Palladaelectro-catalyzed olefination reaction: distal and asymmetric approach

Indian Institute of Science Education and Research Pune

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Certificate

This is to certify that this dissertation entitled "Palladaelectro-catalyzed olefination reaction: distal and asymmetric approach" towards the partial fulfilment of the BS-MS dual degree programme at the Indian Institute of Science Education and Research, Fune represents work carried out by Swastik Biswas at Indian Institute of Technology(IIT) Bombay under the supervision of Prof. Debabrata Maiti, Professor, Department of Chemistry during the academic year 2022-2023

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Declaration

I hereby declare that the matter embodied in the report entitled "Palladaelectro-catalyzed olefination of arenes with dual faceted selectivity: distal and enantioselectivity are the results of the work carried out by me at the Department of Chemistry, Indian Institute of Technology (IIT) Bombay, under the supervision of Prof. Debabrata Maiti and the same has not been submitted elsewhere for any other degree

NAME OF STUDENT : SWASTIK BISWAS

(Swastik Biswas, 14/05/23)

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Finally, I would also like to express my deepest gratitude to my parents, Tinni and Mimi for their unwavering support and encouragement throughout my academic journey. Their love and encouragement have been a constant source of motivation for me, and I am truly grateful for their presence in my life.

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Abstract

One of the most traditional C-H activation reaction, Fujiwara-Moritani reaction requires stoichiometric metal oxidant. Electro-organic chemistry provides a greener alternative, where electron is used as the redox equivalent. Site specific C-H activation coud be achieved through the usage of directing groups (DGs). However, in thermal condition, site specificity could be severely hampered due to molecular bending/rotating motion of DGs and cleavage of DGs through trans esterification with the solvent molecules.

Electro-organic reaction proceeds through benign reaction conditions so C-H activation can even occur in room temperature avoiding thus circumventing all issues related to thermal C-H activation. We envisioned that we might obtain superior site selectivity in meta-para sp^2-H activation. Similarly improved enantioselectivity could be observed in case of biryl oxime which is designed to have internal DG. Using phenylacetic acid scaffold as model substrate, m-exclusive (meta: others > 20:1) and para-exclusive (para: others> 20:1) olefinated product was obtained at respective current conditions. Superior enantioselectivity of e.r. 99:1 was obtained for atroposelective olefination for biaryl-oxime (5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde O-methyl oxime) at 0.4 mA using C as anode and Ni as cathode. Few substrate scopes were explored based on the current optimized electrochemical condition.

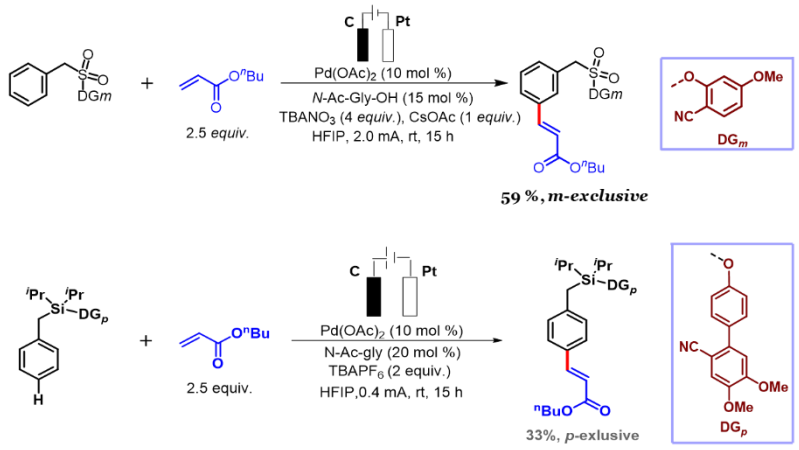

Figure 1 Distal olefination summary

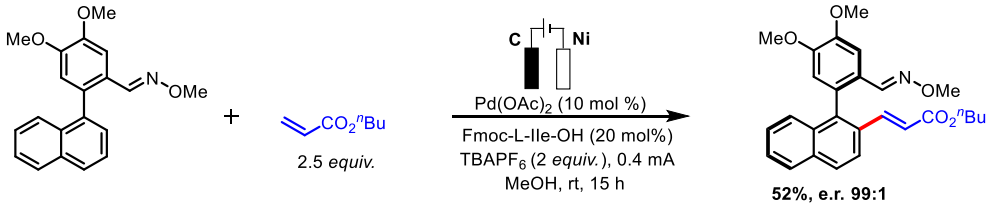

Figure 2 Atroposelective olefination summary

1. INTRODUCTION

1.1 Moving towards C-H activation strategy

Organic molecules play a crucial part in our daily life, ranging from medicines to fertilizers, are made of these molecules.

Synthesis of these molecules always requires functionalization at a specific site. C-C bond formation is the most important transformation among them. Since the early 1950s, functional group interconversion was utilized for C-C bond formation. However, the selectivity and atom economy of the reaction was highly compromised. Later in the 1970s, cross-coupling reactions were introduced which was more efficient than the former strategy and subsequently it was awarded the Nobel prize in chemistry in 2010. C-H bonds are inert and thermodynamically stable, activation of these bonds leads to increased atom economy and minimum metallic waste. Catalytic C-H activation developed in the 1990s has gained a reputation for its superior atom and step economy.(1) Transition metals like Pd and Ir were popularly used for C-H activation due to their variable oxidation states. Recently,3d metal systems such as Co, Mn, Fe, and Ni, have been developed as complementary catalysts. In addition to it, this strategy requires high temperature, metal oxidants, and directing group templates to achieve the desirable site selectivity. Nowadays, substitutes for metal-based oxidants have been developed in photo redox and electrochemical conditions.(2)

1.2 Template-assisted C-H functionalization

The C-H activation was primarily controlled by steric and electronic biases and site selectivity always remained as a major concern. To enhance the site-specificity, directing group (DG) strategy is employed that can even activate non-activated positions of a particular molecule. In this DG strategy, a rigid molecular template is linked to the parent substrate through a suitable linker. This directing group is capable of directing the metal catalyst to the predetermined site in the substrate molecule after weakly coordinating with it. For directing group-assisted C–H functionalization, activating *ortho*-C-H is relatively easier owing to the formation of energetically-favorable, rigid five- to seven-membered metallacycles as intermediates. Nonetheless activating *meta*- or *para*-C–H was inherently challenging as it requires the formation of entropically and enthalpically disfavoured 11-13 membered palladacycles. Distal C-H activation was first achieved in 2012 by Yu's group where meta-selective olefination of benzyl alcohol was reported.(3) Since then, several directing groups were designed for activating specific sites.(4)

The existence of multiple bonds with different chemical reactivity patterns makes the selective functionalization of aromatic compounds challenging. (5) Site-selective C-H bond transformation has been accomplished through a variety of methods for a long time. The introduction of steric bias by bulky groups leads to the direct installation of incoming functionality to a region with less steric demand. (6) However, if there is a steric conflict between the incoming group and the target molecule, the whole process may not be as selective. This may severely restrict the kind of functional groups that could be compatible with the reaction. The addition of electronic biasness provides a successful alternative method for site selectivity. A preinstalled group controls the addition of an incoming

functional group according to the electronic interaction with the specific sites inside the target molecule, this is known as electronic bias. Such preinstalled substituents may generate alternate electronically enriched and deficient locations inside the aromatic molecule as a result of their electronic activity.

These strategies were utilized by Phipps and Gaunt group to establish a copper-catalyzed *meta*-arylation on electron-deficient arenes in 2009.[7] Similar to this, Frost and Ackermann reported the meta-sulfonation of 2-phenyl pyridines and *meta*-alkylation using secondary halides respectively.[8] However, the majority of them were controlled by a known electrical or chelating effect. As a result, the substrate scope was restricted. The concept of a covalently bonded multiatomic molecular framework carrying out a selective functionalization on the target molecule by promoting agostic interactions between the metal catalyst and the target site to be activated opened up new possibilities for C-H activation. The metal may be more easily and specific access to the target spot within the molecule with the help of a distantly positioned coordinating group on the attached chain.[9]

This resulted in the development of a new class of groups known as "directing groups" (DG), which were linked to the target molecule through a bridging linker but had a donor moiety in their tail that could coordinate to the metal catalyst either strongly or weakly. [10]

The employment of the directing group technique resulted in good to exceptional final product yields and enhanced functionalization selectivity. Because the directing groups are so simple to install and remove, this strategy's applicability has grown more and more popular. The directing groups have been discovered to be recyclable in some circumstances.[11]

The Yu group did groundbreaking work in this area when they stated in 2012 that they had successfully used a directing group-based technique to selectively functionalize the meta position of benzyl alcohols and other arenes. Due to its geometrically restricted transition state, selective para-C-H functionalization in arenes was problematic in nature. Using a biphenyl-silyl-tethered D-shaped template, remote *para* C-H functionalization of arene was accomplished by our group (Maiti and coworkers in 2015), allowing for site selectivity in para-olefination and acetoxylation.[12]

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1.3 Origin of Electro-organic chemistry

The first reaction in electrochemistry was invented in 1800.The development of Kolbe electrolysis and Schoebein's dehalogenation of trichloromethane sulfonic acid were influenced by Faraday's early work in electrochemistry, which inspired interest in using electricity to drive organic reactions.

In an electrochemistry setup, a reactive intermediate for further functionalization is produced when the working electrode is coupled to a reaction mixture. For organic electrosynthesis, electrodes are important, however, heterogeneous processes might produce high energy species and passivation that leads to obstruction of further reactions. To prevent this, redox catalysts or mediators were used to oxidize or reduce substrate molecules and form stabilized intermediates. [13,14]

1.4 Importance of Electrocatalysis

Sustainable organic synthesis can be established using alternative energy sources like wind, solar, and hydropower, but using daylight directly is difficult due to changes in energy levels between day and night. The usage of electrochemistry is favourable and is an alluring way to enable chemical reactions compared to others, with the potential for redox transformations in particular, Waldvogel, Baran, Yoshida, and Xu have made significant contributions to the electro-organic synthesis, which has gained momentum. It has the potential to replace expensive stoichiometric redox reagents in organic-synthesis with convenient, affordable electricity.

Other important developments include electrogenerated base and acid syntheses which use electromotive force to carry out proton transfers in a sustainable way. In 1975, Miller was the first to postulate a fresh approach to chiral electrodes for asymmetric catalysis. This led to the invention of shono oxidation in the same year where α-functionalization of alkyl amide was achieved. The bulkiness of a protecting group is considered as prime determining factor of stereochemistry in electrochemical oxidation reactions. Matsumura et al. found that methoxylated serine derivatives exhibited "memory of chirality" due to the presence of a bulky o-phenyl benzoyl-protecting group in the electrochemical oxidation of N-acylated serine derivative. [15,16]

1.5 Developments in Pd assisted electrocatalytic C-H activation

Throughout the past few decades, palladium-catalyzed processes have become more important in all areas of synthetic chemistry. Regeneration of Pd(II) catalysts from palladium(0), stoichiometric oxidants are necessary and electrochemical oxidation has emerged as an affordable substitute for it. One of the classical examples is Wacker oxidation, which needs huge amounts of copper and palladium salts for the former process. Tsuji and coworkers revealed an electrochemical Wacker process that converted palladium using a benzoquinone mediator. TEMPO was also used as a mediator in anodic oxidations to convert Pd(II) from Pd(0)·.When $Pd(OAc)_2$ undergoes Kolbe's decarboxylation a highly reactive Pd(II) species is generated. Cross-coupling between terminal alkynes and aryl boronic acids is a more recent use of the $Pd(OAc)_2$/TEMPO system. Amatore, Jutand, and colleagues identified an electrochemical Heck reaction involving N-acetylcarnitine and a redox mediator such as benzoquinone or hydroquinone. The process starts with the initial C-H palladation which is an electrophilic palladation, followed by olefin addition and hydride removal. The Pd(II) catalyst becomes Pd(0), and a benzoquinone oxidant is needed to restart the catalytic cycle. This led to the invention of the anodic protocol using anaerobic conditions and molecular oxygen
For the first time, Mei and coworkers showed that anodic oxidation can be used to support Pd (II) to catalyze sp^3 C-H functionalization (acetylation). By activating C-H with $Pd(OAc)_2$, this transition makes use of an oxime-ether-based directing group to produce a palladacycle. This Pd (II) complex may be directly anodized, producing a Pd(IV) intermediate that is susceptible to reductive elimination and providing C-H acetylation

products while renewing Pd(II) catalyst. The incorporation of alternative oxygenated functions like OTFA, $OCOC_3H_7$, OTs, or OMe taken in gram scale by replacing the acetate group on the palladium catalyst, the reaction has also been seen in action. Soon after, a similar procedure for acetoxylating sp^2 C-H bonds was also revealed.

Even though the Fujiwara-Moritani reaction is a potent tool for the Pd-catalyzed C-H activation, the reaction is unappealing from an environmental and atom-economical perspective due to the super stoichiometric concentrations of hazardous chemical oxidants. Our group reported the first electrooxidation Fujiwara-Moritani reaction used to olefinate simple arenes in a non-directed and regioselective manner. The ligand-aided oxidative C-H alkenylation of arenes without the use of directing ligands has recently gained recognition due to its improved reactivity and substrate scope expansion. Yu and van Gemmeren independently presented the most recent investigations on the non-directed oxidative C-H olefination of arenes. However, the usage of dangerous and waste-producing oxidants in super stoichiometric concentrations (Ag salts) was unavoidable. Our approach uses a user-friendly undivided cell arrangement and doesn't call for any additional chemical oxidizing agents. This transformation offers a different path for the traditional Fujiwara-Moritani reactions by using electric current in place of hazardous chemical oxidants. Huge functional group tolerance and strong regioselectivities demonstrated the efficacy of this non-directed method. The mechanistic studies indicated that a Pd(III) intermediate connected to a Pd(II)/Pd(IV) catalytic cycle was responsible for the following transformation.[17-30]

1.6 Atropisomerism

Atropisomerism is one of the well-known forms of axial chirality which known to have restricted rotation along a single σ bond either due to steric or electronic effects of the flanking group that raises the rotational barrier more than 23.3 kcal/mol and extended half-life[31]. The first report of atropisomers was experimentally isolated for 6,6'-dinitro-2,2'-diphenic acid by Christie and Kenner[32]. Since then, it have been detected in several natural products having heterobiaryl backbone like Ancistrocladinium A and Marinopyrrole A. It is also found in FDA approved drugs like vancomycin. Another use of atropisomeric skeleton is to make chiral ligand such as BINAP which is used for rhodium-catalyzed asymmetric hydrogenation of acrylic acids. The construction of axially chiral biaryl scaffolds can be accessed through four types of synthetic strategies: atroposelective coupling, prochiral transformation, central-to-axial chirality conversion, and de novo construction[31].

1.7 Asymmetric electrocatalysis

Asymmetric catalysis has been extensively explored to modulate stereochemistry of organic synthesis. On the other hand, electrochemical synthesis is well-known for its sustainable way of controlling reactivity and selectivity of various functionalization reaction in a precise manner. Asymmetric electrochemical synthesis is a merger of these two fields that results refers to the introduction of new elements of chirality into a target

compound through an electroorganic reaction. However, only limited examples of highly enantioselective catalysis of electrochemical reactions have been reported to date. Strategies for catalytic asymmetric electrosynthesis include electrochemical activation of chiral catalyst-bound substrate, asymmetric cascade electrochemical process, chiral media, and chemically modified chiral electrodes (refer **figure 1**)[33-34].

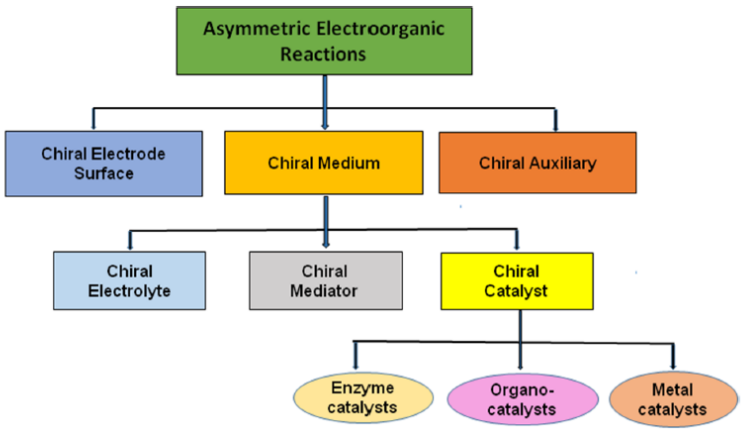


Figure 3 Types of assymmetric Electroorganic reactions

1.8 Electro-organic methods to access Atropoisomers

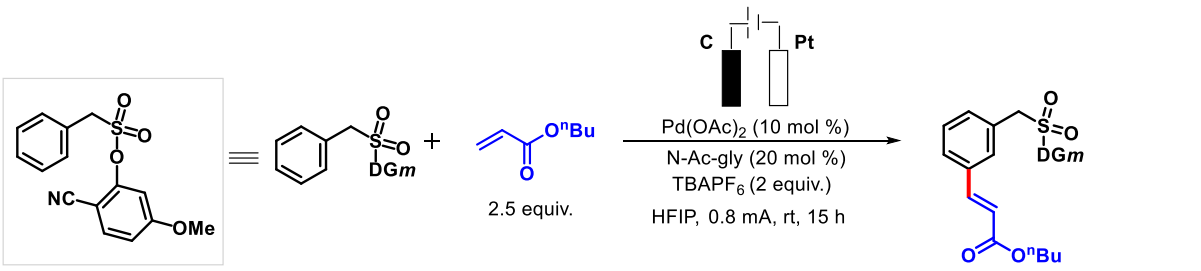
Osa and coworkers first developed an enantioselective approach for the electrocatalytic oxidative coupling of Naphthol, Naphthyl Ether and Phenanthrol utilizing constant voltage, on a graphite felt electrode that has been TEMPO-modified in the presence of (-)-sparteine, to access binaphthyl atropisomers in high enantiomeric excess and yield[35]. The first palladelectro-catalyzed atroposelective C-H activation using transient directing group was reported by Ackerman group for synthesis of axially-chiral olefinated biaryls with high enantioselectivities that could later be transformed into BINOLs, dicarboxylic acids, and helicenes[36]. In continuation of the previous work, the same group has reported the N-C atroposelective olefinations and allylations of indole heterobiaryls utilizing common amino acids as transient directing groups in palladaelectrochemical conditions[37]. The aforementioned two works laid the foundation of the current work in this thesis of atroposelective electrooxidative olefination of biaryl imines, in absence of chemical oxidants.

1.9 Motivation: to address distal selectivity issue and axial enantioselectivity

We envisioned electrochemical condition is one of the possible alternatives to avoid selectivity issues and substrate decomposition due to harsh thermal conditions. It also removes the absolute requirement of stoichiometric amount of silver salt or any oxidant to complete the Fujiwara-Moritani catalytic cycle as anodic oxidation compensates for the oxidation step of Pd(0). The hydrogen evolution reaction also negates the requirement of base for such CMD (Concerted metalation deprotonation)-mediated reaction.

To test our hypothesis, a trial reaction was setup using phenyl-acetic acid sulphoyl ester of 2-hydroxy-4-methoxybenzonitrile (Maiti-Bera-Modak auxillary) with butyl acrylate as the coupling partner. Palladium acetate and N-Acetyl glycine were used as metal catalyst

and ligand respectively in HFIP as solvent and tetrabutyl-ammonium hexafluorophosphate as electrolyte. The current was set at 0.8mA in room temperature conditions. Exclusive yield of meta-olefinated product was obtained of 23% yield.

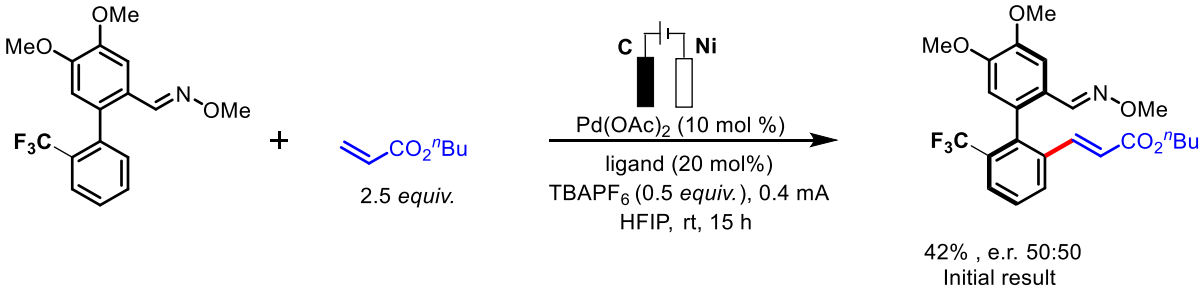


23%

[*m*eta: others = 100:1]

characterized by ^{1}H, ^{13}C, ^{13}C DEPT, mass

Similarly, we initiated a trial reaction for atroposelective C-H olefination of 4,5-dimethoxy-biphenyl 2-trifluoromethyl oxime utilizing metal catalyst complex of Palladium acetate and *N*-acetyl-L-alanine. HFIP was used as solvent, *n-butyl* acrylate as olefinating partner and tetrabutyl-ammonium hexafluorophosphate as electrolyte. Keeping carbon foam as anode and nickel foam as cathode,at 1.2mA current for 16 hours, 42% of olefinated product was obtained with no appreciable enantioselectivity.



42% , e.r. 50:50

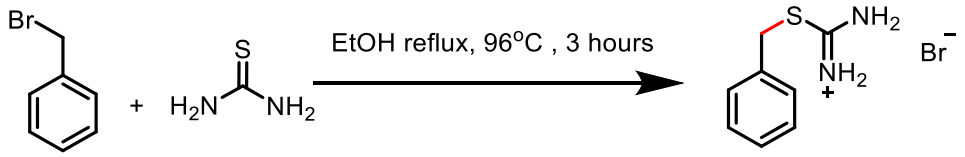
Initial result

Further optimizations of reaction parameters were done to improve the yield and selectivity.

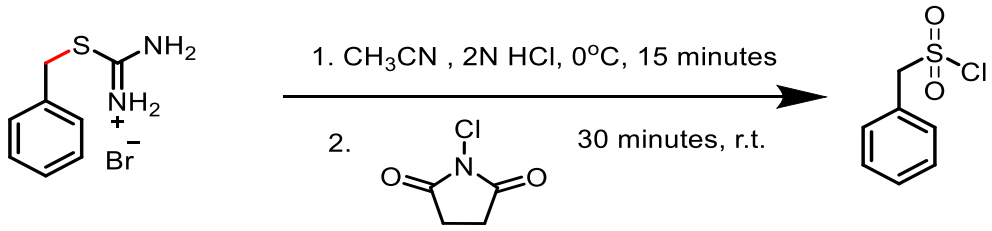
2. METHODS

2.1. Experimental Section – General procedure for preparation of meta-scaffold

- **Preparation of phenylmethanesulfonyl chloride**

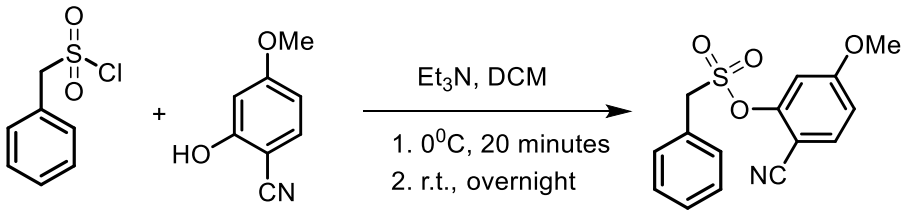


Benzyl bromide (50.0 mmol, 11.895 ml) and thiourea(50.0 mmol, 7.6g) weighed in a 250 ml clean round bottom flask charged with a magnetic stir bar.100 mL of Absolute ethanol was added to it and the mixture was refluxed at 96 °C for three hours. The solvent was evaporated under reduced pressure to produce white solid thiouric salt.



Then, 70 ml of acetonitrile is added to it with 30 ml of 2N HCl under ice-cold condition. It was allowed to stir for 15 minutes at 0 °C. N-chlorosuccinimide (NCS) (400 mmol; 53.4 g) was added portion-wise to the suspension until a clear solution is obtained. At room temperature, the mixture was stirred for an additional 30 minutes. The aqueous layer was then obtained from the solution by evaporating CH_3CN under reduced pressure. The remaining aqueous component after being extracted with ethyl acetate and dried over anhydrous Na_2SO_4, it was purified by column chromatography using silica gel (100-200 mesh size) and petroleum ether/ethyl acetate as the eluent.

- **Preparation of phenylmethanesulfonyl meta-scaffold**



Phenylsulfonyl chloride was added part-wise to an ice-cold solution of 2-hydroxy-4-methoxybenzonitrile (70 mmol, 13.3mg) and TEA (20 equiv., 4.16 ml) in 40 mL dichloromethane under nitrogen atmosphere. After 20 minutes of stirring in the ice bath was removed, and the reaction mixture was kept at room temperature overnight. DCM was evaporated under decreased pressure once the reaction was finished, and the leftover material was extracted with ethyl acetate (3 x 20 mL). Drying of the organic layer was done over anhydrous Na_2SO_4. The crude compound was refined by column chromatography using neutral alumina and petroleum ether/ethyl acetate (85/15, v/v) as the eluent after filtering and solvent evaporation.

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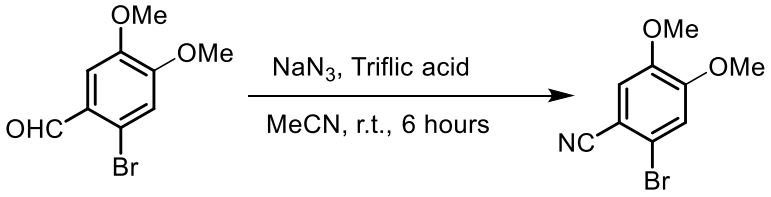
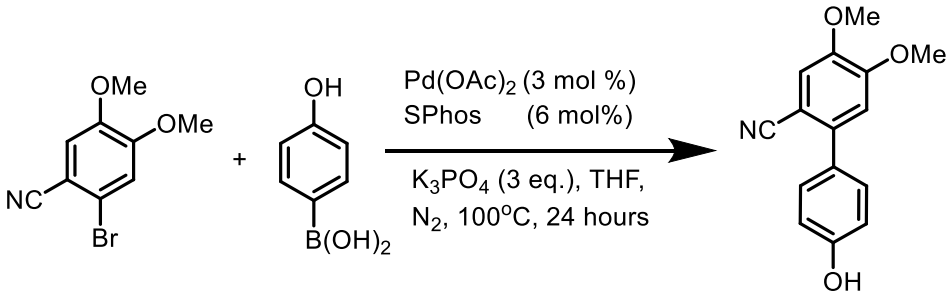
2.2. Experimental Section – Preparation of para-scaffold

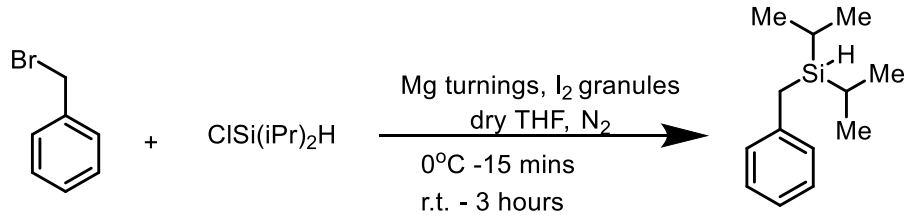
- **Synthesis of para-directing group**



2-Bromo-4,5-dimethoxybenzaldehyde (50.0 mmol) and NaN_3 (3.0 equiv., 150 mmol) were placed in a 250 mL oven-dried round bottom flask charged with a stir bar. CHCN (100 mL) was then added, and the mixture was stirred at room temperature for 15 minutes. Following that, 3.5 equiv. (13.39 ml) of trifluoromethanesulphonic acid was added to the mixture dropwise. The reaction was allowed to stir at room temperature for 12 hours. After the completion of the reaction, the solvent was evaporated under low pressure. The solid residue obtained is dissolved in ethyl acetate, and was extracted in a saturated $NaHCO_3$ solution (3 times). After that, the organic fraction was dried over anhydrous Na_2SO_4 and purified using column chromatography at 4%(v/v) ethyl acetate/pet ether.

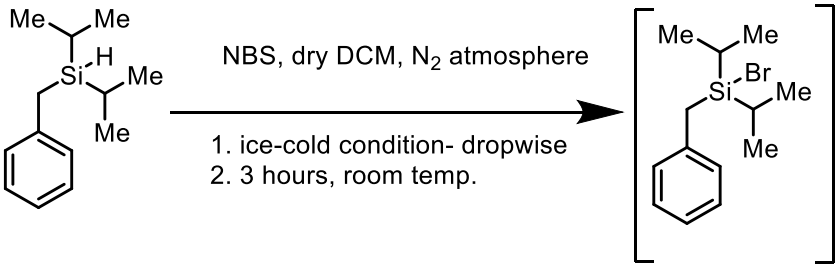


- **Synthesis of silyl ether scaffold**

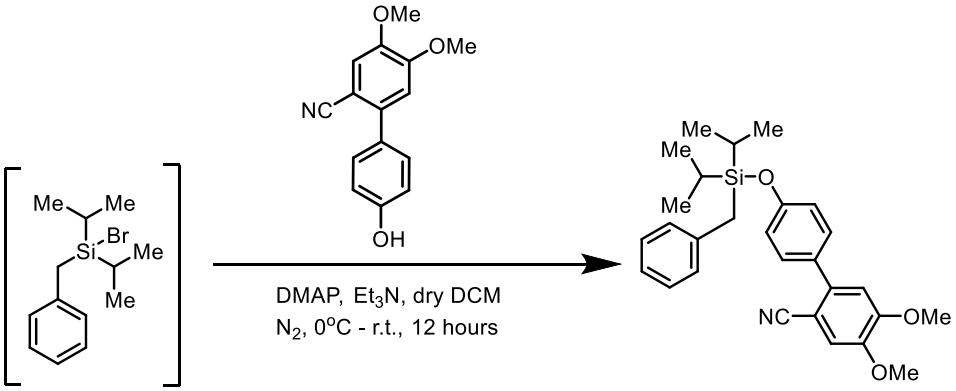


Activated magnesium turnings (30.0 mmol, 3.0 equiv), and one bead of I2, were placed in a clean, oven-dried screw cap reaction tube that was also charged with a magnetic stir bar. Three times, the reaction tube was evacuated and then refilled with nitrogen. Dry THF of 15 mL is then added. Di-isopropylchlorosilane (12 mmol, 1.2 equiv.) was added to it dropwise and stirred for 15 minutes at room temperature. In an ice-cold environment, benzyl bromide (10 mmol, 1 equivalence) in dry THF (10 mL) solution was added to the solution dropwise. For three hours, the mixture was stirred. The reaction mixture quenched upon completion using 10ml brine solution three times.The aqueous part was washed with 20ml ethyl acetate three times., Later, the combined organic layer to dried by passing it through anhydrous Na2SO4. The crude mixture was purified using column chromatography with petroleum ether as the eluent and silica gel (60-120/100-200 mesh size) as the stationary phase. The product was used for the subsequent steps**.**

- **Synthesis of phenylacetic para-directing scaffold**



Under an atmosphere of N_2, benzyldiisopropylsilane (10 mmol, 1.0 equiv.) was added dropwise into an ice-cold suspension of N-bromosuccinimide (12 mmol, 1.2 equiv.) in 10 mL dry DCM. At room temperature, the reaction was stirred continuously for three hours.

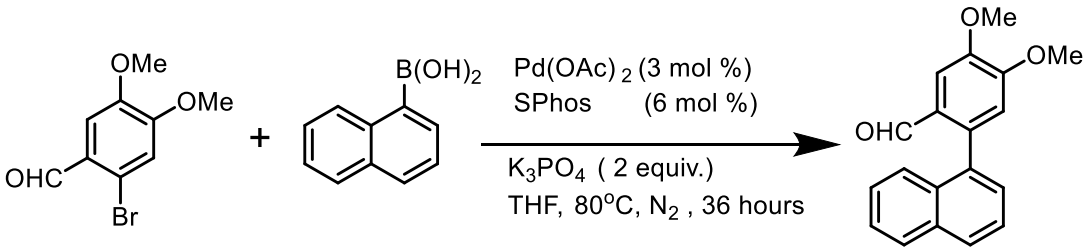


4-hydroxy-4, 5-dimethoxybiphenyl-2-carbonitrile (7.0 mmol, 0.7 equiv.) and 4-dimethylaminopyridine (10 mol%) were placed in a clean round-bottomed flask that was charged with a magnetic stir bar. The apparatus was taken down and then refilled with N2.

The mixture was then given a drop-by-drop addition of TEA (30 mmol, 3.0 equiv.) after receiving 5 mL of dry DCM. The entire mixture was kept warm while being stirred until all of the 4'-hydroxy-4,5-dimethoxybiphenyl-2-carbonitrile was dissolved. Drop by drop, the aforementioned benzylbromodiisopropylsilane solution was added in an ice-cold environment. Following that, the reaction mixture was stirred all night long at room temperature. The mixture was then finished by being quenched with water (20 mL) and extracted three times with ethyl acetate (3 x 30 mL).

2.3. Experimental Section – Preparation of atroposelective-scaffold

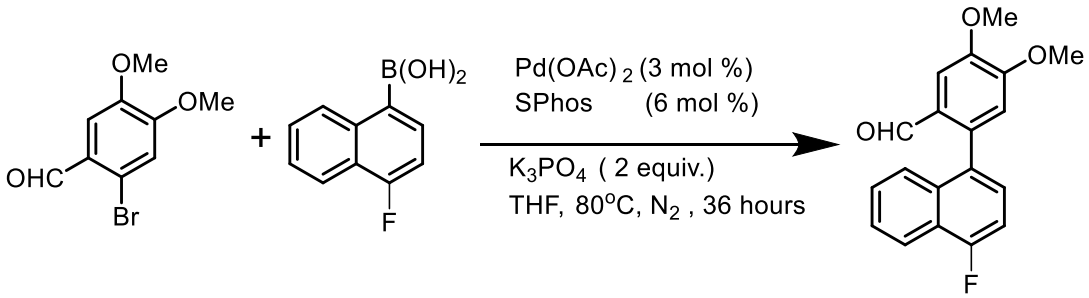
- **Synthesis of biaryl scaffold (4,5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde**



For synthesis of 4,5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde, following the Suzuki cross coupling reaction conditions were followed. A clean, oven-dried screw cap reaction tube was charged with magnetic bead and 2-bromo-4,5-dimethoxybenzaldehyde (1 equiv., 2mmole), naphthalen-1-ylboronic acid (1.2

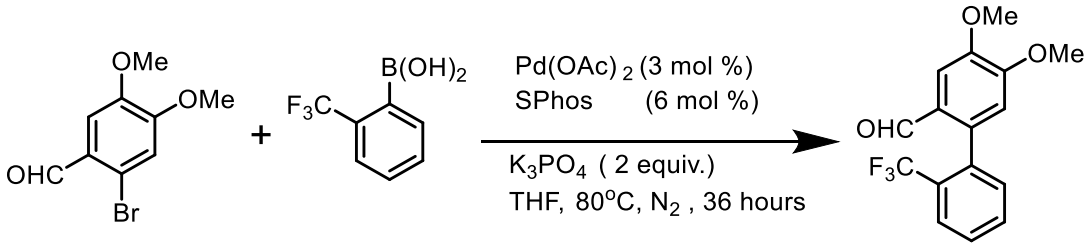
equivalent), palladium (II) acetate (3 mol%), SPhos (6 mol%), and K_3PO_4 (2 equiv.) were added. The cap was then fitted with a rubber septum. The reaction tube was evacuated, filled back up with nitrogen, and this process was repeated three more times. 6 mL of THF was then added to the reaction mixture in presence of the nitrogen. The reaction mixture was vigorously stirred at 75°C on an oil bath for 24 hours. Now, a rotary evaporator was used to evaporate THF from the reaction mixture. The reaction mixture was extracted three times using brine solution (3 x 20 mL) and ethyl acetate (3 x 10 mL). Over anhydrous Na_2SO_4, the organic layer was collected and dried. Under low pressure, the solvent evaporated. By using neutral alumina and ethyl acetate/petroleum ether (20/80, v/v) as the eluent, column chromatographic technique was utilized to purify the product and it was obtained as a white solid.

- **Synthesis of 2-(4-fluoronaphthalen-1-yl)-4,5-dimethoxybenzaldehyde scaffold**



To synthesize 2-(4-fluoronaphthalen-1-yl)-4,5-dimethoxybenzaldehyde, the Suzuki coupling reaction conditions were followed. A clean, oven-dried screw cap reaction tube was charged with magnetic bead and 2-bromo-4,5-dimethoxybenzaldehyde (1 equiv., 2mmole), (4-fluoronaphthalen-1-yl)boronic acid (1.2 equivalent), palladium (II) acetate (3 mol%), SPhos (6 mol%), and K_3PO_4 (2 equiv.) were added. The cap was then fitted with a rubber septum. The reaction tube was evacuated, filled back up with nitrogen, and this process was repeated three more times. 6 mL of THF was then added to the reaction mixture in presence of the nitrogen.
The reaction mixture was vigorously stirred at 75°C on an oil bath for 24 hours. Now, a rotary evaporator was used to evaporate THF from the reaction mixture. The reaction mixture was extracted three times using brine solution (3 x 20 mL) and ethyl acetate (3 x 10 mL). Over anhydrous Na_2SO_4, the organic layer was collected and dried. Under low pressure, the solvent evaporated. By using neutral alumina and ethyl acetate/petroleum ether (20/80, v/v) as the eluent, column chromatographic technique was utilized to purify the product.

- **Synthesis of 4,5-dimethoxy-2'-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde**



Conditions for the Suzuki coupling reaction were followed to synthesie 4,5-dimethoxy-2'-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde. Magnetic beads were added to a clean, oven-dried screw cap reaction tube along with 2-bromo-4,5-dimethoxybenzaldehyde (1 equivalent, 2 mmole), (2-(trifluoromethyl)phenyl)boronic acid (1.2 equivalent), palladium (II) acetate (3 mol%), SPhos (6 mol%), and K_3PO_4 (2 equivalent). A rubber septum was then attached to the cap. The reaction tube was emptied, then refilled with nitrogen. This procedure was then carried out three more times. Then, to the nitrogen filled reaction tubes, 6 mL of THF was added.
For 24 hours, the reaction mixture was stirred at 75°C on an oil bath. THF was then removed from the reaction mixture using a rotary evaporator. Using ethyl acetate(3 x 10 mL) and three separate 20 mL portions of brine solution, the reaction mixture was extracted three times The organic layer was collected and dried over anhydrous Na2SO4. The solvent evaporated under reduced pressure. The product was purified by column chromatography using neutral alumina and ethyl acetate/petroleum ether (20/80, v/v) as the eluent.

- **General synthetic of biaryl-methoxy-oxime**

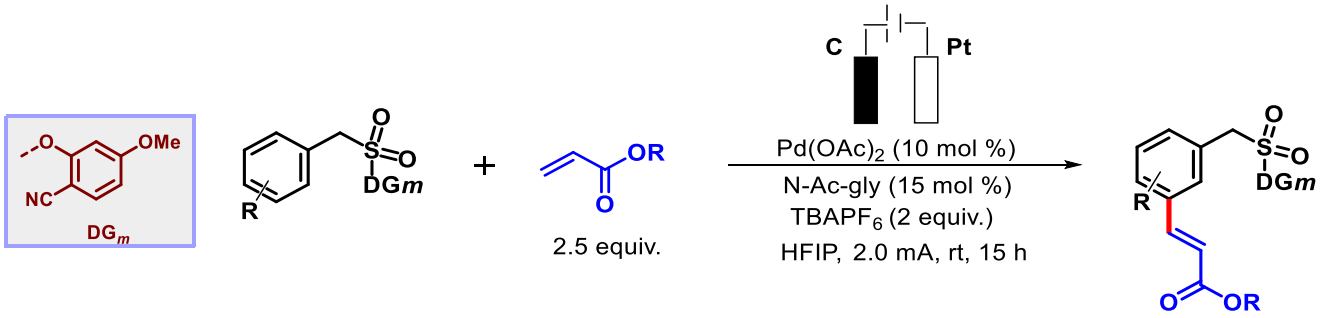
To 1 equivalent of 4,5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde, 1.5 equivalence of O-methylamine hydrochloride is added in a clean round-bottomed flask charged with magnetic bead. To it DCM is added and 4 equivalence of pyridine. It is allowed stir for 2 hours.

2.4. General Procedure for directed electroolefination

For meta-olefination: A carbon wool(GF) anode and a platinum cathode were used in an undivided cell with air to conduct the electrooxidative olefination. In an oven-dried sample vial was charged with magnetic stir-bar, corresponding arene DG adduct (0.05 mmol), $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (15 mol%), electrolyte

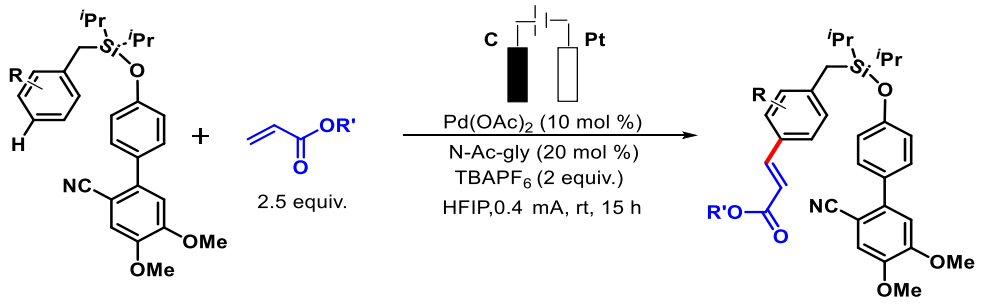
tetra-n-butyl ammonium nitrate(TBANO3) (4 equiv.), and olefinic coupling partner (2.5 equiv.) in 3 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), were added.

The reaction mixture was electrolyzed for 15 hours at room temperature using electrodes that had a surface area of 0.7 cm x 0.7 cm and a constant current of 2.0 mA. After completion of reaction, the graphite anode was filtered through a celite pad and washed with 10 ml of ethyl acetate. After the filtrate was evaporated under reduced pressure, the crude mixture was purified using column chromatography with silica (100–200 mesh size) and petroleum ether/ethyl acetate as the eluent to produce the desired products. the selectivity was observed utilizing the ^{1}H NMR signal and 1,3,5-trimethoxybenzene as an internal standard. The ^{1}H NMR spectra of the olefinated product were used to calculate the regioselectivity.



For para-olefination: A carbon wool(GF) anode and a platinum cathode were used in an undivided cell with air to conduct the electrooxidative olefination. In an oven-dried sample vial was charged with magnetic stir-bar, corresponding arene DG adduct (0.05 mmol), $Pd(OAc)_2$ (10 mol%), N-Ac-Gly-OH (20 mol%), electrolyte tetra-n-butyl ammonium hexafluorophosphate ($TBAPF_6$) (2 equiv.), and olefinic coupling partner (2.5 equiv.) in 3 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), were added.

The reaction mixture was electrolyzed for 15 hours at room temperature using electrodes that had a surface area of 0.7 cm x 0.7 cm and a constant current of 0.4 mA. After completion of reaction, the graphite anode was filtered through a celite pad and washed with 10 ml of ethyl acetate. After the filtrate was evaporated under reduced pressure, the crude mixture was purified using column chromatography with silica (100–200 mesh size) and petroleum ether/ethyl acetate as the eluent to produce the desired products. the selectivity was observed utilizing the ^{1}H NMR signal and 1,3,5-trimethoxybenzene as an internal standard. The ^{1}H NMR spectra of the olefinated product were used to calculate the regioselectivity.



(**a**)

(**b**)

(**c**)

Figure 4 : Photograph of the electro set up (**a**) Electrode used in the reaction (**b**) Reaction vial set up (**c**) Set up during reaction time.

3. RESULTS AND DISCUSSION

(This work is part of an ongoing research work of Prof. D. Maiti's lab. This section is included in my thesis with due permission.)

❖ Results – Optimization of meta C-H olefination

Directing group variation

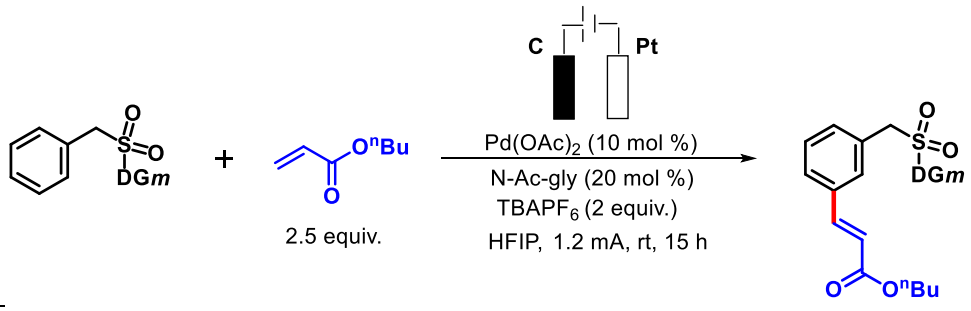
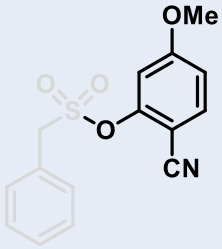
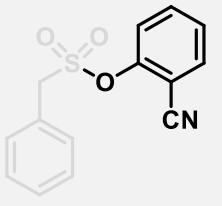
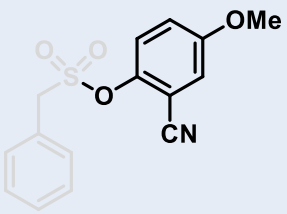
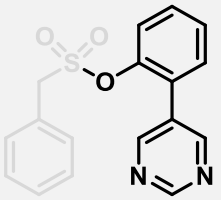
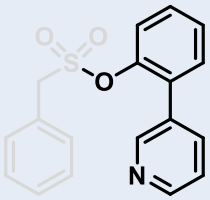
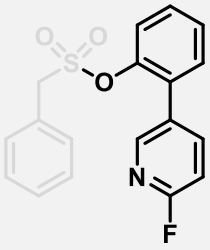
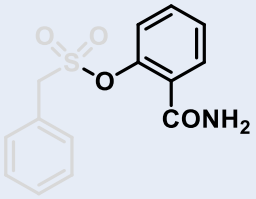
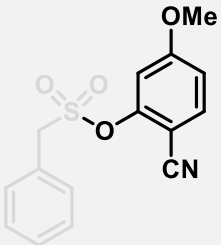
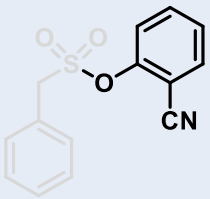


Table 1 Directing group variation

Directing group	Yields
	**23%**
	16%

	18%
	7%
	No Reaction
	No Reaction
	No Reaction
	23%
	16%

Several meta-directing templates were screened ranging from benzonitrile derivatives to benzamide directing group to pyrimidine to pyridine directing groups. Among those meta directing groups, **2-hydroxy-4-methoxybenzonitrile** best yield and selectivity was observed.

Current variation

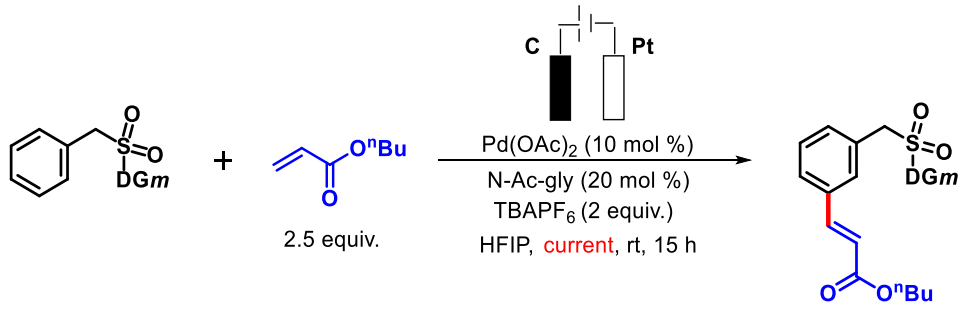


Table 2 Current variation

Current	Yields	Selectivity (*m*:others)
No current	12 %	exclusive
0.4 Ma	31 %	exclusive
0.7 Ma	32 %	exclusive
1.0 Ma	36 %	exclusive
1.2 Ma	21 %	exclusive
1.6 Ma	24 %	exclusive
2.0 Ma	**43 %**	**exclusive**
3.0 Ma	n.r.	-
4.0 Ma	n.r.	-
5.0 Ma	n.r.	-
6.0 Ma	n.r.	-
7.0 Ma	n.r.	-

8.0 Ma	n.r.	-
9.0 Ma	n.r.	-
10.0 Ma	n.r.	-
1.7 Ma	n.r.	-
1.8 Ma	27 %	exclusive
1.9 Ma	40 %	exclusive
2.1 Ma	28 %	exclusive
2.2 Ma	22 %	exclusive
2.3 Ma	n.r.	-
2.4 Ma	n.r.	-
2.5 Ma	n.r.	-

Current was screened from 0Ma (control reaction) to 2.5Ma keeping voltage (30V) constant. At **2.0Ma** highest yield and selectivity was obtained.

Olefin-type variation

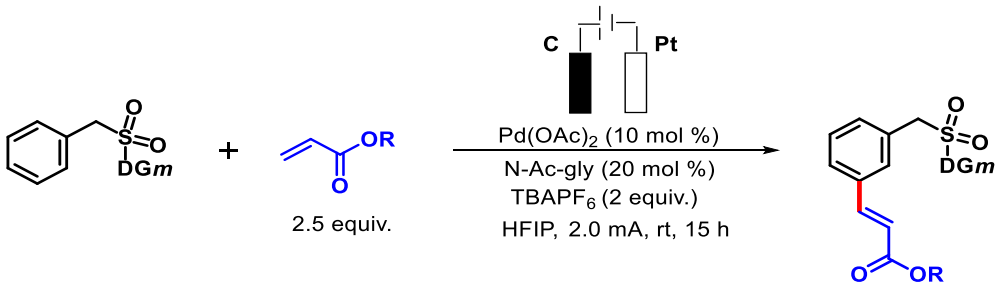


Table 3 Olefin type variation

R	Yields	Selectivity (m:others)
Me	37 %	exclusive
Et	41 %	exclusive
***n*-Bu**	**43 %**	**exclusive**

Olefin coupling partners were screened. Among the available alkyl acrylates, **n-butyl acrylate** gave highest meta-exclusive product.

Metal catalyst complex variation

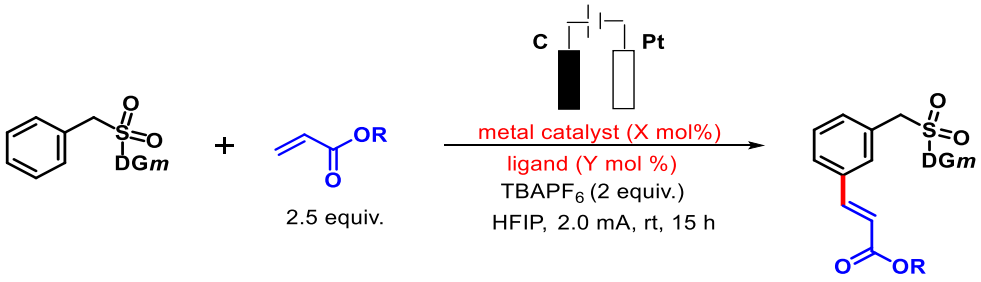
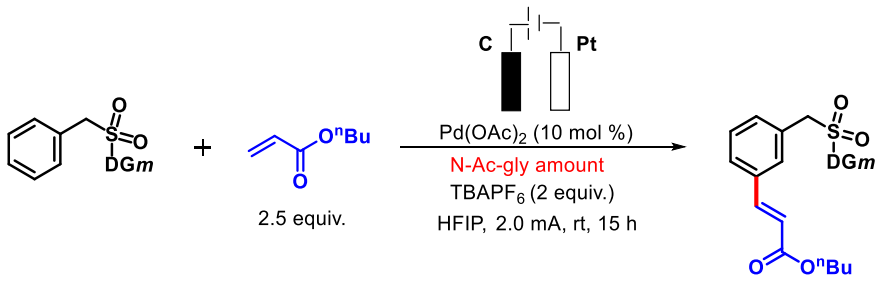


Table 4 Metal catalyst complex variation

Metal catalyst	Ligand	Yields
no catalyst	N-Ac-gly (20 mol%)	no reaction
$Pd(Oac)_2$ (10 mol%)	N-Ac-gly (20 mol%)	43 % [exclusive]
$Ni(acac)_2$ (10 mol%)	-	no reaction
$[Ru(p\text{-}cymene)_2Cl_2]$ (5 mol%)	-	no reaction
$Co(Oac)_2.4H_2O$ (10 mol%)	-	no reaction
$Rh(COD)Cl_2$ (5 mol%)	Xphos (5 mol%)	no reaction
Cp*RhCl2 (5 mol%)	-	11 % [>30:1]

Several permutations of metal catalyst and corresponding ligand were initially screen for their yield and selectivity. Only the combination of $Pd(Oac)_2$ – N-Ac-Gly and $Rh(COD)Cl_2$- Xphos gave appreciable yield. Between these two catalyst complex, **$Pd(Oac)_2$ of 10 mol% and N-Ac-Gly of 20 mol %** gave highest yield and selectivity.

N-Acetyl glycine ligand loading variation



Ligand amount	Yields	Selectivity (*m*:others)
No ligand	n.r.	-
5 mol%	n.r.	-
10 mol%	39 %	exclusive
15 mol%	**47 %**	**exclusive**
20 mol%	43 %	exclusive
25 mol%	24 %	exclusive
30 mol%	n.r.	-
35 mol%	-	-
40 mol%	-	-

N-acetyl glycine ligand loading for screened from 0 mol % to 40 mol %. At **15 mol%** of N-acetyl glycine, highest yield and selectivity was obtained.

Palladium catalyst variation

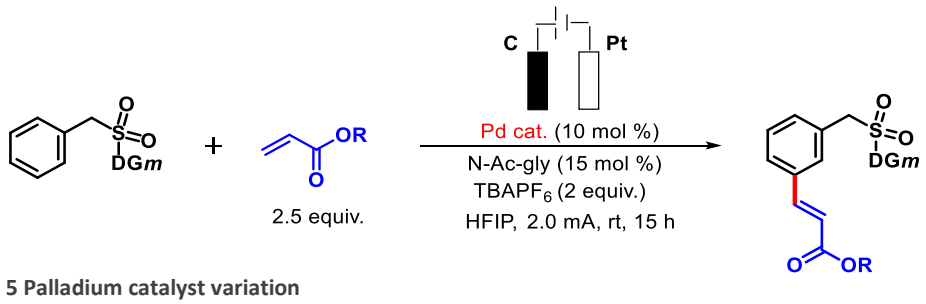


Table 5 Palladium catalyst variation

Pd catalyst	Yields	Selectivity (m:others)
$Pd(Oac)_2$	**47 %**	**exclusive**

$Pd(PPh_3)_2Cl_2$	-	-
$Pd(PhCN)_2Cl_2$	n.r.	-
Pd(π-cinnamyl)chloride	n.r.	-
$Pd(PPh_3)_4$	-	-
$Pd(CH_3CN)_2Cl_2$	n.r.	-
Pd(1,5 cyclooctadiene)Cl_2	n.r.	-
$Pd(Otf)_2$	13 %	exclusive
$Pd(acac)_2$	n.r.	-
$Pd(Opiv)_2$	19 %	exclusive
$PdCl_2$	n.r.	-

Several palladium salts and complexes were screened. Among those Pd salts, **$Pd(Oac)_2$** gave highest yield and selectivity.

Palladium acetate loading variation

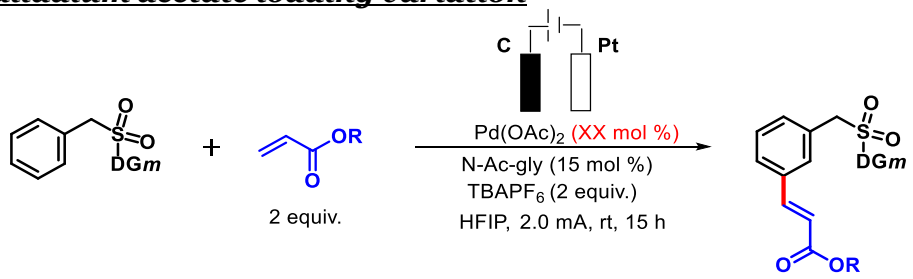


Table 6 Palladium acetate loading variation

Pd cat. Loading	Yields	Selectivity (m:others)
1 mol%	n.r.	-
3 mol%	n.r.	-
5 mol%	21 %	exclusive
7 mol%	19 %	exclusive
10 mol%	**47 %**	**exclusive**
15 mol%	38 %	exclusive
20 mol%	41 %	exclusive
25 mol%	-	-
30 mol%	-	-

Palladium catalyst loading was screened from 1 mol % to 30 mol %. At **10 mol %** of palladium acetate loading, highest meta-exclusive yield was observed.

Electrolyte variation

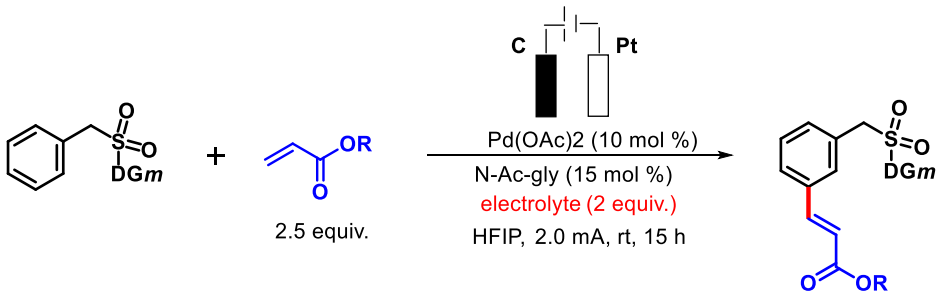


Table 7 Electrolyte variation

Electrolyte	Yields	Selectivity (m:others)
TBAI	n.r.	-
$TBABF_4$	23 %	-
$TBAHSO_4$	20 %	-
NH_4PF_6	n.r.	-
$TBABH_4$	-	-
Choline chloride	-	-
TBAOAc	43 %	exclusive
$TBANO_3$	**53 %**	**exclusive**
TEAP	36 %	exclusive
TMABr	-	-
$TBAClO_4$	no reaction	-
TBABr	31%	exclusive

TBACl	16 %	-
NH_4Cl	no reaction	-
LiClO4	no reaction	-
LiCl	no reaction	-
LiOAc	30 %	exclusive
$NaClO_4$	38 %	exclusive
TPAOH	40 %	exclusive
$(CH_3)_{15}(CH_3)_3NBr$	7 %	-
NH_4Br	no reaction	-
NH_4VO_3	22 %	exclusive
NH_4I	no reaction	-
$(NH_4)_6Mo_7O_{24}.4H_2O$	20 %	exclusive
NH_4SCN	no reaction	-
NH_4F	25 %	exclusive
$(NH_4)_2Ce(NO_3)_6$	no reaction	-
$(NH_4)_2CO_3$	no reaction	-
(Di-n-dodecyl) dimethyl ammonium bromide	no reaction	-

Electrolyte amount variation

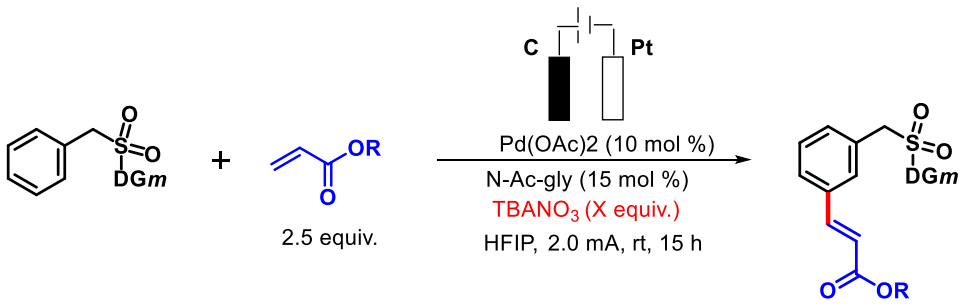


Table 8 Electrolyte amount variation

Electrolyte amount	Yields	Selectivity (m:others)
No electrolyte	8 %	-
1 equiv.	19 %	-
2 equiv.	**53 %**	**exclusive**
3 equiv.	42 %	exclusive
4 equiv.	47 %	exclusive
5 equiv.	n.r.	n.r.
6 equiv.	12 %	-
7 equiv.	n.r.	n.r.
8 equiv.	n.r.	n.r.
9 equiv.	n.r.	n.r.
10 equiv.	n.r.	n.r.

Olefin (n-butyl acrylate) amount variation

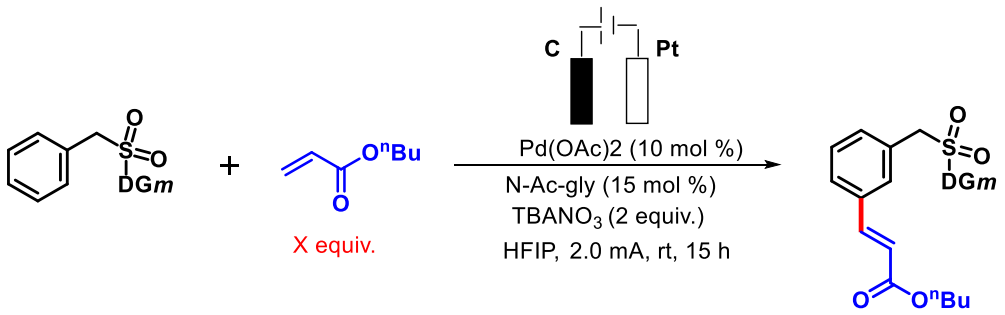


Table 9 Olefin (n-butyl acrylate) amount variation

Olefin amount	Yields	Selectivity (m:others)
0.5 equiv.	7 %	-
1 equiv.	28 %	exclusive
1.5 equiv.	40 %	exclusive
2 equiv.	45 %	exclusive
2.5 equiv.	**53 %**	**exclusive**
3 equiv.	50 %	exclusive
3.5 equiv.	33 %	exclusive
4 equiv.	35 %	exclusive
4.5 equiv.	n.r.	n.r.
5 equiv.	n.r.	n.r.

Ligand type variation

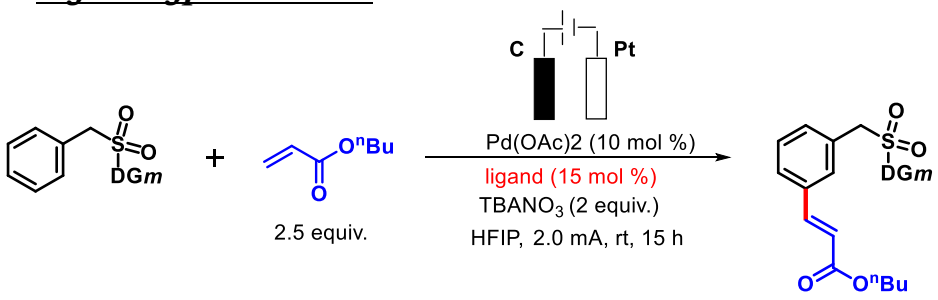
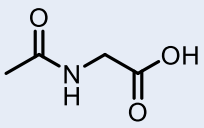
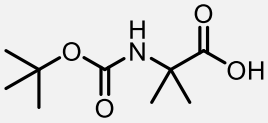
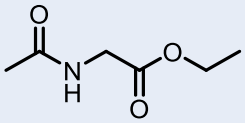
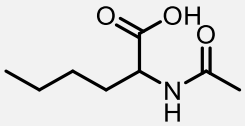
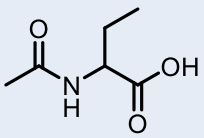
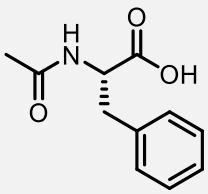
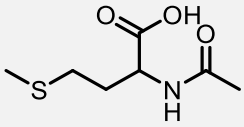
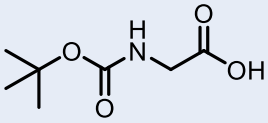
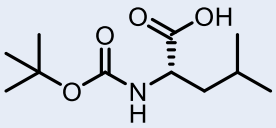
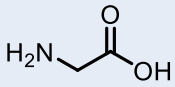


Table 10 Ligand type variation

Ligands	Yields
	**53 %, exclusive**
	no reaction
	43 %, exclusive
	no reaction
	no reaction

	no reaction
	19 %, exclusive
	no reaction
	26 %, exclusive
	19 %, exclusive
	no reaction

Electrode variation

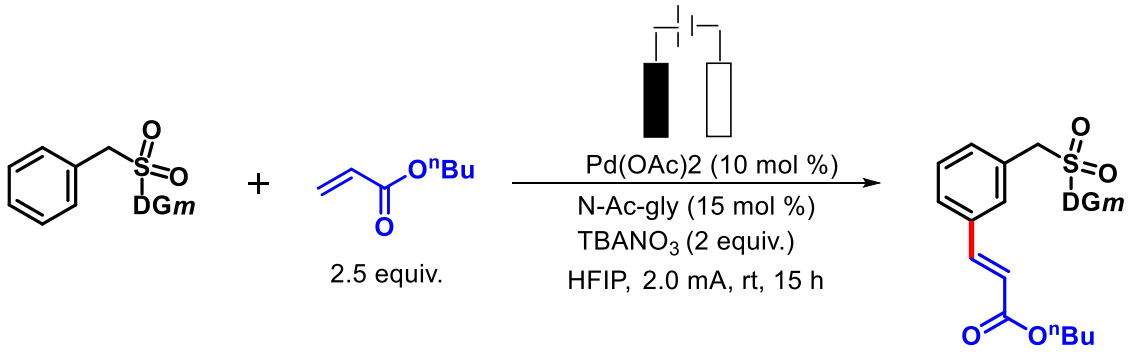


Table 11 Electrode variation

Electrode (anode vs cathode)	Yields	Selectivity (m:others)
C-C	n.r.	n.r.
Pt plate-C	n.r.	n.r.
C-Pt plate	**53 %**	**exclusive**
Pt plate-Pt plate	48 %	exclusive
C-Ni	46 %	exclusive
Ni-C	n.r.	n.r.
Ni-Ni	n.r.	n.r.
C-Pt mesh	n.r.	n.r.
C-Pt wire	41 %	exclusive
C-Pt ring	n.r.	n.r.
C-steel	n.r.	n.r.
C-Cu foam	36 %	exclusive

Cu foam-C	29 %	-
C cloth-Pt plate	48 %	exclusive
Cu foam-Cu foam	29 %	exclusive
Ni-Pt plate	44 %	exclusive
Pt plate-Ni	n.r.	n.r.
Pt plate-Pt mesh	-	-

Solvent variation

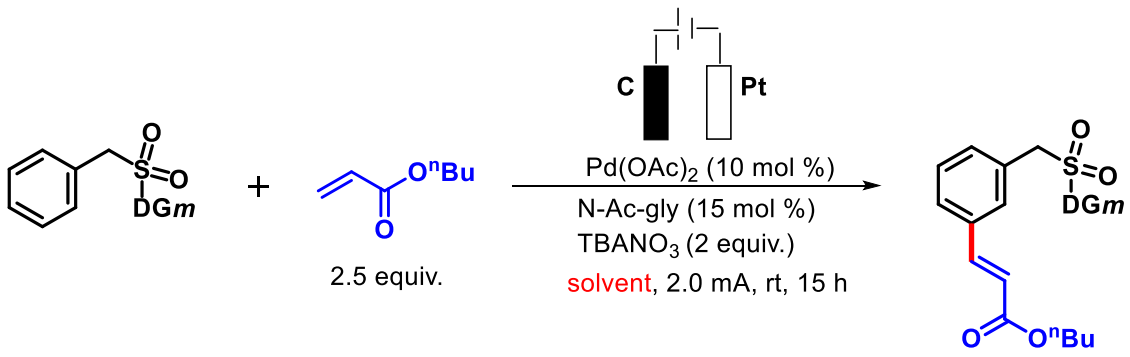


Table 12 Solvent variation

Solvent	Yields	Selectivity (m:others)
HFIP	53 %	exclusive
DCE	21 %	exclusive
CH_3CN	n.r.	n.r.
DCM	n.r.	n.r.
MeOH	n.r.	n.r.

THF	n.r.	n.r.
Toluene	n.r.	n.r.
DMA	n.r.	n.r.
γ-valerolactone	n.r.	n.r.
γ-butylrolactone	n.r.	n.r.
TFT	n.r.	n.r.
DMSO	n.r.	n.r.
t-BuOH	n.r.	n.r.
DMF	n.r.	n.r.

HFIP-DCE mixture variation

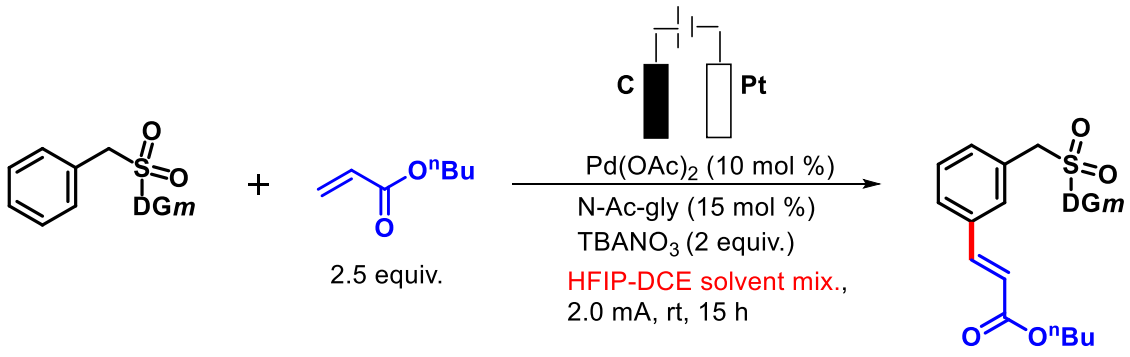


Table 13 HFIP-DCE mixture variation

Solvent	Yields	Selectivity (*m*:others)
HFIP: DCE (1:1)	n.r.	n.r.
HFIP: DCE (2:1)	n.r.	n.r.
HFIP: DCE (3:1)	27 %	>30:1

HFIP: DCE (5:1)	34 %	>30:1
HFIP: DCE (10:1)	42 %	exclusive

Time period variation

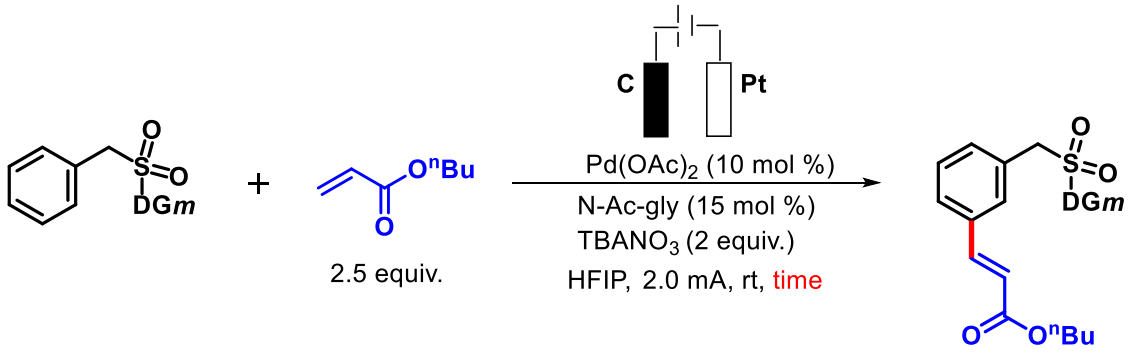


Table 14 Time period variation

Time	Yields	Selectivity (m:others)
3 h	14 %	>20:1
6 h	35 %	>30:1
9 h	41 %	exclusive
12 h	**56 %**	**exclusive**
15 h	53 %	exclusive
18 h	48 %	exclusive
21 h	46 %	exclusive
24 h	43 %	exclusive
26 h	43 %	exclusive
30 h	**57 %**	**exclusive**
33 h	40 %	exclusive
42 h	40 %	exclusive
45 h	n.r.	n.r.
48 h	n.r.	n.r.

60 h	n.r.	n.r.
72 h	n.r.	n.r.

Oxidant variation

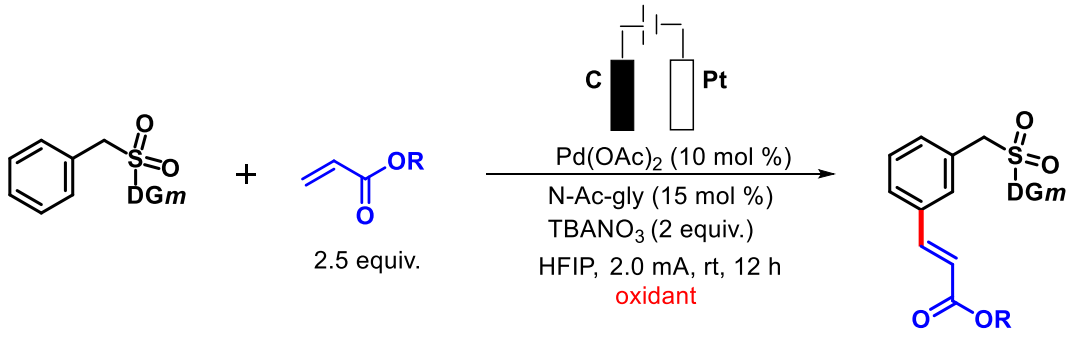


Table 15 Oxidant variation

Oxidant	Yields	Selectivity (m:others)
no oxidant	**56 %**	**exclusive**
BQ- 0.1 equiv.	n.r.	n.r.
BQ- 0.25 equiv.	12 %	>30:1
BQ- 0.5 equiv.	22 %	>30:1
BQ- 0.75 equiv.	n.r.	n.r.
BQ- 1.0 equiv.	34 %	>30:1
BQ- 1.5 equiv.	n.r.	n.r.
BQ- 2.0 equiv.	n.r.	n.r.
BQ- 2.5 equiv.	n.r.	n.r.
BQ- 3.0 equiv.	n.r.	n.r.
Ag_2CO_3- 0.1 equiv.	n.r.	n.r.
Ag_2CO_3- 0.25 equiv.	16 %	>30:1

Ag_2CO_3- 0.5 equiv.	42 %	exclusive
Ag_2CO_3- 1.0 equiv.	46 %	exclusive
Ag_2CO_3- 2.0 equiv.	n.r.	n.r.
AgOAc- 0.1 equiv.	n.r.	n.r.
AgOAc- 0.5 equiv.	n.r.	n.r.
AgOAc- 1.0 equiv.	40 %	exclusive
AgOAc- 2.0 equiv.	n.r.	n.r.

Base variation

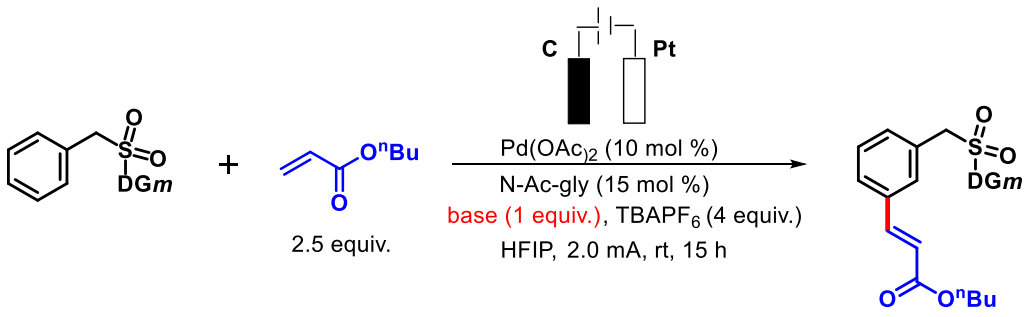


Table 16 Base variation

Base	Yields	Selectivity (*m*:others)
Cs_2CO_3	10 %	n.r.
KOAc	21 %	> 30:1
NaOAc	**45 %**	exclusive
NaO^tBu	17 %	n.r.
NaHCO3	no rxn	-
Na_2HPO_4	**52 %**	exclusive
$KHCO_3$	5 %	n.r.
NH_4Oac	no rxn	-
NaOTf	n.r.	-
KH_2PO_4	n.r.	-
NaH_2PO_4	12 %	n.r.
K_2CO_3	23 %	> 30:1
KOH	no rxn	-
HCO_2Na	**45 %**	exclusive
Na_2CO_3	no rxn	-
NaOMe	no rxn	-
$PhCO_2Na$	**49 %**	exclusive
K_3PO_4	no rxn	-
HCO_2K	no rxn	-
NaOTf	n.r.	-
NaOPiv	no rxn	exclusive
Lio^tBu	15 %	n.r.

LiOAc	8 %	-
CsF	12 %	-
CF_3CO_2Na	no rxn	-
KF	**46 %**	exclusive
NaOMe	15 %	-
CsOAc	**59 %**	exclusive
NaOTs	no rxn	-
NaF	5 %	-

Base equivalence variation

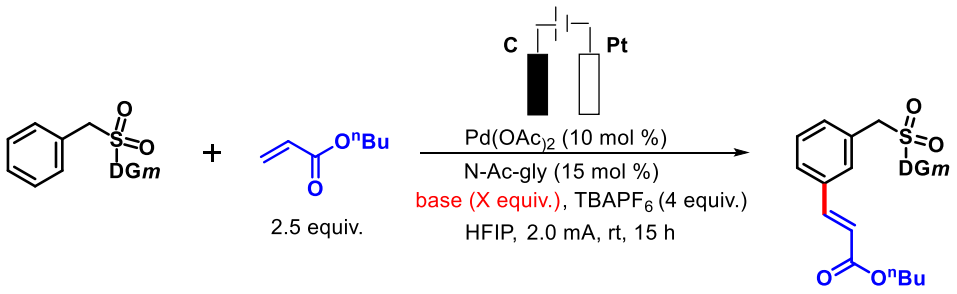


Table 17 Base equivalence variation

Base	Yields	Selectivity (*m*:others)
NaOAc (2 equiv.)	41 %	exclusive
NaOAc (3 equiv.)	35 %	> 30:1
Na_2HPO_4 (2 equiv.)	45 %	exclusive

Na_2HPO_4 (3 equiv.)	32 %	> 30:1
HCO_2Na (2 equiv.)	37 %	exclusive
HCO_2Na (3 equiv.)	30 %	> 30:1
$PhCO_2Na$ (2 equiv.)	45 %	exclusive
$PhCO_2Na$ (3 equiv.)	23 %	> 30:1

❖ Results – Optimization of atroposelective C-H olefination

1. Directing group variation

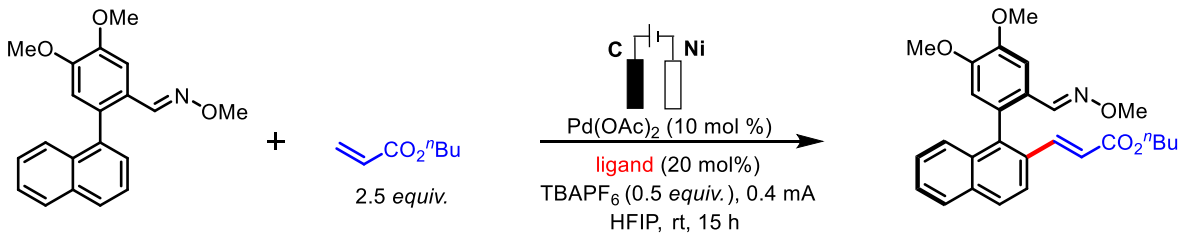
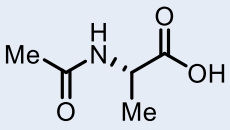
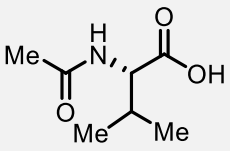
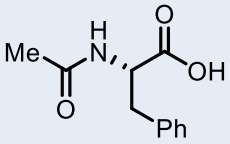
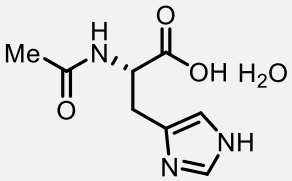
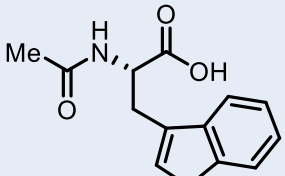
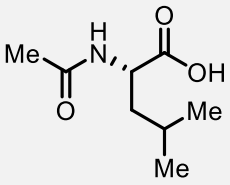
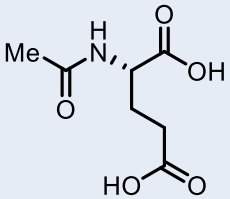
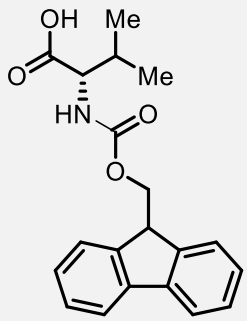
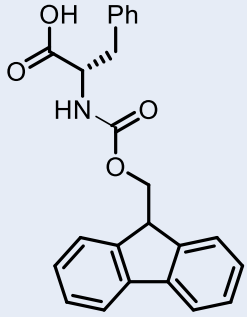
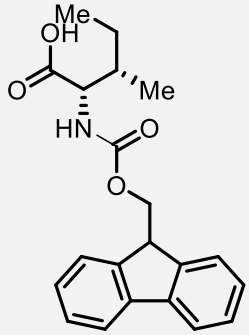
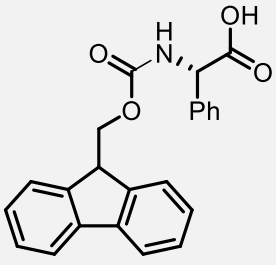
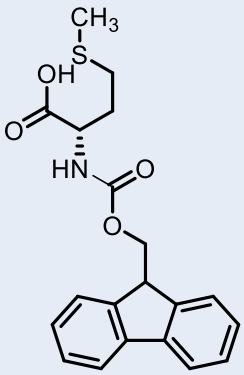
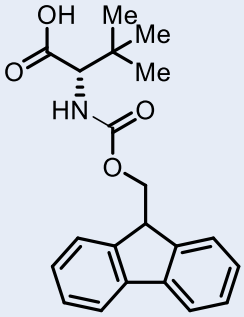
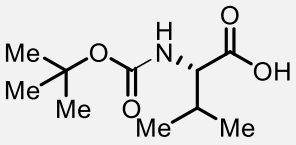


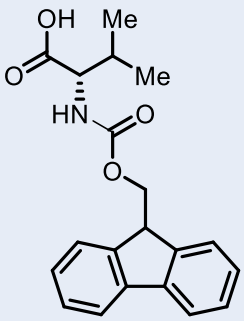
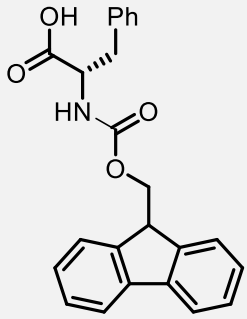
Table 18 Directing group variation

Ligand	Yields	er
 N-Ac-L-Ala-OH	46 %	92:8

 N-Ac-L-Val-OH	53 %	51:49
 N-Ac-L-Phe-OH	48 %	60:40
 N-Ac-L-His-OH. H_2O	42%	51:49
 N-Ac-L-Trp-OH	45 %	53:47
 N-Ac-L-Leu-OH	No Reaction	Not Determined
 N-Ac-L-Glu-OH	No Reaction	Not Determined

 Fmoc-L-Val-OH	52 %	55:45
 Fmoc-L-Phe-OH	50 %	49:51
 Fmoc-L-Ile-OH	57 %	65:35
 Fmoc-L-Phg-OH	51 %	46:54

 Fmoc-L-Met-OH	No reaction	Not determined
 Fmoc-L-Thr-OH. H_2O	**66 %**	**52:48**
 Fmoc-L-Tle-OH	53 %	51:49
 N-Boc-Val-OH		

 Fmoc-L-Val-OH	52 %	55:45
 Fmoc-L-Phe-OH	50 %	49:51

2. Solvent variation

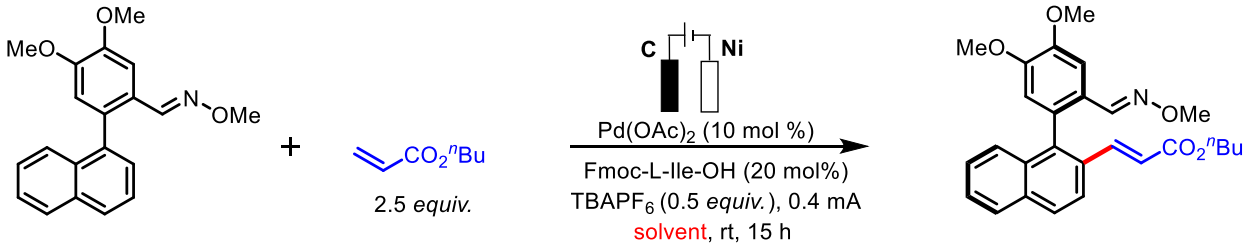


Table 19 Solvent variation

Solvent	Yields	er
HFIP	**46 %**	**92:8**
1,4-dioxane	27 %	77:23
Tetrahydrofuran	22 %	73:27

Dimethyl Formamide	-	-
Toluene	36 %	93:7
Dichloromethane	30 %	63:37
Acetonitrile	-	-
Dichloroethane	34 %	74:26
Methanol	**45 %**	**94:6**
^{t}Butanol	**44 %**	**97:3**
Dimethylacetamide	-	-

3. Solvent HFIP/DCM mixture variation

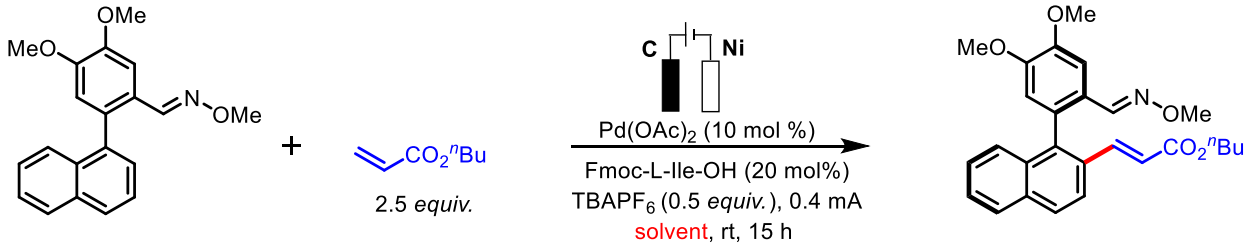


Table 20 Solvent HFIP/DCM mixture variation

Solvent	Yields	er
HFIP: DCM (5:1)	46 %	64:26
HFIP: DCM (2:1)	50 %	55:45
HFIP: DCM (1:1)	47 %	63:37

HFIP: DCM (1:2)	40 %	80:20
HFIP: DCM (1:5)	40 %	64:36
HFIP: DCE (5:1)	47 %	62:38
HFIP: DCE (2:1)	62 %	55:45
HFIP: DCE (1:1)	49 %	60:40
HFIP: DCE (1:2)	60 %	57:43
HFIP: DCE (1:5)	46 %	64:36

4. Ligand-solvent mixture variation

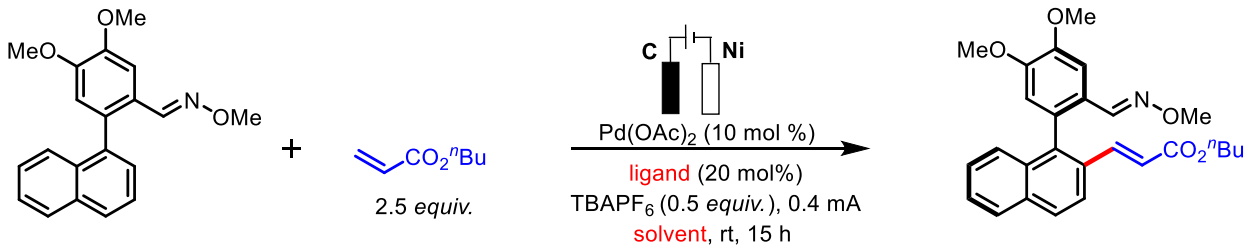


Table 21 Ligand-solvent mixture variation

Ligand	Solvent	Yields	er
Fmoc-L-Thr-OH. H_2O	Methanol	NR	-
Fmoc-L-Thr-OH. H_2O	^{t}Butanol	NR	-
Fmoc-L-Ile-OH	**Methanol**	**45 %**	**99:1**
Fmoc-L-Ile-OH	**^{t}Butanol**	**36 %**	**99:1**
N-Boc-Val-OH	Methanol	48 %	95:5

N-Boc-Val-OH	^{t}Butanol	37 %	98:2
Na-Boc-L-Arg-OH.HCl	Methanol	16 %	-
Na-Boc-L-Arg-OH.HCl	^{t}Butanol	18 %	-
N-Boc-L-His(Ots)-OH	Methanol	NR	-
N-Boc-L-His(Ots)-OH	^{t}Butanol	NR	-
Ne-Boc-L-Lys-OH	Methanol	NR	-

5. Palladium catalyst variation

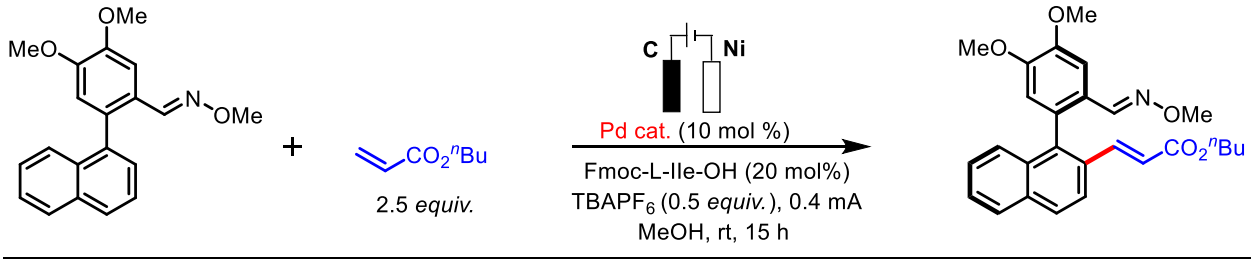


Table 22 Palladium catalyst variation

Pd cat. variation	Yields	er
$Pd(OAc)_2$	**52 %**	**99:1**
$Pd(PPh_3)_2Cl_2$	-	-
$PdCl_2$	-	-
$Pd(PPh_3)_4$	-	-
$Pd_2(dba)_3$	-	-
$Pd(PhCN)_2Cl_2$	-	-

$Pd(acac)_2Cl_2$	23 %	99:1
$[Pd(\ p\text{-cinnamyl})Cl]_2$	28 %	98:2
$Pd(CH_3CN)_2Cl_2$	-	-
$Pd(TFA)_2$	-	-
$Pd(OPiv)_2$	28 %	99:1

6. Electrode variation

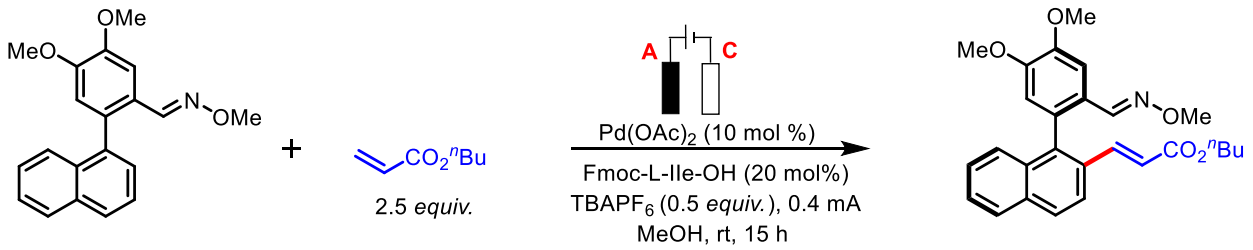


Table 23 Electrode variation

Electrode (anode vs cathode)	Yields	er
C-Ni	**45 %**	**99:1**
C-Pt Plate	35 %	98:2
C-Pt Wire Gauze	38 %	98:2
C-Pt ring	52 %	96:4
C-Pt string	49 %	96:4
C-Cu foam	36 %	96:4
C-Zn Plate	34 %	97:3

C-Mg Plate	no rxn	-
C-Steel	43 %	97:3
C-C	38 %	96:4

7. Electrolyte variation

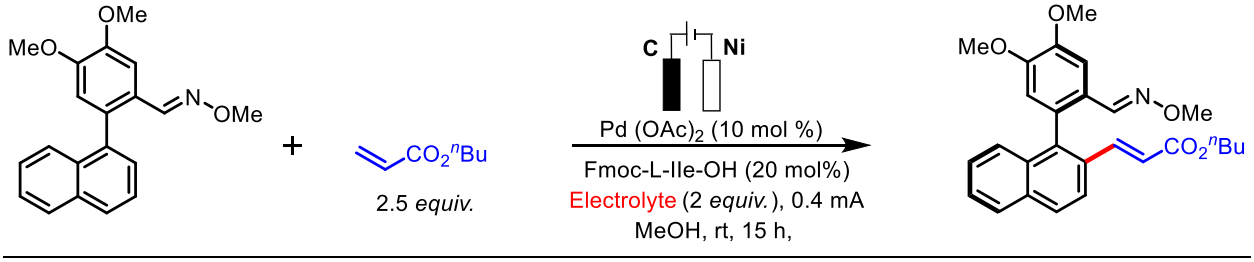


Table 24 Electrolyte variation

Electrolyte	Yields	er
$TBAPF_6$	**52 %**	**99:1**
$TBANO_3$	41 %	98:2
$TBABF_4$	-	-
TBAF	-	-
TBACl	16 %	-
TBABr	trace	-
$TBABH_4$	-	-
$TBAClO_4$	22 %	-
TEAP	37 %	97:3
TMABr	14 %	-
NH_4SCN	-	-

NH_4F	-	-
NH_4Br	12 %	-

8. Current variation

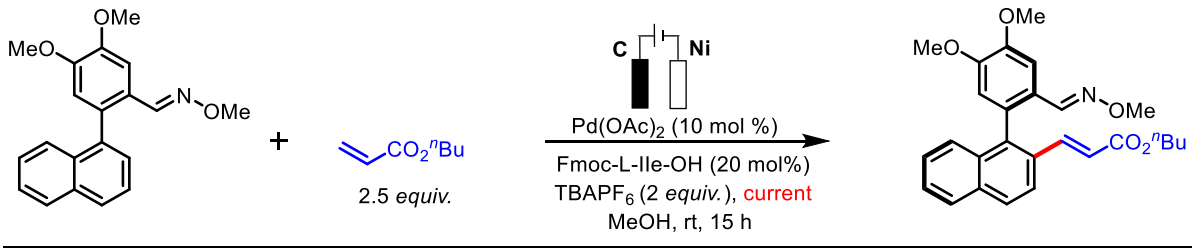


Table 25 Current variation

Current (mA)	Yields	er
no current	20 % (mix. of prd.)	NR
0.1	26 %	97:3
0.2	28 %	96:4
0.4	**52 %**	**99:1**
0.7	38 %	98:2
1.2	34 %	95:5
1.5	34 %	95:5
1.8	NR	-
1.9	36 %	92:8
2	34 %	93:7
2.5	trace	-

❖ Discussion

- ***Meta -olefination***

We have studied meta-olefination using two substrate linkers namely sulphonyl ester and carbonyl ester with acrylates as coupling partners.

For the former linker, sulfonyl ester scaffold, several optimizations were done. Initially, the directing group was varied ranging from cyano-arene directing groups to pyrimidine and pyridine directing group. It was observed that 2-hydroxy-4-methoxybenzonitrile was the best among the directing groups varied providing highest yield. Current variation was studied ranging from 1.6mA to 2.4mA. Highest yield of 43% at an exclusive selectivity was obtained at 2.0 mA.

Olefin variation was done using different kinds of acrylate as coupling partner. Better yield was obtained for butyl acrylate so it was kept as reference for further optimizations. In metal catalyst variation, it was observed that $Pd(OAc)_2$ with N-Acetyl glycine combination gave best yield among all metal complexes including Ni, Rh, Co and Ru. When ligand amount variation was done using N-Acetyl glycine, it was observed that 15 mol% gave the best yield. Similarly, palladium catalyst variation was done, among which palladium acetate was best suited for this reaction. When palladium catalyst loading was done, 10 mol% of $Pd(OAc)_2$ gave the best result.

During electrolyte variation, it was noted that the salts of tetrabutyl-ammonium(TBA) generally gave better yield and among those TBA-nitrate gave the highest yield of 53%. Alkali metal salts and ammonium salts were also screened but no improvement in yield was observed. In electrolyte amount variation which was done from 0 equivalent to 10 equivalents with respect to the sulphonyl-ester of phenylacetic acid, 2 equivalents of $TBANO_3$ had provided with highest yield.

Keeping all other parameters same, 2.5 equivalence of n-butyl acrylate as a coupling partner yielded best result in the optimization of olefin amount. In the same manner, among all N-protected amino acid were screened as a ligand, N-acetyl glycine was found to be most suitable.

For electrode variation, several permutations were tried out using carbon foam, carbon cloth, platinum plate, platinum mesh, platinum ring, steel nickel foam, copper foam as cathode and anode. A highest yield of 53% was obtained for the combination using carbon as anode and platinum as cathode.

When solvent variation was carried out, meta-olefinated product was only formed in HFIP and DCE. Thus, different ratio of HFIP and DCE solution were tried as solvent for this reaction. However, pure HFIP gave the highest yield.

While performing time variation ranging from 3 hours to 72 hours, 15 hours was found to be most suitable time period in terms of yields. In order to improve yield, oxidants like

benzoquinone, silver acetate and silver carboxylate in different amount were added yet no improvement in the yield was observed.

- ***Para -olefination***

  Using 4'-((benzyldiisopropylsilyl)oxy)-4,5-dimethoxy-[1,1'-biphenyl]-2-carbonitrile as model substrate; current, electrode and olefin amount was varied. Those parameters were optimized to 0.4mA, C-Pt (Anode vs. Cathode) and 2.5 equivalence of olefin respectively.

- ***Atroposelective olefination***

The reaction was initially designed to olefinate 4,5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde O-methyl oxime with n-butyl acrylate using 10 mol% palladium acetate and 20 mol% of N-acetyl-l-alanine. Carbon is used as anode and nickel is used as cathode.

Several parameters were screened like ligand, solvent, solvent-ligand combination, electrode combination, metal catalyst, Pd catalyst variation, Pd catalyst loading, ligand loading, base variation, additive variation, electrolyte amount, olefin amount, current, temperature and time period.

Among several N-protected amino acids, N-Acetyl-L-Alaline gave highest enantioselectivity of 92:8 and Fmoc-L-Threonine gave 66% of yield however enantioselectivity was found to be 52:48.

Similarly, various solvents were screened among those HFIP gave highest yield of 46% with enantioselectivity of 92:8. Methanol and tert-butanol gave better enantioselectivities of 94:6 and 97:3 respectively. Hence, using methanol and tert-butanol, few working ligands were screened. Fmoc-L-Ile-OH with methanol was found to best combination among all.

Different electrode combinations were tested. C as anode and Ni as cathode was found to best suited. Among several transition metal catalyst screened, palladium salt is most suitable and among all palladium salts, $Pd(OAc)_2$ is optimum metal catalyst. The loading was optimized to 10 mol % and ligand loading was optimized to 20 mol%. Different bases were tried out, however no significant increase in yield was observed. Electrolyte loading and olefin loading was optimized to 2 equivalence and 2.5 equivalence respectively. Current in the reaction medium was scanned from 0A to 10A, at 0.4mA highest yield was observed. Upon temperature variation from 40 oC to 100 ^{o}C, no role of temperature was observed. In time period variation which was checked from 3 hours to 48 hours, 15 hours was the most appropriate time period.

4. CONCLUSIONS

After initial set of optimizations, it was found that 2-hydroxy-4-methoxy-benzonitrile (abbreviated as DG_m) was the best performing meta-directing group and N-acetyl glycine as the best ligand for this olefination. Sulphonyl ester gave 56% yield with exclusive meta-selectivity at 2.0 mA.

Para-selective olefination was also studied using silyl ether as the linker and 4'-hydroxy-4,5-dimethoxybiphenyl-2-carbonitrile as the para-directing group (abbreviated as DG_p). A yield of 33% with exclusive para selectivity was obtained at 10 mol% Pd catalyst loading and at current of 0.4mA. Tetrabutyl-ammonium hexafluorophosphate was found to be the optimum electrolyte in this case.

The advantage of this method is that only mono-olefination occurs over bis-olefination and the site selectivity for meta: others and para: others in respective cases is greater than 100 :1. It was deduced from the relative peak heights of the olefinic proton doublet at 6.5ppm. This extent of selectivity could not be achieved by similar reports of olefination in thermal condition.

In thermal distal olefination, Yu group has suggested the presence of Pd-Ag heterodimeric cluster to responsible for C-H activation.[37]

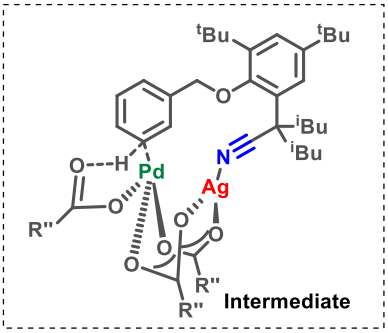


Figure 5 : Proposed Pd-Ag heterobimetalllic cluster for distal C-H activation

In our oxidant-free electro C-H olefination, there is no presence of silver salt. The exact metallocycle formed in this case is still not known. It is also being investigated through spectrochemical and computational techniques.

Biaryl-oxime (5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde O-methyl oxime) was atroposelectively olefinated with superior axiochiral-selectivity of e.r. 99:1 at electric current of 0.4 mA using C as the anode and Ni as the cathode in solvent methanol.

In summary, exceptional distal site selectivity and atropselectivity was achieved in palladaelectric conditions. More substrates to be explored to check applicability of the current reaction schemes over wide range of substrates having different functionalities and deduce the actual mechanism of the olefination reaction.

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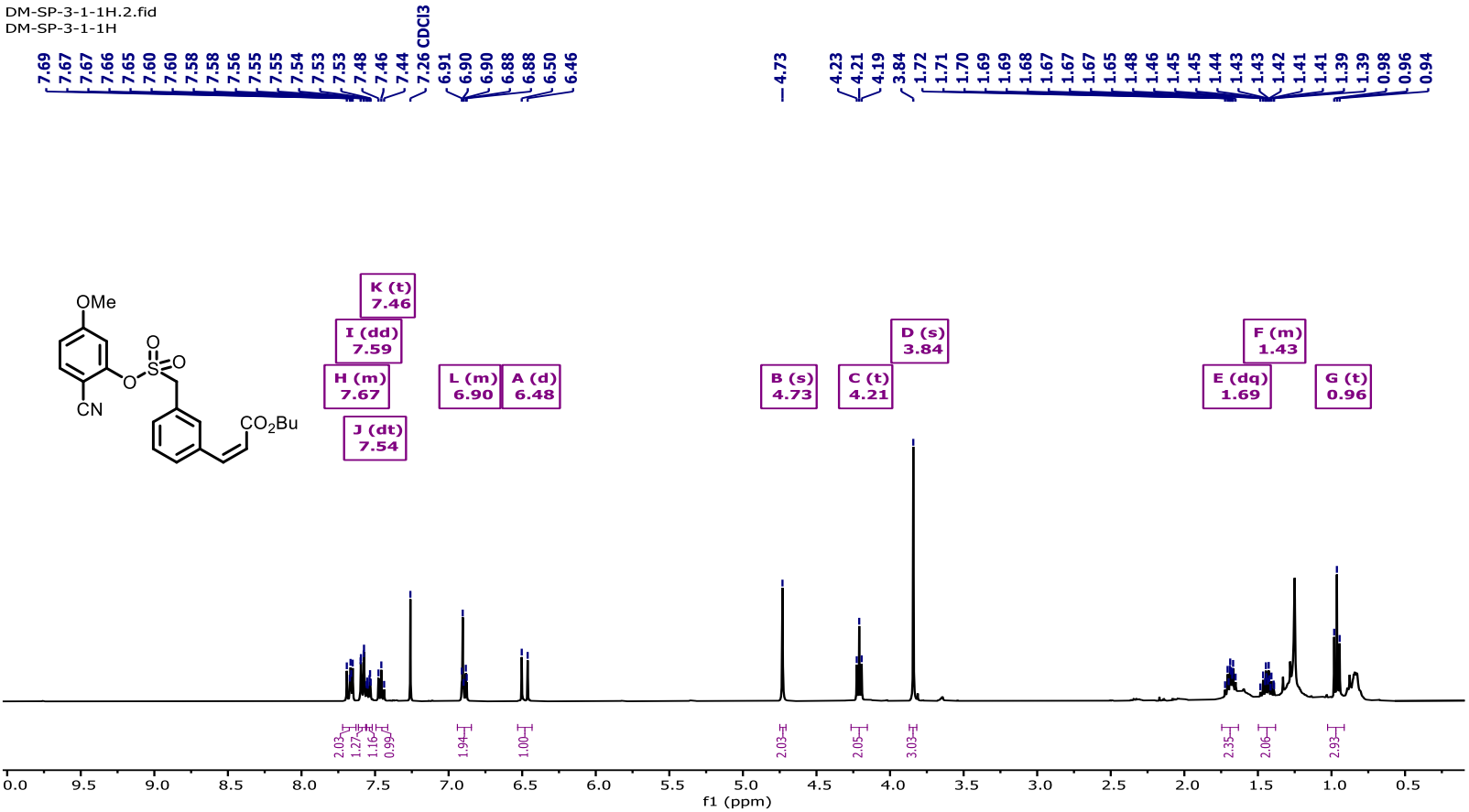
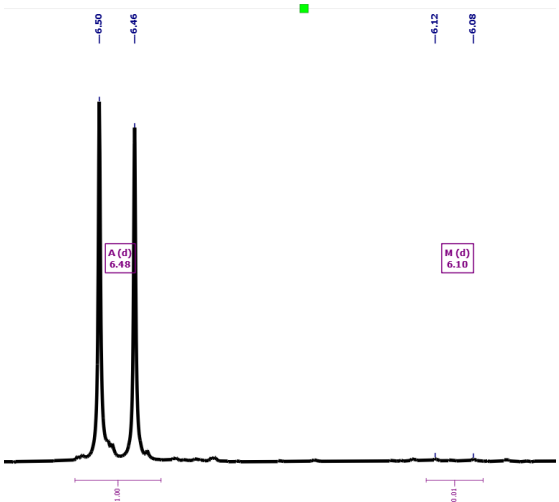
6. APPENDIX

¹H NMR of meta-olefinated product (2-cyano-5-methoxyphenyl (3-(prop-1-en-1-yl)phenyl)methanesulfonate)

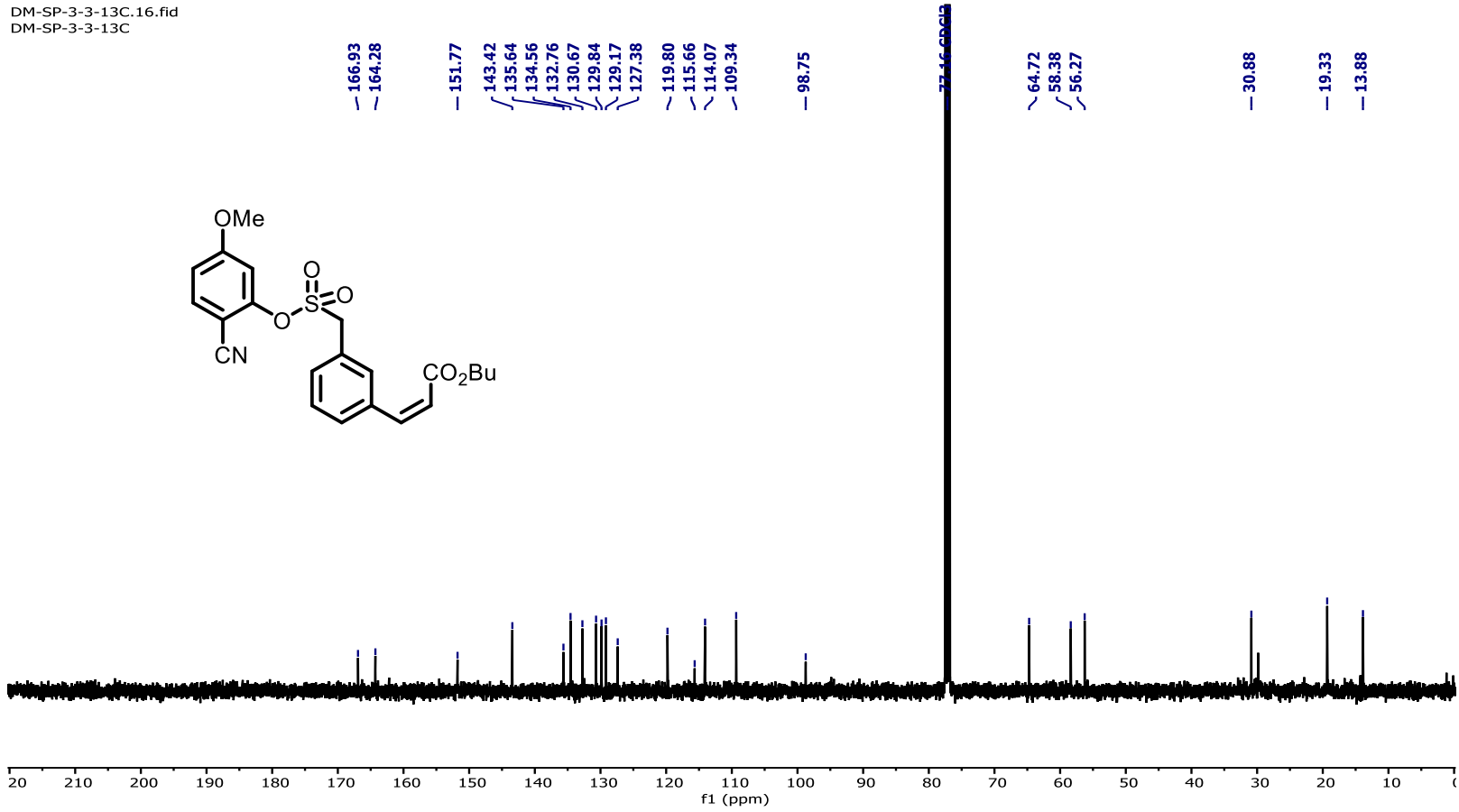


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.63 (m, 2H), 7.59 (dd, J = 8.3, 0.8 Hz, 1H), 7.54 (dt, J = 7.8, 1.5 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.48 (d, J = 16.1 Hz, 1H), 4.73 (s, 2H), 4.21 (t, J = 6.7 Hz, 2H), 3.84 (s, 3H), 1.69 (dq, J = 8.0, 6.7 Hz, 2H), 1.50 – 1.38 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H).

Olefin peak at ∂6.5 – meta vs. others (~ 100 : 1)

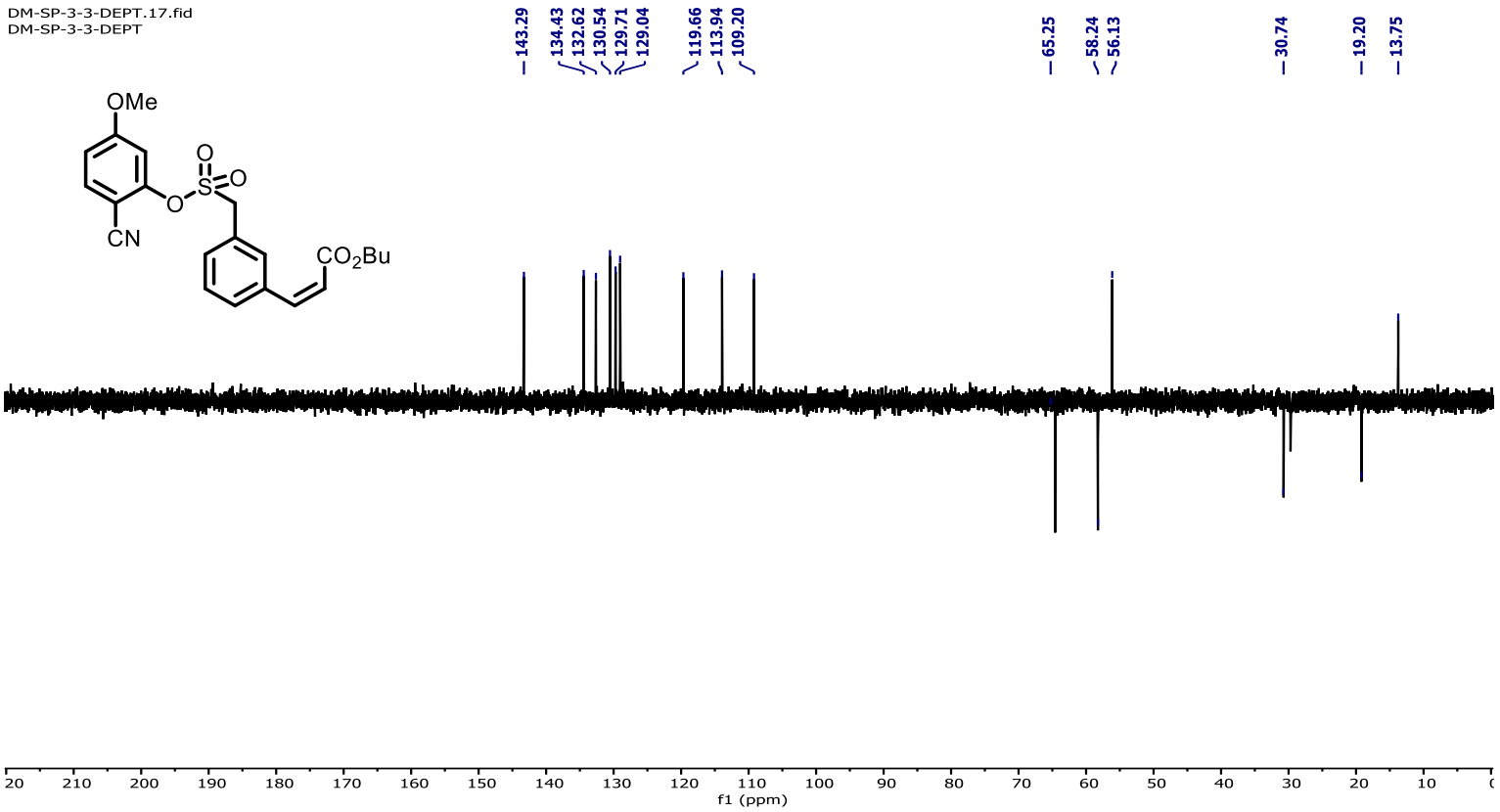


^{13}C NMR of meta-olefinated product (2-cyano-5-methoxyphenyl (3-(prop-1-en-1-yl)phenyl)methanesulfonate)



^{13}C NMR (101 MHz, $CDCl_3$) δ 166.93, 164.28, 151.77, 143.42, 135.64, 134.56, 132.76, 130.67, 129.84, 129.17, 127.38, 119.80, 115.66, 114.07, 109.34, 98.75, 64.72, 58.38, 56.27, 30.88, 19.33, 13.88

^{13}C DEPT NMR of meta-olefinated product (2-cyano-5-methoxyphenyl (3-(prop-1-en-1-yl)phenyl)methanesulfonate)



^{13}C DEPT NMR (101 MHz, $CDCl_3$) δ 143.29, 134.43, 132.62, 130.54, 129.71, 129.04, 119.66, 113.94, 109.20, 65.25, 58.24, 56.13, 30.74, 19.20, 13.75**.**

Mass Spec. of meta-olefinated product (2-cyano-5-methoxyphenyl (3-(prop-1-en-1-yl)phenyl)methanesulfonate)

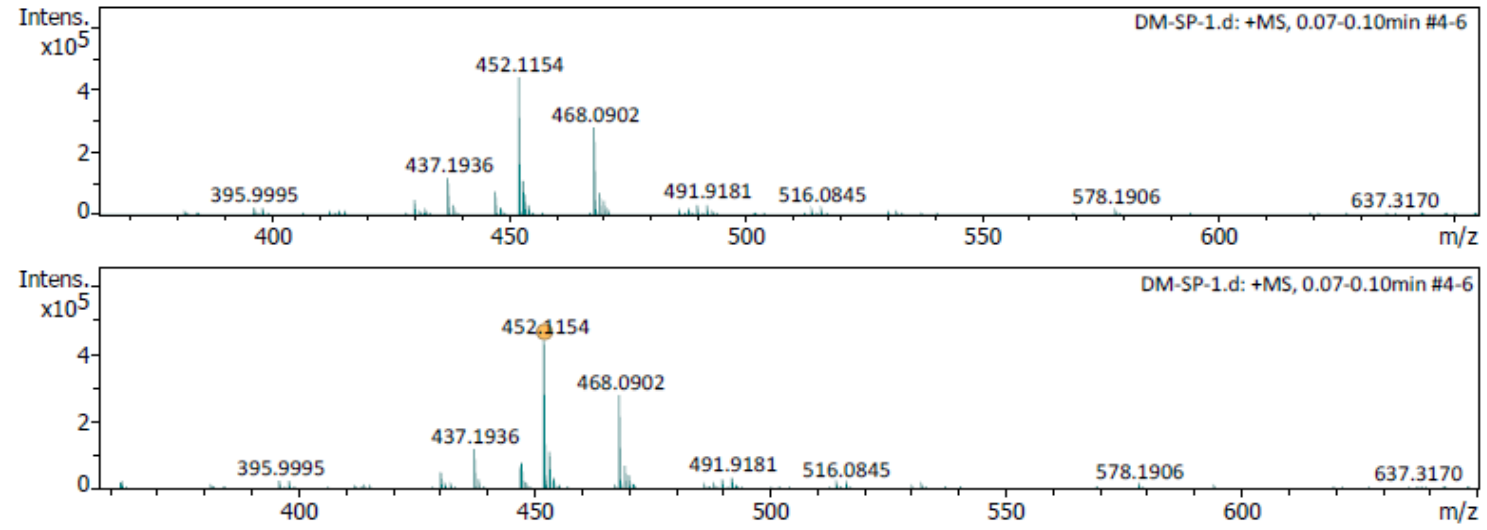
DEPARTMENT OF CHEMISTRY, I.I.T.(B)

Analysis Info

Analysis Name	D:\Data\SEP 21\DM-SP-1.d	Acquisition Date	9/16/2021 9:55:43 AM
Method	NaICsI_pos_1500.m	Operator	GKL-IN
Sample Name	DM-SP-1	Instrument	maXis impact 282001.00081
Comment	C22H23NO6S		

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Not active	Set Capillary	3700 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1500 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Source
		Set Corona	0 nA	Set APCI Heater	0 °C



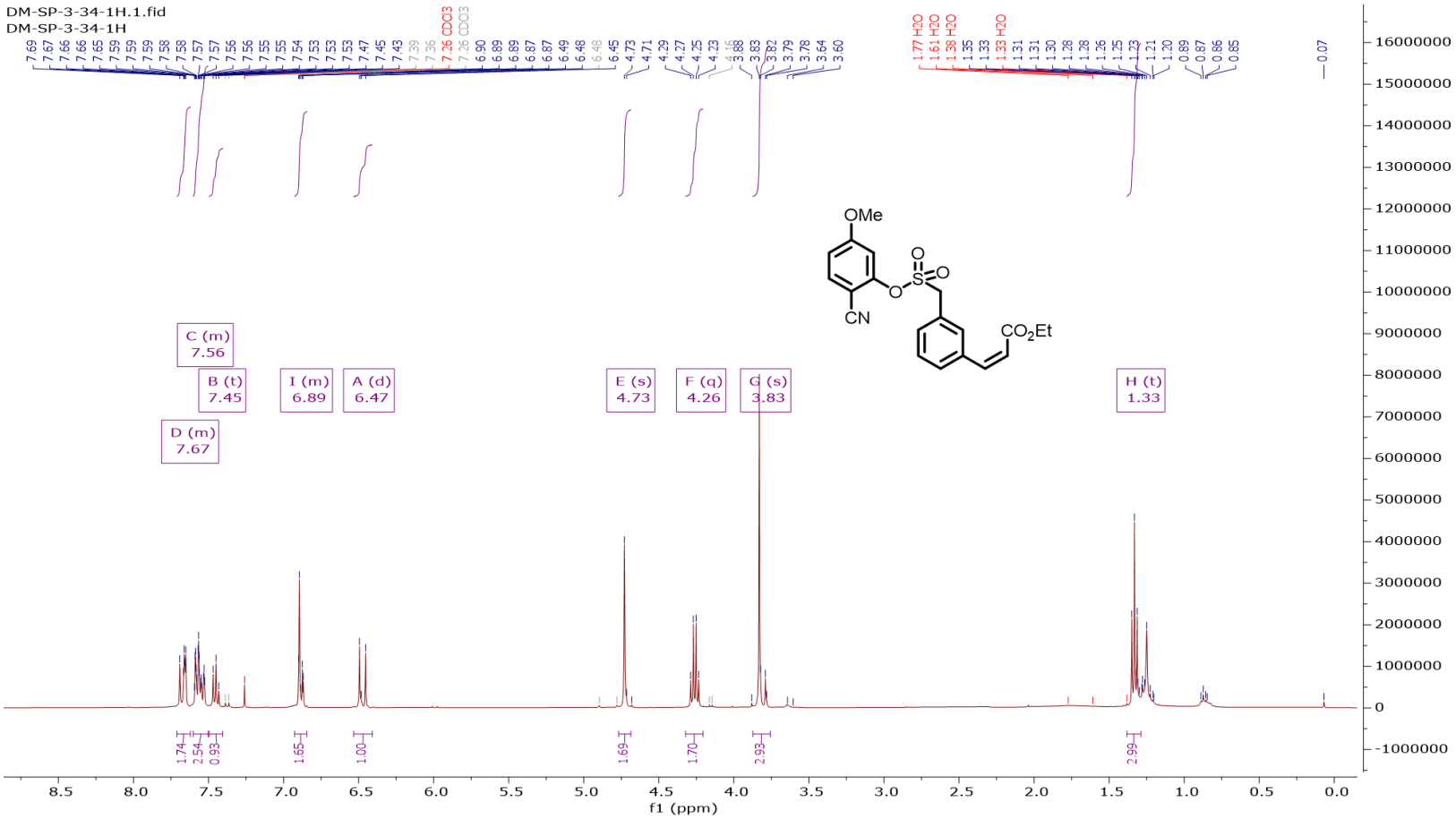
Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e⁻ Conf	N-Rule
452.1154	1	C22H23NNaO6S	452.1138	-3.5	8.4	1	100.00	14.0	even	ok

Chemical Formula: $C_{22}H_{23}NO_6S$

Exact Mass: 429.12

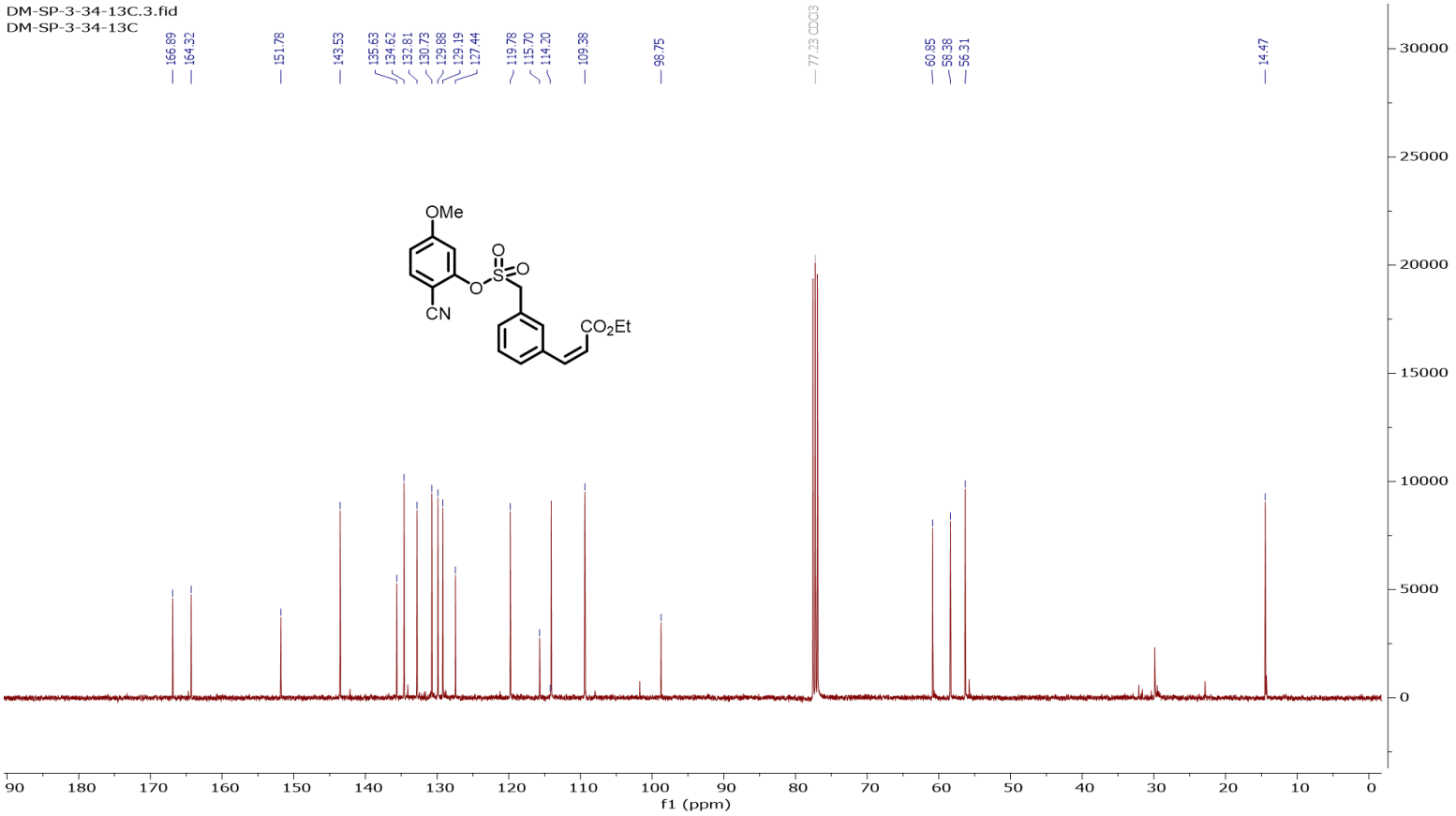
Molecular Weight: 429.49

¹H NMR OF meta-olefinated product (ethyl-3-(3-(((2-cyano-5-methoxyphenoxy)sulfonyl)methyl)phenyl) acrylate)



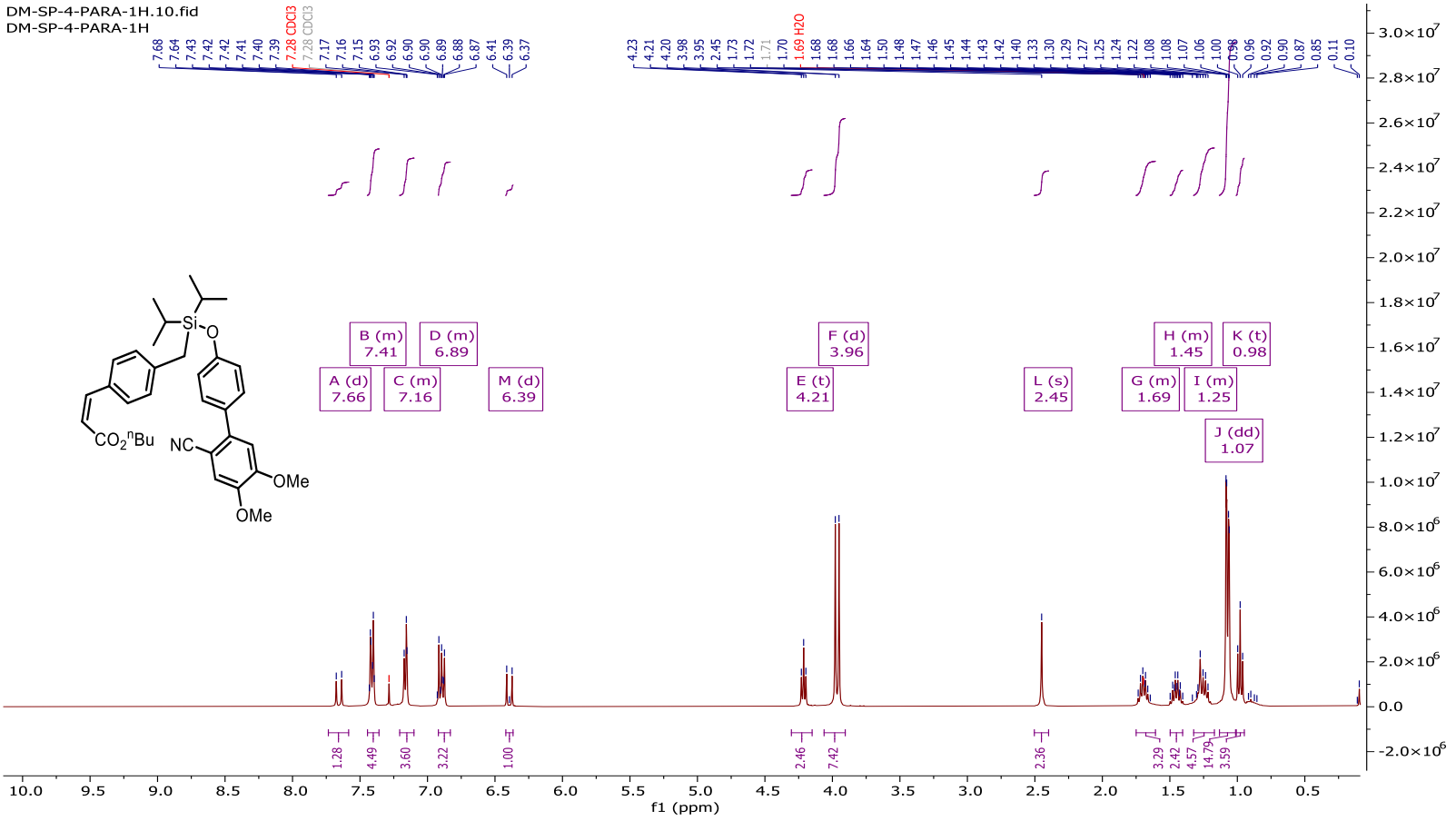
¹H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 2H), 7.60 – 7.50 (m, 3H), 7.45 (t, J = 7.7 Hz, 1H), 6.93 – 6.85 (m, 2H), 6.47 (d, J = 16.1 Hz, 1H), 4.73 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

^{13}C NMR OF meta-olefinated product (ethyl-3-(3-(((2-cyano-5-methoxyphenoxy)sulfonyl)methyl)phenyl) acrylate)



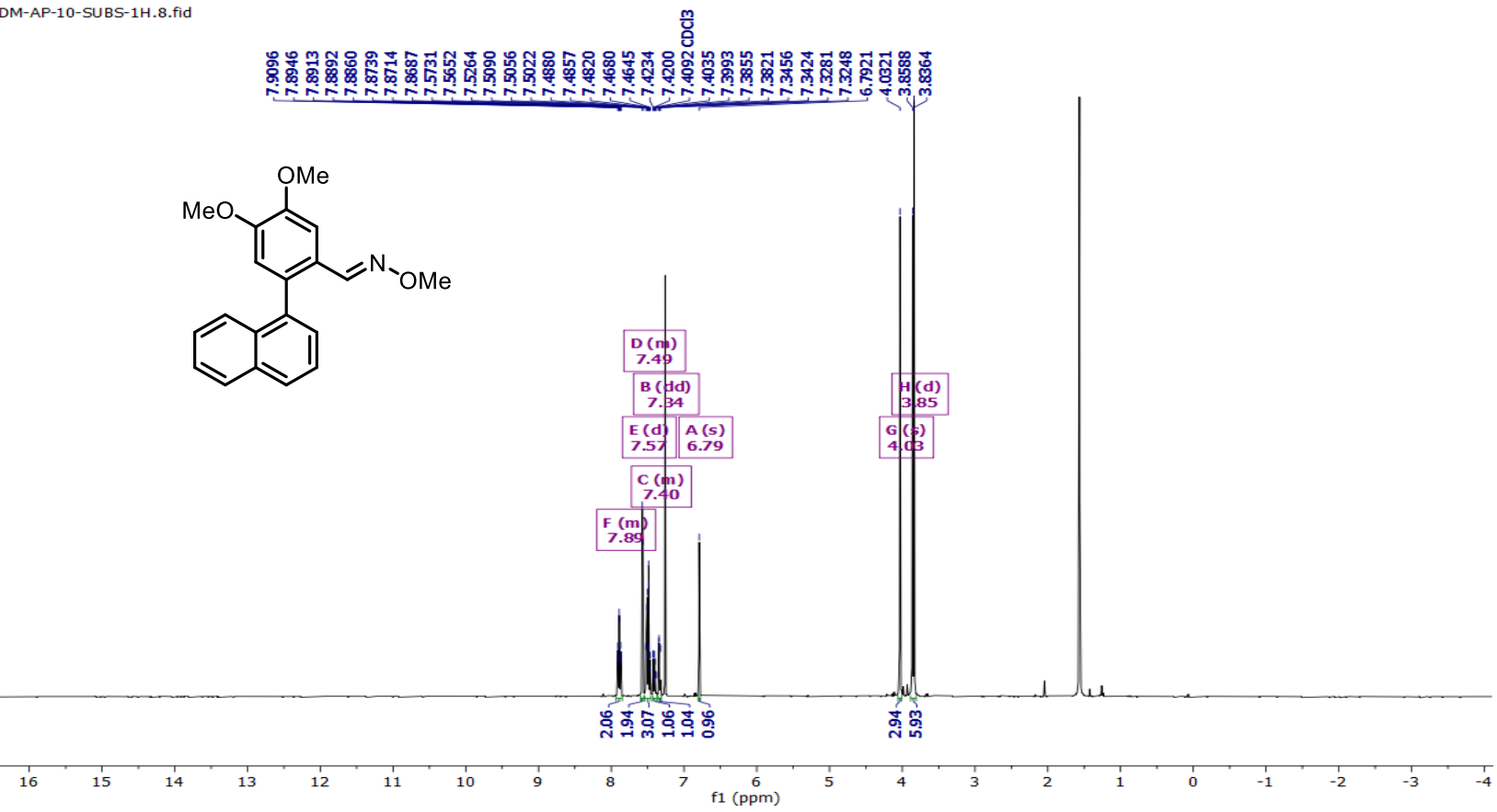
^{13}C NMR (101 MHz, $CDCl_3$) δ 166.89, 164.32, 151.78, 143.53, 135.63, 134.62, 132.81, 130.73, 129.88, 129.19, 127.44, 119.78, 115.70, 114.20, 109.38, 98.75, 60.85, 58.38, 56.31, 14.47.

¹H NMR OF para-olefinated product (*butyl 3-(4-((((2'-cyano-4',5'-dimethoxy-[1,1'-biphenyl]-4-yl)oxy)diisopropylsilyl)methyl)phenyl)acrylate****)***

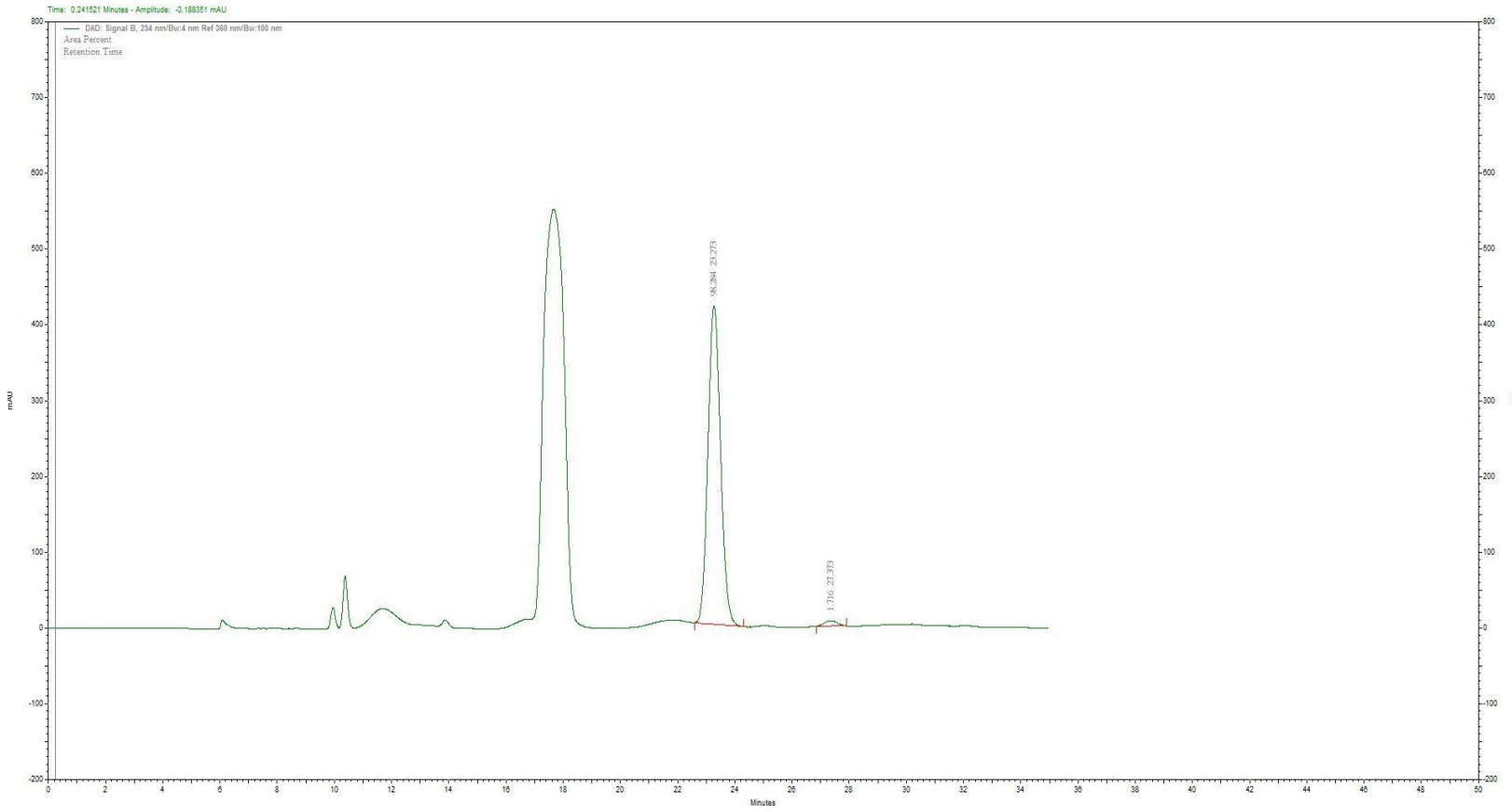


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 16.0 Hz, 1H), 7.44 – 7.36 (m, 4H), 7.21 – 7.10 (m, 4H), 6.92 – 6.83 (m, 3H), 6.39 (d, J = 16.0 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 3.96 (d, J = 11.0 Hz, 7H), 2.45 (s, 2H), 1.75 – 1.61 (m, 3H), 1.50 – 1.41 (m, 2H), 1.32 – 1.17 (m, 5H), 1.07 (dd, J = 7.5, 2.1 Hz, 15H), 0.98 (t, J = 7.4 Hz, 4H).

¹H NMR OF dimethoxy biaryl scaffold (4,5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde O-methyl oxime)



HPLC Of atroposelective olefinated biaryl imine product (*4,5-dimethoxy-2-(naphthalen-1-yl)benzaldehyde O-methyl oxime)*



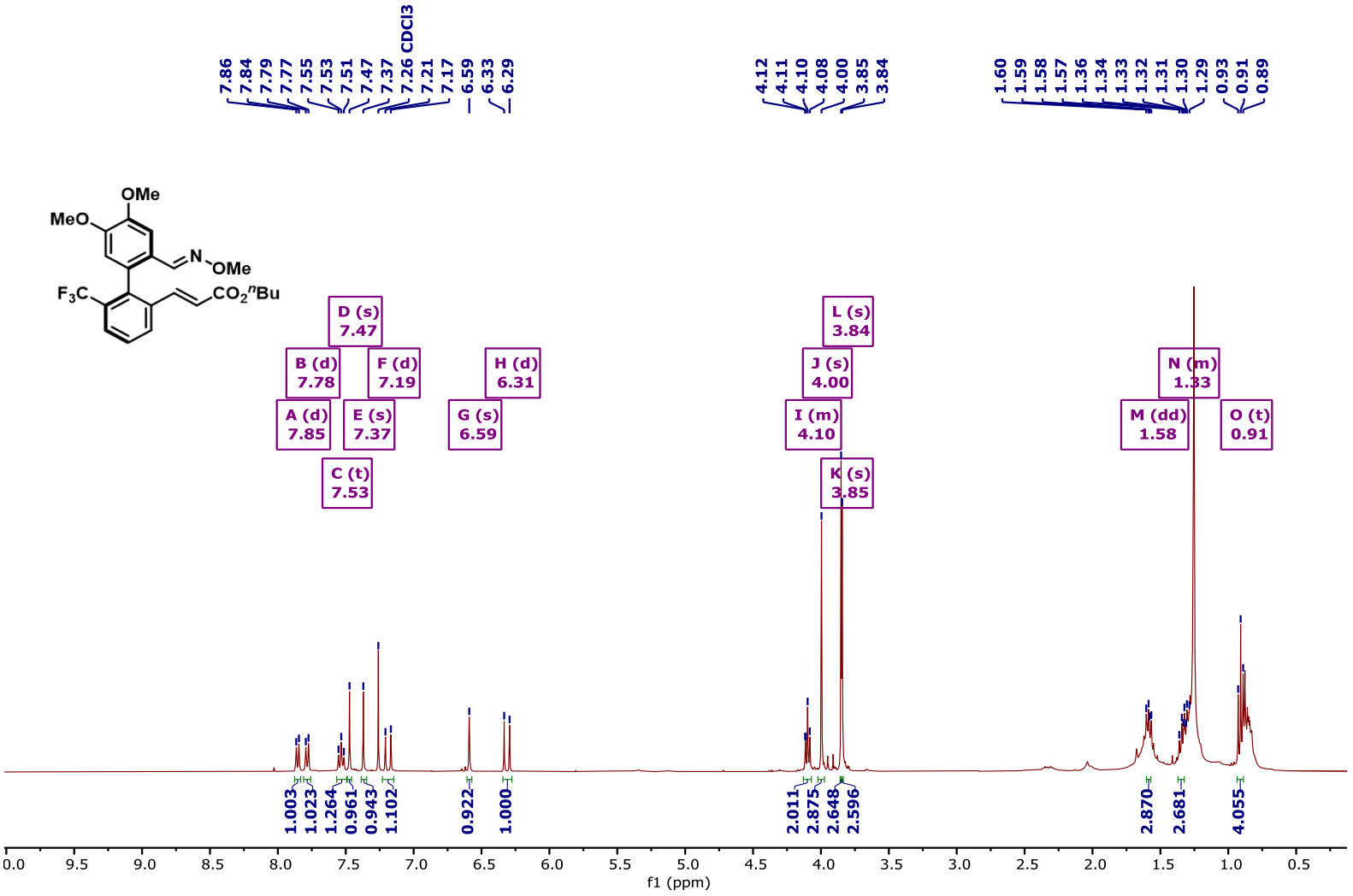
Chiral HPLC analysis:

Wavelength : 254 nm ; Column : CHIRALPAK AD-H; Elution percentage : 4 %

Method: 35 minutes; Flow rate : 1ml per minute

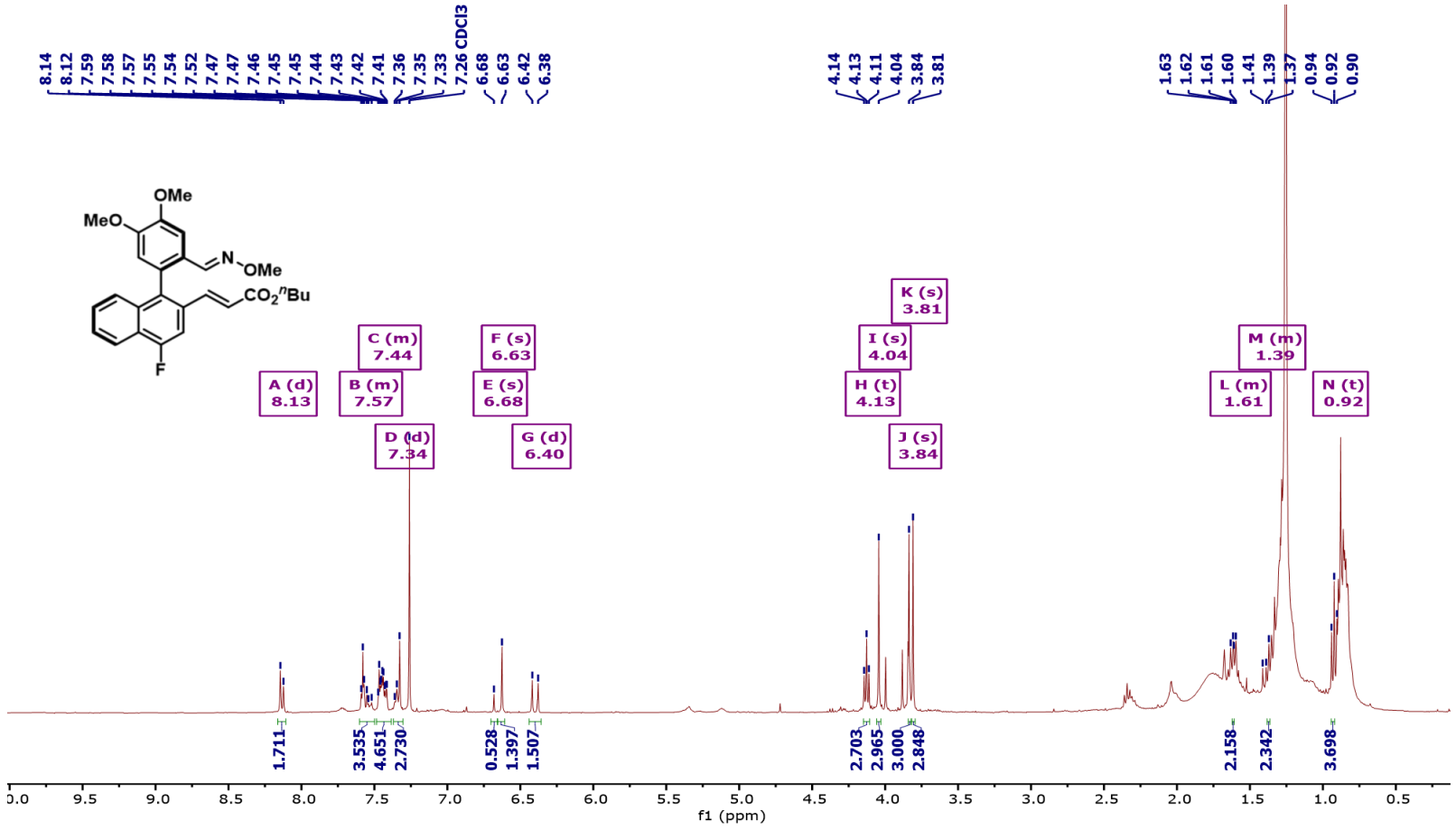
At retention time of 18 minutes, reactant peak was observed. At retention time 24 minutes and 28 minutes , two respective peaks of enantiomeric products were observed.

¹H NMR OF dimethoxy biaryl scaffold (4,5-dimethoxy-2'-(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde O-methyl oxime)



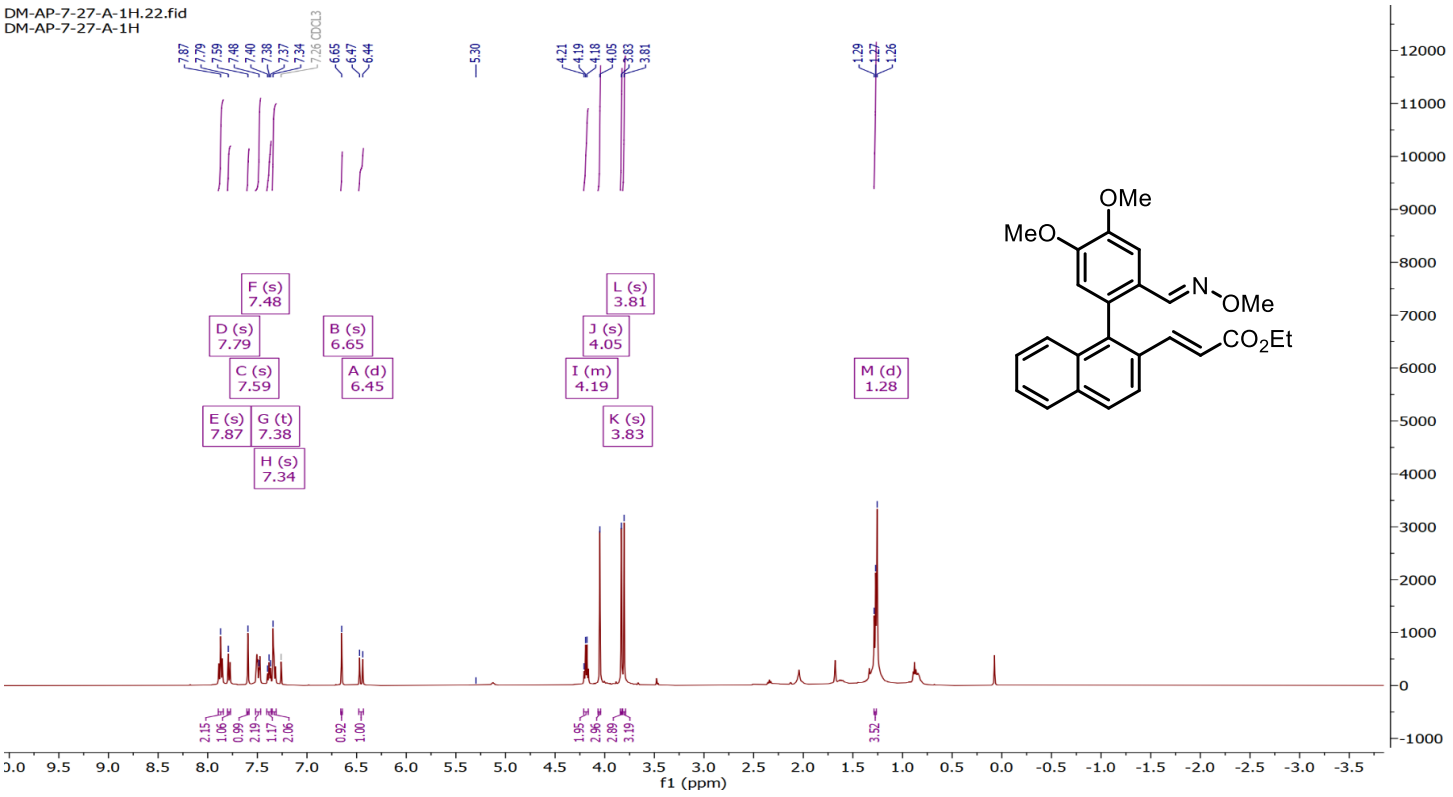
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.47 (s, 1H), 7.37 (s, 1H), 7.19 (d, *J* = 16.0 Hz, 1H), 6.59 (s, 1H), 6.31 (d, *J* = 15.9 Hz, 1H), 4.16 – 4.06 (m, 2H), 4.00 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 1.58 (dd, *J* = 8.6, 6.4 Hz, 3H), 1.37 – 1.29 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H).

¹H NMR OF biaryl olefinated product (butyl-3-(1-(4,5-dimethoxy-2-((E)-(methoxyimino)methyl)phenyl)-4-fluoronaphthalen-2-yl)acrylate)



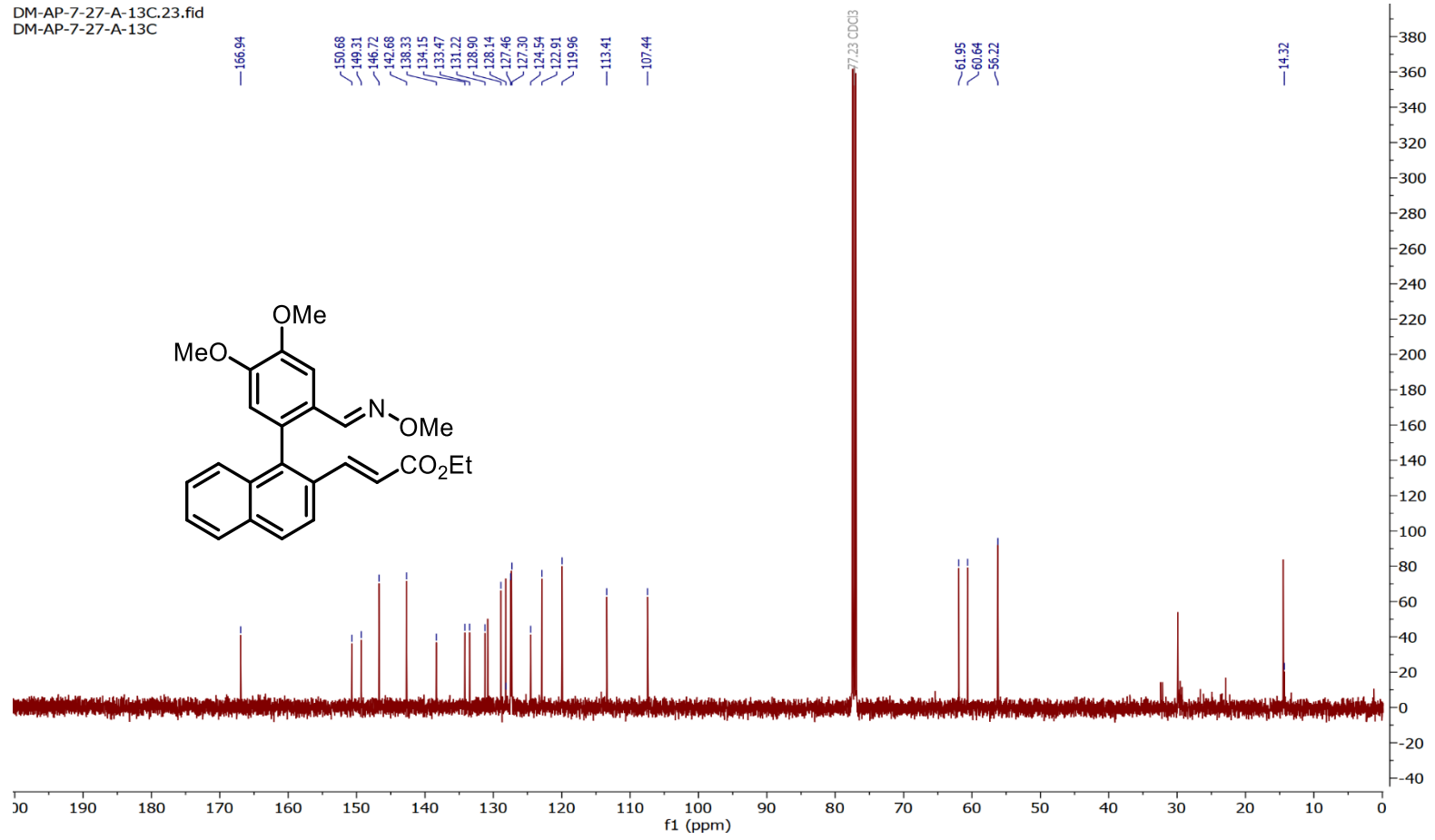
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.49 – 7.39 (m, 3H), 7.34 (d, J = 7.4 Hz, 1H), 6.68 (s, 0H), 6.63 (s, 1H), 6.40 (d, J = 15.9 Hz, 1H), 4.13 (t, J = 6.6 Hz, 2H), 4.04 (s, 2H), 3.84 (s, 2H), 3.81 (s, 2H), 1.63 – 1.59 (m, 2H), 1.45 – 1.36 (m, 2H), 0.92 (t, J = 7.4 Hz, 2H).

¹H NMR OF dimethoxy biaryl olefinated product (ethyl-3-(1-(4,5-dimethoxy-2-((E)-(methoxyimino)methyl)phenyl)naphthalen-2-yl)acrylate)



1H NMR (500 MHz, CDCl3) δ 7.87 (s, 2H), 7.79 (s, 1H), 7.59 (s, 1H), 7.48 (s, 2H), 7.38 (t, J = 7.6 Hz, 1H), 7.34 (s, 2H), 6.65 (s, 1H), 6.45 (d, J = 15.9 Hz, 1H), 4.21 – 4.17 (m, 2H), 4.05 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 1.28 (d, J = 7.1 Hz, 4H).

¹³C NMR OF dimethoxy biaryl olefinated product (ethyl-3-(1-(4,5-dimethoxy-2-((E)-(methoxyimino)methyl)phenyl)naphthalen-2-yl)acrylate)



^{13}C NMR (101 MHz, CDCl3) δ 166.89, 164.32, 151.78, 143.53, 135.63, 134.62, 132.81, 130.73, 129.88, 129.19, 127.44, 119.78, 115.70, 114.20, 109.38, 98.75, 60.85, 58.38, 56.31, 14.47.