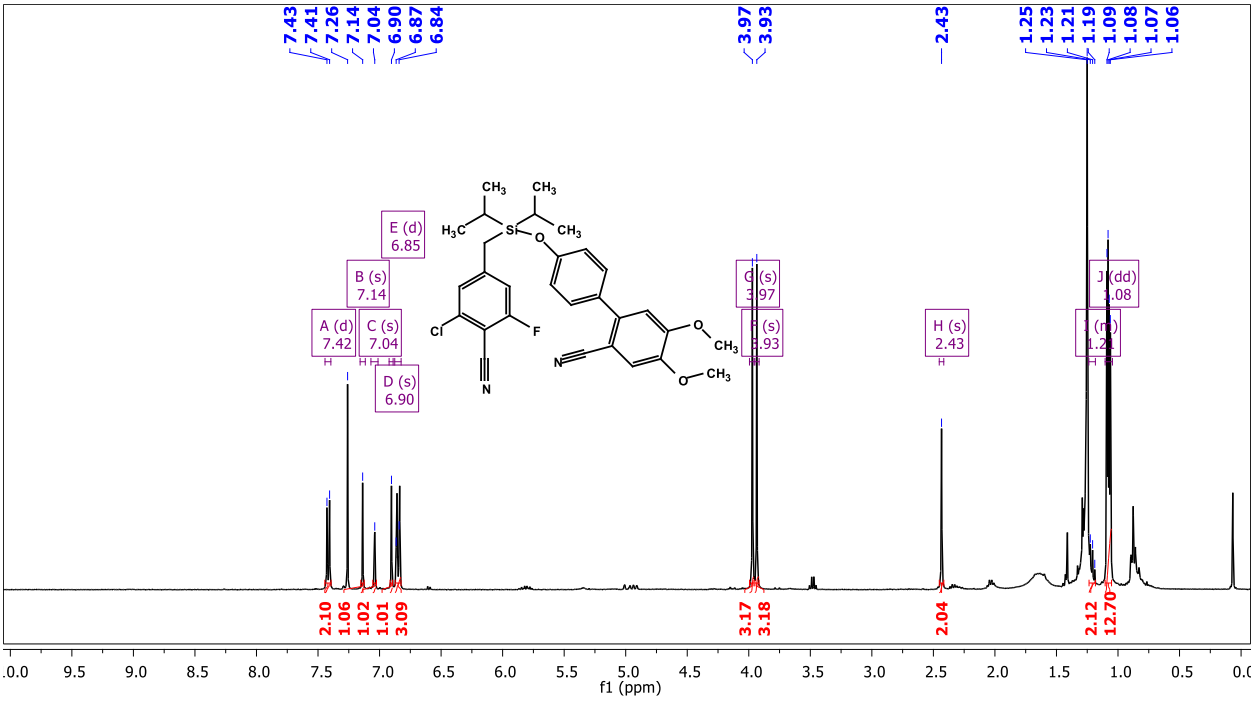
^{1}H spectra of 4m:


7.32
7.30
7.30
7.29
7.28
7.28
7.26 CDCl3
7.12
6.89
6.73
6.71
3.96
3.93
2.80
1.41
1.39
1.37
1.17
1.15
1.11
1.09
B (s) 7.12
D (d) 6.72
A (dt) 7.29
C (s) 6.89
F (s) 3.93
E (s) 3.96
G (s) 2.80
I (d) 1.16
H (m) 1.39
J (d) 1.10
4.00
1.02
1.00
2.03
3.03
3.01
2.00
2.07
6.00
6.01
f1 (ppm)

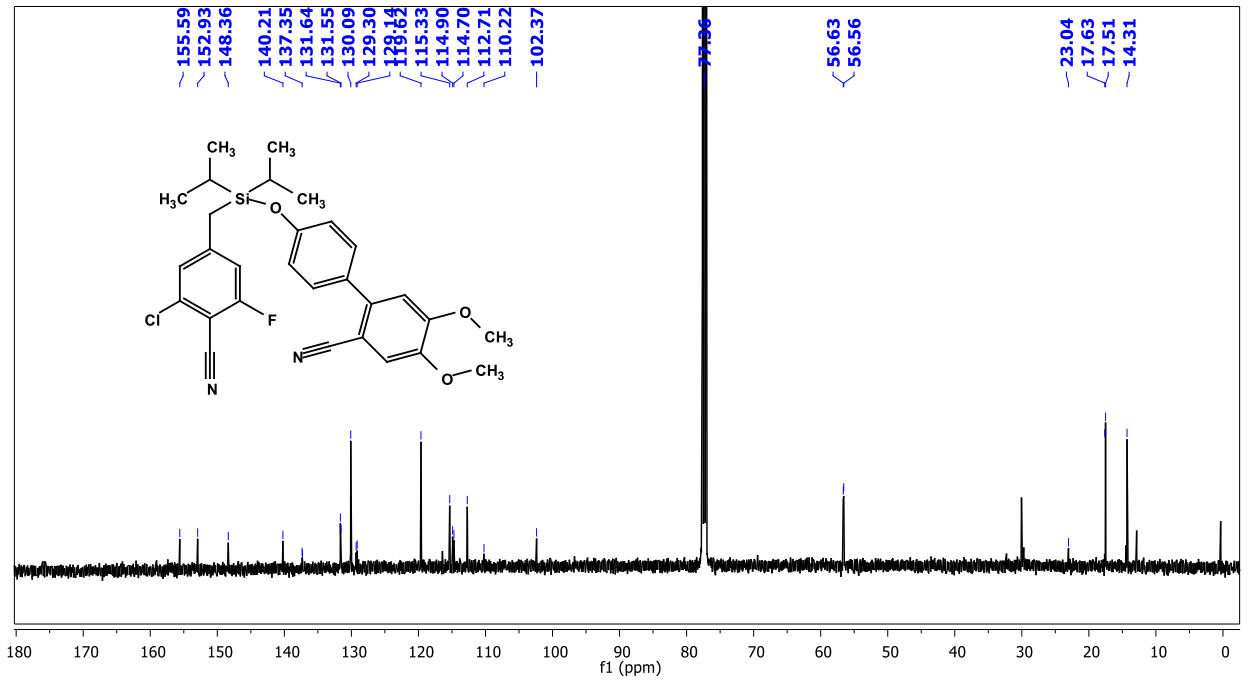
^{13}C NMR of 4m


155.47
152.84
148.27
140.11
139.43
139.30
136.51
131.40
130.44
129.91
128.72
119.38
116.28
115.28
112.62
112.59
102.26
77.58
77.26
76.94
56.54
56.46
22.94
17.64
17.52
14.75
f1 (ppm)

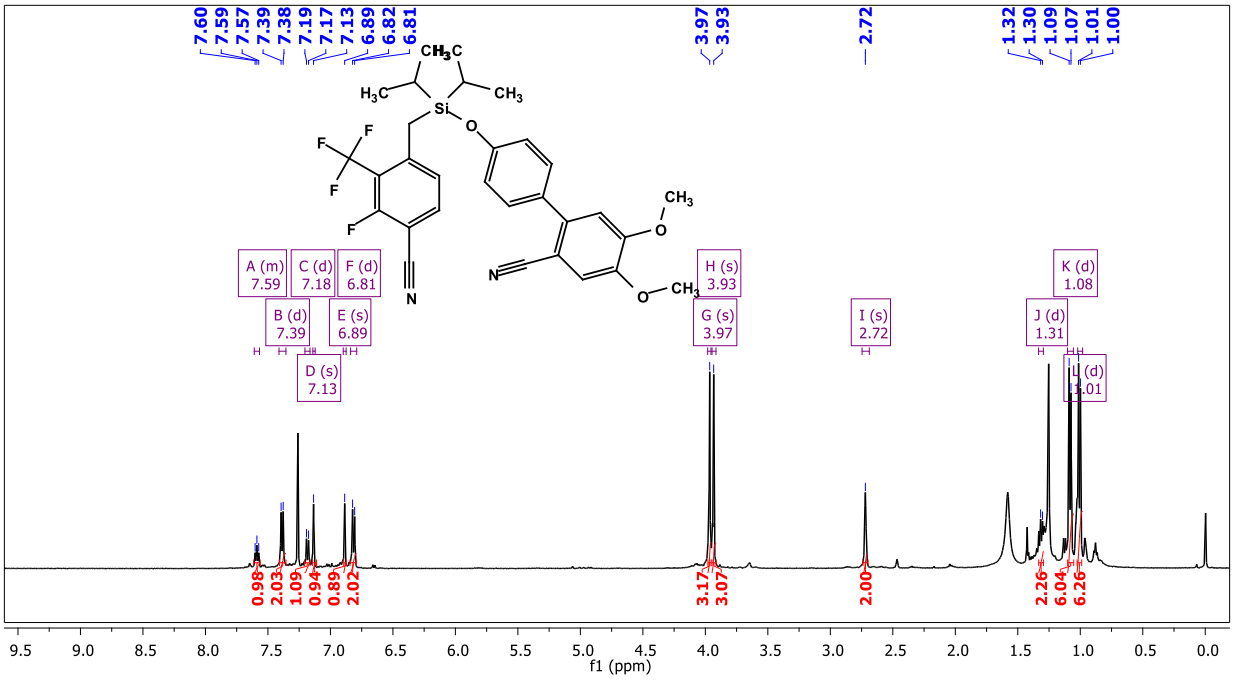
^{1}H NMR of 4o:



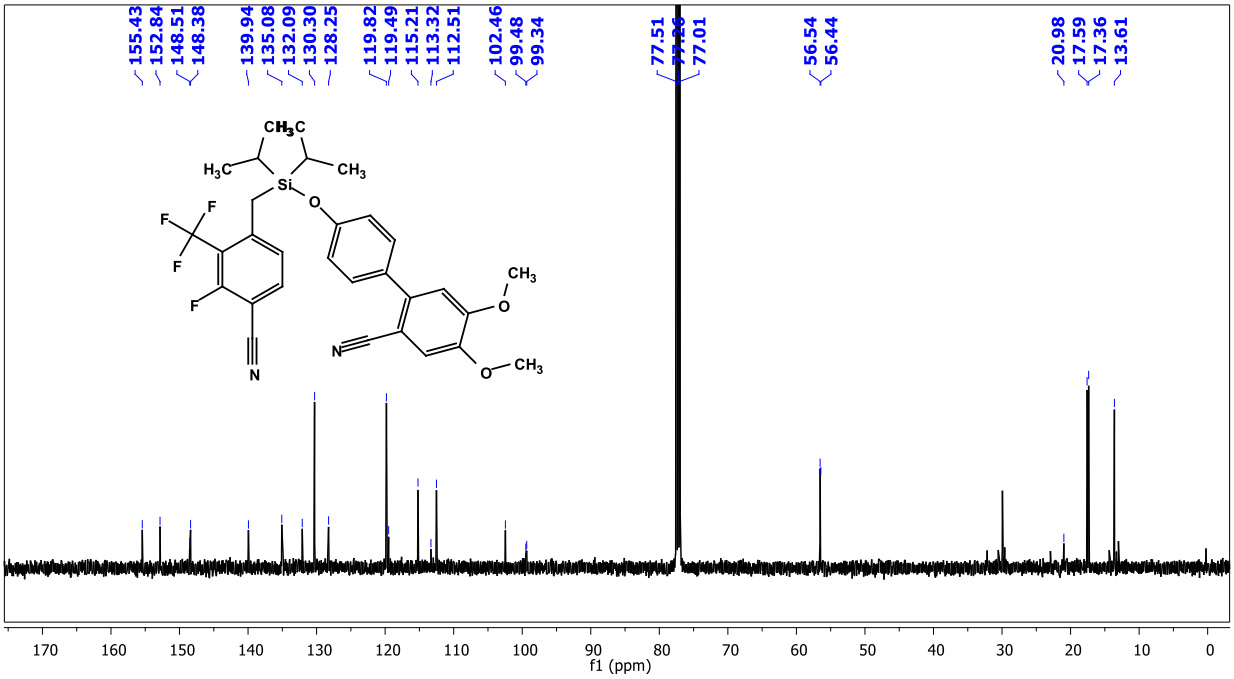
^{13}C NMR 4o



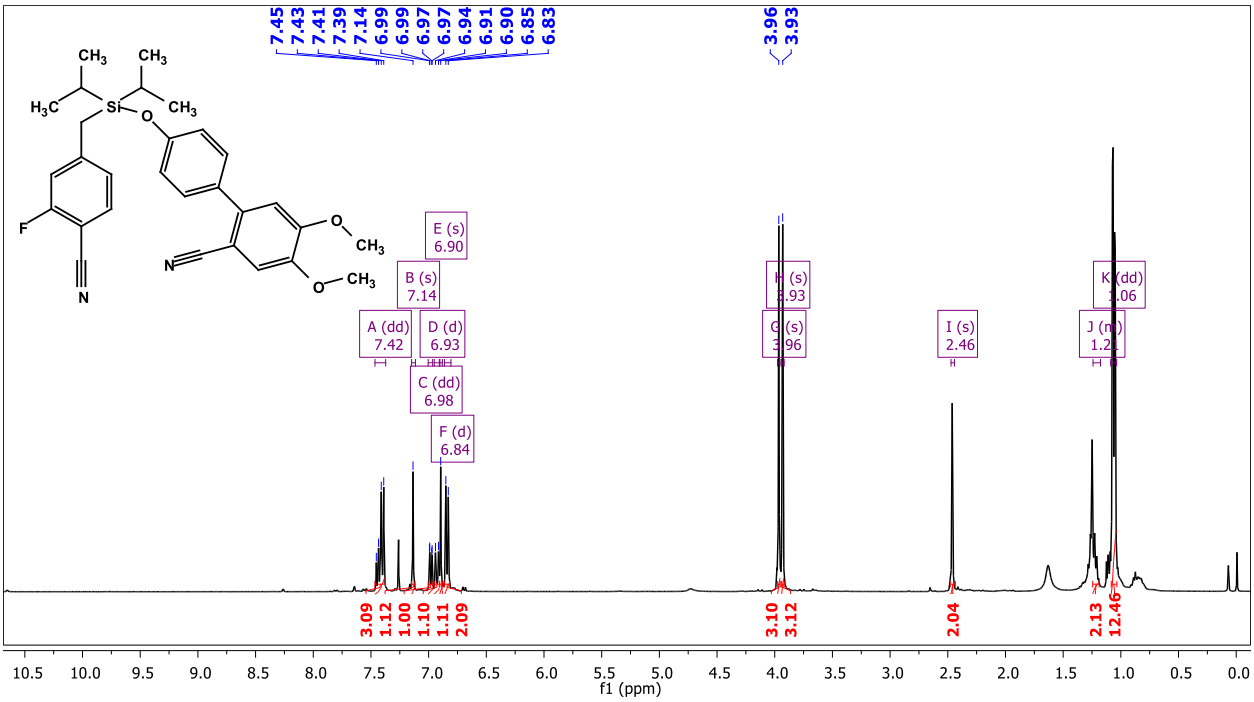
^{1}H NMR of 4p:



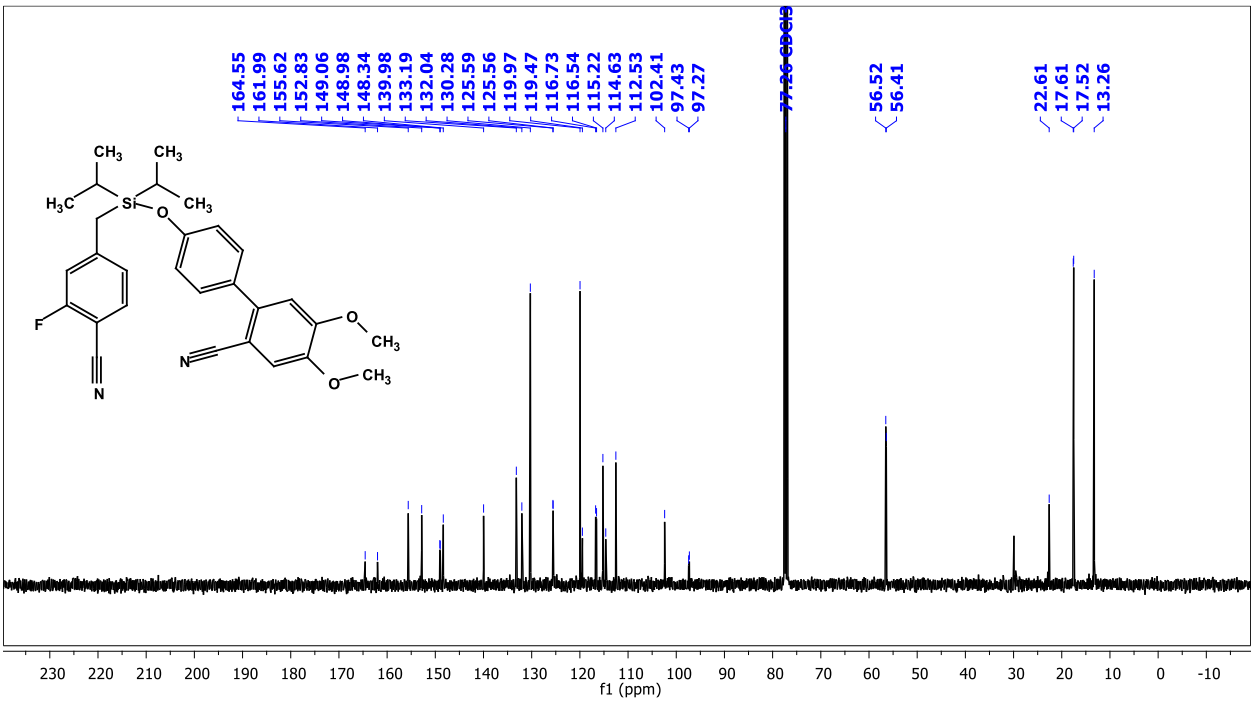
^{13}C NMR of 4p:



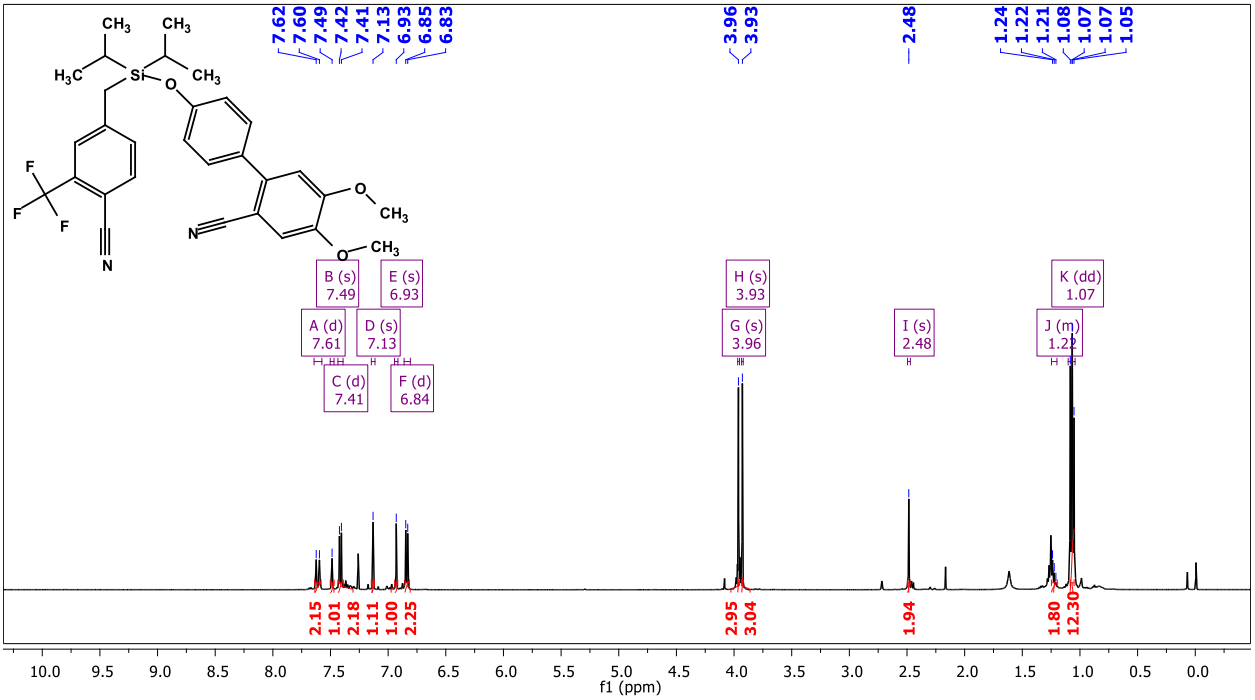
^{1}H NMR of 4q:



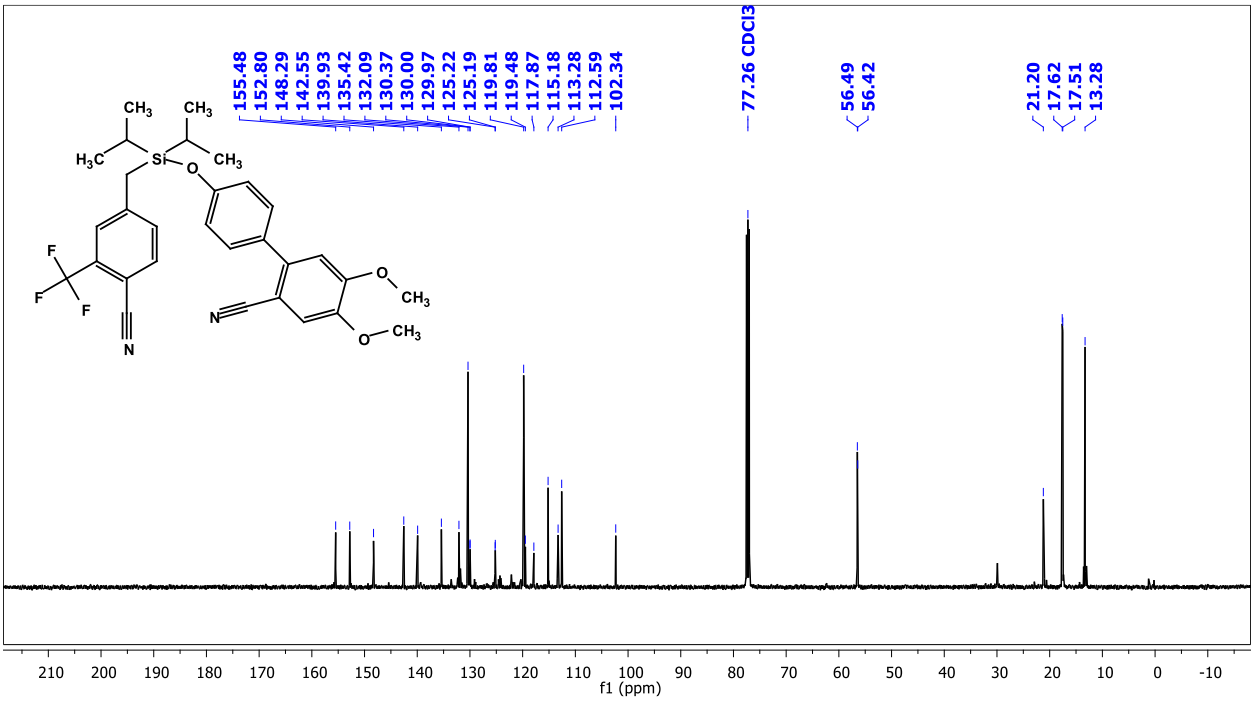
^{13}C NMR of 4q:



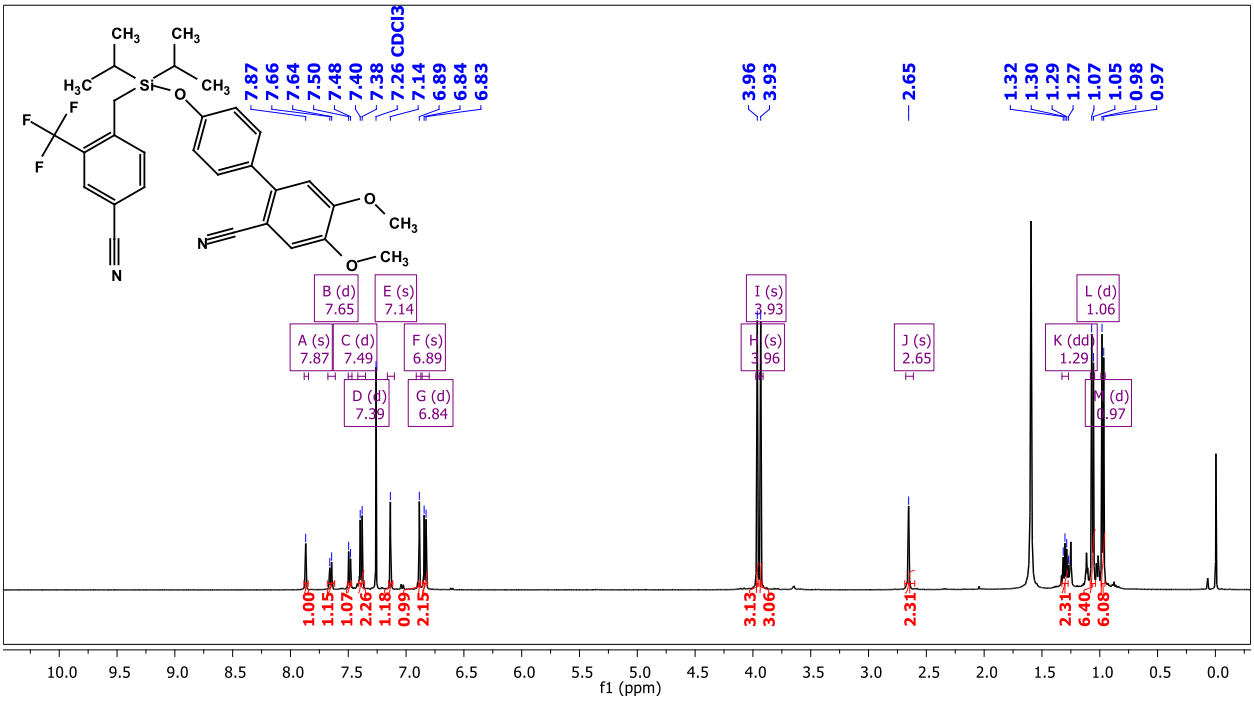
^{1}H NMR of 4r:



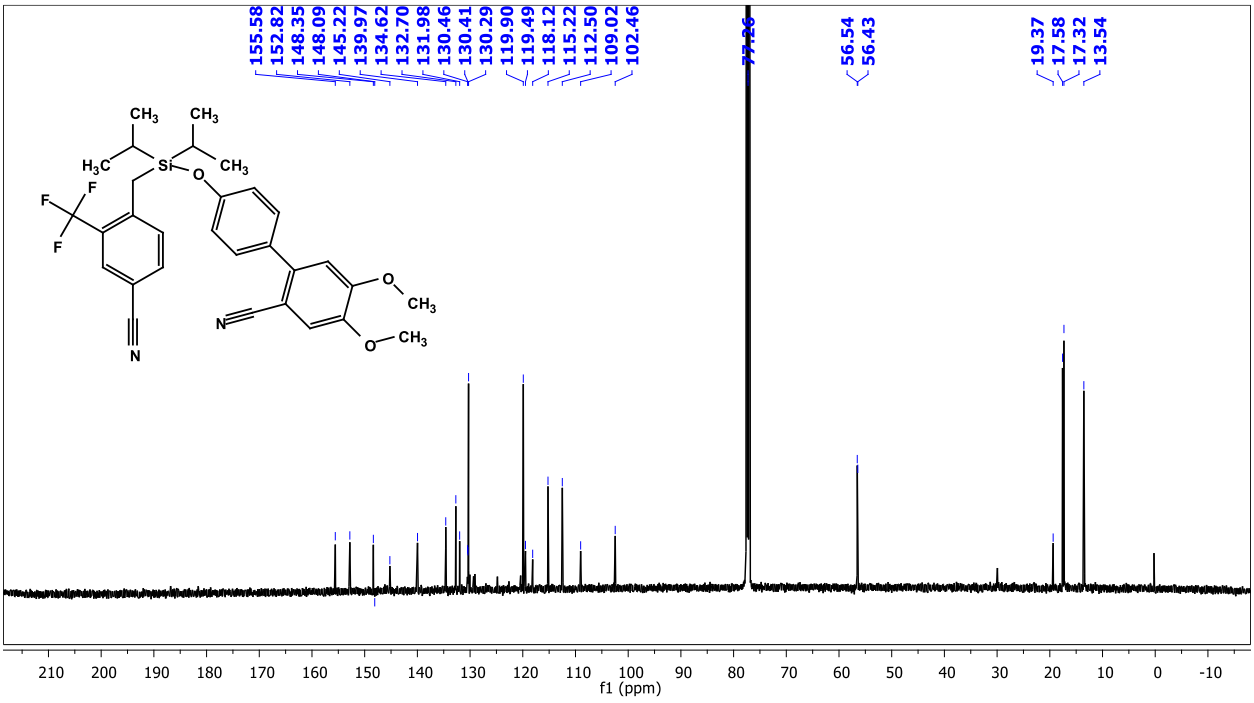
^{13}C NMR of 4r:



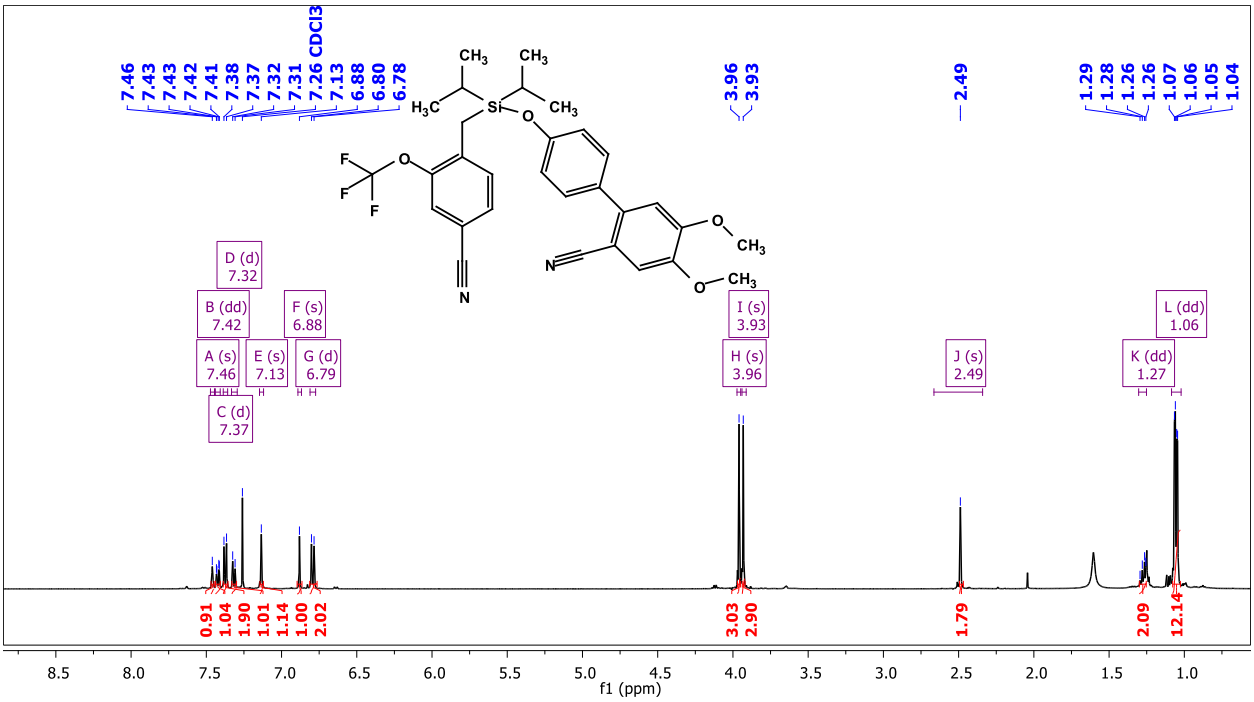
^{1}H NMR of 4s:



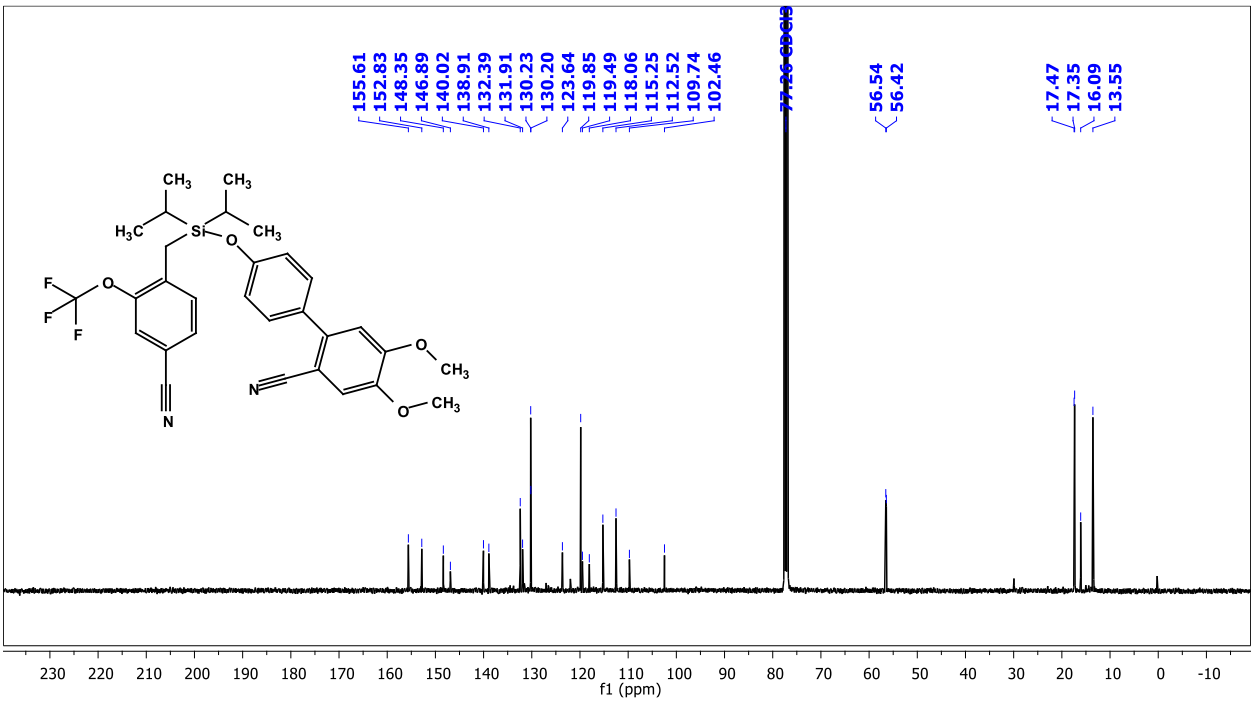
^{13}C NMR of 4s:



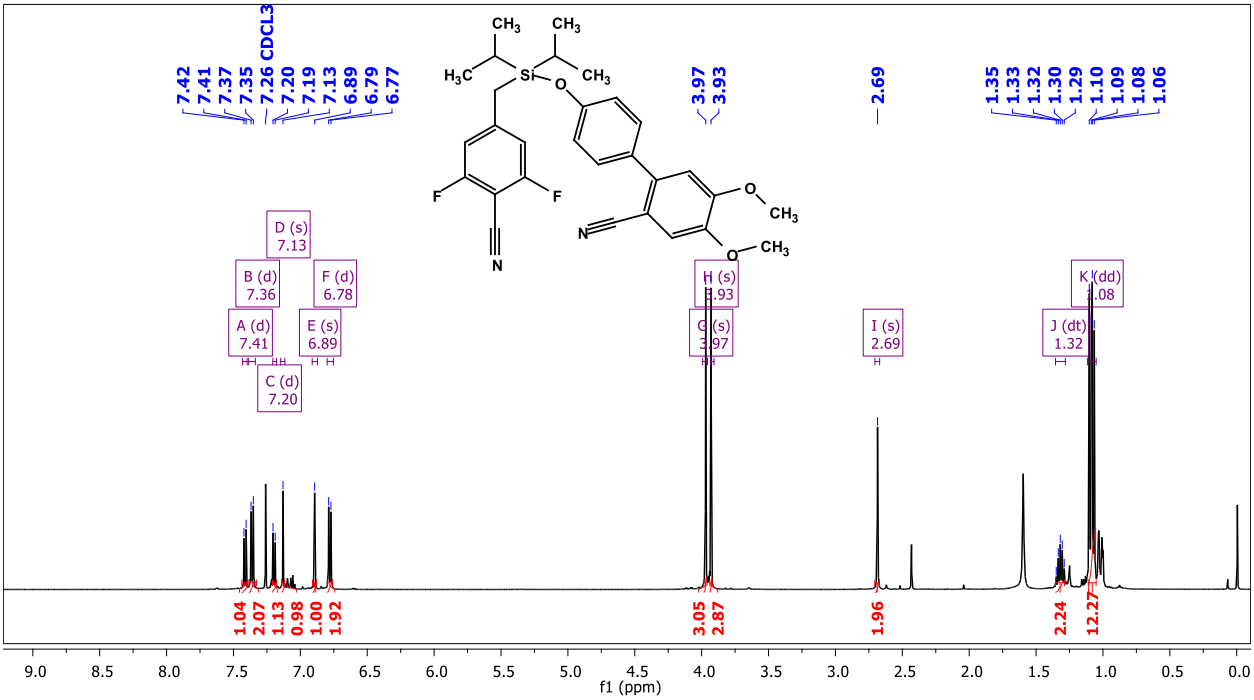
^{1}H NMR of 4t:



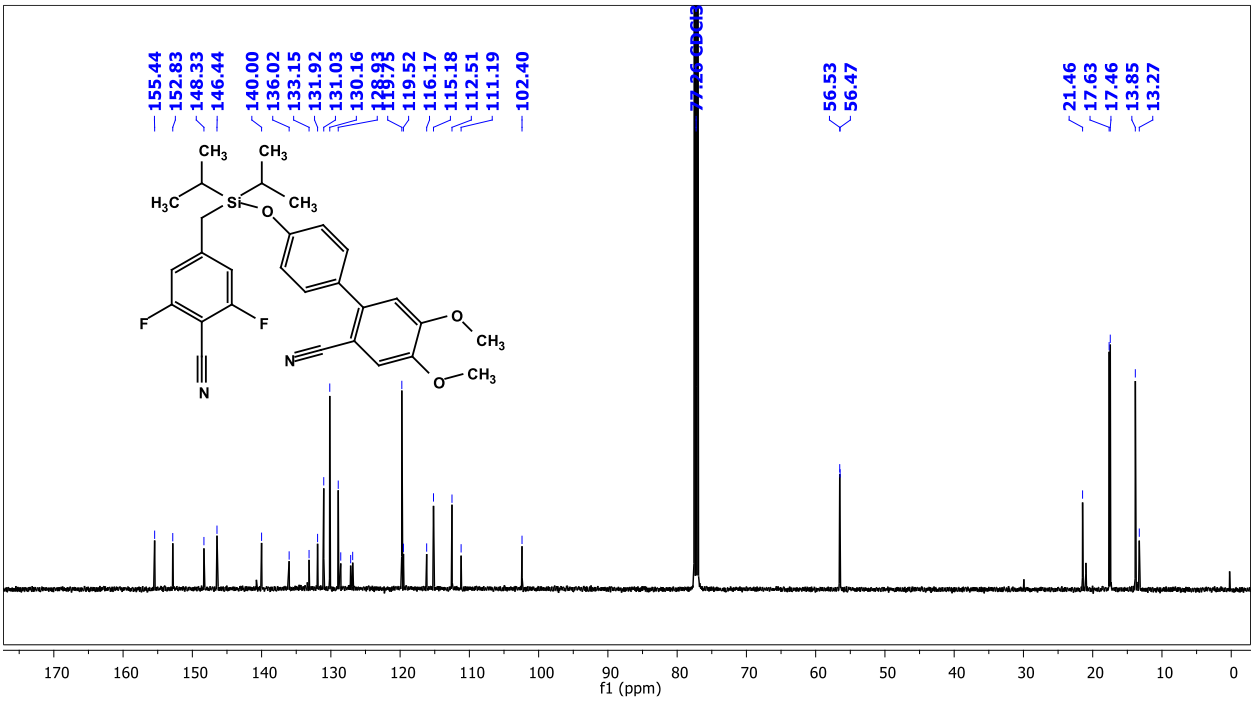
^{13}C NMR of 4t:



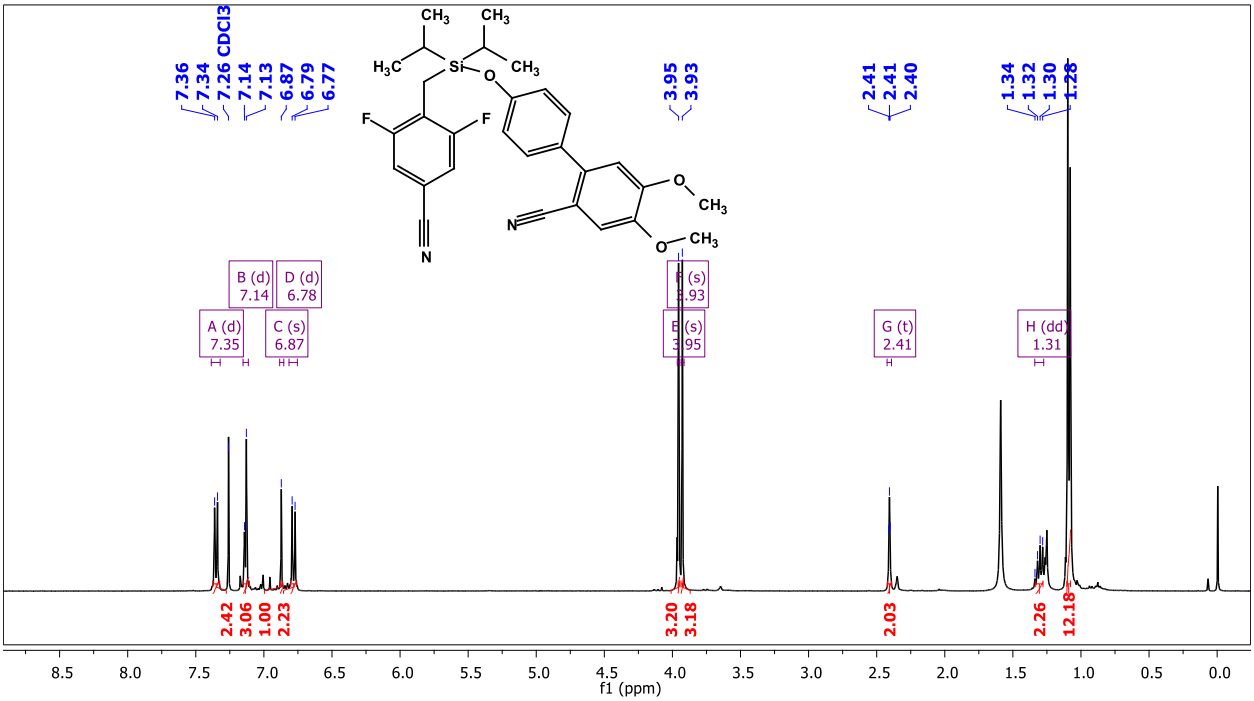
^{1}H NMR of 4u:



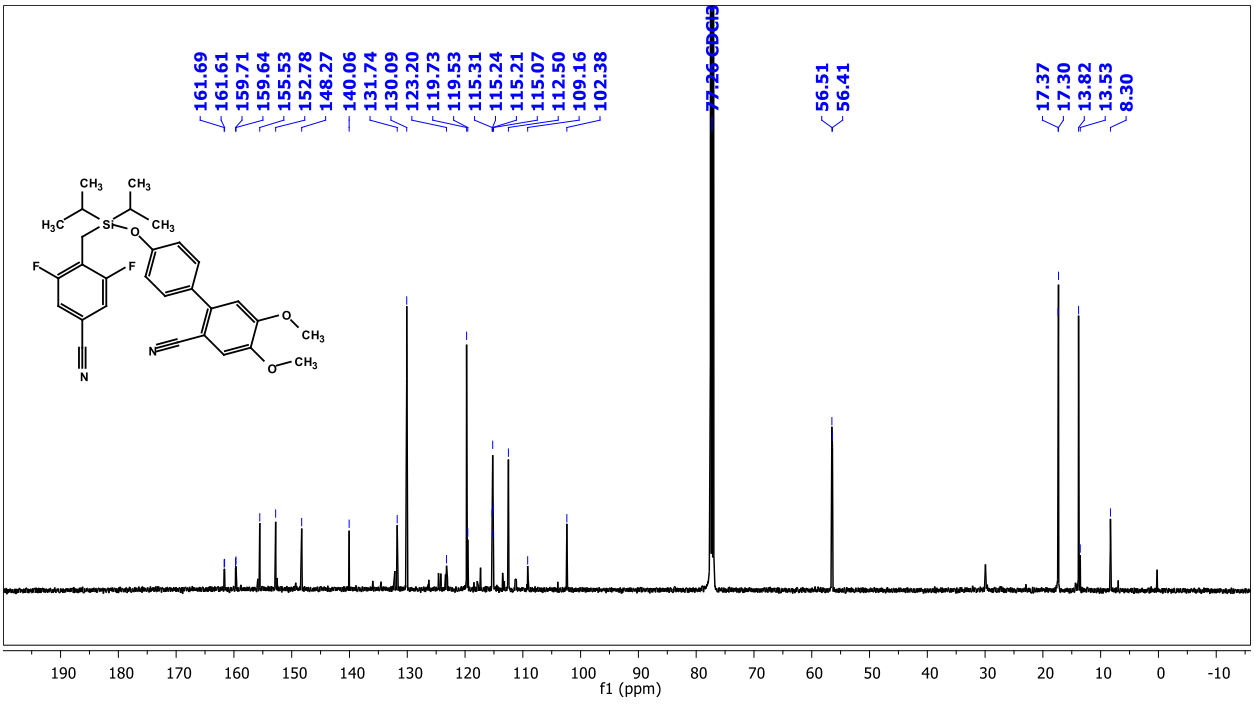
^{13}C NMR OF 4u:



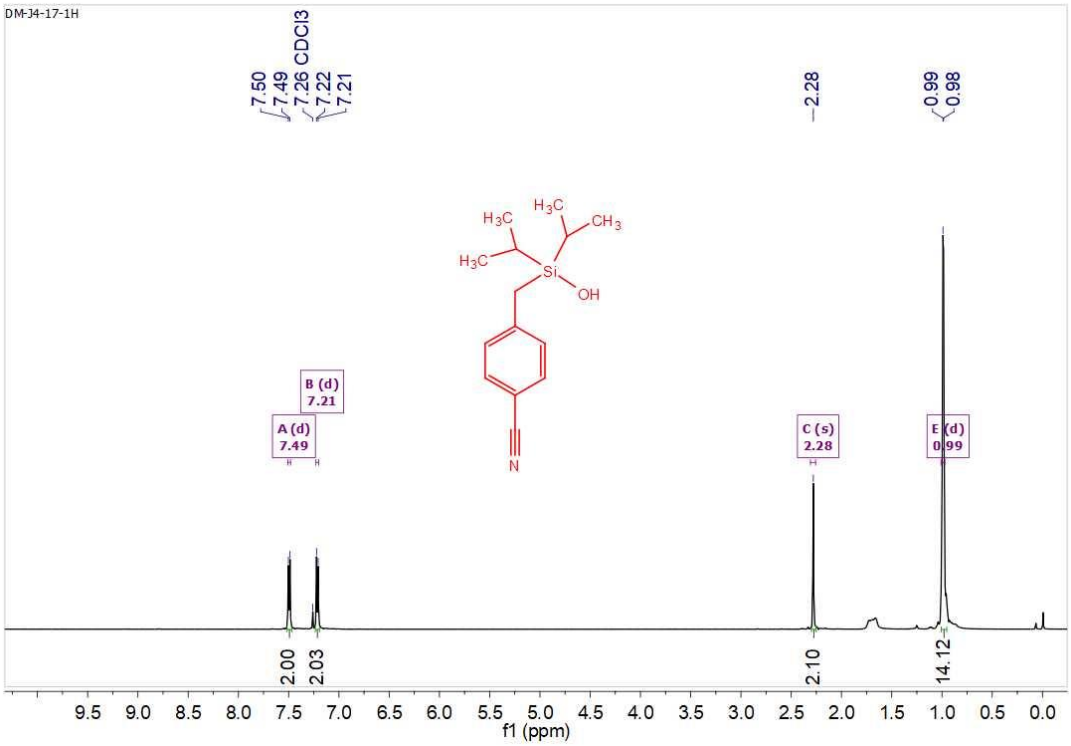
^{1}H NMR of 4v:



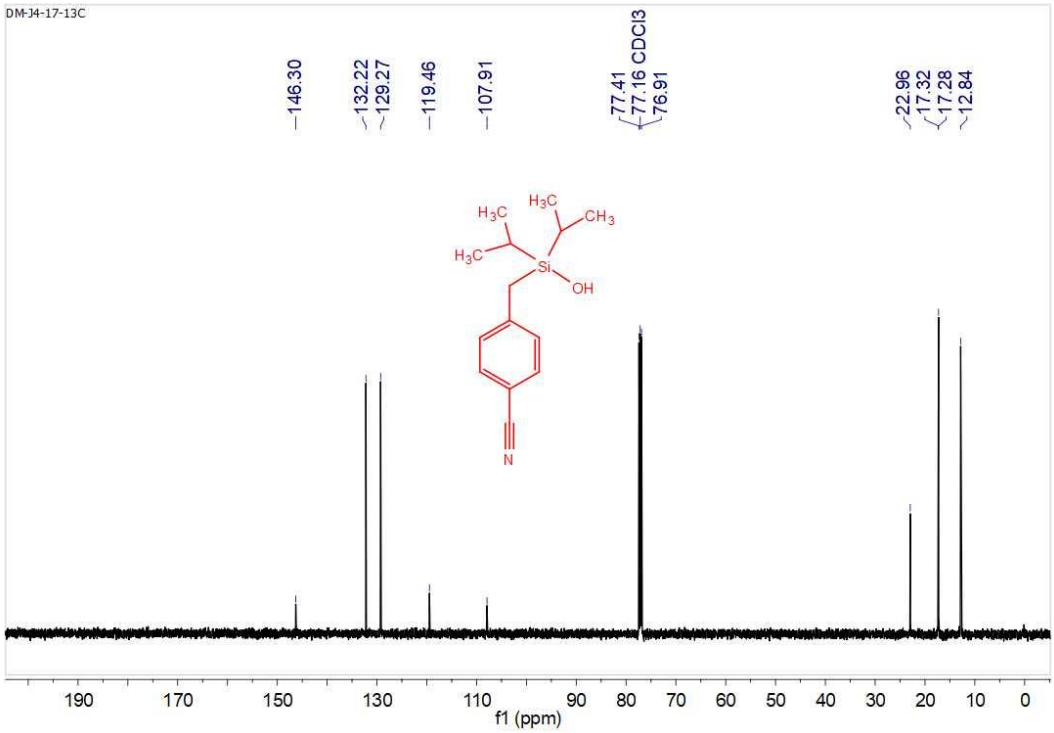
^{13}C NMR 4v**:**



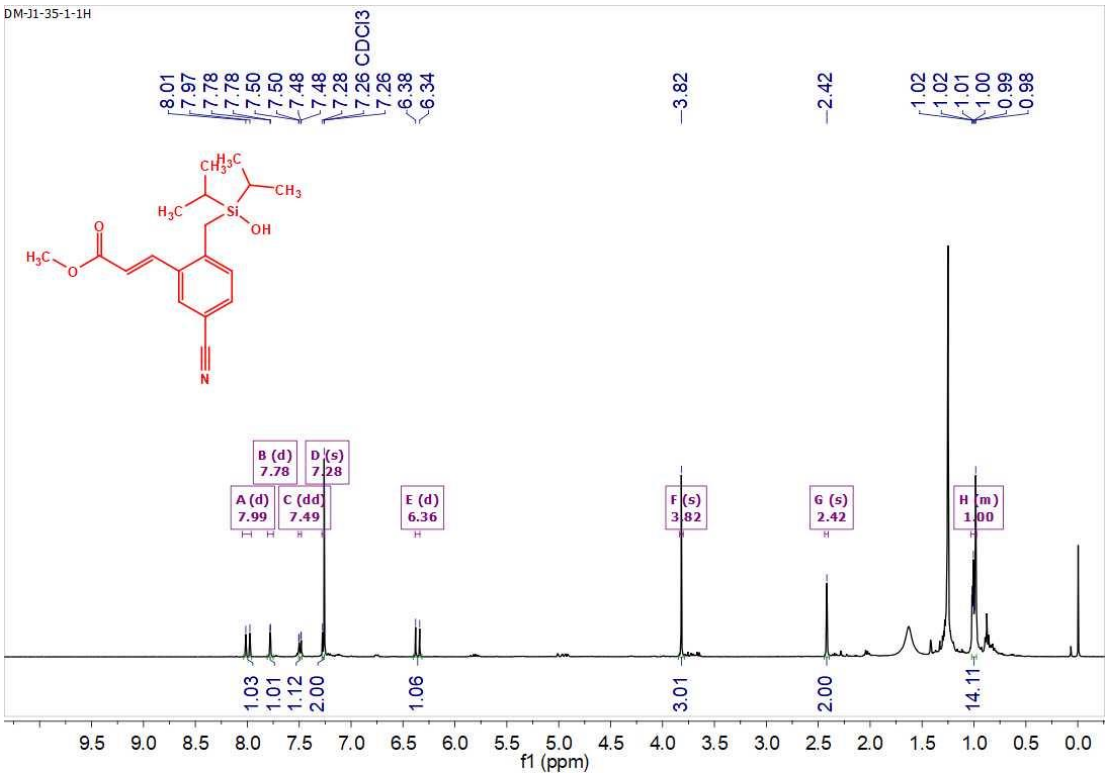
^{1}H NMR of 6:



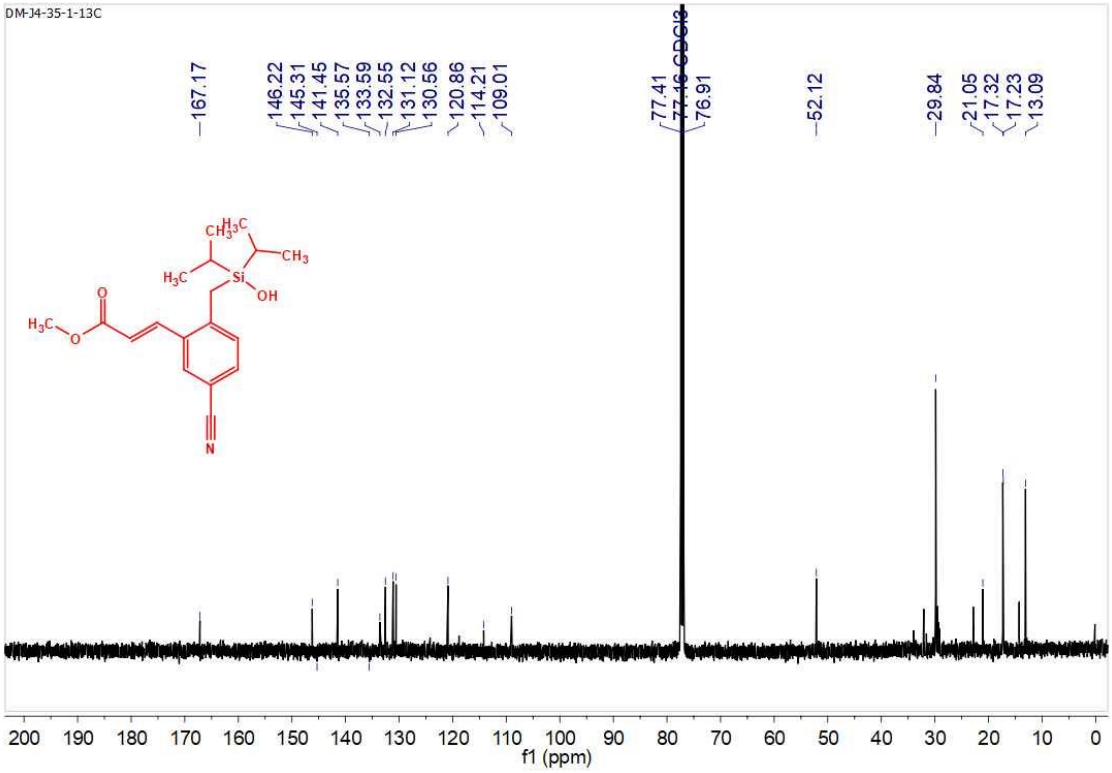
^{13}C NMR of 6:



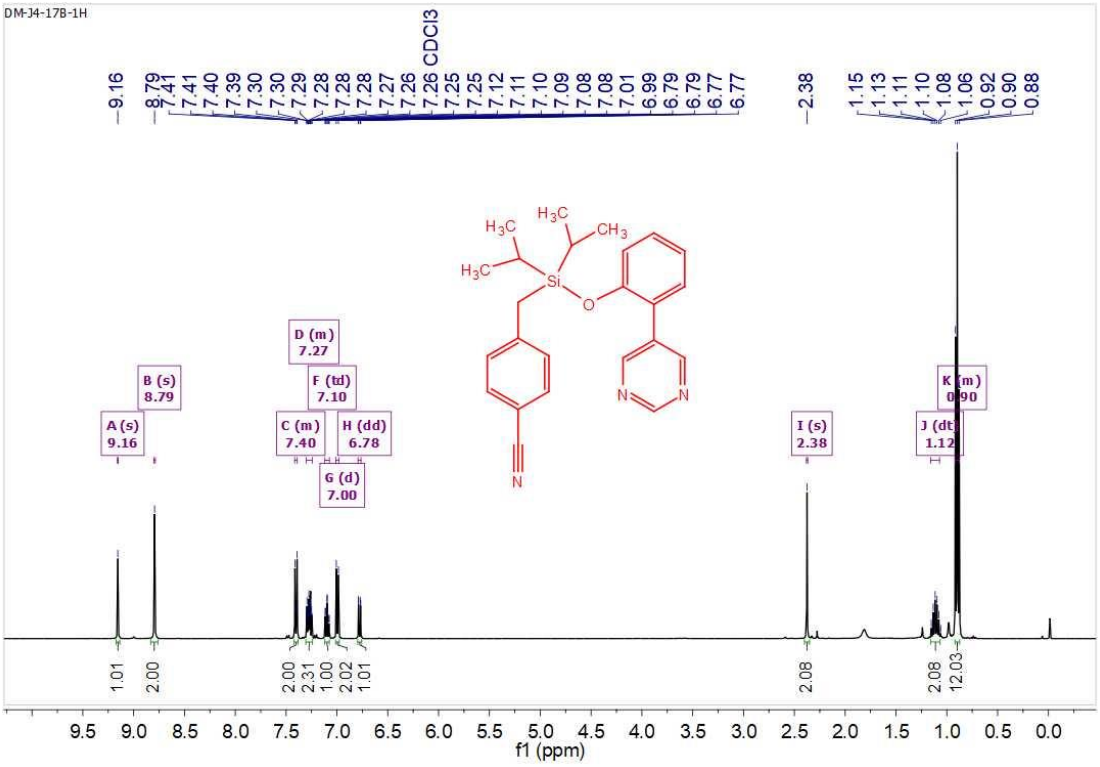
^{1}H NMR of 7:



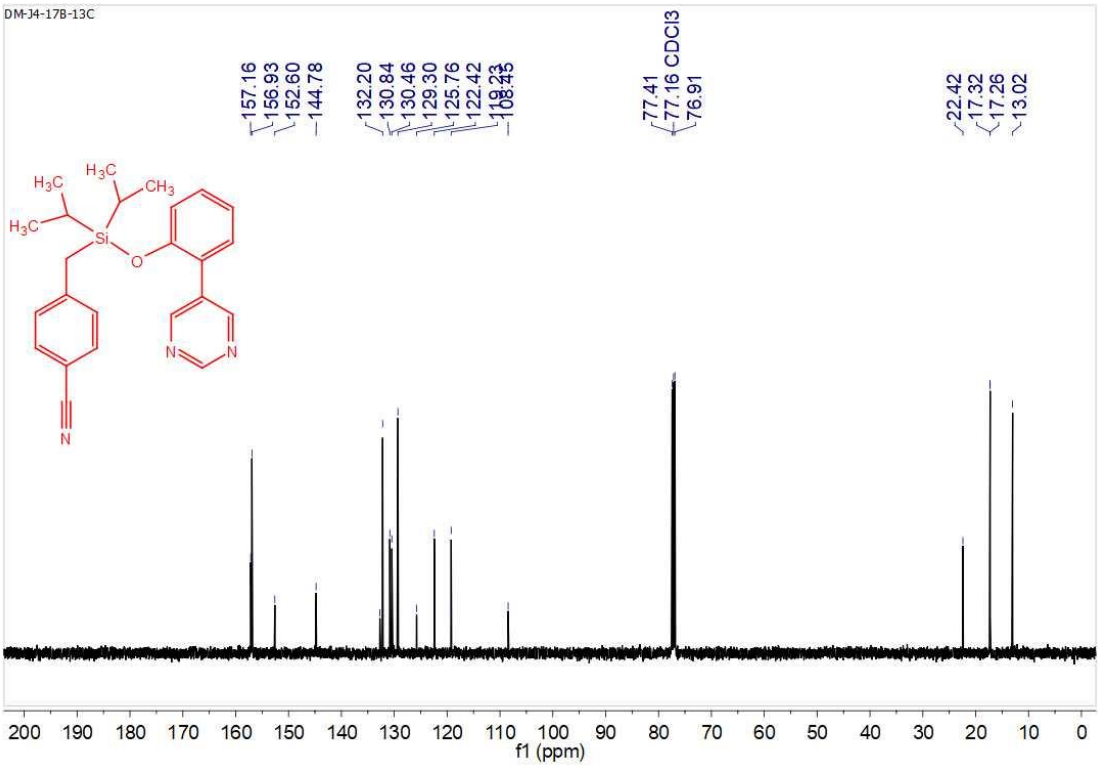
^{13}C NMR of 7:



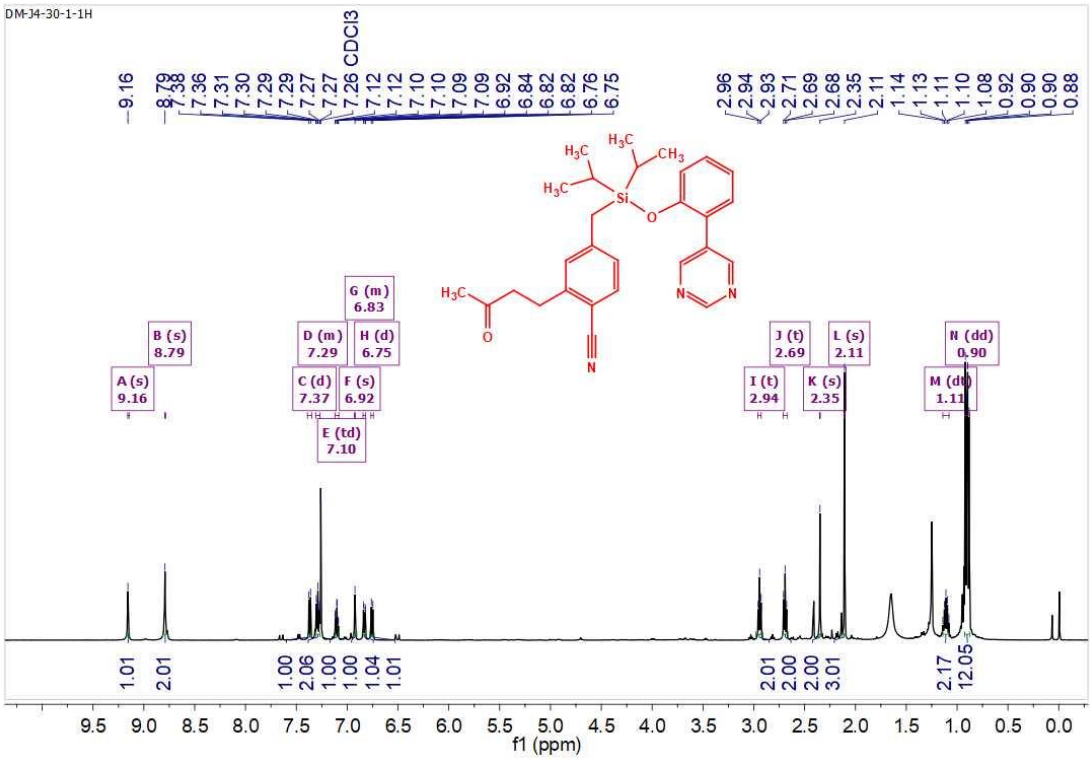
^{1}H NMR of 8:



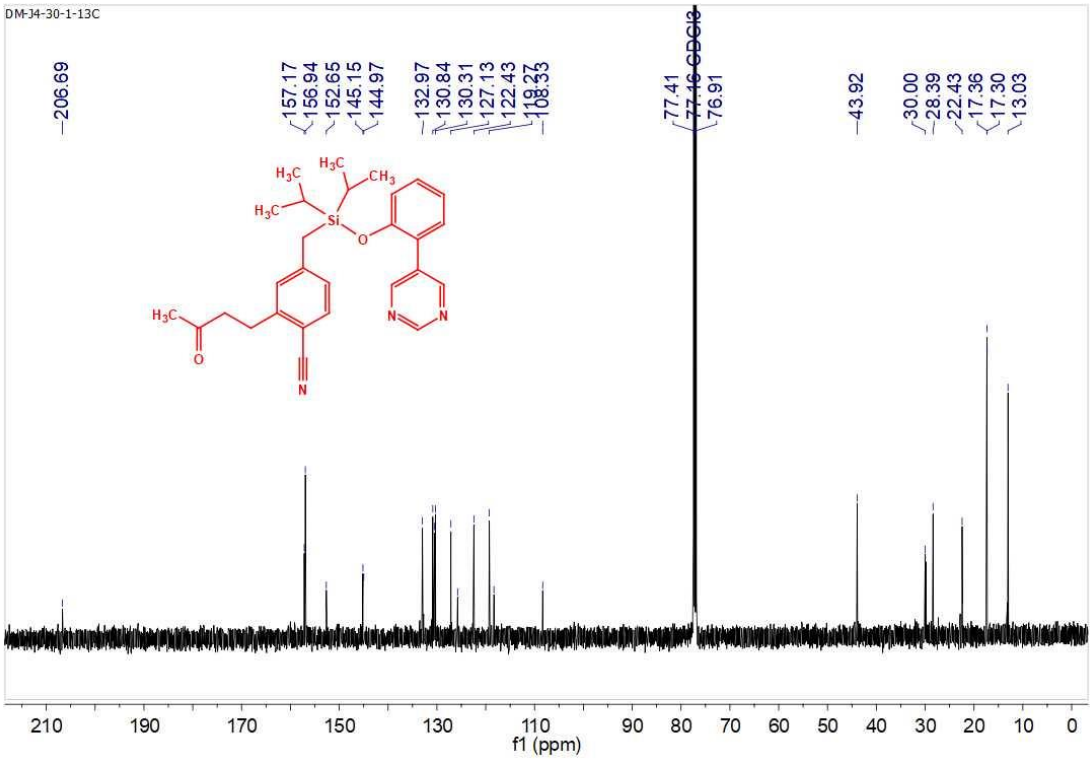
^{13}C NMR of 8:



^{1}H NMR of 9:


DM-J4-30-1-1H
CDCl3
A (s) 9.16
B (s) 8.79
C (d) 7.37
D (m) 7.29
E (td) 7.10
F (s) 6.92
G (m) 6.83
H (d) 6.75
I (t) 2.94
J (t) 2.69
K (s) 2.35
L (s) 2.11
M (dd) 1.11
N (dd) 0.90
f1 (ppm)

^{13}C NMR of 9:


DM-J4-30-1-13C
CDCl3
f1 (ppm)

4.8. Reference:

(1) (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res*. **2009**, *42*, 1074. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (d) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (e) Sigman, M. S.; Werner, E. W. *Acc. Chem. Res.* **2012**, *45*, 874 (f) Ackermann, L. *Acc. Chem. Res*. **2014**, *47*, 281. g) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. h) Tobisu, M.; Chatani, N. *Science* **2014**, *343*, 850. i) Takamatsu, K.; Hirano, K.; Miura, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 5353. j) Gemoets, H. P. L.; Kalvet, I.; Nyuchev, A. V.; Erdmann, N.; Hessel, V.; Schoenebeck, F.; Noel, T. *Chem. Sci.* **2017**, *8*, 1046. For selected reviews on C-H activation, see: h) Arockiam, P. B., Bruneau, C. & Dixneuf, P. H. *Chem. Rev.* **112**, 5879-5918 i) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; *Angew. Chem.* **2009**, *121*, 9976; j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q.; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; *Angew. Chem.* **2009**, *121*, 5196; k) Yeung, C. S.; Dong, V. M.; *Chem. Rev.* **2011**, *111*, 1215; l) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F.; *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; *Angew. Chem.* **2012**, *124*, 10382; m) Sarkar, S. D.; Liu, W.; Kozhushkov, S. I.; Ackermann, L.; *Adv. Synth. Catal.* **2014**, *356*, 1461; n) Li, J.; Sarkar, S. D.; Ackermann, L.; *Top. Organomet. Chem.* **2016**, *55*, 217. o) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **110**, 1147

2) For other *meta*- C-H functionalization examples see: a) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518–522. b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. c) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **2013**, *135*, 5877. d) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem*. **2015**, *7*, 712. e) Li, J.; Warratz, S.; Zell, D.; De Sarkar, S.; Ishikawa, E. E.; Ackermann, L. *J. Am. Chem. Soc.* **2015**, *137*, 13894. f) Kumar, N. Y. P.; Bechtoldt, A.; Raghuvanshi, K.; Ackermann, L. *Angew. Chem. Int. Ed.* **2016**, *55*, 6929. g) Bisht, R.; Chattopadhyay, B. *J. Am. Chem. Soc.* **2016**, *138*, 84. h) Wang, P.; Farmer, M. E.; Huo, X.; Jain, P.; Shen, P.-X.; Ishoey, M.; Bradner, J. E.; Wisniewski, S. R.; Eastgate, M. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 9269. i) Gemoets, H. P. L.; Laudadio, G.; Verstraete, K.; Hessel, V.; Noel, T. *Angew.*

Chem. Int. Ed. **2017**, *56*, 7161. j) Hoque, M. E.; Bisht, R.; Haldar, C.; Chattopadhyay, B. *J. Am. Chem. Soc.* **2017**, *139*, 7745. k) Li, J.; Korvorapun, K.; De Sarkar, S.; Rogge, T.; Burns, D. J.; Warratz, S.; Ackermann, L. *Nat. Commun*. **2017**, *8*, 15430. l) Hofmann, N.; Ackermann, L. *J. Am. Chem. Soc.* **135**, 5877-5884 m) Li, J. *Nat. Commun.* **8**, 15430. n) Bhattacharya, T.; Pimparkar, S.; Maiti, D. *RSC Advances*, **2018**, *8*, 19456.

3) Yang, Y. F.; Cheng, G. J.; Liu, P.; Leow, D.; Sun, T. Y.; Chen, P.; Zhang, X.; Yu, J. Q.; Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344–355.

4) Lee, S.; Lee, H.; Tan, K. L. *J. Am. Chem. Soc.* **2013**, *135*, 18778–18781.

5) Dai, H.; Li, G.; Zhang, X.; Stepan, A. F.; Yu, J. Q. *J. Am. Chem., Soc.* **2013**, *135*, 7567–7571.

6) Wan, L.; Dastbaravardeh, N.; Li, G.; Yu, J. Q. *J. Am. Chem. Soc.* **2013**, *135*, 18056–18059.

7) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215–220.

8) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R. Y.; Movassaghi, M.; Yu, J. Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807–10813.

9) Bera, M.; Modak, A.; Patra, T.; Maji, A.; Maiti, D. *Org. Lett.* **2014**, *16*, 5760.

10) Deng, Y.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 888–891.

11) Bera, M.; Maji, A.; Sahoo, S. K.; Maiti, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 8515–8519.

12) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature,* **2015**, *519*, 334–338.

(12) Li, S.; Ji, H.; Cai, L.; Li, G. *Chem. Sci.* **2015**, *6*, 5595–5600.

13) a) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. *J. Am. Chem. Soc.* **2015**, *137*, 11888. b) Patra, T.;

Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A, Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751 –7755.

14) a) Maji, A.; Dahiya, A.; Lu, G.; Bhattacharya, T.; Brochetta, M.; Liu, P.; Zanoni, G.; Maiti, D. *Nat Commun*. 2018, DOI: 10.1038/s41467-018-06018-2 b) Maji, A.; Guin, S.; Feng, S.; Dahiya, A.; Singh, V. K.; Liu, P.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 14903–14907. c) Dutta, U.; Maiti, S.; Pimparkar, S.; Maiti, S.; Gahan, L. R.; Krenske, E. H.; Lupton, D. W.; Maiti, D. *Chem. Sci.,* **2019,** DOI: 10.1039/C9SC01824G

15) a) Ping, Y.; Ding, Q.; Peng, Y. *ACS Catal.*, **2016**, *6*, 5989-6005. b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shoo, B. C. *J. Med. Chem.* **2010**, *53*, 7902. c) Hyland, J.; O'Connor, C. *J. Chem. Soc. Perkin Trans. 2,* **1973**, 223. b) Swain, C. *J. Am. Chem. Soc.* **1947**, *69*, 2306. d) Das, B.; Reddy, C.; Kumar, D.; Krishnaiah, M.; Narender, R. *Synlett* **2010**, 391. e) Finholt, A. E.; Jacobson, E. C.; Ogard, A. E.; Thompson, P. *J. Am. Chem. Soc. 1955*, *77*, 4163 f) Rappoport, Z. *The Chemistry of the Cyano Group*, Interscience Publishers, New York, **1970**. g) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, *4*, 277. h) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn*. **1975**, *48*, 3298. i) Dalton, J. R.; Regen, S. L.; *J. Org. Chem.* **1979**, *44*, 4443. j) Akita, Y.; Shimazaki, M.; Ohta, A. *Synthesis,* **1981**, 974. k) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714. l) Sato, N.; Suzuki, M. *J. Heterocycl. Chem.* **1987**, *24*, 1371. m) Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118. o) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887.

16) For selected examples of Pd, Ru, Rh, co-catalyzed directed C(sp^2)-H cyanation, see: a) Jia, X. F.; Yang, D. P.; Zhang, S. H.; Cheng, J. *Org. Lett.* **2009**, *11*, 4716. b) Jia, X. F.; Yang, D. P.; Wang, W. H.; Luo, F.; Cheng, J. *J. Org. Chem.* **2009**, *74*, 9470. c) Mishra, A.; Vats, T. K.; Deb, I. *J. Org. Chem.* **2016**, *81*, 6525. d) Chaitanya, M.; Anbarasan, P. *Org. Lett.* **2015**, *17*, 3766. e) Gong, T. J.; Xiao, B.; Cheng, W.-M.; Sun, W.; Xu, J.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 10630. f) Yu, D.-G.; Gensch, T.; Azambuja, F.; Vasquez-Cespedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722.

SYNOPSIS

of the PhD thesis

Exploration for Distal C–H Functionalization of Aliphatic and Aromatics by Pd Catalysis

Proposed to be submitted in partial fulfillment of the requirements of

The degree of
Doctor of Philosophy
of the
Indian Institute of Technology, Bombay, India
and
Monash University, Australia

by

Sandeep Yadavrao Pimparkar

Supervisors:

Prof. Debabrata Maiti (IIT Bombay)

Prof. David Lupton (Monash University)

The course of study for this award was developed jointly by
Monash University, Australia and the Indian Institute of Technology, Bombay
and was given academic recognition by each of them.
The programme was administrated by The IITB-Monash Research Academy

(Year 2019)

Current thesis entitled "**Exploration for distal C–H functionalization of aliphatic and aromatics by Pd catalysis**" has been divided into four chapters.

Research for my graduate degree was mainly focused on distal C–H activation of aliphatic and aromatic substrates with the aid of directing groups for Pd catalysis to enable the delivery of palladium selectively at gamma (γ) position of aliphatic carboxylic acids and *para* position of aromatic toluens. At the earliest of my Ph. D work, I started to look closely at distal C–H activation strategies of aliphatic acid for β, γ C–H functionalization. During a literature survey, I found that although few directing groups been utilized to activate beta (β) and gamma (γ) C–H bond of aliphatic acid but most of the methodologies have certain limitation of use of exogenous ligand to γ selective arylation, so the newer strategy was needed to develop attend this challenge. To achieve site selective γ C–H activation a bidentate 8-aminoquinoline as the directing group was introduced which not only served as internal ligand but also formed stable 6 membered metallacycle with aliphatic sp^3 center to deliver the Palladium selectively at γ position enabling C(sp3)-H functionalization with wide array of iodoarenes and bromo alkynes.

Various directing group developed, played an important role in enabling proximal *ortho* C–H activation by Pd, Rh & Ru catalysis and are well explored in literature. Also, few of templates were designed for *meta* C–H functionalization by Pd & Rh catalysis. But *para* C–H functionalization remained challenge mainly due to unfavorable geometrically constrained metallacycle as it had to deliver metal selectively at *para* position by overriding *ortho* and *meta* positions. This was made possible by designing a U-shaped template which took advantage of Thorpe-Ingold and was allowed to bend biphenyl directing template ring to deliver palladium at *para* position of substrate ring for selective cyanation reaction.

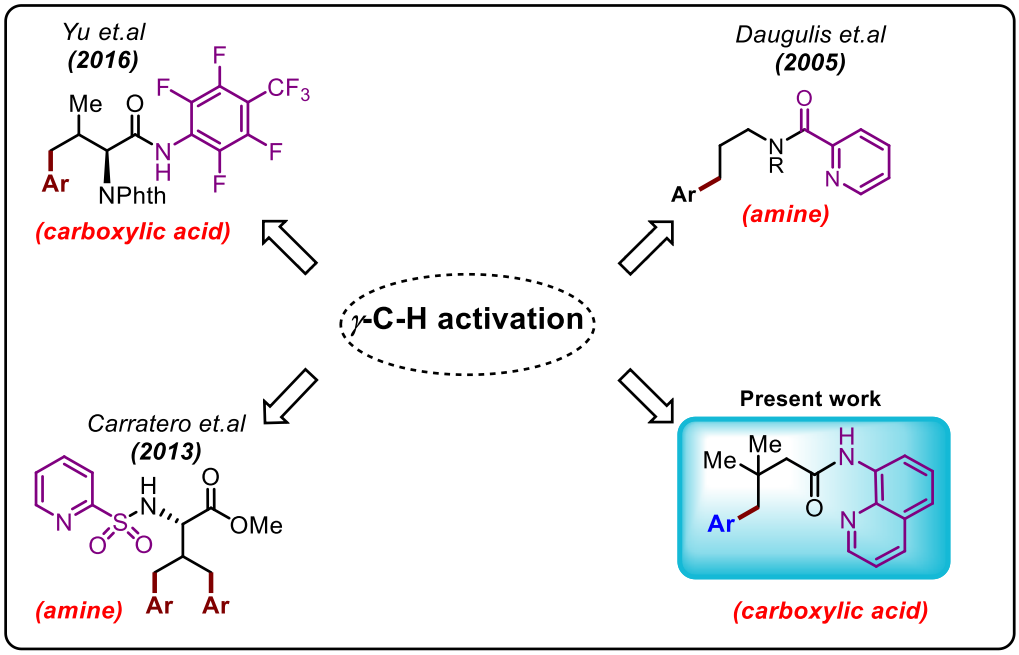
Chapter 1

The thesis begins with background of work described in thesis. The prior reported literature, its limitation and solutions are organized in this chapter. The development of methods to solve problem for scope of thesis is described in subsequent chapters.

Chapter 2

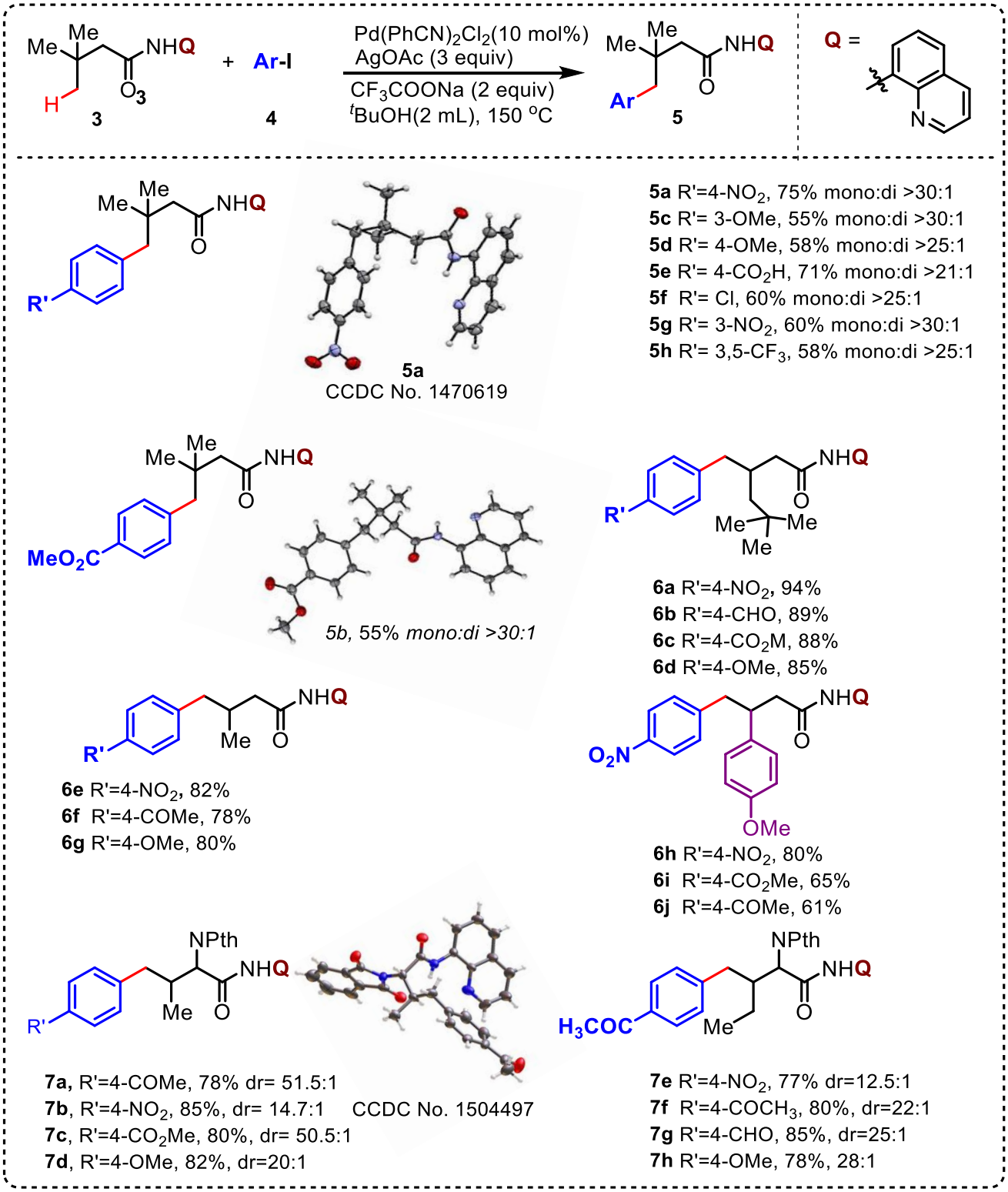
Over a decade success stories shown a paradigm shift in aliphatic sp^3 C-H activation which reflected the applicative potential of C–H bond and this has allowed superior scope of selective functionalization at sp^2/sp^3 carbon centres with aid of organometallic catalyst even in complex molecular environment. But till date still activating sp^3 carbon centre is quite challenging due to its high bond dissociation energy (415 kJ/mol for C-H bond for methane) and abundance of C-H bonds in aliphatic molecule. A series of strategies implemented over the years has thus helped in the formidable task of making this inert class of C–H bonds participate actively in chemical transformations. Formation of a five-membered metallacycle with bidentate 8-aminoquinoline directing group has led to many highly selective β-C–H functionalization. So, I wish to farther the scope of this protocol into attracting more distal γ-C–H bonds. After many unsuccessful attempts I was able to fine tune reaction condition for selective arylation of the remote γ-position of aliphatic carboxylic acids using 8-aminoquinoline as bidentate chelating auxiliary with help of palladium(II) catalyst in which both amine and quinoline nitrogen chelate with the palladium. Most significant importance for this reaction is that it does not require any exogeneous expensive ligand as directing group serve both purposes by ligating with metal intramolecularly. After screening preliminary reaction conditions with *tert*-butylacetic acid with 8-aminoquinoline via amide linkage for arylation with 4-nitroiodobenzene as arylating source in presence of $Pd(OAc)_2$ as catalyst and AgOAc as oxidant interestingly, regioselective γ-arylation was observed (NMR yield, 50%) with a near exclusive formation of mono-arylated product (*mono*:*di*>30:1). After optimizing various reaction parameters, it was concluded that $Pd(PhCN)_2Cl_2$ and AgOAc as the perfect catalyst-oxidant combination for the reaction. Use of a bulky polar hydroxylic solvent like *t*-BuOH was found to be beneficial for the reaction. Presence of a bulky anion

like trifluoroacetate was useful for the reaction. Also, Inclusion of exogenous ligand failed to provide any additional improvements on the reaction condition. After optimisation reaction was tested for various aryl iodides and different aliphatic acid and was found in good to excellent yields (scheme 2). To gain more insight into the plausible reaction mechanistic pathway control experiments were performed to understand the rol of AgOAc. In the independent set of reactions, replacement of AgOAc either by air, oxygen or N_2 did not give corresponding product



Scheme 1: Overview and present work on γ-C–H arylation of carboxylic acid amides

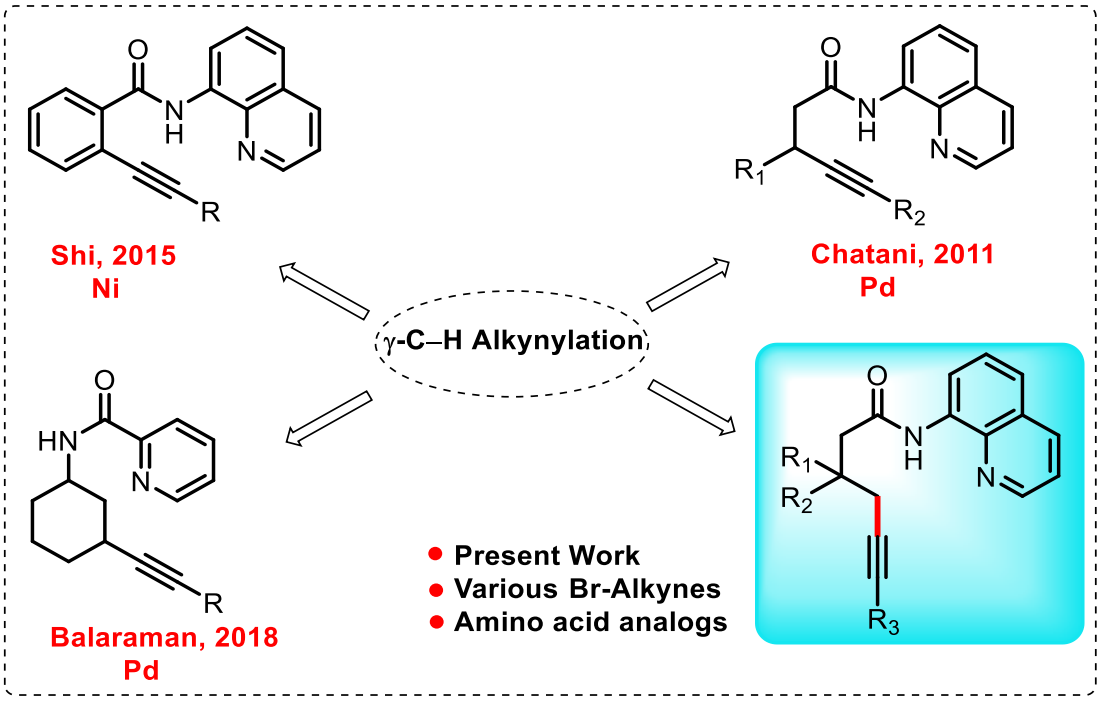
Replacing AgOAc with *p*-benzoquinone as an oxidant also did not yield any product. Along with that replacing aryliodide with aryltriflate and using *p*-benzoquinone as the oxidant failed to product. Thus, arylhalide is a potent arylating source for this protocol. Moreover, AgOAc exhibits a dual role by probably acting as halide scavenger as well as oxidant. Further application of the protocol was demonstrated by facile removal of the 8--aminoquinoline directing group that furnished the corresponding ester in 80% yield along with recovery of the 8-aminoquinoline auxiliary in 75% yield. The latter could be reinstalled again to farther the γ-arylation on other substrates.



Scheme 2: Variation of amide and aryl iodide for γ-arylation

Chapter 3

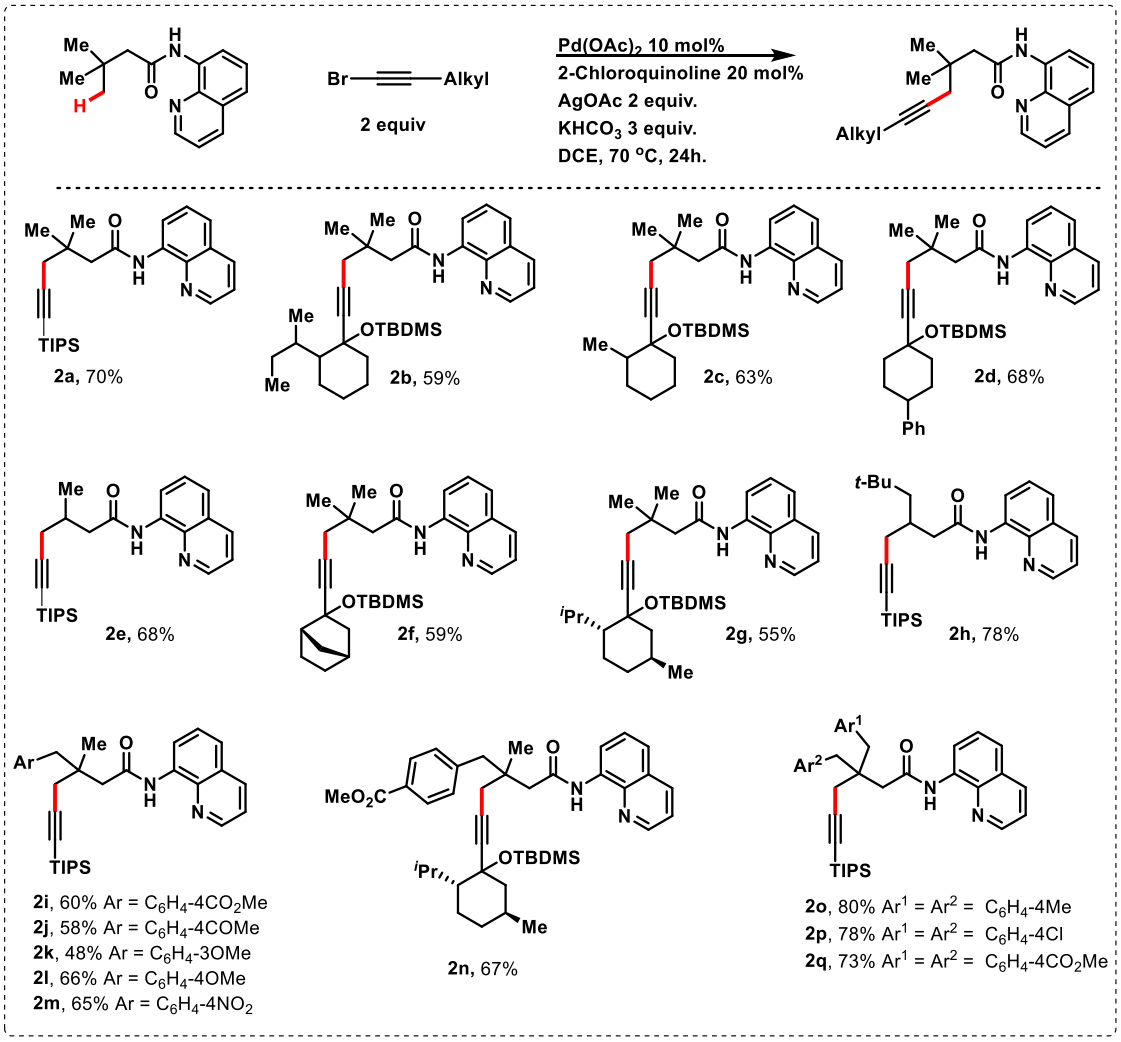
Selective functionalization of aliphatic C-H bond is always challenging due to i) abundance of C-H bond in aliphatic substrates ii) high bond dissociation energy iii) site selectivity due to presence of multiple active sites in molecules (α, β, γ, δ, ε etc). But over the past decade selective functionalization of aliphatic C- H bond has emerged a tool to synthesize complex structures. if one can think to utilize such abundant raw feed stock materials to transform them into valuable product, one must overcome such limitations by employing newer strategies. One of way that can solve such problem is attaching a suitable directing group and activating the C-H bond by forming favorable metallacycle intermediate. In the literature Pd, Ni are known to utilized for C-H activation of β-C-H bonds alkynylation but nonetheless γ-C-H alkynylation is remained unattended. Alkynes are such a powerful building block for synthesis of diverse nature of motifs which can facilitates various addition, metathesis or cycloaddition reactions.



Scheme 3: Overview and present work on γ-C–H alkynylation of carboxylic acid amides

To start with, I started to screen various reaction conditions to employ 8-aminoquinoline as directing group for carboxylic acids to react with (bromoethynyl)triisopropylsilane.

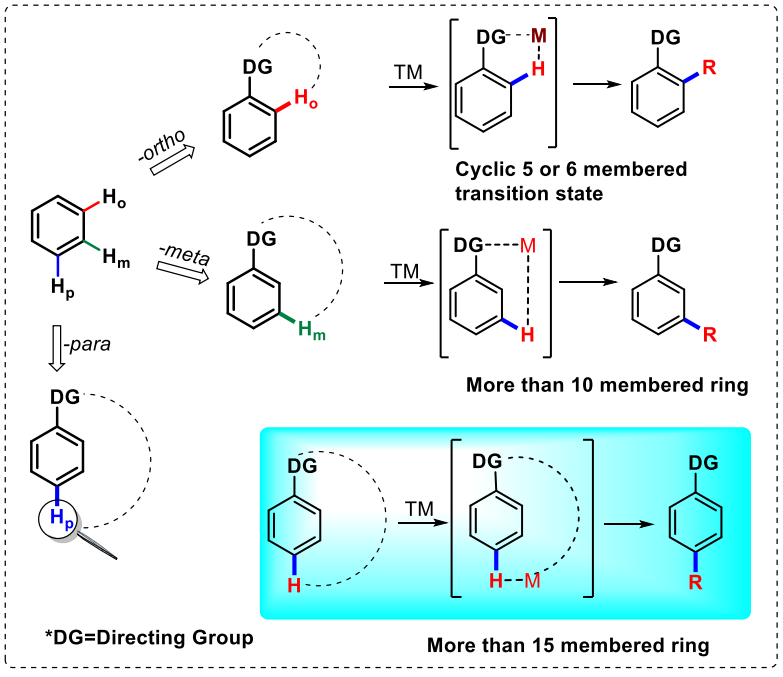
Initially attempt were less successful with NMR yields of 30% with *mono:di* as 2:1 alkynylated product. For this reaction role of ligand was very crucial and screening of various pyridine, pyrimidine, quinolone based ligands gave 2-Chloroquinoline as best ligand. After optimizing reaction conditions, $Pd(OAc)_2$ 10 mol% was found to be best along AgOAc as oxidant in 2 equiv., $KHCO_3$ as base in 3 equiv., in DCE as solvent at 70 °C for 24 hour. Reaction tolerated various carboxylic acid amides including amino acid backbone, to make reaction efficient in such complex substrates NH_2 group of amino acid was protected with pthalimide protection. The efficacy of reaction was very well among different substituted bromo-alkynes which exhibited wide array of complexity which is previously unattended in literature.



Scheme 4: Efficiency of reaction for various amide and bromo-alkynes

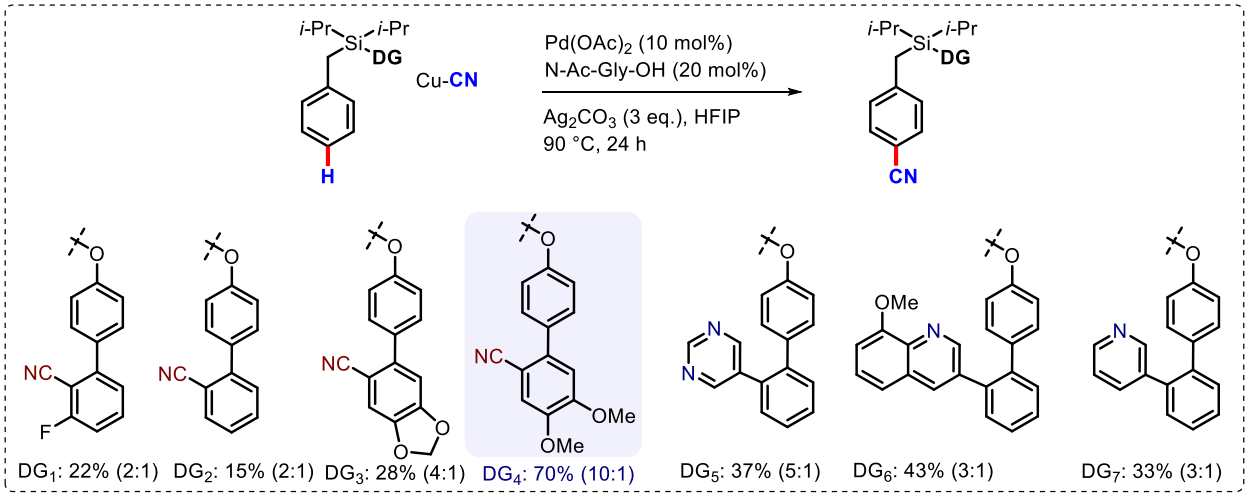
Chapter 4

Site selectivity in aromatic systems is always a critical challenge for C–H activation reactions. Simple monosubstituted benzene has three different C(sp^2) aromatic sites for functionalization and it often leads to multiple functionalized product when reacted as a substrate. Since two decades and more, various groups around the globe have solved this problem by introducing directing group on the arenes to facilitate the chelation for transition metal and specifically activating the *ortho* C–H bond which is present in *close* proximity. This strategy is now well diversified with various directing groups like amides, anilides, aldehydes, ketones, carboxylates to give olefinated, arylated, hydroxylated, alkenylated arenes and heteroarenes. This approach is well studied for different transition metals Rh, Ru & Pd, Ni, Cu, Ir. Also it has been utilized to synthesize different heterocycles by annulation reaction with alkynes and alkenes. It is always a difficult task to approach the '*distal*' C–H bond due to instability of macrocyclic transition states or limitation of 5 or 6 membered transition states.



Scheme 5: Site selectivity for *ortho, meta* & *para* C–H activation by directing group

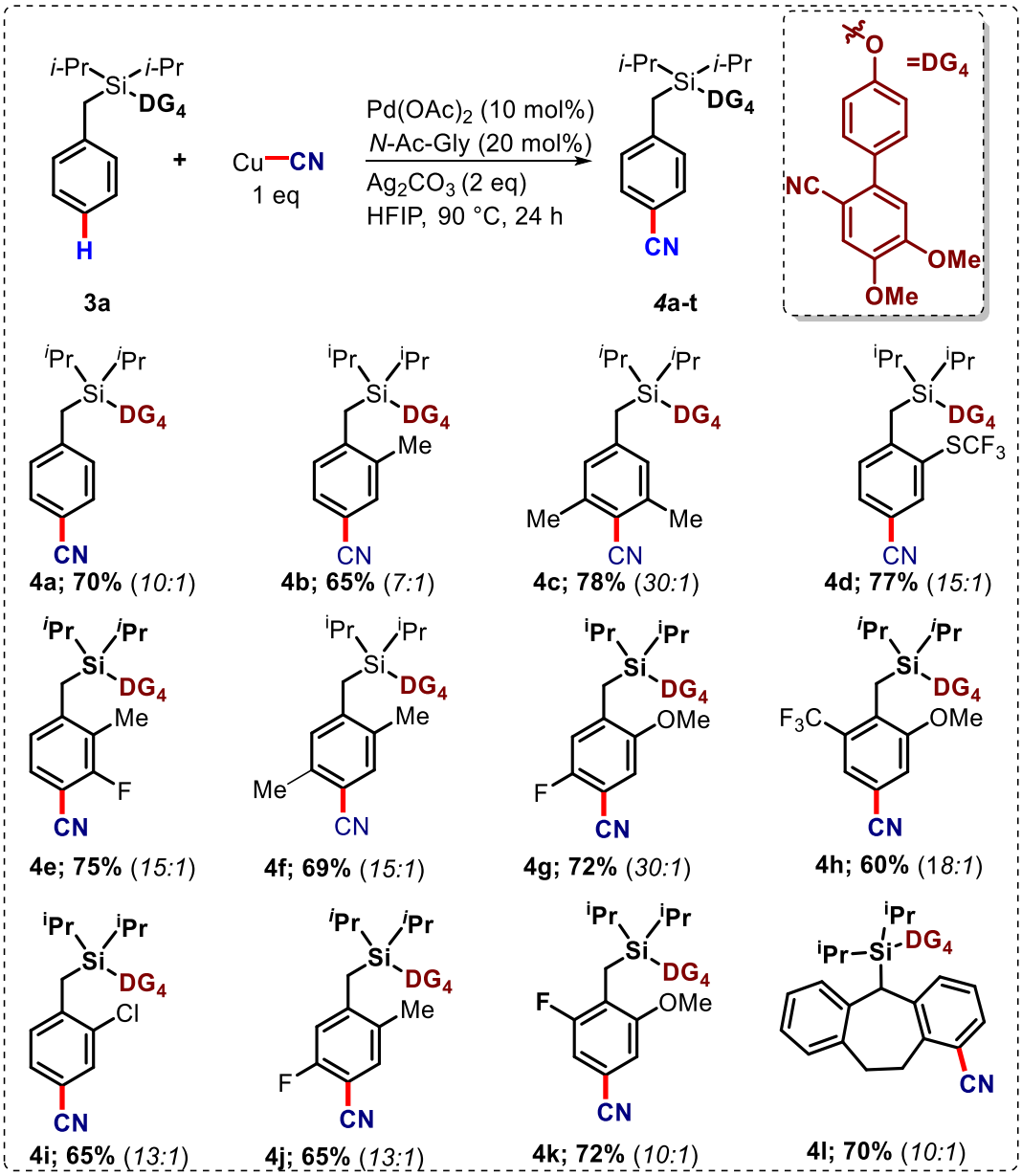
Yu et al in 2012 overruled this limitation by employing "*end-on*" nitrile-based template for *distal meta* C–H activation with Pd catalyst and subsequently newer templates were reported by same group for *meta* C–H functionalization reactions. Maiti's group also developed newer nitrile-based template and later superior pyrimidine template for various meta C–H functionalization reactions. But still activating far *distal* position *i.e*. *para* C–H bond was one of the challenges for synthetic community. Maiti's group successfully developed U-shaped *para* directing template for olefination of toluene and phenol. But this template was practically not applicable for other types of reactions one can think or attempted so far. I tried to develop newer U-shaped template to reach distal para C–H bond of toluene for selectively introduce CN (Nitrile) group at *para* C–H bond.



Scheme 6: Screening of templates for site selectivity and yield

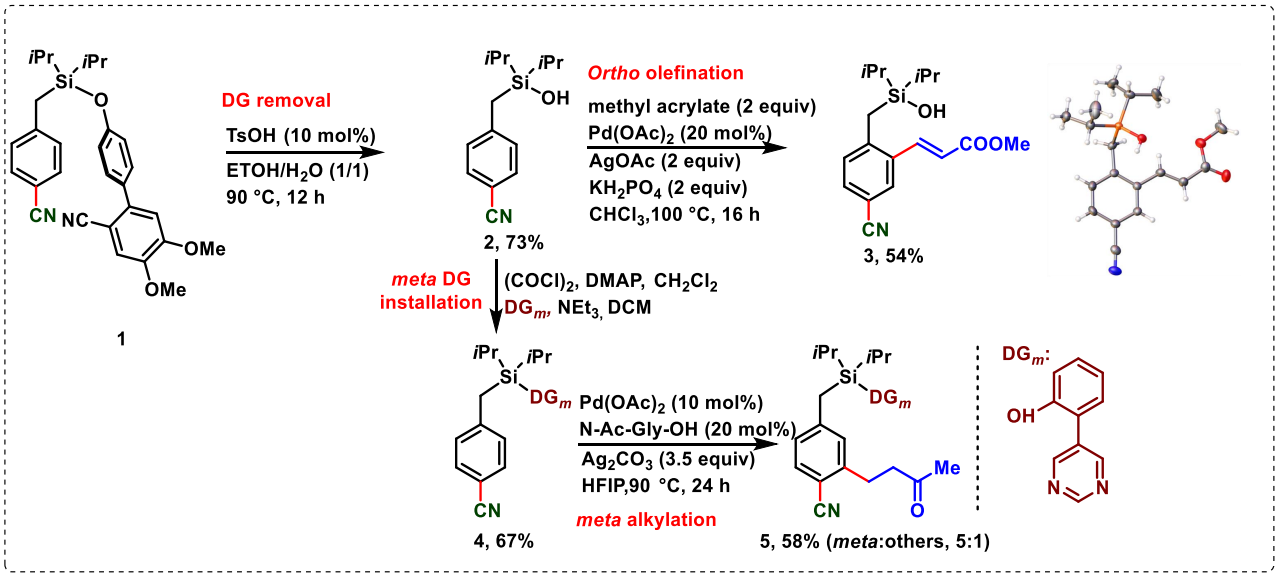
Initially I started investigating with 1st generation template DG_2 (Scheme **6)**. Optimization initial reaction parameters offered a yield of 30% with 2:1 *para* selectivity. During the screening of directing templates from strong coordinating pyridine and quinoline (DG_5-DG_7) improved the yield yet compromised the selectivity. Modification of the electronic environment around the nitrile group showed further improvements ($DG_{1/3/4}$). Maximum output was obtained with dimethoxy substituted template (DG_4). Enhanced electron density due to the presence of dimethoxy group justified the better metal binding and whereas H-bonding interaction with the solvent is likely to provide optimal structural rigidity for superior *para* selectivity. Cuprous cyanide was found to be most effective cyanation agent and N-aceyl-glycine was found best mono-protected amino acid ligand

to enhance the catalytic activity. Among various silver oxidants, Ag_2CO_3 was better suitable with combination of HFIP as solvent to increase the H-bonding interaction. I also optimize the amount of CuCN required and found to be 1 equiv. as optimum and an overall yield of 70% of cyanation product with 10:1 *para:other* selectivity was obtained in presence of 10 mol% $Pd(OAc)_2$, 20 mol% *N*-Ac-Gly-OH, 1 equiv. of CuCN and 2 equiv. of Ag_2CO_3 in hexafluoroisopropanol (HFIP) as solvent.



Scheme 7: *para* selective cyanation of tolyl substrates

Reaction tolerated wide array of substrates with good yields with moderate *p:other* selectivity. To demonstrate synthetic utility of method various post stage synthetic modification is carried out to demonstrate that directing group can be cleaved and product can serve substrate for *meta* selective reactions after installing *meta* directing group. Also, equimolar mixture of deuterated and normal substrate was reacted in present reaction condition indicated pH/pD 1:1 indicating C–H activation step is not rate determining step. Computational studies were carried out in collaboration which indicated that Cu–CN can bind with the carbonate anion (from Ag_2CO_3) to form a stable $CuCN(CO_3)$ species. The transmetallation between the Pd(II) intermediate after C–H activation with $CuCN(CO_3)$ has a high barrier (29 kcal/mol), representing the rate-determining step. While the C–H activation step (24.7 kcal/mol) is reversible. The product showed ability to diversify by removing directing group and it can be used for sequential functionalization as well.



Scheme 8: Recycling of template and iterative functionalization

Publications:

Peer review papers:

1. **Palladium catalyzed distal *para* selective C–H Cyanation of Arene by H–bonded template**
   Pimparkar, S.; Bhattacharya, T.; Maji, A.; Saha, A.; Dutta, U.; Jayarajan, R.; Lu, G.; Lupton, D. W.; Maiti, D.
   (Manuscript Submittted for peer review publication)
   Preprint: https://doi.org/10.26434/chemrxiv.11448690.v1

2. **Ligand enabled chelation assisted C(sp^3)-Alkynylation of Aliphatic Carboxymides**
   Pimparkar, S.; Maiti, D.
   (Manuscript under preparation)

3. **Ligand free Rhodium Catalyzed Selective *para*-C–H Olefination**
   Dutta, U.; Maiti, S.; **Pimparkar, S**.; Maiti, S.; Gahan, L. R.; Krenske, E. H.; Lupton, D. W.; Maiti, D. *Chem. Sci.***, 2019**, *10*, 7426-7432.

4. **Combining Transition Metals and Transient Directing Groups for C–H Functionalizations**
   Bhattacharya, T.; **Pimparkar, S**.; Maiti, D. *RSC Advances*, **2018**, *8*, 19456- 19464 ("Invited Contribution")

5. **Experimental and Computational Studies on Remote γ-C(sp^3)–H Silylation and Germanylation of Aliphatic Carboxamides**
   Deb, A.; Singh, S.; Seth, A.; **Pimparkar, S**.; Bhaskararao, B.; Guin, S.; Sunoj, R. B.; Maiti, D. *ACS Catal*. **2017**, *7*, 8171-8175.

6. **Chelation assisted palladium catalyzed arylation of aliphatic carboxylic acid derivatives** (One of the most downloaded paper in the journal)
   Dey, A[†].; **Pimparkar, S**[†].; Deb, A.; Guin, S.; Maiti, D. *Adv. Synth. Catal.* **2017**, *359*, 1301-1307.
   [†]Contributed equally

7. **Switch to Allylic Selectivity in Cobalt-Catalyzed Dehydrogenative Heck Reactions with Unbiased Aliphatic Olefins**
   Maity, S.; Kancherla, R.; Dhawa, U.; Hoque, E.; **Pimparkar, S**.; Maiti, D.; *ACS Catal.* **2016**, *6*, 5493-5499.

8. **Palladium-Catalyzed Directed *para* C–H Functionalization of Phenols**
   Patra, T.; Bag, S.; Kancherla, R.; Mondal, A.; Dey, A.; **Pimparkar, S**.; Agasti, S.; Modak, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751-7755